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Editor-in-Chief
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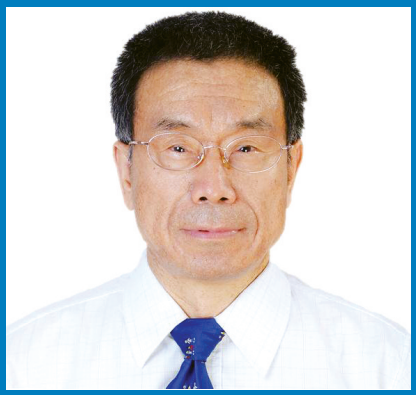
MD,PhD,DSc,
Professor, Academician
(Georgia)

GEORGIAN PEDIATRIC CARDIOLOGY ASSOCIATION

GPCA was founded on the base of TSMU pediatric clinics in 1992 and was registered in 1999. Association was founded by five persons according to Georgian Civil Codex Regulation in 1997. Association work is not limited, has independent balance in Georgian and foreign banks. Main goals of this association is early diagnostics of diseases like – Rheumatic and None-Rheumatic Cardiovascular diseases, heart ischemic diseases, myocardial infarction, different cardiomyopathy diseases, children hypertensions, Athlete's Heart and etc. Also, one of the main goals of GPCA is to help all young people who are interested in Pediatric Cardiology. Association works include bloodless instrumental research like – ECG in 15 inclinations, PCG– during load, electric velometry, capillaroscopy, rheography, echocardiography and others, research ofimmunological and genetic markers. Members of Association can be lawyers who share the goals and main principles of work. Members of GPCA have determined rights and duties: to participate in governing of Association and various projects, use the consultations and recommendations of Association, get financial support from Association funds and leave Association. The governing system of Association is represented by general meeting of the members which is held once in a year. Each member has one vote. These charters are in action after registration. So, this association has important duties and function, which is stimulated by doctor's sensitiveness and creative work in this field.

Address: LublianaN21 TBILISI(Georgia) E-mail: euscigeo@yahoo.comContact: Goerge Chakhunashvili



Editor-in-Chief
FUYONG JIAO
MD Prof and Head Children's Hospital of Shaanxi Provincial People's Hospital of Xi, an Jiaotong University, The Society of Promotion Children's Health of Shaanxi Province. Executive Councillor of ISPCAN (CHINA)

1. Shaanxi International Medical Exchange Promotion Association（SIMEA）

Date of establishment: June 1994

Registration number: 51610000520157511D

Address: No. 22, Huancheng East Road, Xincheng District, Xi'an City, Shaanxi Province

E-mail: 3105089948@qq.com

Contact: Fuyong Jiao

SIMEA was established in 1994 with the approval of the Shaanxi Provincial Department of Civil Affairs. It is a first-level social organization under the charge of the Shaanxi Provincial Health and Family Planning Commission. The concept of "seeking well-being" will give full play to the advantages and characteristics of the gathering of experts, a wide range of disciplines, and a sound network, aiming to build a platform for international medical exchanges and mutual learning.

2. Children's Hospital of Shaanxi Provincial People's Hospital

Date of establishment: 1950

Address: No. 256, Youyi West Road, Beilin District, Shaanxi Province

Contact: Fuyong Jiao

Since its establishment in 1950, the Children's Hospital of Shaanxi Provincial People's Hospital has experienced more than 70 years of development. It is now the Children's Hospital of the Third Affiliated Hospital of Xi'an Jiaotong University. It is a children's hospital integrating medical treatment, teaching, and scientific research. Shaanxi Province Kawasaki Disease Diagnosis and Treatment Center, Shaanxi Province Pediatrics Clinical Medicine Research Center, National Drug Research Institute (Children Neuromedicine Specialty), Shanghai Cooperation Organization Hospital Cooperative Alliance International Exchange Center, and China Kawasaki Disease Website (ww.chinakd.org) have been established.), European Center for Traditional Chinese Medicine (Prague). Insist on innovating the "send out and invite in" communication methods for academic exchanges and scientific research cooperation.

3.The Institution of Shaanxi Province Clinical Medicine Demonstration International Science and Technology Cooperation

Established time: 2020

Address: No. 256, Youyi West Road, Beilin District, Xi'an City, Shaanxi Province

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The Shaanxi Provincial Clinical Medicine Demonstration International Science and Technology Cooperation Base was established in 2020. It is an organization approved by the Shaanxi Provincial Department of Science and Technology to promote international cooperation and exchanges in clinical medicine and guide the province to carry out international cooperation and exchanges in clinical medicine. The cooperation base is set up in Shaanxi Provincial People's Hospital. Actively expand foreign medical resources, and provide a lasting communication channel for domestic medical and health institutions and public health service units to learn international advanced management experience and strengthen the training of talent teams.

GEORGIAN PEDIATRIC CARDIOLOGY ASSOCIATION

Shaanxi International Medical Exchange Promotion Association (SIMEA)
Children's Hospital of Shaanxi Provincial People's Hospital
Institution of Shaanxi Province Clinical Medicine Demonstration International
Science and Technology Cooperation

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PREFACE

Children is the hope of society, the future of world and mankind!

Strong children make the world strong! In order to strengthen international medical academic exchanges and improve the diagnostic and therapeutic skills of pediatricians, nurses and general practitioners around the world, the international Journal of Pediatrics was organized by the joint efforts of pediatricians and general practitioners from China, Georgia, Poland, The Czech Republic, Turkmenistan and India et al. This journal is of great clinical significance and academic value to promote international communication among pediatric medical staff and improve the diagnostic and treatment technology level of pediatric diseases. We hope that with our joint efforts and hard work, this journal will take root, sprout and grow in the world, bringing good news to the health of children around the world and benefiting children all over the world!

GEORGE CHAKHUNASHVILI (Georgia) and
FUYONG JIAO (China)

INTERNATIONAL JOURNAL OF PEDIATRIC CARDIOLOGY

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ADVANCED ARTICLE

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(PREVENTIVE CARDIOLOGY IMPORTANT CLINICAL VALUE OF ECG (ELECTROCARDIOGRAPHY) DURING THE USE OF GEORGIAN DRUGS - "APIVIT", "APIKOR", "APIPULMO" AND "APIHEPAT" IN THE POST-COVID PERIOD)

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N. JOBAVA,
K. S. CHAKHUNASHVILI,
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The possibility of initial diagnosis of the beginning of heart remodeling, i.e., right and left sided hypertrophies and dilatations, with the help of detailed analysis of ECG (electrocardiogram) is given a great role in modern preventive cardiology. In particular, the "Child Cardio-Rheumatological" service professionally implemented in children and adolescents. The "Children's Cardio-Rheumatological" service is based on staffing it with professionals and organizationally correct management. One of the most important determinants of the professionalism of doctors is the ability to meticulously analyze the methods of bloodless instrumental research of the cardiovascular system and their results.

ECG (electrocardiography) belongs to such researches, which due to its ease of use and cheapness, has not been able to find a proper place in pediatrics.

ECG is a routine method of bloodless instrumental research of the cardiovascular system available to everyone, which, with its most important data, complements the presentation of the blood circulation apparatus and, together with other studies, completes the diagnosis (1,2,3,4,5,6,7,8,9,.....71).

The aim of our research was:

Possibilities of initial diagnosis of the beginning of heart remodeling, i.e. right and left sided hypertrophies and dilatations, with the help of scopulosic analysis of ECG (electrocardiogram), during treatment with "Apivit", "Apikor", "Apipulmo" and "Apihepatis" in the post-covid period. It will definitely play an important role in preventive cardiology.

The design of the labor study included 450 children aged 0 to 18 years, who were consulted in 2020-2023 in Tbilisi, both as outpatients and in various clinics. All of them had an ECG in the post-Covid period, and in the said contingent, along with other drugs, the Georgian drugs "Apivit", "Apikor", "Apipulmo" and "Apihepati" were used, about which we read accordingly in the instructions:

APIVITI

/Registration and date R-020845 2016-11-22 - 2021-11-22/ Pharmacological group/subgroup: JG.: immunomodulators.

kv/jg.: plant origin

It is a natural high-quality and biologically active product. Each pill consists of: valine _ 5.5-6%, lysine _ 5.9-7%, leucine _ 5.8-6.7%, glutamine mg. 9.1%, cystine _ 0.6% other. on average 20% of protein in the form of albumins,

Vitamins: A, B1, B2, B5, B6, C, E, D, PP, folic acid biotin, thyrisine and others. glucoside rutin. Minerals: Fe, Mg, Cha and others.

Indication: 1. to fill the deficiency of vitamins, minerals and amino acids (in case of hypovitaminosis); 2. When adults grow in height, since it ensures the growth and development processes of the body; 3. During immunodeficiency conditions, because it has immunomodulating, immunostimulating and antimicrobial properties. 4. In case of chronic fatigue syndrome: fatigue, decrease in mental and physical performance; 5. During pregnancy and lactation. 6. During diabetes and thyroid gland pathology.; 7. During stress and nervous tension

Dosage: up to 1 year 1/4 tablet 2 times; from 1 to 3 years 1/3 tablet twice a day; from 3 to 5 years: 1/2 tablet 2 times a day; From 5 to 12 years, 1 tablet twice a day; from 12 years, 2-3 tablets. 3 times a day; The course of treatment is one month. Repeated course is recommended once every 3 months. If necessary, it is allowed to double the doses. Contraindications: individual intolerance Release form: tablet 0.35; Not covered with paint. There are 60 (30X2) tablets in the package.

APIKOR

registration # and date #p-024217 2018-09-01 - 2023-09-01 Natural complete complex is a mixture of bee (pollen,

bee milk) and grape product containing two biologically active components. It is rich in all the substances that determine the normal activity of the body.

Mechanism of action: improves the contractile function of the myocardium, enhances the cardiotrophic and therapeutic effect of cardiac glycosides; has anticholesterolemic and antioxidant effect, protects vascular walls from atherosclerotic damage, reduces the risk of developing ischemic heart disease; improves vision; regulates the exchange of vitamins, amino acids and microelements; has immunomodulating, immunostimulating and antimicrobial properties; helps to cleanse the body, improves fat metabolism and weight loss; relieves nervous tension during stress, improves sleep; Explains "Pakhmelia". Normalizes blood pressure, improves vascular regulation, stimulates hemopoiesis. A P I K O R vitamins + amino acids + microelements + grape seed contains: 22 types of amino acids, 20% protein in the form of albumins, vitamins (A, B1, B2, B5, B6, C, D, PP, E, K, folic acid), biotin, rutin, beta-sitosterol (phosphoterin), microelements (Fe, Cha, Mg, Dzn, Chu, F), glycosides, fatty acids.

Used for:

1. As an antioxidant complex during the combined treatment of diseases of the cardiovascular system and their prevention;

2. to regulate cholesterol and lipid metabolism, which protects vascular walls from atherosclerotic damage and reduces the risk of developing ischemic heart diseases, prevents the development of excess weight and premature aging processes;

3. In case of eco and radiation pathologies, it has anti-radiation and anti-carcinogenic properties.

4. for the purpose of immunocorrection;

5. To regulate protein metabolism and during hypovitaminosis (insufficient food)

6. During mental and physical overload (athletes).

Dosage: up to 1 year 1/4 tablet 2 times a day; from 1 to 3 years 1/3 tablet twice a day; from 3 to 5 years: 1/2 tablet 2 times a day; from 5 to 12 years, 1 tablet twice a day; From 12 years, 2-3 tab. 3 times a day; The course of treatment is one month. Repeated course is recommended once every 3 months. If necessary, it is allowed to double the doses. Contraindications: individual intolerance Release form: tablet 0.35; Not covered with paint. There are 60 (30X2) tablets in the package.

APIPULMO

/ Registration # and date #p-024219 2018-09-01 - 2023-09-01 /

The natural full-fledged complex contains a mixture of two products rich in biologically active components: Georgian bee products (pollen, bee milk) and conifer extract, which is rich in substances necessary for the body's construction, development and life.

Mechanism of action: regulates the exchange of vitamins, amino acids and trace elements, redox processes; enhances the utilization of oxygen by the tissue and as a result increases mental and physical performance; ensures growth and development processes of the body; improves the functioning of the reproductive system; Strengthens the body's ability to adapt to extreme and stressful factors and its protective mechanisms. has immunomodulating, immunostimulating and antimicrobial properties; Amino acids contained in the drug are easily absorbed, which helps to maintain the nitrogen balance and the growth and development of the body; Prevents premature aging. Live happily and courageously

It is a natural complete complex - vitamins + minerals + amino acids; Contains: 22 types of amino acids, 20% protein in the form of albumins, vitamins (A, B1, B2, B5, B6, C, D, PP, E, K, folic acid), biotin, rutin, beta-sitosterol (phosphoterin), trace elements (Fe, Cha, Mg, Dzn, Chu, F), glycosides, chlorophyll. It is effective: 1. during acute and chronic inflammatory diseases of the respiratory system, bronchitis, pneumonia, tuberculosis; 2. during chronic hypoxia; 4. to fill the deficiency of vitamins, minerals and amino acids (in case of hypovitaminosis); 5. When adults grow in height, since it ensures the growth and development processes of the body; 6. During immunodeficiency conditions, because it has immunomodulating, immunostimulating and antimicrobial properties. 7. In case of chronic fatigue syndrome: fatigue, decrease in mental and physical performance; 8. During pregnancy and lactation. 9. During diabetes and thyroid gland pathology.; 10. During stress and nervous tension

Dosage: up to 1 year 1/4 tablet 2 times a day; from 1 year to 3 years 1/3 tablet 2 times a day; from 3 to 5 years: 1/2 tablet 2 times a day; from 5 to 12 years, 1 tablet twice a day; from 12 years 2-3 tablets 3 times a day; The course of treatment is one month. A repeat course is recommended once every 3 months. If necessary, it is allowed to double the doses. Contraindications: individual intolerance Release form: tablet 0.35; Not covered with paint. There are 60 (30X2) tablets in the package.

APIHEPATI registration # and date #p-024218 2018-09-01 - 2023-09-01 natural complete complex is a sum of natural, natural plant components: conifer extract, bee (pollen, bee milk) and a mixture of grape products, which are necessary for the normal animal activity of the body and the prevention of various diseases

Mechanism of action: increases the body's physical and mental performance; regulates the exchange of vitamins, amino acids and microelements, redox processes; has a radioprotective effect, ensures removal of heavy metals, neutralization of free radicals and toxins; The amino acids contained in the drug are easily absorbed, which helps to maintain the nitrogen balance and ensures the growth and development processes of the body; Improves the function of the gastrointestinal tract, stomach, liver, spleen. The drug has a lipotrophic effect (removes excess fat from liver cells), restores the function of hepatocytes, prevents premature aging; has anti-radiation and anti-carcinogenic properties; has immunomodulating, immunostimulating and antimicrobial properties; APIHEPATI contains: 22 types of amino acids, 20% protein in the form of albumins, vitamins (A, B1, B2, B5, B6, C, D, PP, E, K, folic acid), biotin, rutin, beta-sitosterol (phosphoterin), microelements (Fe, Cha, Mg, Dzn, Chu, F), glycosides, chlorophyll. Fatty acids are used: 1. as a hepatoprotector, radioprotector to expel heavy metals, to neutralize free radicals and toxins; 2. In case of environmental and radiation pathologies, it has anti-radiation and anti-carcinogenic properties.; 3. To regulate protein metabolism and during hypovotamonosis (malnutrition) 4. During immunodeficiency conditions

(chronic fatigue syndrome) 5. During fatigue, mental and physical work capacity reduction and overload (athletes); 6. During the recovery period (rehabilitation) after severe and chronic diseases, infectious pathologies, operative interventions, injuries, radiation and chemotherapy; 7. In case of vision impairment, during chronic inflammatory diseases and dystrophic changes of the organ of vision; 8. During the climacteric period, infertility and impotence; 9. During diabetes and thyroid gland pathology.; 10. For the prevention of viral infections; Dosage: up to 1 year 1/4 tablet 2 times; from 1 to 3 years 1/3 tablet twice a day; from 3 to 5 years: 1/2 tablet 2 times a day; From 5 to 12 years, 1 tablet twice a day; from 12 years, 2-3 tablets. 3 times a day; The course of treatment is one month. Repeated course is recommended once every 3 months. If necessary, it is allowed to double the doses. Contraindications: individual intolerance Release form: tablet 0.35; Not covered with paint. There are 60 (30X2) tablets in the package.

Depending on the indications, in the course of treatment, we use the following combinations of drugs additionally or in isolation for a duration of 2 months:

"Apivit" + L-Carnitine + Jamgbad (in drops),

"Apicor" + L-Carnitine + Zhamgbadi (in drops),

"Apipulmo" + L-Carnitine + Jamgbad (in drops),

"Apihepati" + L-Carnitine + Zhamgbadi (in drops),

In the above-mentioned studies, along with the ECG data in the complex, a lot of attention was paid to fatigue, general weakness and cardialgia in the anamnesis.

We evaluated the reliability of quantitative indicators in work with Student's criterion (t), qualitative with x^2 criterion, comparison between groups with Pearson. The difference was considered reliable if $t>1.96$ $p<0.05$ and $x^2>3.84$, $p<0.05$ (10,11). $t>1.96$ $p<0.05$ and >3 $x^2.84$, $p<0.05$ (10,11) Mathematical assurance was carried out using SPSS software package.

In the process of reviewing the obtained results, it was found that the phases of ECG changes described by us (G.Chakhunashvili, N.Jobava at. 2019-2020-2021) in the post-covid period of children and adolescents - 0-Ia.b-IIa.b-III-IV:

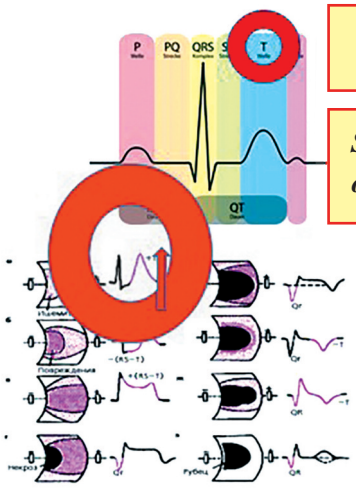
0

Thus, our many years of clinical with experience to ventricular hypertrophy, which Classically, it already exists, with all its ECGs with signs for preventive cardiology
We separate
Four possible phases of ECG changes:

- 0
- Ia - Ib
- IIa - IIb
- III
- IV

0

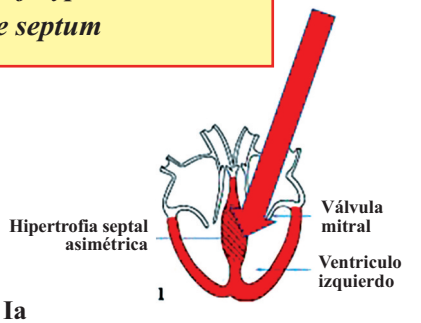
O phase
ECG signs of hypoxia and coronary without failure changes
... on the septalarea so
ECG within the age norm



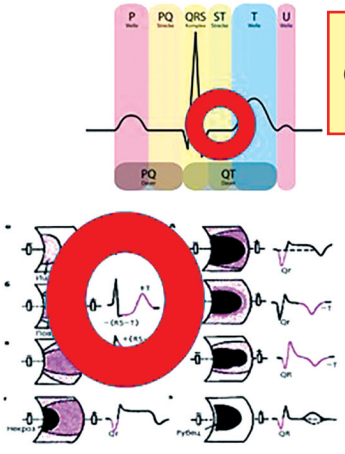
IA phase

Signs of hypoxia on the septum

$T_{V_{34}}$

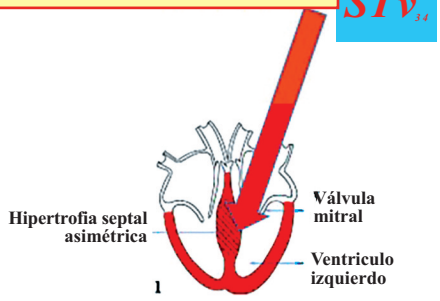


Ia



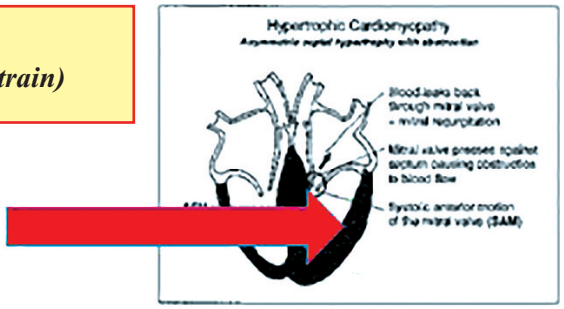
IB phase
(the ST segment is already changing)

STv_{34}



Ib

IIA phase
(left ventricular strain)

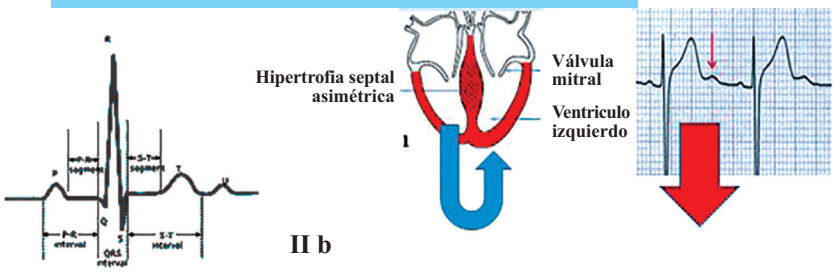


IIa

IIB phase

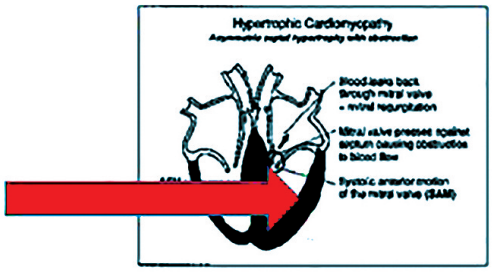
It is near the right ventricle related to - Signs of hypertension in a small circle

S V 3456



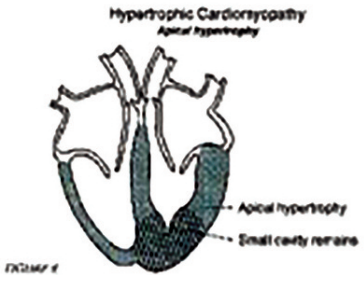
II b

III phase
(left ventricular overload)



III

***And* IV phase**
is the classical hypertrophy of the left ventricle, which should be avoided as much as possible.



IV

The percentage distribution of the number of cases according to the phases of the ECG change is as follows:

0-10%,Ia - 25%,Ib - 5%,IIa - 19%,IIb-35%,III - 5%.IV – 1%.

In these patients, the drugs "Apivit", "Apicor", "Apipulmo" and "Apihepati" were prescribed according to the relevant indications mentioned in the instructions.

The results of positive dynamics on the ECG are shown in the corresponding images:

Thus, based on the analysis of clinical and instrumental data of the material, where at $P<0.05$, we recommend the following combinations taking into account the phases of ECG changes:

0 - "Apivit" + L-Carnitine + Jamgbad (in drops)

Ia.b. - "Apicor" + L-Carnitine + Zhamgbadi (in drops)

II A.b. - "Apipulmo" + L-Carnitine + Zhamgbadi (in drops)

III. - "Apicor" + L-Carnitine + Zhamgbadi (in drops)

IV. - "Apihepati"+L-Carnitine+-Zhamgbadi (in drops)

The above examples clearly show the possibility of early diagnosis of the beginning of heart remodeling, i.e. right and left sided hypertrophies and dilatations, with the help of scopulosic analysis of ECG (electrocardiogram).

And in preventive cardiology, ECG (electrocardiography) gives significant clinical value not only in the use of Georgian drugs - "Apivit", "Apikor", "Apipulmo" and "Apihepati" in the post-covid period.

CONCLUSION:

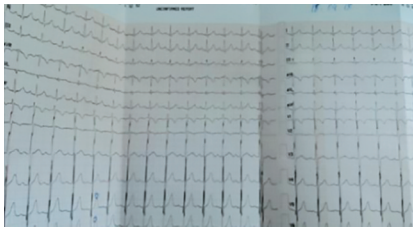
Thus, our studies have shown that

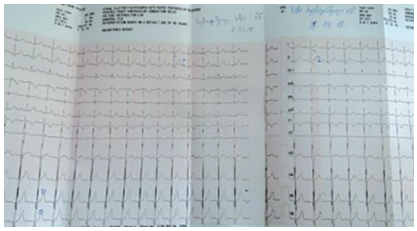
- In the age of children and adolescents, the possibility of early diagnosis of the beginning of heart remodeling, i.e. right and left sided hypertrophies and dilatations, with the help of scopule analysis of ECG (electrocardiogram) is very great.
- The diagnostic value of ECG (electrocardiography) in the use of "Apivit", "Apikor", "Apipulmo" and "Apihepati" in the post-Covid period is definitely assigned the most important role in preventive cardiology.
- "Apivit", "Apikor", "Apipulmo" and "Apihepati" are distinguished by a particularly wide range of action in children and adolescents.
- In preventive cardiology, ECG (electrocardiography) is given significant clinical value not only in the use of Georgian drugs - "Apivit", "Apikor", "Apipulmos" and "Apihepat" in the post-covid period.

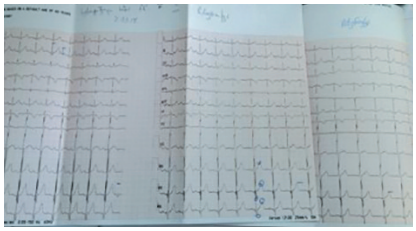
And finally, exactly such studies:

- assigns ECG (electrocardiography), with its ease of use and cheapness,

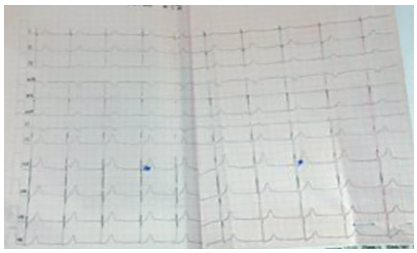
Ia

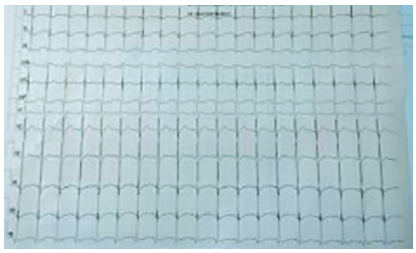




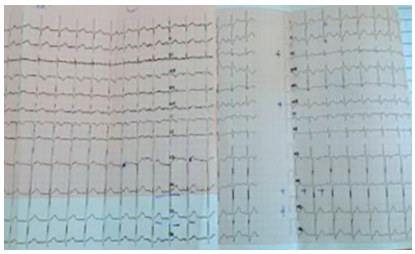


I b

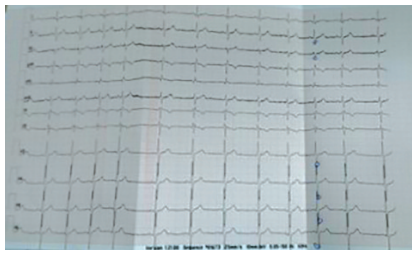




II b



III



to a dignified and appropriate place in pediatrics.

- and will defeat ECG (electrocardiographic) phobia in pediatrics.

LITERATURE:

1. "Children's Cardiology" N 13. 2019.42-46 p. Fundamentals of preventive cardiology of children and adolescents for athletes and dancers G.S. Chakhunash Vili, district Fagava, N. better Ir. Corintheli, K. Cha Khu Nash Wi Lee, d. Hug you (Tbilisi State Medical University, Association of Children's Cardiologists of Georgia) http://sppf.info/pdf/cardio-2019.pdf

2. Chemical study of a set of plants with antioxidant activity / V. Khositashvili, L. Khositashvili, N. Mindiashvili, G. Chakhunashvili, M. Sutiashvili // Georgian Chemical Journal. - Tbilisi, 2008. - ISSN 1512-0686. - N8(2). - pp. 184-185. - Resume by Kart. Rus. and Engl. in languages [MFN: 16499]

3. The science of medicine and the necessary way to its development in the XXI century "The child has the right to be protected from the germ" / Giorgi Chakhunashvili //Social, ecological and clinical pediatrics. - Tbilisi, 2009. - N11-6-5. - pp. 54-60 [MFN: 35033]

4. Development of technology, recipe and standardization method of new drug form of "Forest Nobat" / V. Khositashvili, P.A. Yavichi, G. Chakhunashvili, L. Khositashvili, L. Churadze, T. Rukhadze //Social, ecological and clinical pediatrics. - Tbilisi, 2009. - N11-6-5. - pp. 66-70 [MFN: 35042]

5. Study of general toxic action of herbal syrup "Menj-un" / G. Chakhunashvili, V. Khositashvili, L. Khositashvili, K. Mulkijanian //Social, ecological and clinical pediatrics. - Tbilisi, 2008. - N10-5-4. - pp. 29-33 [MFN: 35060]

6. The perspective of the use of pharmacological agents and biologically active nutritional supplements (Cartan, Apivit, Apicor, Apipin-Apipulmo, Apipinko-Apihepat) in athletes in the XXI century / G. Chakhunashvili, K. Chakhunashvili, N. Jobava, Kh. Lasareishvili, Z. Kakhabrishvili, D. Tabutsadze //Social, ecological and clinical pediatrics. - Tbilisi, 2007. - N9-4-3. - pp. 27-31 [MFN: 35144]

7. Georgian nutritional supplements and their physico-chemical characterization / G. Chakhunashvili, V. Khositashvili, L. Khositashvili, N. Jobava // Social, ecological and clinical pediatrics. - Tbilisi, 2005. - N7-2-1. - pp. 39-40. - Resume by Kart. [MFN: 35307]

8. Clinical-instrumental characteristics of the cardiovascular system during mucoviscidosis in children / N. Badriashvili, G. Chakhunashvili, N. Topuridze, N. Jobava, M. Khetsuriani, T. Chkheidze, st. Kvatchadze // Children's cardiology. - Tbilisi, 2007. - N1. - pp. 29-31 [MFN: 35377]

9. Euthyroid hyperplasia of the thyroid gland in children: (condition of the cardiovascular system) / L. Komshiashvili, L. Gujabidze, T. Abuladze, G. Chakhunashvili, T. Marinashvili // Children's cardiology. - Tbilisi, 2007. - N1. - pp. 46-48 [MFN: 35410]

10. Children's cardiology in the XXI century: for the prevention of cardiovascular disease in children (coronary insufficiency and its pediatric aspect) / G. Chakhunashvili, N. Jobava, K. Chakhunashvili // Children's cardiology. - Tbilisi, 2008. - N2. - pp. 9-12 [MFN: 35444]

11. Feedback on the global direction "Cardinc Risk in the Young": timely detection of premature morphofunctional changes of the cardiovascular system and modern management of training processes in adolescent athletes (footballers) / Maya Altunashvili, Giorgi Chakhunashvili // Children's Cardiology. - Tbilisi, 2008. - N2. - p. 13-14 [MFN: 35449]

12. Transient hypoxia and diagnostic value of EKG in perinatology / T. Mchedlishvili, G. Chakhunashvili, M. Jobava // Children's cardiology. - Tbilisi, 2008. - N2. - p. 19 [MFN: 35464]

13. A modern view of the management of diseases of the cardiovascular system in children and adolescents / G. Chakhunashvili, N. Jobava, K. Chakhunashvili // Children's Cardiology. - Tbilisi, 2009. - N3. - pp. 9-17 [MFN: 35489]

14. The perspective of using lectins in the medicine of the 21st century / E. Bairamov, G. Chakhunashvili // Children's cardiology. - Tbilisi, 2009. - N3. - p. 38-39 [MFN: 35502]

15. Management of training processes of highly qualified wrestlers / z. Kakhabrishvili, G. Chakhunashvili, K. Chakhunashvili // Children's cardiology. - Tbilisi, 2009. - N3. - p. 40-41 [MFN: 35514]

16. Selection of plants rich in phenolic compounds with radioprotective properties and their use for obtaining

paramedical preparations / Vazha Khositashvili, Levan Khositashvili, Nanuli Mindiashvili, Giorgi Chakhunashvili, Marine Sutiashvili // News of the Academy of Agricultural Sciences of Georgia. - Tbilisi, 2007. - ISSN 1512-2743. - December. - N21. - pp. 250-253. - Res. Rus. and Engl. [MFN: 37320]

17. Current issues of children's cardiology in Georgia and its development prospects in the 21st century / G. Chakhunashvili // Social Pediatrics. - Tbilisi, 2003. - N4. - p. 13-14 [MFN: 37543]

18. Course of the Georgian National Section of Eurosciences (safety of children and adolescents in a scientific way, medicine and sports) / G. Chakhunashvili // Social, ecological and clinical pediatrics. - Tbilisi, 2010. - N12-7-6. - pp. 29-30. - Text in Kart. and Engl. in language [MFN: 55626]

19. Necessity of drinking "Iveriuliphyto" in the process of sports training / K. Chakhunashvili, N. Jobava, N. Topuridze, Z. Shakarashvili, G. Chakhunashvili //Social, ecological and clinical pediatrics. - Tbilisi, 2010. - N12-7-6. - p. 35 [MFN: 55634]

20. ST-segment and T-tooth in healthy children and some inflammatory and non-inflammatory diseases in pediatrics (prospects of using NEHB sections in pediatrics issues of preventive cardiology) / G. Chakhunashvili, K. Chakhunashvili, N. Jobava // Children's cardiology. - Tbilisi, 2010. - N4. - pp. 9-23 [MFN: 55728]

21. Functional state of the cardiovascular system during hidden vegetative dysfunction and vascular hyperreactivity in sports children and adolescents: [in issues of diagnosis, treatment and prevention] / G. Chakhunashvili, I. Dolidze, T. Gogatishvili // Children's cardiology. - Tbilisi, 2010. - N4. - pp. 39-41 [MFN: 55738]

22. Unified management of medicine, sports and education system is necessary: interview / Giorgi Chakhunashvili; Interviewed by Neli Darbaidze // Georgian elite: public and political magazine. - Tbilisi, 2010. - August. - N5(65). - pp. 57-58 [MFN: 70789]

23. Cardiovascular system damage in juvenile rheumatoid arthritis: (review) / G. Chakhunashvili, N. Jobava, M. Lekishvili and K. Chakhunashvili // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2011. - ISSN 1987-9857. - N5. - pp. 8-16. - Children's cardiology. - Summary in Eng. and Kart. [MFN: 81401]

24. Characterization of the data obtained by capillaroscopy and cardiointervalography / G. Chakhunashvili, N. Jobava // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2011. - ISSN 1987-9857. - N5. - pp. 16-24. - Children's cardiology. - Resume by Kart. and Engl. [MFN: 81403]

25. Anthropometric, physical and functional characteristics of athletes and the functional state of the cardiovascular system against the background of the action of "Iveriuli-phytos" energy drink enriched with amino acids / G. Chakhunashvili, N. Jobava, N. Topuridze, K. Chakhunashvili, N. Badriashvili, Z. Shakrashvili, G. Tskvediashvili, Ir. Kalandia, Z. Pkhaladze // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2011. - ISSN 1987-9857. - N5. - pp. 24-32. - Children's cardiology. - Summary in Eng. and Kart. [MFN: 81405]

26. Immune status during bronchopneumonias developed on the background of thymomegaly in children / G. Chakhunashvili, M. Topuridze, N. Badriashvili, N. Jobava, N. Tofuridze //Georgian Respiratory Journal. - Tbilisi, 2010. - ISSN 1512-2778. - Volume 6. Addendum 1, Sat. resp. Assoc. II joint. Congress abstracts. - p. 16. - Summary in Eng. [MFN: 108151]

27. Timely detection of early morphofunctional (adaptive, pathological) changes in the cardiovascular system and modern management of training processes in adolescent athletes (football players): (literature review) / G. Chakhunashvili, N. Jobava, K. Chakhunashvili, Ig. Dolidze, Z. Pkhaladze, T. Gogatishvili // Children's Cardiology / Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2012. - ISSN 1987-9857. - N6. - pp. 15-20. - Summary in Eng. and Kart. En.. - list of scientific literature cited in the work p. 18-19 [MFN: 116808]

28. Functional state of the cardiovascular system during hidden vegetative dysfunction and vascular hyperreactivity in sports children and adolescents (issues of diagnosis, treatment and prevention): (literature review) / G. Chakhunashvili, N. Jobava, K. Chakhunashvili, Ig. Dolidze, Z. Pkhaladze, T. Gogatishvili // Children's Cardiology / Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2012. - ISSN 1987-9857. - N6. - pp. 20-24. - Resume by Kart. and Engl. En.. - list of scientific literature cited in the work p. 22-24 [MFN: 116812]

29. Diagnostic value of arrhythmias and mitral valve prolapse in children and adolescents in modern pediatric cardiology / G. Chakhunashvili, N. Jobava, M. Shvangiradze, M. Inasaridze, A. Bliadze, T. Gogatishvili // Children's Cardiology / Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2012. - ISSN 1987-9857. - N6. - pp. 25-27. - Res. Geo. and Mngl. En.. - scientific lit. List p. 26 [MFN: 116816]

30. Comparative analysis of physical and functional indicators of basketball players against the background of the action of "Apikori" / G. Chakhunashvili, N. Jobava, N. Topuridze, N. Badriashvili, Z. Shakarashvili, K. Chakhunashvili // Children's Cardiology / Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2012. - ISSN 1987-9857. - N6. - pp. 30-32. - Res. Geo. and Engl. En.. - lit. p. 32 [MFN:

31. Immune homeostasis and its correction with apipulmot during acute respiratory viral infections in children / G. Chakhunashvili, N. Topuridze, N. Jobava, N. Badriashvili, K. Chakhunashvili, T. Khodel // Social, ecological and clinical pediatrics. - Tbilisi, 2012. - ISSN 1987-9865. - N14-9-8. - pp. 27-29. - Original articles. - Resume by Kart. and Engl. En.. - lit. p. 28. - nine 1. - Nine. 2. - Nine. 3[MFN: 116890]

32. Efficacy of "Apihepat" in the complex treatment of bronchopneumonia / G. Chakhunashvili, N. Topuridze, N. Jobava, N. Badriashvili, K. Chakhunashvili // Social, ecological and clinical pediatrics. - Tbilisi, 2012. - ISSN 1987-9865. - N14-9-8. - pp. 30-32. - Original articles. - Resume by Kart. and Engl. En.. - lit. p. 31. - Table 1 [MFN: 116892]

33. Changes of ST segment and T tooth in different age groups of healthy children / G. Chakhunashvili, N. Jobava // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 11-18. - Summary in Eng. and Kart. in language [MFN: 143888]

34. Assessment of the physical and functional condition of athletes against the background of Api Pulmo and Apicor / D. Chakhunashvili, K. Chakhunashvili, G. Chakhunashvili, N. Jobava, N. Topuridze, N. Badriashvili, Z. Shakarashvili, Z. Pkhaladze // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 19-22. - Summary in Eng. and Kart. in the language. - lit. p. 22 [MFN: 143894]

35. EKG parameters (ST and T wave) and capillaroscopic parameters during diabetes mellitus type I in children / d. Chakhunashvili, K. Chakhunashvili, G. Chakhunashvili, N. Jobava // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 23-26. - Summary in Eng. and Kart. in language [MFN: 143895]

36. ECG Parameters (ST segment and T tooth) in diabetes mellitus type I, some inflammatory and other non-inflammatory diseases in childhood / d. Chakhunashvili, K. Chakhunashvili, G. Chakhunashvili, N. Jobava // Children's Cardiol-

ogy: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 26-32. - Summary in Eng. and Kart. in the language. - lit. pp. 30-31 [MFN: 143900]

37. The frequency of mitral valve prolapse, etiopathogenesis, determination of the degree of involvement in the pathogenic process of diseases and its discussion in the context of arrhythmias / D. Chakhunashvili, K. Chakhunashvili, G. Chakhunashvili, N. Jobava, M. Shvangiradze, M. Inasaridze // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 32-37. - Summary in Eng. and Kart. in the language. - Three too. Lit. pp. 36-37 [MFN: 143902]

38. Necessity of deep clinical analysis of ST segment and T tooth changes, in the presence of ventricular repolarization, premature partial syndromes and P-Q interval shortening in children and adolescents / d. Chakhunashvili, K. Chakhunashvili, G. Chakhunashvili, N. Jobava // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 39-41. - Summary in Eng. and Kart. in the language. - lit. pp. 39-40 [MFN: 143904]

39. Arterial hypertension in children's age/ c. Chakhunashvili, R. Svanadze, A. Bliadze // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 41-48. - Summary in Eng. and Kart. in the language. - lit. p. 47 [MFN: 143926]

40. Violation of heart rhythm and conduction in children: (modern principles of their management) / G. Chakhunashvili, M. Khutsuriani, N. Jobava // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 48-56. - Summary in Eng. and Kart. in language [MFN: 143928]

41. Possibilities of including the immunotherapeutic drug "GA-40" in the treatment of infectious pathologies in pediatric cardiology / D. Chakhunashvili, K. Chakhunashvili, G. Chakhunashvili, N. Jobava // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 77-78. - Summary in Eng. and Kart. in language [MFN: 143940]

42. Development prospects of sports valeology / Ib. Dolidze, G. Chakhunashvili // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2013. - ISSN 1987-9857. - N7. - pp. 79-81. - Resume in Russian. English and Kart. in the language. - lit. pp. 80-81 [MFN: 143941]

43. The state of the immune system and its correction with Apivit during euthyroid gout / G. Chakhunashvili, K. Chakhunashvili, N. Topuridze, N. Badriashvili, S. Ghlonti // Social, ecological and clinical pediatrics. - Tbilisi, 2013. - ISSN 1987-9865. - N15-10-9. - pp. 49-51. - Resume by Kart. and Engl. in the language. - lit.

44. Necessity of "Api Puri" in the diet of athletes and pregnant women / G. Chakhunashvili, K. Chakhunashvili, D. Chakhunashvili, N. Badriashvili, M. Topuridze, N. Jobava, Z. Pkhaladze, Ir. Kalandia // Social, ecological and clinical pediatrics. - Tbilisi, 2013. - ISSN 1987-9865. - N15-10-9. - pp. 54-62. - Resume by Kart. and Engl. in language [MFN: 144073]

45. Immune homeostasis during ongoing bronchopneumonia with thymomegaly in children against the background of apihepatitis treatment/ c. Chakhunashvili, K. Chakhunashvili, N. Topuridze, N. Badriashvili // Social, ecological and clinical pediatrics. - Tbilisi, 2013. - ISSN 1987-9865. - N15-10-9. - pp. 84-86. - Summary in Eng. and Kart. in language [MFN: 144152]

46. The condition of basketball players before inclusion in the Epicurit diet: (Stage I of the study) / G. Chakhunashvili, D. Chakhunashvili, K. Chakhunashvili, N. Jobava, N. Topuridze, Ir. Kalandia, Z. Pkhaladze //Social, ecological and clinical pediatrics. - Tbilisi, 2013. - ISSN 1987-9865. - N15-10-9. - pp. 86-88. - Summary in Eng. and Kart. in language [MFN: 144159]

47. The condition of basketball players after joining the "Apipur" nutrition program: (Stage I-II of the study) / G. Chakhunashvili, D. Chakhunashvili, K. Chakhunashvili, N. Badriashvili, M. Topuridze, N. Jobava, Ir. Kalandia, Z. Pkhaladze // Children's Cardiology: Journal of the Association of Children's Cardiologists of Georgia. - Tbilisi, 2014. - ISSN 1987-9857. - N8. - pp. 18-20. - Original articles and scientific activities. - Resume by Kart. and Engl. in language [MFN: 162677]

48. Assessment of anthropological, physical and functional indices in sportsmen (basketball players) against the background of high physical loading.

Chakhunashvili G, Jobava N, Guchashvili M, Chakhunashvili K, Gogilashvili T, Shvangiradze M, Pagava K.

Georgian Med News. 2011 Jul-Aug; (196-197):12-8.

49. The 26th International Pediatric Association Congress of Pediatrics; South Africa, August 4-9.2010 "The clinical significance of ST-segment deviation and T wave changes in children" (abstract). - G. Chakhunashvili, n, jobava, k. Chakhunashvili

50. "USE OF BNP AND NT_PROBNP IN EARLY STAGE DIAGNOSIS OF ATHLETE'S CARDIOVASCULAR PATHOLOGIES : LITERATURE OVERVIEW." - Ilia NadareiSvili, George Chakhunashvili; journal of the Georgian pediatric cardiology association #4 pages:30-38 2010

51. „ST სეგმენტის, T კბილის, და Q-T ინტერვალის თანამედროვე პრობლემები ბავშვთა და მოზარდთა კარდიოლოგიაში" — გ.ჩახუნაშვილი, ნ.ჯობავა, კ.ჩახუნაშვილი - საქართველოს ბავშვთა კარდიოლოგითა ასოციაციის ჟურნალი №4 გვ:9-28 2010წ

52. „გულ-სისხლძარღვთა სისტემის ფუნქციური მდგომარეობა ფარული ვეგეტატიური დისფუნქციისა და სისხლძარღვოვანი ჰიპერრეაქტიულობის დროს სპორტსმენ ბავშვებსა და მოზარდებში (დიაგნოსტიკის, მკურნალობისა და პრევენციის საკითხები)" - გ.ჩახუნაშვილი, ი.დოლიძე, თ.გოგატიშვილი; საქართველოს ბავშვთა ცარდიოლოგთა ასოციაციის ჟურნალი №4 გვ:39-41 2010წ

54. „ბავშვთა კარდიოლოგია XXI საუკუნეში, კორონარული უკმარისობა და მისი პედიტრიული ასპექტი" - გ.ჩახუნაშვილი, ნ.ჯობავა, კ.ჩახუნაშვილი; საქართველოს ბავშვთა კარდიოლოგითა ასოციაციის ჟურნალი №2 გვ:9-12; 2008

55. „გულ-სისხლძარღვთა სისტემის ნაადრევ მორფო-ფუნქციურ ცვლილებათა დროული გამოვლენა დასაწვრთო პროცესების თანამედროვე მართვა მოზარდ სპორტსმენებში" - მ.ალთუნაშვილი, გ.ჩახუნაშვილი; საქართველოს ბავშვთა კარდიოლოგთა ასოციაციის ჟურნალი №2 გვ:13-14; 2008წ

56. "cardiovascular system in the sports-children holding prevention arrangments against week rings" - G.chakhunashvili, N.jobava, D.fruidze, D.tabutsadze,M.chkhaidze; journal of the Georgian pediatric cardiology association # 2; page:15-18; 2008

57. Martin A: Apports nutritionnels conseillés pour la population française. (3ème Ed). Paris, Ed Tec & Doc 608p.2001.

58. Rokitzki L, Logemann E, Sagredos AN, Murphy M, Wetzel-Roth W, Keul. J: Lipid peroxidation and antioxidant vitamins under extreme endurance stress. Acta Physiol Scand151 :149– 158,1994

59. Hill AC, Miyake CY, Grady S, Dubin AM. 2011

60. Effects of a single session of resistance exercise training on specific cardiac and oxidative stress markers

61. Tschan Harald, Vidotto Claudia, Atamaniuk Johanna, Kinzelbauer Markus, Wessner Barbara and Bachl Norbert - Center of Sport Sciences and Univversity Sports – Department Sport-

physiology, University of Vienna, Austria, BKW Laboratory Medicine, Vienna, Austria, 3 Social Medical Center South – Department of Laboratory Diagnostics, Vienna, Austria

62. "Cardiovascular system in the sports – children holding prevention arrangements against week rings". G. Chakhunashvili, N. Jobava, D. Pruidze, D. Tabutsadze, V. Kandelaki, M. Chichaidze. Pediatric clinic of State Medical University Tbilisi, Georgia. Profilactic Center for Mother and Child Tbilisi, Georgia

63. Функциональные изменения сердца юных спортсменов: профилактика и коррекция. Медицинский научный и учебно-методический журнал. Корнеева И.Т., Поляков С.Д., НЦЗД РАМН, Москва 2005г.

64. Детская спортивная медицина. Андреева Т. Г., Феникс, Москва 2007г.

65. Pediatric Cardiology. Walter H. Johnson, James H. Moller. ISBN-13: 9780781728782. 2001 y. 326 pages.

66. Pediatric Cardiology. Victoria Vetter, MD; Professor of Pediatrics; The University of Pennsylvania School of Medicine; Chief; Division of Cardiology; The Children's Hospital of Philadelphia, Philadelphia, PA., publication date: FEB-2006 y. 384 pages.

67. Hill AC, Miyake CY, Grady S, Dubin AM. Accuracy of interpretation of preparticipation screening electrocardiograms. J Pediatr. 2011, Jul 9.

68. . Мурашко, В.В. Электрокардиография: Учебн. пособие / В.В. Мурашко, А.В. Струтынский. – 8-е изд. – М.: МЕДпресс-информ, 2007. – 320 с.: ил

69. D.Corrado Publications http://www.labome.org/expert/italy/university/corrado/d-corrado-202830.html

70. Nino Jobava, George chakhunashvili-"clInIcal-InStruMental cHaracterIZatIonS of carDIoVaScular SYSteM DurInG SoMe conGenItal, InflaMMatorY anD acQuIreD nonInflaMMatorY DISeaSeS In cHIlDHooD anD PoSSIbIlItIeS of tHe InvolveMent of PreParatIon Ga-40 In tHe treatment" International Journal OF Pediatric Cardiology"2021.N1 p5-15

71. "Pediatric Cardiology" N 19. 2022.11-19p. "Important clinical value of ECG (electrocardiography) during the use of Georgian drugs - "Apivit", "Apikor", "Apipulmo" and "Apihepat" in the post-covid period(Preventive cardiology)

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SUMMARY

POSSIBILITIES OF INITIAL DIAGNOSIS OF THE BEGINNING OF HEART REMODELING, I.E. RIGHT AND LEFT SIDED HYPERTROPHIES AND DILATATIONS, WITH THE HELP OF SCOPULOSIC ANALYSIS OF ECG (ELECTROCARDIOGRAM).

(PREVENTIVE CARDIOLOGY - SIGNIFICANT CLINICAL VALUE OF ECG (ELECTROCARDIOGRAPHY) IN THE USE OF GEORGIAN DRUGS - "APIVIT", "APIKOR", "APIPULMOS" AND "APIHEPAT" IN THE POST-COVID PERIOD)

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The possibility of initial diagnosis of the beginning of heart remodeling, i.e. right and left sided hypertrophies and dilatations, with the help of scopulosic analysis of ECG (electrocardiogram) is given a great role in modern preventive cardiology.

Based on the above, the aim of the research was to

Possibilities of initial diagnosis of the beginning of heart remodeling - i.e. right and left sided hypertrophies and dilatations, with the help of scopulosic analysis of ECG (electrocardiogram). And this was demonstrated by the diagnostic value of ECG (electrocardiography) in "epivitis", "apikor", "apipulmos" and "epihepatitis". "When used in the post-Covid period, which will definitely be given the most important role in preventive cardiology.

The design of the labor study included 450 children aged 0 to 18 years, who were consulted in 2020-2023 in Tbilisi, both as outpatients and in various clinics. All of them had an ECG taken in the post-Covid period in 12 normal sections, and Georgian drugs "Apivit", "Apikor", "Apipulmo" and "Apihepati" were used along with other drugs in the said contingent. In the studies, along with the ECG data in the anamnesis, great attention was paid to fatigue, general weakness and cardialgia. In the work, we evaluated the reliability of the quantitative indicators with the Student's criterion (t), the qualitative one with the □2 criterion, and the comparison between groups with Pearson. The difference was considered reliable if t>1.96 p<0.05 and □2>3.84, p<0.05 (10,11). t>1.96 p<0.05 and >3□2.84, p<0.05 (10,11) Mathematical assurance was carried out using SPSS software package.

In the process of reviewing the obtained results, it was found that the phases of ECG changes described by us (G.Chakhunashvili, N.Jobava at. 2019-2020-2021) in the post-covid period of children and adolescents - 0-Ia.b-IIa. B-III-IV:

The percentage distribution of the number of cases according to the phases of the ECG change is as follows:

0-10%,Ia - 25%,Ib - 5%,IIa - 19%,IIb-35%,III - 5%.IV – 1%.

Our studies have shown that

- In the age of children and adolescents, the possibility of early diagnosis of the beginning of heart remodeling, i.e. right and left sided hypertrophies and dilatations, with the help of scopule analysis of ECG (electrocardiogram) is very great.
- The diagnostic value of ECG (electrocardiography) in the use of "Apivit", "Apikor", "Apipulmo" and "Apihepat" in the post-Covid period is definitely assigned the most important role in preventive cardiology.
- "Apivit", "Apikor", "Apipulmo" and "Apihepati" are distinguished by a particularly wide range of action in children and adolescents.
- In preventive cardiology, ECG (electrocardiography) is given significant clinical value not only in the use of Georgian drugs - "Apivit", "Apikor", "Apipulmos" and "Apihepat" in the post-covid period.

And finally, exactly such studies:

- assigns ECG (electrocardiography), with its ease of use and cheapness, to a dignified and appropriate place in pediatrics.
- and will defeat ECG (electrocardiographic) phobia in pediatrics.

ORIGINAL ARTICLES AND SCIENTIFIC ACTIVITIES IN PEDIATRICS

RESEARCH PROGRESS IN TRADITIONAL CHINESE MEDICINE OF KAWASAKI DISEASE

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ABSTRACT:

Objective: This review is to explore the role of TCM in the management of KD.

The pathogenesis of KD is still unclear, and it is mainly believed to be related to genetics, immunity and infection there is no specific drug in treatment, and the overall principle is to control inflammation and minimize the risk of coronary aneurysm.

Methods: The relevan published articles, data and information of KD at home and abroad were collected from the Internet,and management of KD were compared and analyzed to compare the role of TCM.

Results: there is no unified standard for the usage and dosage of gamma globulin, aspirin and glucocorticoid in the acute stage, and they have certain toxic and side effects, and they are different in different countries.

CONCLUSION

As a traditional medical means in China, traditional Chinese medicine has shown advantages in the treatment of this disease, and its research progress is summarized as follows.

KEY WORDS: Kawasaki Disease, management,traditional Chinese medicine

INTRODUCTION

Kawasaki Disease (KD) is a kind of acute fever mucocutaneous lymph node syndrome with lymph node involvement and finger and toe peeling [1]. It was first diagnosed and studied by Japanese doctor Tomisaku Kawasaki [2], and it is the main cause of acquired heart disease in children in many countries, among which Japan is the leader. The incidence rate of children within 5 years of age is about 1% [3]. Currently, there is no accurate national data on KD incidence in China [4]. A survey shows that Kawasaki disease is a relatively common disease in Shaanxi Province of China, and Xi 'an is a high incidence area [5], with the characteristics of the morbidity group similar to Japan [6].

The pathogenesis of KD is still unclear, and it is mainly believed to be related to genetics, immunity and infection [8]. There is no specific drug in treatment, and the overall principle is to control inflammation and minimize the risk of coronary aneurysm [1]. Although its acute usage and dosage have no uniform standard, and present great differences in various countries [2]. As a traditional medical means in our country, TCM presents advantages in the treatment process of this disease, and its research progress is summarized as follows.

1, ETIOLOGY AND PATHOGENESIS

There is no corresponding name for Kawasaki disease in traditional Chinese medicine books. According to its clinical characteristics, such as acute fever, chapped lips, strawberry tongue, rash, erythema, and stiff and swollen limbs, most scholars treat Kawasaki disease as "warm disease" [9], and some scholars think it belongs to the category of "epidemic rash" [10] or "macular rash" [11], which is caused by warm and hot pathogenic poison that impinges on human body and damages lung and stomach. Changes in the course of the disease disturb blood flow and involve all viscera [2].

SECOND, TREATMENT

(1) Treatment by stages

Chen [12] divided the stages of disease into three stages according to the dialectical theory of Weiqi and blood camp, and gave different TCM decoction respectively. The study found that the symptoms, TNF-α, IL-6, CRP, etc. of the group treated with TCM decoction had advantages compared with the group treated with Western medicine alone. Wang [13] used the same syndrome differentiation method for staging, and added 5, 10 and 21 days as the course of the disease. He studied 72 patients and found that the combination of TCM treatment had advantages in improving clinical symptoms, shortening the course of the disease, and improving coronary artery dilation. Zhang [14] conducted a clinical study on 109 patients and found that compared with western medicine alone, the recovery of white blood cells, platelets, sedimenta-

tion rate and so on had obvious advantages in the integrated treatment of Chinese and western medicine combined with the staging treatment of Weiqi and Yingxue dialectical treatment, and the incidence of myocardial injury was significantly reduced. In general, the staging theory of KD takes the syndrome differentiation of qi and blood as the key line, and determines the staging according to the law of disease course. Although it is against the idea of TCM individualized syndrome differentiation, it is more convenient for clinical promotion and application

2. Treatment based on symptom differentiation

Li [15] carried out stage treatment according to syndrome differentiation of Weiqi and blood. Yinqiao SAN was selected in the early stage of the disease, Qingwen and Duduyin was selected in the middle stage, and Zhuye Plaster Decoction and Qinghao Bijia decoction were selected in the convalesce stage. The combination of traditional Chinese and Western medicine has advantages in improving clinical symptoms and regulating immune disorders compared with simple western medicine. Wang [16] applied Qingying Decoction to the treatment of burnt KD of Qi Ying and found that the treatment effect was better than that of Western medicine alone. Sha's [17] treated burnt KD with Huanglian Jiedu Decoction and Baihu decoction, and found that it had advantages in inhibiting the levels of peripheral blood NT-proBNP, PCT and CRP, improving the symptoms of the children, and reducing the incidence of coronary artery injury. Wang [18] used Fuzheng Xiaoyu method to treat KD with Qi and Yin injuries and found that there was no statistical difference between intravenous injection of Danshen injection combined with Fuzheng Xiaoyu Decoction and aspirin. Wang [19] treated 60 cases of convalescent Kawasaki disease syndrome with Danshen Shengmai Decoction and found that it had significant effects on improving symptoms, reducing platelet and esR, restoring abnormal electrocardiography, and improving coronary artery dilation. Yang [20] searched KD related theme words based on TCM syndrome differentiation, collected and built a database, and statistically found that the syndrome types of Wei Qi with the same disease, Qi ying with burnt and qi Yin with two injuries were the most common. In the initial treatment, most of them were Xin Liang to clear the surface, clearing heat and detoxifying, in the extreme stage, Qi Liang ying and detoxifying, and in the later stage, Qi qi and Yin were mainly used. Liang's [21] collected and collated the data of 92 KD patients with Qi-ying burnt syndrome and found that most of them used traditional Chinese medicine to treat pain, cold and return to lung and stomach channels, and the treatment was mainly to clear heat, detoxify and cool blood and promote blood circulation.

(3) specific treatment

Li [22] used Qianjin Wushi Decoction to clear heat and detoxify the heart and calm the mind to treat Kawasaki disease, and the clinical symptoms and serum factor recovery level were better than that of Western medicine alone. Zheng [23] used Huanglian Jiedu Decoction combined with Baihu decoction to treat Kawasaki disease, and the combined treatment of Chinese and Western medicine has advantages over the simple western medicine group in terms of clinical symptoms and recovery of inflammatory factors. Fu [24] applied Jiedu Huayu Decoction in combination with conventional western medicine and found that the combination of Chinese and western medicine could significantly reduce the rate of coronary artery dilation. Chen's [25], Zhao's [26] and Wang's [27] all chose traditional Chinese medicine for clearing heat and detoxifying, nourishing Yin and invigorating qi combined with Western medicine for conventional treatment, and found that the combination of traditional Chinese and Western medicine had significant differences in improving clinical symptoms. Zhang believed that blockage of stasis and injury of Qi and Yin were the basic causes, and the treatment of Taohong Siwu Decoction combined with Shengmai Yin to promote blood circulation and remove blood stasis, qi and Yin had remarkable effect.

(4) Chinese medicine preparation

Coronary artery dilation is a major complication of Kawasaki disease. Yan [28] conducted serological tests on KD children with coronary artery injury under different treatment regimens. matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1) and mRNA were quantitatively monitored. It was found that tanshinone □A can inhibit the expression of MMP-9 and TIMP-1 mRNA and protein in Kawasaki disease patients to a certain extent, so as to reduce the vasculitis injury and reduce the coronary artery damage in Kawasaki disease. Wang [29] selected 20 healthy children of Kawasaki disease and 20 healthy children of the same age to isolate mononuclear cells from venous blood for culture, and found that tanshinone □A and aspirin had similar anti-inflammatory pathways and effects. Zhang [30] established a Kawasaki disease coronary artery injury model in mice to study the effects of gamma globulin and astragaloside IV on coronary tissue and found that they could up-regulate the expression of interleukin-35 (IL-35) and inhibit the Janus kinase 1(JAK1)/ signal transduction and transcriptional activator 1(STAT1) pathway to reduce the inflammatory response and coronary artery injury in Kawasaki disease. It has a protective effect on coronary arteries. Liu [31] prepared the model with the same method and took normal salt as reference, and found that ginsenoside Rb1 could improve the pathological injury of coronary artery in Kawasaki disease mice, inhibit the content of inflammatory factors, and down-regulate the expression of nuclear factor-κB (NF-κB) and matrix metalloproteinase-9 (MMP-9) in heart tissue, so as to inhibit the inflammatory response and play a role. Hu used tumor necrosis factor-α (TNF-α) to induce human coronary endothelial cells (HCAEC) to establish a model of KD coronary injury cells, and found that salidroside can activate phosphatidylinositol 3 kinase (PI3K)/protein kinase B(Akt) and inhibit NF-κB signaling pathway, improve endothelial cell permeability and reduce oxidative stress damage.

With the standardization, standardization and popularization of the diagnosis and treatment of Kawasaki disease, the discovery rate of Kawasaki disease is gradually increasing, and the overall treatment plan tends to be mature. However, the problem of adverse reactions is still easy to be seen in the high-dose impact therapy of Western medicine in the acute stage [32]. At this time, the combination of traditional Chinese medicine is just right, and has good effects in shortening the course of disease and improving the prognosis.

Most Chinese medicine scholars believe KD belongs to the category of warm disease. Regardless of whether the disease is combined with the disease stage, the treatment focuses on the dialectical treatment of qi and blood. With the development of traditional Chinese medicine in recent years, the treatment part of traditional Chinese medicine has gradually changed from decoction to traditional Chinese medicine preparation, which also opens up a new way for the use of traditional Chinese medicine.

REFERENCES:

[1]. Fuyong Jiao, Junzori Suzuki and Zhongdong Du, International Research Progress of Kawasaki Disease. 2022, Xi 'an: Shaanxi Science and Technology Press. 1.

[2] Jiao Fuyong, Kawasaki Disease. 2014, Beijing: People's Medical Publishing House. 2-6; 163-166.

[3]. Elakabawi, K., et al., Kawasaki Disease: Global Burden and Genetic Background. Cardiol Res, 2020. 11(1): p. 9-14.

[4]. Singh, S., A. Sharma and F. Jiao, Kawasaki Disease: Issues in Diagnosis and Treatment--A Developing Country Perspective. Indian J Pediatr, 2016. 83(2): p. 140-5.

[5]. Jiao, F., et al., Epidemiologic and clinical characteristics of Kawasaki disease in Shaanxi Province, China, 1993-1997. J Trop Pediatr, 2001. 47(1): p. 54-6.

[6]. Jiao, F., X. Yan and X. Wu, The Xi'an Experience of Kawasaki Disease - Lessons Learnt over 5 years. Indian J Pediatr, 2016. 83(10): p. 1195-6.

[7]. Jiao, F.Y., [Kawasaki disease - a new manifestation of COVID-19 in children]. Zhongguo Dang Dai Er Ke Za Zhi, 2020. 22(7): p. 677-678.

[8]. Agarwal, S. and D.K. Agrawal, Kawasaki disease: etiopathogenesis and novel treatment strategies. Expert Rev Clin Immunol, 2017. 13(3): p. 247-258.

[9]. Wang Wenge. The understanding of Kawasaki disease in ancient books of traditional Chinese Medicine. In the 27th National Academic Seminar on Pediatrics of Traditional Chinese Medicine of Pediatrics Branch of China Association of Traditional Chinese Medicine and the second International Academic Exchange Conference on Pediatrics of Traditional Chinese Medicine of World Federation of Traditional Chinese Medicine Societies, Learning class on the Progress of Theory and Practice of Traditional Chinese Medicine Pediatrics. 2010. Shanghai, China.

[10]. Liu Bichen et al., TCM Syndrome Treatment of Kawasaki disease. Beijing Traditional Chinese Medicine, 1990(04): pp. 10-11.

[11]. Zhou Liujuan. Treatment of 5 cases of Kawasaki disease with integrated Chinese and Western medicine. Journal of Integrative Chinese and Western Medicine, 1990(05): 305.

[12]. Chen Fuju et al., Effect of integrated Chinese and Western medicine on serum TNF-α IL-6 CRP level in children with Kawasaki disease. Primary Medicine Forum, 2019(02): pp. 244-246.

[13] Wang Xuehui, He Feng, Zhang Dengli, Clinical observation of staging treatment of coronary artery disease in Kawasaki disease. Journal of Clinical Rational Drug Use, 2018(16): 100-102.

[14] Zhang Qin, Liu Dian, Su Min, Clinical effect of integrated Chinese and Western medicine on Kawasaki disease. Clinical Medicine Research and Practice, 2017(17): pp. 123-124.

[15]. Li Kai and Yan Suqi, Clinical study of TCM Weiqi Ying blood syndrome differentiation combined with gamma globulin in the treatment of Kawasaki disease in children. Chinese Journal of Traditional Chinese Medicine, 2016(10): 2527-2531.

[16] Wang Xu et al. Qingying Decoction combined with Propyl granules in the treatment of 30 cases of burnt Kawasaki disease. Guangming Chinese Medicine, 2022(12): pp. 2161-2163+2179.

[17] Sha Bangwu and Zhao Dingming, Huanglian Jiedu Decoction combined with Baihu Decoction in the treatment of Kawasaki disease in children and the effect on the levels of NT-proBNP, PCT and CRP in peripheral blood of children. Chinese Journal of Emergency Medicine, 2021(03): pp. 524-526.

[18]. Wang Shuang. Clinical study on Fuzheng and Eliminating Blood stasis in children with Kawasaki disease (Qi and Yin injury with blood stasis), 2010, Changchun University of Traditional Chinese Medicine.

[19]. Wang Jianxin and Qiu Tingting. Clinical study on the treatment of 60 cases of convalescent Kawasaki disease syndrome with Danshen Shengmai Decoction. Shi Zhen Chinese Medicine, 2009. 20(08): pp. 2073-2074.

[20] Yang Xiangna et al., Literature study on the treatment of Kawasaki disease based on syndrome differentiation of Weiqi Ying blood. Chinese Ethnic and Folk Medicine, 2021(21): pp. 76-83.

[21]. Liang Yanni, Analysis of risk factors of KD combined with CAL and study on medication rule of Traditional Chinese Medicine in the treatment of KD burnt syndrome, 2021, Guangzhou University of Traditional Chinese Medicine.

[22]. Li Lin et al., Effect of Qianjin Wushi Decoction on Kawasaki disease and its effect on TCM symptom score and serum inflammatory factor levels. Sichuan Traditional Chinese Medicine, 2022. 40(10): pp. 70-73.

[23]. Zheng Tao, Analysis of Huanglian Jiedu Decoction combined with Baihu Decoction combined with gamma globulin in the treatment of Kawasaki disease in children. Knowledge of Prevention and Treatment of cardiovascular Diseases, 2022(21): pp. 12-15.

[24]. Fu Aixue and Meng Yingying, Clinical effect of Traditional Chinese medicine Jiedu Huayu Decoction combined with gamma globulin on Kawasaki disease. Clinical Research of Chinese Medicine, 2020. 12(26): pp. 42-45.

[25] Chen H Yang, Combined application of gamma globulin and nutritional myocardial decoction in the treatment of Kawasaki disease in children. Chinese and Foreign Medical Science, 2019(36): 22-24.

[26] Zhao Fangfang. Effect of integrated Chinese and Western medicine on Kawasaki disease in children. Asia Pacific Traditional Medicine, 2014(23): pp. 52-53.

[27] Wang R J, Combined application of gamma globulin and nutritional myocardium decoction in the treatment of Kawasaki disease in children. Journal of Contemporary Medicine, 2014(18): pp. 233-234.

[28] Yan Hongxia et al., Effect of Tanshinone □A on matrix metalloproteinase 9 and its inhibitor TIMP-1 in children with Kawasaki disease complicated with coronary artery damage. Chinese Journal of Arteriosclerosis, 2013. 21(09): pp. 831-835.

[29] Wang Yan et al., Effect of Tanshinone □A on NF-κB activation and inflammatory cytokine expression in peripheral blood mononuclear cells of children with Kawasaki disease, in the 17th National Pediatric Academic Congress of Chinese Medical Association 2012: Zhengzhou, Henan, China. Page 1.

[30] Zhang F, et al., Protective effect of astragaloside IV on coronary artery injury in Kawasaki disease mice. Chinese Patent Medicine, 2022. 44(05): pp. 1454-1459.

[31] Liu Qian, Wu Shengwei, Jiang Hongyu, Ginsenoside Rb1 therapeutic effect on Kawasaki disease mice. Chinese Journal of Clinical Pharmacology, 2020. 36(23): pp. 3914-3917.

[32] Zhang Hui and Liu Jun. Adverse reactions and nursing countermeasures of large dose gamma globulin in the treatment of Kawasaki disease in children. Practical Cardio-cerebral Pulmonary Vascular Diseases, 2017. 25(S1): pp. 146-147.

RESEARCH PROGRESS IN TRADITIONAL CHINESE MEDICINE OF KAWASAKI DISEASE

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ABSTRACT:

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The pathogenesis of KD is still unclear, and it is mainly believed to be related to genetics, immunity and infection [8]. There is no specific drug in treatment, and the overall principle is to control inflammation and minimize the risk of coronary aneurysm [1]. Although its acute usage and dosage have no uniform standard, and present great differences in various countries [2]. As a traditional medical means in our country, TCM presents advantages in the treatment process of this disease, and its research progress is summarized as follows.

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SECOND, TREATMENT

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REFERENCES:

[1]. Fuyong Jiao, Junzori Suzuki and Zhongdong Du, International Research Progress of Kawasaki Disease. 2022, Xi 'an: Shaanxi Science and Technology Press. 1.

[2] Jiao Fuyong, Kawasaki Disease. 2014, Beijing: People's Medical Publishing House. 2-6; 163-166.

[3]. Elakabawi, K., et al., Kawasaki Disease: Global Burden and Genetic Background. Cardiol Res, 2020. 11(1): p. 9-14.

[4]. Singh, S., A. Sharma and F. Jiao, Kawasaki Disease: Issues in Diagnosis and Treatment--A Developing Country Perspective. Indian J Pediatr, 2016. 83(2): p. 140-5.

[5]. Jiao, F., et al., Epidemiologic and clinical characteristics of Kawasaki disease in Shaanxi Province, China, 1993-1997. J Trop Pediatr, 2001. 47(1): p. 54-6.

[6]. Jiao, F., X. Yan and X. Wu, The Xi'an Experience of Kawasaki Disease - Lessons Learnt over 5 years. Indian J Pediatr, 2016. 83(10): p. 1195-6.

[7]. Jiao, F.Y., [Kawasaki disease - a new manifestation of COVID-19 in children]. Zhongguo Dang Dai Er Ke Za Zhi, 2020. 22(7): p. 677-678.

[8]. Agarwal, S. and D.K. Agrawal, Kawasaki disease: etiopathogenesis and novel treatment strategies. Expert Rev Clin Immunol, 2017. 13(3): p. 247-258.

[9]. Wang Wenge. The understanding of Kawasaki disease in ancient books of traditional Chinese Medicine. In the 27th National Academic Seminar on Pediatrics of Traditional Chinese Medicine of Pediatrics Branch of China Association of Traditional Chinese Medicine and the second International Academic Exchange Conference on Pediatrics of Traditional Chinese Medicine of World Federation of Traditional Chinese Medicine Societies, Learning class on the Progress of Theory and Practice of Traditional Chinese Medicine Pediatrics. 2010. Shanghai, China.

[10]. Liu Bichen et al., TCM Syndrome Treatment of Kawasaki disease. Beijing Traditional Chinese Medicine, 1990(04): pp. 10-11.

[11]. Zhou Liujuan. Treatment of 5 cases of Kawasaki disease with integrated Chinese and Western medicine. Journal of Integrative Chinese and Western Medicine, 1990(05): 305.

[12]. Chen Fuju et al., Effect of integrated Chinese and Western medicine on serum TNF-α IL-6 CRP level in children with Kawasaki disease. Primary Medicine Forum, 2019(02): pp. 244-246.

[13] Wang Xuehui, He Feng, Zhang Dengli, Clinical observation of staging treatment of coronary artery disease in Kawasaki disease. Journal of Clinical Rational Drug Use, 2018(16): 100-102.

[14] Zhang Qin, Liu Dian, Su Min, Clinical effect of integrated Chinese and Western medicine on Kawasaki disease. Clinical Medicine Research and Practice, 2017(17): pp. 123-124.

[15]. Li Kai and Yan Suqi, Clinical study of TCM Weiqi Ying blood syndrome differentiation combined with gamma globulin in the treatment of Kawasaki disease in children. Chinese Journal of Traditional Chinese Medicine, 2016(10): 2527-2531.

[16] Wang Xu et al. Qingying Decoction combined with Propyl granules in the treatment of 30 cases of burnt Kawasaki disease. Guangming Chinese Medicine, 2022(12): pp. 2161-2163+2179.

[17] Sha Bangwu and Zhao Dingming, Huanglian Jiedu Decoction combined with Baihu Decoction in the treatment of Kawasaki disease in children and the effect on the levels of NT-

proBNP, PCT and CRP in peripheral blood of children. Chinese Journal of Emergency Medicine, 2021(03): pp. 524-526.

[18]. Wang Shuang. Clinical study on Fuzheng and Eliminating Blood stasis in children with Kawasaki disease (Qi and Yin injury with blood stasis), 2010, Changchun University of Traditional Chinese Medicine.

[19]. Wang Jianxin and Qiu Tingting. Clinical study on the treatment of 60 cases of convalescent Kawasaki disease syndrome with Danshen Shengmai Decoction. Shi Zhen Chinese Medicine, 2009. 20(08): pp. 2073-2074.

[20] Yang Xiangna et al., Literature study on the treatment of Kawasaki disease based on syndrome differentiation of Weiqi Ying blood. Chinese Ethnic and Folk Medicine, 2021(21): pp. 76-83.

[21]. Liang Yanni, Analysis of risk factors of KD combined with CAL and study on medication rule of Traditional Chinese Medicine in the treatment of KD burnt syndrome, 2021, Guangzhou University of Traditional Chinese Medicine.

[22]. Li Lin et al., Effect of Qianjin Wushi Decoction on Kawasaki disease and its effect on TCM symptom score and serum inflammatory factor levels. Sichuan Traditional Chinese Medicine, 2022. 40(10): pp. 70-73.

[23]. Zheng Tao, Analysis of Huanglian Jiedu Decoction combined with Baihu Decoction combined with gamma globulin in the treatment of Kawasaki disease in children. Knowledge of Prevention and Treatment of cardiovascular Diseases, 2022(21): pp. 12-15.

[24]. Fu Aixue and Meng Yingying, Clinical effect of Traditional Chinese medicine Jiedu Huayu Decoction combined with gamma globulin on Kawasaki disease. Clinical Research of Chinese Medicine, 2020. 12(26): pp. 42-45.

[25] Chen H Yang, Combined application of gamma globulin and nutritional myocardial decoction in the treatment of Kawasaki disease in children. Chinese and Foreign Medical Science, 2019(36): 22-24.

[26] Zhao Fangfang. Effect of integrated Chinese and Western medicine on Kawasaki disease in children. Asia Pacific Traditional Medicine, 2014(23): pp. 52-53.

[27] Wang R J, Combined application of gamma globulin and nutritional myocardium decoction in the treatment of Kawasaki disease in children. Journal of Contemporary Medicine, 2014(18): pp. 233-234.

[28] Yan Hongxia et al., Effect of Tanshinone IIA on matrix metalloproteinase 9 and its inhibitor TIMP-1 in children with Kawasaki disease complicated with coronary artery damage. Chinese Journal of Arteriosclerosis, 2013. 21(09): pp. 831-835.

[29] Wang Yan et al., Effect of Tanshinone IIA on NF-κB activation and inflammatory cytokine expression in peripheral blood mononuclear cells of children with Kawasaki disease, in the 17th National Pediatric Academic Congress of Chinese Medical Association 2012: Zhengzhou, Henan, China. Page 1.

[30] Zhang F, et al., Protective effect of astragaloside IV on coronary artery injury in Kawasaki disease mice. Chinese Patent Medicine, 2022. 44(05): pp. 1454-1459.

[31] Liu Qian, Wu Shengwei, Jiang Hongyu, Ginsenoside Rb1 therapeutic effect on Kawasaki disease mice. Chinese Journal of Clinical Pharmacology, 2020. 36(23): pp. 3914-3917.

[32] Zhang Hui and Liu Jun. Adverse reactions and nursing countermeasures of large dose gamma globulin in the treatment of Kawasaki disease in children. Practical Cardio-cerebral Pulmonary Vascular Diseases, 2017. 25(S1): pp. 146-147.

ENHANCE THE PREVENTION AND TREATMENT OF SECONDARY CORONARY ARTERY INJURY IN CHILDREN

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The etiological mechanism of coronary artery lesions (CAL) coronary artery dilatation disease is not completely clear, and its pathological manifestations are mainly the destruction of the middle layer of the coronary artery vessel wall structure and the degradation of elastic fibers. Possible causes include atherosclerosis, autoimmune or inflammatory reactions, vascular infectious diseases, and overexpression of gene susceptibility [1]. The disease is prevalent in patients with autoimmune diseases or Kawasaki disease in childhood, in men with dyslipidemia, in

men with hypertension, in men who are chronic smokers, and can be triggered by infections with autoimmune abnormalities and emotional agitation. A variety of childhood rheumatic immune diseases can lead to coronary artery damage (CAL). By understanding the immunological pathogenesis of the disease and broadening the diagnosis and differentiation of the disease, we can help improve the diagnosis and treatment of CAL-related rheumatologic diseases.

I. MAIN ETIOLOGY

1. atherosclerosis: coronary artery dilatation disease is a variant of obstructive coronary artery disease.

2. autoimmune or inflammatory response: Coronary artery dilatation disease in children and adolescents is usually a complication of Kawasaki disease, and connective tissue diseases, systemic arteritis and Marfan syndrome can lead to coronary artery dilatation disease.

3. vascular infectious diseases: infections such as fungal or septic emboli, syphilis, spirochete disease, etc. can damage coronary vessels and lead to coronary artery dilation.

4. The etiology of simple coronary artery dilation disease is unknown and may be related to genetic susceptibility (e.g., specific HLA class II genotype, matrix metalloproteinase gene variants), angiotensin-converting enzyme overexpression, etc.

5. coronary arteriovenous fistula

6. hereditary family cluster nesting hypercholesterolemia

Second, the predisposing factors

1. infection and autoimmune abnormalities: infection may directly or indirectly damage coronary arteries by stimulating autoimmune reactions.

2. emotional excitement or after strenuous activity can trigger the disease, appearing chest pain and discomfort.

3. In addition, smoking, high blood pressure, cocaine use, etc. may trigger this disease.

I. KAWASAKI DISEASE

Kawasaki disease is an infection-induced systemic inflammatory disease in children, in which vasculitis is the main feature, mainly involving small and medium-sized arteries [2]. Clinical manifestations include fever, rash, congestion of the conjunctiva of the eye and oral mucosa, palmoplantar erythema, hard edema of the finger (toe) ends and enlarged cervical lymph nodes, etc. A few children may even have Kawasaki disease shock syndrome (KDSS) or macrophage activation syndrome (MAS). A few children may even have life-threatening complications such as Kawasaki disease shock syndrome (KDSS) or macrophage activation syndrome (MAS)[2]. The disease usually has a good prognosis, with most temporary changes in CAL and long-term complications mainly related to the degree of coronary artery involvement. Coronary artery dilatation to an internal diameter <8 mm and a Z value <10 often results in gradual recovery, whereas giant coronary aneurysms (maximum internal diameter ≥8 mm) are highly susceptible to myocardial infarction, arrhythmia, or sudden death due to coronary occlusion [3-4].

The exact etiology of Kawasaki disease has not been elucidated. It has been found that Kawasaki disease may be associated with infection by different pathogens and genetic susceptibility. The pathology of Kawasaki disease shows inflammatory cells infiltrating the vascular tissue and destroying the luminal endothelium, elastic fiber layer and middle smooth muscle cells, which eventually leads to luminal dilation and aneurysm formation [5]. Inflammatory cells infiltrating the arterial vasculature include neutrophils, T cells (especially CD8+ T cells), eosinophils, plasma cells (especially IgA-secreting plasma cells), and macrophages [6]. Early in the course of the disease, mainly neutrophils infiltrate the arterial wall, and after 2 weeks, monocytes and CD8+ T cells predominate [7]. Thus, Kawasaki disease may be a systemic inflammatory disease with a predominantly intrinsic immune disorder due to exposure of genetically susceptible individuals to various infections and/or environmental triggers.

II. MULTISYSTEM INFLAMMATORY SYNDROME (MIS) IN CHILDREN

Since April 2020 several countries have reported the clinical features of cohorts of childhood MIS cases, which occur mostly in previously healthy children and adolescents with a clinical presentation similar to KDSS, presenting with systemic multisystem damage and evidence of novel coronavirus pneumonia (COVID-19). The World Health Organization defines MIS in children [8] as (1) age <19 years. (2) Fever ≥3 d. (3) Evidence of multisystem injury (≥2): (i) rash, bilateral nonpurulent conjunctivitis, or skin mucosal symptoms; (ii) hypotension or shock; (iii) cardiovascular dysfunction, pericarditis, valvulitis, or CAL; (iv) coagulation abnormalities; and (v) acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain). (4) Elevated inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein, or calcitoninogen. (5) Inflammation due to infection by other pathogens is excluded. (6) Evidence related to COVID-19.

Cardiac involvement is a common manifestation of MIS in children, with 32% of patients having a left ventricular ejection fraction of less than 55% and 11% of them having an ejection fraction of less than 30%. 23% of patients have myocarditis. 23.4% of patients with KD-like symptoms have coronary artery dilatation/aneurysm [9]. 93% of coronary artery aneurysms are mild and 7% are moderate [10]. 40% to 50% of children with MIS meet the diagnostic criteria for Kawasaki disease or incomplete Kawasaki disease, which is very similar to KDSS [10], Key differences between childhood MIS and Kawasaki disease include a predominantly non-Hispanic black, Hispanic, or Latino population for childhood MIS, mostly in children aged 6-15 years [11]; more prominent gastrointestinal symptoms (especially abdominal pain), more significant elevation of inflammatory markers, lower absolute lymphocyte and platelet counts, and evidence of COVID-19 associated with childhood MIS [12-14].

The climb in the number of cases of childhood MIS occurred several weeks after the peak of COVID-19 community onset, and studies have shown persistent monocyte activation, elevated levels of anti-severe acute respiratory syndrome coronavirus IgG antibodies, enhanced CD8+ T cell activation, and elevated levels of inflammatory cytokines, interleukin (IL), gamma interferon, and tumor necrosis factor TNF and ferritin levels are significantly elevated, among others [11,15-16]. Therefore, MIS in children is an inflammatory cytokine storm disease caused by abnormal immune response induced after viral infection.

III. MULTIPLE AORTITIS (TAKAYASU ARTERITIS, TA)

TA is a chronic nonspecific inflammatory disease of large and medium-sized vessels, mainly involving the aorta and its major branches, but also the pulmonary and coronary arteries [17].TA often has nonspecific systemic symptoms in its early stages, such as fever, rash, and malaise; while symptoms such as ischemic limb pain and/or cyanosis, dizziness, and hypertension due to arterial stenosis, occlusion, or dilation are not evident in infants and children [17-18]. The disease is similar to Kawasaki disease and may be associated with abnormal inflammatory indicators, such as elevated levels of acute phase reactants, anemia, leukocytosis and/or thrombocytosis; histopathology shows a predominantly cytotoxic lymphocyte infiltration in the arterial tissue, especially γδ T cells; other inflammatory cells include histiocytes, macrophages and plasma cells [19]. These cells cause vascular damage by releasing large amounts of the cytolytic protein perforin, which disrupts the vascular elastic membrane and mesothelial muscle layer, leading to aneurysmal dilatation [19-20]. the incidence of TA CAL is 10%-30%, which manifests as focal or diffuse inflammation, dilation, stenosis or occlusion [21], and IVIG treatment unresponsive to Kawasaki disease should be distinguished from this disease.

IV. SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (JIA)

Systemic JIA is a systemic auto-inflammatory disease [22], which may have no early manifestations of arthritis, but more prominent extra-articular manifestations, including daily intermittent fever (fever peak ≥38.5 °C), pale red maculopapular rash, enlarged liver and spleen lymph nodes, and plasmacytitis, and is easily complicated by MAS [23]. Laboratory features of systemic JIA include increased white blood cell count, elevated granulocyte count and ratio, thrombocytosis, anemia, increased erythrocyte sedimentation rate, and elevated C-reactive protein and serum ferritin, while being negative for autoantibodies [24]. Several papers have reported the finding of coronary artery dilation on cardiac ultrasonography in children with systemic JIA [25-26], which is easily misdiagnosed as Kawasaki disease or incomplete Kawasaki disease similar to Kawasaki disease, and the immunopathogenesis of systemic JIA in individuals with a certain genetic background, in which the intrinsic immune system is dysregulated and overactivated by various promotive factors, producing large amounts of inflammatory cytokines (IL-1, IL- 6 and IL-10, IL-17, IL-21, etc.) and pro-inflammatory proteins (S100-A8, S100-A9 and S100A-12), which in turn lead to systemic multisystemic inflammation and even complications of MAS [27-28]. Given that systemic JIA does not respond to IVIG therapy, children with IVIG-naïve Kawasaki disease need to be differentiated from systemic JIA, even if coronary artery dilatation is present.

V. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

SLE in children is a chronic recurrent autoimmune disease that presents with multisystemic multi-organ involvement, positive signature autoantibodies, and decreased complement [29-30]. children with SLE are at significantly higher risk of CAL than the healthy population, and systemic inflammation is an independent risk factor for CAL [31]. children with SLE have larger coronary artery diameters than healthy children, and a small number of children with SLE can be complicated by coronary arteritis and/or coronary artery dilation [31], which may be diagnosed early as Kawasaki disease or incomplete Kawasaki disease. It has been suggested that coronary arteritis may be a more common clinical feature of childhood SLE than currently recognized, and early recognition and management would be beneficial in improving long-term cardiovascular outcomes in children with SLE [32-33].

VI. PRIMARY IMMUNODEFICIENCY DISEASES (PID)

Some primary immunodeficiency diseases may also involve coronary arteries, including autosomal dominant hyperimmunoglobulin E syndrome (AD-HIE), which is caused by a subtractive variant of the STAT3 gene [34-35], and X-linked lymphoproliferative disease (X-linked HIE), which is caused by a variant of the XIAP gene. X-linked lymphoproliferative disease 2 (XLP-2) and partially monogenic auto-inflammatory disease (AID) [36].AD-HIE coronary artery involvement can manifest as atherosclerosis, tortuosity, dilatation and local aneurysms [35].XLP-2 often presents as EBV-associated fulminant infectious mononucleosis and phagocytic syndrome, which can lead to Kawasaki disease-like CAL, and the underlying mechanism may be related to excessive activation of CD8+ T cells and inflammatory cytokine storm in EBV infection [37].AID often presents as recurrent or persistent inflammation of unknown origin, and the clinical features of the exacerbation phase are similar to those of Kawasaki disease has many overlapping clinical features, such as fever, rash, plasma membrane inflammation, arthritis, aseptic meningitis, conjunctivitis and uveitis, among which hyper IgD syndrome caused by MVK gene variants can present with coronary artery dilation [36], which is easily misdiagnosed as Kawasaki disease or incomplete Kawasaki disease in early stages, and recurrent Kawasaki disease should be distinguished from AID in particular.

VII. CHRONIC ACTIVE EPSTEIN-BARR VIRUS (CAEBV) INFECTION

CAEBV infection is a rare, life-threatening lymphoproliferative disorder that manifests as persistent infectious mononucleosis-like syndrome, EBV viremia, or EBV-associated phagocytic syndrome [38]. Untreated T-cell CAEBV-infected patients often develop systemic organ lesions due to T-cell infiltration of tissues, phagocytic lymphocytosis, hepatic failure, and CAL [39].The incidence of coronary artery dilation in CAEBV is approximately 8.5% [40], with some early misdiagnosis as incomplete Kawasaki disease.The mechanism by which CAL occurs in CAEBV may be related to abnormal secretion of inflammatory factors (e.g. tumor necrosis factor α, IL-16 and IL-10), and T-cell immune imbalance [41]. In children with persistent fever, hepatosplenomegaly, and abnormal liver enzymes with coronary artery dilatation, especially those without the typical clinical manifestations of Kawasaki disease, care needs to be taken to differentiate from CAEBV.

A variety of rheumatic immune and cardiovascular diseases in children can lead to CAL, and in individuals with a specific genetic background, over-activation of intrinsic immunity and/or imbalance of adaptive immunity in the presence of infection or other triggers, leading to acute or chronic inflammatory injury, are the key immunologic mechanisms leading to CAL. Based on a deep understanding of the pathogenesis of the disease, clinicians should broaden the diagnosis and differentiation of the disease in all aspects to avoid falling into the trap of diagnosing Kawasaki disease or incomplete Kawasaki disease; at the same time, they should pay high attention to CAL secondary to rheumatic immune diseases and cardiovascular diseases, and actively manage coronary complications based on multidisciplinary cooperation to further improve the diagnosis and treatment of CAL lesions in children with related diseases.

CAL is not uncommon in pediatrics but has a complex etiology. congenital coronary artery disease, atherosclerosis, infectious diseases and rheumatic immune diseases can all cause CAL. the core pathogenesis is focal or diffuse inflammation leading to destruction of the intima and mesostructure of the coronary artery wall, degradation of the elastic fibers and subsequent dilatation, stenosis or occlusion of the coronary arteries. The incidence of CAL due to Kawasaki disease is most common in pediatrics, and timely treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of CAL from 25% to approximately 4%[42]. CAL is not unique to Kawasaki disease, and many rheumatic immune diseases in children can lead to coronary artery involvement. Clinicians need to have a better understanding of the immunological mechanisms of the disease and to broaden their thinking about diagnosis and treatment to avoid misdiagnosis and underdiagnosis.

REFERENCE

[1] Islam A-K-M-Monwarul,Majumder A-A-S. Coronary artery disease in Bangladesh: a review.[J]. Indian heart journal, 2013, (4): 424-35.

[2] Mccrindle Brian-W,Rowley Anne-H,Newburger Jane-W, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.[J]. Circulation, 2017, (17): e927-e999.

[3] Taichi Kato,Masaru Miura,Tohru Kobayashi, et al. Analysis of Coronary Arterial Aneurysm Regression in Patients With Kawasaki Disease by Aneurysm Severity: Factors Associated With Regression.[J]. Journal of the American Heart Association, 2023, 12(3): e022417.

[4] Mccrindle Brian-W,Manlhiot Cedric,Newburger Jane-W, et al. Medium-Term Complications Associated With Coronary Artery Aneurysms After Kawasaki Disease: A Study From the International Kawasaki Disease Registry.[J]. Journal of the American Heart Association, 2020, (15): e016440.

[5] Orenstein Jan-Marc,Shulman Stanford-T,Fox Linda-M, et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study.[J]. PloS one, 2012, (6): e38998.

[6] Kei Takahashi,Toshiaki Oharaseki,Yuki Yokouchi, et al. Kawasaki disease: basic and pathological findings.[J]. Clinical and Experimental Nephrology, 2012, 17(5): 690-693.

[7] Sato Wakana,Yokouchi Yuki,Oharaseki Toshiaki, et al. The pathology of Kawasaki disease aortitis: a study of 37 cases.[J]. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology, 2020: 107303.

[8] Yue-Hin Loke,Charles I Berul,Ashraf S Harahsheh. Multisystem inflammatory syndrome in children: Is there a linkage to Kawasaki disease?[J]. Trends in Cardiovascular Medicine, 2020, 30(7): 389-396.

[9] Kaushik Ashlesha,Gupta Sandeep,Sood Mangla, et al. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection.[J]. The Pediatric infectious disease journal, 2020, (11): e340-e346.

[10] Lee Min-Sheng,Liu Yi-Ching,Tsai Ching-Chung, et al. Similarities and Differences Between COVID-19-Related Multisystem Inflammatory Syndrome in Children and Kawasaki Disease.[J]. Frontiers in pediatrics, 2021: 640118.

[11] Cheung Eva-W,Zachariah Philip,Gorelik Mark, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City.[J]. JAMA, 2020, (3): 294-296.

[12] Jerin Jose,Elif Seda Selamet Tierney,Ashraf S Harahsheh, et al. COVID-19 Positive Versus Negative Complete Kawasaki Disease: A Study from the International Kawasaki Disease Registry.[J]. Pediatric Cardiology, 2023: 1-9.

[13] Alberto García-Salido,Juan Carlos de Carlos Vicente,Sylvia Belda Hofheinz, et al. Severe manifestations of SARS-CoV-2 in children and adolescents: from COVID-19 pneumonia to multisystem inflammatory syndrome: a multicentre study in pediatric intensive care units in Spain.[J]. Critical Care (london, England), 2020, 24(1): 666.

[14] Elizabeth Whittaker,Alasdair Bamford, Julia Kenny, et al. Clinical

Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2.[J]. Jama, 2020, 324(3): 259-269.

[15] Consiglio Camila-Rosat,Cotugno Nicola,Sardh Fabian, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19.[J]. Cell, 2020, (4): 968-981.e7.

[16] Conor N Gruber,Roosheel S Patel,Rebecca Trachtman, et al. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C).[J]. Cell, 2020, 183(4): 982-995.e14.

[17] Souza Alexandre-Wagner-Silva-de,Carvalho Jozélio-Freire-de. Diagnostic and classification criteria of Takayasu arteritis.[J]. Journal of autoimmunity, 2014: 79-83.

[18] Seza Ozen,Angela Pistorio,Silvia M Iusan, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria.[J]. Annals of the Rheumatic Diseases, 2010, 69(5): 798-806.

[19] Aeschlimann Florence-A,Yeung Rae-S-M,Laxer Ronald-M. An Update on Childhood-Onset Takayasu Arteritis.[J]. Frontiers in pediatrics, 2022: 872313.

[20] Podgorska Dominika,Podgorski Rafal,Aebisher David, et al. Takayasu arteritis - epidemiology, pathogenesis, diagnosis and treatment.[J]. Journal of applied biomedicine, 2019, (1): 20.

[21] Aeschlimann Florence-A,Twilt Marinka,Yeung Rae-S-M. Childhood-onset Takayasu Arteritis.[J]. European journal of rheumatology, 2020, (Suppl1): S58-S66.

[22] Ravelli Angelo,Martini Alberto. Juvenile idiopathic arthritis.[J]. Lancet (London, England), 2007, (9563): 767-778.

[23] Erdal Sağ,Berna Uzunoğlu, Fatma Bal, et al. Systemic onset juvenile idiopathic arthritis: a single center experience.[J]. The Turkish Journal of Pediatrics, 2019, 61(6): 852-858.

[24] Kumar Sathish. Systemic Juvenile Idiopathic Arthritis: Diagnosis and Management.[J]. Indian journal of pediatrics, 2016, (4): 322-7.

[25] A Felix,F Delion,B Suzon, et al. Systemic juvenile idiopathic arthritis in French Afro-Caribbean children, a retrospective cohort study.[J]. Pediatric Rheumatology Online Journal, 2022, 20(1): 98.

[26] Arsenaki Elisavet,Georgakopoulos Panagiotis,Mitropoulou Panagiota, et al. Cardiovascular Disease in Juvenile Idiopathic Arthritis.[J]. Current vascular pharmacology, 2020, (6): 580-591.

[27] Saverio La Bella,Marta Rinaldi,Armando Di Ludovico, et al. Genetic Background and Molecular Mechanisms of Juvenile Idiopathic Arthritis.[J]. International Journal of Molecular Sciences, 2023, 24(3).

[28] Yu-Tsan Lin,Chen-Ti Wang, M Eric Gershwin, et al. The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis.[J]. Autoimmunity Reviews, 2011, 10(8): 482-9.

[29] Silva Clovis-A,Avcin Tadej, Brunner Hermine-I. Taxonomy for systemic lupus erythematosus with onset before adulthood.[J]. Arthritis care & research, 2012, (12): 1787-93.

[30] Ohara Asami,Iwata Naomi,Sugiura Shiro, et al. Evaluation of the European League Against Rheumatism/-American College of Rheumatology-2019 classification criteria in patients with childhood-onset systemic lupus erythematosus: a single-center retrospective study.[J]. Clinical rheumatology, 2022, (8): 2483-2489.

[31] Shen C-C,Chung H-T,Huang Y-L, et al. Coronary artery dilation among patients with paediatric-onset systemic lupus erythematosus.[J]. Scandinavian journal of rheumatology, 2012, (6): 458-65.

[32] Sherif M Gamal,Sally S Mohamed,Marwa Tantawy, et al. Lupus-related vasculitis in a cohort of systemic lupus erythematosus patients. [J]. Archives of Rheumatology, 2021, 36(4): 595-692.

[33] Agarwal Arunima,Student Stephanie-Biglarian-Medical,Limstavros Sophia, et al. Pediatric systemic lupus erythematosus presenting with coronary arteritis: A case series and review of the literature.[Z], 2015: 42-7.

[34] Khaled Z Abd-Elmoniem,Nadine Ramos,Saami K Yazdani, et al. Coronary atherosclerosis and dilation in hyper IgE syndrome patients: Depiction by magnetic resonance vessel wall imaging and pathological correlation.[J]. Atherosclerosis, 2017, 258: 20-25.

[35] Alexandra F Freeman, Elizabeth Mannino Avila, Pamela A Shaw, et al. Coronary artery abnormalities in Hyper-IgE syndrome.[J]. Journal of Clinical Immunology, 2011, 31(3): 338-45.

[36] Sandra Hansmann,Elke Lainka,Gerd Horneff, et al. Consensus protocols for the diagnosis and management of the hereditary autoinflammatory syndromes CAPS, TRAPS and MKD/-HIDS: a German PRO-KIND initiative. [J]. Pediatric Rheumatology Online Journal, 2020, 18(1): 17.

[37] Ru-Yue Chen,Xiao-Zhong Li,Qiang Lin, et al. Epstein-Barr virus-related hemophagocytic lymphohistiocytosis complicated with coronary artery dilation and acute renal injury in a boy with a novel X-linked inhibitor of apoptosis protein (XIAP) variant: a case report.[J]. Bmc Pediatrics, 2020, 20(1): 456.

[38] Cohen Jeffrey-I,Jaffe Elaine-S,Dale Janet-K, et al. Characterization and treatment of chronic active Epstein-Barr virus disease: a 28-year experience in the United States.[J]. Blood, 2011, (22): 5835-49.

[39] Quintanilla-martinez Leticia, Swerdlow Steven-H,Tousseyn Thomas, et al. New concepts in EBV-associated B, T, and NK cell lymphoproliferative disorders.[J]. Virchows Archiv : an international journal of pathology, 2022, (1): 227-244.

[40] Kimura Hiroshi,Morishima Tsuneo,Kanegane Hirokazu, et al. Prognostic factors for chronic active Epstein-Barr virus infection.[J]. The Journal of infectious diseases, 2003, (4): 527-33.

[41] Muneuchi Jun,Ohga Shouichi, Ishimura Masataka, et al. Cardiovascular complications associated with chronic active Epstein-Barr virus infection.[Z], 2009: 274-81.

[42] Correction to: Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.[J]. Circulation, 2019, (5): e181-e184.

KALEIDOSCOPE OF INTERESTING WORKS

NEW PROGRESS IN TREATMENT OF TOURETTE'S DISEASE

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Tourette treatment progress ?

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ABSTRACT

Tourette is a chronic neuropsychiatric disorders affect children with normal learningjiving, social interaction. Treatment were divided into two categories,including drug treatment and non-drug treatment, and mainly drug treatment.This paper literature on treatment are reviewed.

[Key words] Tourette; Child; Nervous and mental diseases; Clinical treatment;
Progress tourette syndrome (TS), also known as Tourette syndrome or "Tourette syndrome", is a syndrome characterized by multiple involuntary tic, speech or behavior disorders. The disease usually occurs at the age of 3-15 years, with more males than females, with a ratio of (3-4) : 1 Although some scholars have studied some risk factors as factors of Tourette's disease, the specific cause of Tourette's disease is unknown at present,but Role of histidine decarboxylase gene in the pathogenesis of Tourette syndrome. Histidine decarboxylase (HDC) mutation is a rare genetic cause with high penetrance in patients with TS. HDC□knockout (KO) mice have similar behavioral and neurochemical abnormalities as patients with TS.[1]

1. PATHOPHYSIOLOGY

Clinically, they are usually divided into three categories: motor twitch, vocal twitch and sensory twitch. Movement twitch finger face, neck and shoulders, trunk and limbs muscles involuntary, sudden, rapid contraction movement, manifested is blinking, frowning, mouth, nose, tongue, mouth, head shaking, nodding, neck stretching, shoulders shrugs, chest and other movements. Motor convulsions last for a certain period of time, usually within 2 years, and develop into vocal convulsions, most commonly in the throat, but also in the tongue muscles and nose. At the same time, patients will show abnormal mood changes and other manifestations, and have different degrees of decline in learning ability. In terms of treatment, classical drugs such as haloperidol, risperidone and thiapride are the main choices[2]. In addition, psychological and behavioral therapy, mental stimulation of the brain, traditional Chinese medicine acupuncture and moxibustion are also widely concerned. In this study, the progress in the treatment of Tourette's syndrome was described.

2. BIOCHEMISTRY

This chapter comprehensively reviews the published record for neurosurgical, neurostimulatory, and neuroimaging evidence of the involvement of the cingulate gyrus in Gilles de la Tourette syndrome (TS). The most noteworthy evidence comes from neuroimaging. Neuroimaging findings were rarely exclusive to the cingulate cortex and tended to implicate multiple other cortices as well. Some results are reflective of obsessive-compulsive (OC) symptoms of TS. Copious findings, however, drawn from structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), resting-state functional magnetic resonance imaging (rsfMRI), task fMRI, and positron emission tomography (PET) implicate six of the eight cingulate subregions in TS. Gauged by MRI, cortical thinning and/or below-normal volume are seen in subgenual anterior cingulate cortex (sACC), pregenual anterior cingulate cortex (pACC), anterior middle cingulate cortex (aMCC), and posterior middle cingulate cortex (pMCC), correlating with tic severity in sACC, pACC, and aMCC. Moreover, in pMCC, dorsal posterior cingulate cortex (dPCC), and ventral posterior cingulate cortex (vPCC), cortical thickness is a candidate biomarker shared across siblings with TS. Loss of cortex may reflect excitotoxicity secondary to insuf-

ficient local GABAergic inhibition, a notion supported by the few relevant MRS and PET studies conducted to date, recommending continued development of GABAergic and glutamatergic pharmacologic agents to treat TS. Measurements of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) obtained with DTI indicate that the white matter proximal to sACC, pACC, pMCC, and dPCC may also represent a seat of pathology in TS. rsfMRI reveals abnormal functional connectivity of pACC and dPCC with the globus pallidus internus, a favored target of therapeutic deep brain stimulation (DBS) for TS. In whole-brain network (graph theory) analysis, dPCC functional connectivity is related to the severity and complexity of tics. In task fMRI, in contrast, the pMCC seems to play a preeminent role in premonitory urges and preparation for tics as well as normal urges to urinate, swallow, and yawn. Strong monkey PET and EEG evidence ties vocal tics to spike discharges, α-activity, and regional blood flow in the pACC unleashed by failure of GABAergic inhibition in the ventral striatum. Tic suppression in fMRI scans is associated with increased blood oxygenation level-dependent activity in sACC, pACC, and aMCC, but decreased activity in pMCC and dPCC. Activity in the former three subregions may represent volitional effort, physical discomfort, and emotional distress that accompanies mounting tic urges; pMCC and dPCC may be more instrumental in amplifying than suppressing urges. Needs for future neuroimaging work in TS include longitudinal studies-particularly those striving to predict which individual pediatric patients will continue to suffer from TS as adults and studies of treatment response-particularly of behavioral therapies, which are as efficacious as pharmacology. Transcranial magnetic stimulation and related therapies such as cranial electrotherapy stimulation, which showed good efficacy in a recent trial, merit continued exploration. TS research using DTI, MRS, and PET will no doubt continue to benefit in coming years from technological advances such as ultrahigh-field scanners, multichannel head coils, and novel (including GABAergic and glutamatergic) ligands. [3]

3. TREATMENT

3.1 Drug therapy

3.1.1 Dopamine receptor blockers

Neuroanatomical and neuroimaging studies suggest that frontal cortical-basal ganglia circuit disorders, especially dopaminergic neurotransmitter system and serotonin system dysfunction, play an important role in the pathogenesis of TS. Long-term randomized, double-blind, placebo-matched studies have confirmed that classical dopamine (D2) blockers fluopectlebore and pimozide can significantly reduce the frequency of convulsions in children with TS. The effective rate of treatment with fluopectlebore 2-20 mg/d or pimozide 2-48 mg/d can be up to 80%[4], but the adverse reactions are large. For example, extrapyramidal reactions, lethargy, and cognitive bluntness, many patients stop taking the drug during the course of treatment. Currently, low-dose long-term therapy is generally used in clinical practice, such as fluopectlebore 1-4 mg/d and pimozide 2-8 mg/d.

Typilide is a benzamide derivative that selectively blocks basal ganglia dopamine receptors[5]. In a prospective study of 69 children with TS aged 4-16 years, Zheng Yabing et al., showed that compared with haloperidol, the adverse reactions of TS in the treatment of children with TS were fewer and less severe, and the patients' compliance was better, and there was no significant difference in the efficacy. However, Beiyan Wu et al. reported that the efficacy of Tiride was not as good as haloperidol, and its clinical efficacy still needed further observation.

Aripetic dopamine system stabilizers are novel atypical antipsychotics with high affinity to dopamine D2, D3, 5-HT1A, and 5-HT2A receptors, so they play a particularly important role in the treatment of TS. A prospective multicentered controlled study of 195 children with TS aged 5-17 years in China showed that the YGTSS (yale global tic severity scale) score of TS children was significantly improved after 12 weeks of aripiperol treatment (5-25 mg/d). The clinical efficacy and incidence of adverse reactions were similar to those of Tipilide (100-500 mg/d)[6]. LMurphy et al. Retrospective analysis of 6 patients aged 8-19 years with TS complicated with OCD showed that aripiperol was treated with 5-20 mg/d After 12 weeks, the YGTSS score and C-YBOCS score decreased by 56% and 71%, respectively. Meanwhile, Winter et al. reported that a female patient with TS and OCD was treated with oral aripebi (5-7.5 mg/d) for only 2 weeks, and her tic and OCD symptoms were significantly relieved. In the study of 7 patients with refractory TS (refractory to other antipsychotics or unable to tolerate severe adverse drug reactions), Frolich et al. found that aripebi 5-30 mg/d for 8 weeks could significantly alleviate motor and vocal tic seizures in children, but had no significant effect on OCD and ADHD. It has been reported that the common side effects of Aripebi are drowsiness, weight gain, inability to sit still, headache and vomiting. About 20.7% to 25.0% of patients discontinue treatment because they cannot tolerate the medication. The clinical efficacy and drug tolerance of aripebi in TS with OCD and especially refractory TS need to be further discussed. In a randomized, double-blind, placebo-controlled study, Jankovic et al. found that topivate was effective in the treatment of moderate to severe Tourette's disease, but the principle of topivate in the treatment of tourette's disease is not very clear.

3.1.2 Monoaminergic antagonists

Selective monoaminergic antagonists such as risperidone, clozapine, olanzapine, and zilapidone are also effective in treating TS. Currently the most widely research of risperidone, it can simultaneously antagonism serotonin 5 - HT2 receptors and dopamine D2 receptors, a large number of studies have shown It can significantly reduce TS patients with different age twitch, curative effect is similar or even better than fluorine sent several alcohols, horse mo qi, especially for TS with anxiety, depression, OCD[7-8] heart 1. Randomized, double-blind, placebo-controlled studies and open experimental studies have shown that chilapidone can effectively treat TS in children and adolescents without adverse effects of weight gain. However, it is worth noting that Scahill et al. reported that a patient with TS died suddenly during clinical trial treatment with zirapperidone, and its safety and tolerability need to be investigated with a large sample. Clinical application of this drug should be cautious, close observation and monitoring of patients with discomfort.

3.1.3 Levetiracetam

Levetiracetam is a pirolidine derivative whose chemical structure has no correlation with existing antiepileptic drugs. In vitro and in vivo tests showed that levetiracetam inhibited epileptiform burst discharges in hippocampus, but had no effect on the excitability of normal neurons, suggesting that levetiracetam may selectively inhibit the hypersynchrone of epileptiform burst discharges and the propagation of seizures. A prospective open study showed that 72% of children with Tourette's disease responded to treatment after 12 weeks of levetiracetam. However, levetiracetam does not directly facilitate GABAergic neurotransmission, but has been shown to have adverse effects on GABA and glycine-gated current negative regulator activity in cultured neurons.

3. 1.4 Norepinephrine

In addition to dopamine and serotonin neurotransmitter systems, other neurotransmitter systems such as cholinergic, noradrenergic, glutamatergic, aminobutyric acid neurotransmitter system imbalance may also be involved in the pathogenesis of TS. Some scholars believe that decreased dopamine and increased norepinephrine in the central nervous system may be associated with ADHD-related pores in TS patients[9], which provides a theoretical basis for the treatment of TS patients with ADHD. Clonidine is a mesoaxis a2 adrenergic blocker, available in oral tablets and percutaneous patches, which reduces norepinephrine activity in the central nervous system. Clonidine has been used in the treatment of TS since 1980, but its clinical efficacy is still controversial. Atomoxetine, a selective norepinephrine reuptake inhibitor, has been shown to be effective in children and adolescents with ADHD in multiple randomized, double-blind, placebo-controlled studies. Spencer TJ[10]and others lost in a prospective study on 117 children aged 7-17 years with TS complicated with ADHD showed that atomoxetine can significantly improve the symptoms of ADHD in children and reduce their tic attacks. During the treatment, adverse reactions such as rapid pulse, nausea, anorexia and weight loss were observed. Moreover, some studies have reported that some children with TS suffer from exacerbation of tics and disease recurrence after treatment with atoroxetine. At the same time, the authors should also be aware of the limitations of the efficacy studies of atoroxetine. Children with severe TS (severe tic or ADHD) may not be included in double-blind, placebo-controlled trials because of the high rate of drug withdrawal[11]. Patients with TS and ADHD who are well controlled with other medications may participate in such studies only if they cannot tolerate current treatment. As a clinical drug for the treatment of children with TS complicated with ADHD, the general safety and efficacy of atoroxetine in the population still need to be explored by large sample control.

3.2Anti-inflammatory and immunoregulatory therapy

The pathogenesis of TS is still unclear. Studies have shown that immune dysfunction or inflammatory response may be involved in the pathogenesis of TS. Some studies have reported that celecoxib, a COX-2 inhibitor, combined with antibiotics can significantly improve tic seizures and behavior disorders in TS patients[12]. Zykov et al. treated 7 children with TS who had failed to respond to long-term antipsychotics. After immunomodulatory therapy (intravenous propyl globulin), the symptoms of motor twitch, vocal twitch and behavior disorder were significantly improved, and the remission was maintained for more than 6 months. These meaningful but very preliminary results need further controlled studies.

3.3 Magnesium sulfate and vitamin B6

Approved by the Council of the Government of Andalusia, Spain, Spanish pediatricians and medical experts conducted a randomized, double-blind placebo study of magnesium sulfate 0.5 mg/ (kg • d) and vitamin B62mg/ (kg-d) (nK) in children aged 7-14 years with tic according to DSM-IV criteria (307.23) and clinical data and YGTSS (Yale Scale) The efficacy and safety of magnesium sulfate and vitamin b6 were investigated, and the results suggested that the new treatment could improve and control seizures and help reduce side effects.

3.4 Remote therapy

Kareem Khan etal digital therapy is implemented as a widely accessible first-line treatment using a purely online or therapistsupported approach.

Digital technology evolves at a rapid pace meaning that as technology changes and interfaces are updated it cannot be certain that a program that was efficacious five or ten years ago would be equally efficacious today. Although RCTs are still the gold standard for which to assess the efficacy of DHIs.

It could provide immediate access to these treatments for those who otherwise would not have access due to long waiting lists or their geographical location, which could also potentially free up existing resources and services for those requiring more complex treatment and assessment. Thus,cutting costs and waiting times would be a two-fold benefit for healthcare services and patients alike. There is a need to conduct more robust research in this domain but also an urgency to implement a digital intervention for children with tic disorders in real-world settings[13].

3.5 Psychobehavioral therapy

3.5.1 Habit reversal training

There is also habit reversal training. It is the most widely studied behavior therapy method at present. It mainly enhances children's self-awareness of tic attacks through a series of methods, such as description of tic response, detection response, early warning process and situational awareness training, and then learns to use certain competitive actions to interrupt or inhibit tic attacks. Habit reversal training may also include relaxation training, mutation management, and general training. A large number of studies have shown that habit reversal training combined with or without drug therapy can effectively relieve the lobar onset of TS motor tics and vocal tics in adults or children[14]. However, the large-scale application of habit reversal training is limited due to the need to obtain the informed consent of the families of the affected children, the lack of professionally trained physiotherapists and adequate insurance coverage.

3.5.2 Biofeedback

It is often used in the treatment of ADHD, anxiety disorders and Tourette's. Doctors placed multiple electrodes on

the child's head to record the rhythm changes of the brain's bioelectricity. At the same time, specialized computer equipment converts information about changes in the rhythm of brain currents into cartoon animations that can be displayed on a fluorescent screen. When children's attention is focused, brain waves adjust to a better state, there will be a cartoon character shooting a successful animation. With this kind of reward method, can make the children intuitively feel their own brain current, experience and remember the "shot successful" when their state, so as to achieve the therapeutic effect.

3.5.3 Dietary Adjustment

Strengthen nutrition, avoid the use of food additives, pigments, caffeine and other food, such as food can induce or aggravate twitch symptoms.

3.6 Other treatments

Acupuncture, immunotherapy, deep brain stimulation, transcranial magnetic stimulation and surgical treatment have been tried to treat the disease.

Touretic syndrome is a common neurodevelopmental disorder in children. About 90% of children are combined with neuropsychiatric disorders, the most common of which are OCD and ADHDO. Although the pathogenesis of TS is still unclear, the treatment of TS has become mature. Children with mild TS may only need psychological and behavioral intervention. A large number of studies support the application of habit reversal training as an alternative or auxiliary treatment for some children with TS. However, the vast majority of children still need medical treatment to relieve their tics and related behavior disorders. Classic TS treatment drugs include Tepilide, fluepislebore, pimozide, risperidone, clonidine, etc. Due to poor efficacy or serious adverse reactions, alipetic, attomoxetine, immune agents, etc., have been gradually tried, and significant efficacy has been achieved in some studies. However, both old and new drugs inevitably have adverse reactions, which will inevitably affect the compliance of children and seriously affect the clinical efficacy. How to enhance the clinical efficacy while minimizing the serious adverse reactions of drugs is the focus of current research. Traditional Chinese medicine in the treatment of TS has the characteristics of overall regulation, safety and effectiveness, and recurrence rate, which can not be ignored, but it is still in the preliminary exploration stage. At present, large-scale, multicenter, randomized, double-blind and controlled studies should be conducted more widely to explore the rules of syndrome differentiation and treatment of TS, so as to provide a solid scientific basis for the treatment strategy of TS.

4. DISCUSS

Hyperextension whole bone method is a traditional Chinese medicine treatment of spinal fractures, yuan dynasty wei Lin also in the specialized to effect the "ankles suspension method" is introduced, the method of "door drag climbing stretching method" in Ming dynasty "the party phuket, broken doors," qing "YiZong jin jian • bonesetting loading message" and the "climbing rope stacked bricks method" reset method. In recent years, many domestic scholars have combined hyperextension osteoplasty with PVP in the treatment of OVCF, which has achieved good short-term analgesic effect. However, it often fails to achieve comparable effects with PKP in the recovery of the height of the affected vertebra and correction of kyphosis, and the bone cement leakage rate is still high, and there is a lack of mid-and long-term clinical observation.

Bai B et al[9-10]. found that restoring vertebral height can reduce vertebral kyphosis after fracture and has the potential benefit of reducing malform-related sequelae. In this study, the surgeon followed the principle of anti-trauma mechanism in preoperative manipulative reduction, and used progressive pad elevation restoration method to fix the fracture and exercise the lumbar and back muscles. This can not only restore the height of the vertebral body, correct the deformity, and the occurrence of late chronic low back pain will be greatly reduced back[11].

It is generally believed that PVP in the treatment of OVCF single vertebral bone cement perfusion volume is less than PKP, in this study, the PVP group and PKP group single vertebral bone cement perfusion volume has no significant difference ($P > 0.05$), and the incidence of bone cement leakage is lower than that reported in the literature[12], the reasons are investigated. Comprehensive closed reduction can reduce or return to normal bone density in the compression area of the injured vertebra, and even form local cavities, which greatly increases the volume of the vertebral body and can accommodate more bone cement. Bone cement can at low pressure and high viscous state of dispersion in the vertebral body, seeping into the vertebral body bone trabecular bone cement is increased and the contact area of the vertebral body, effectively reduce hair born of leakage of bone cement and bone trabecular micro fracture risk again because of bone cement has overcome between the vertebral cancellous bone and elastic modulus decrease due to the differences and thus reduce the adjacent vertebral body fracture again hair[14].

In the current economic conditions in our country, postures, manual reduction of OVCF patients treated + PVP is relatively safe, simple operation, less X-ray exposure time, patients with vertebral height restoration and protrusion deformity correction effect after apparent, analgesic effect is good, durable, less cost, and low incidence of diseases, treatment can achieve the maximum price down, It's a good treatment.

[REFERENCES]

[1] WANG Shoubao, Wang Chun, Lin Jin, et al. Advances in treatment of osteoporotic thoracolumbar compression fractures in the elderly [J]. Journal of Clinical & Experimental Medicine,2010,9 (2) : 153-155.

[2] Teng MM, Wei CJ, Wei LC, Kyphosis correction and height restoration effects of percutaneous vertebroplasty [J]. AJNR,2003,24 (9) : 1893-1900.

[3] Joseph O'Neill,John C Piacentini,Bradley S Peterson.Cingulate role in Tourette syndrome[J].Handbook of clinical neurology,2019,166:165-221

[4] Mathis MJ.Percutaneous vertebroplasty or kyphoplasty: which one do I choose? [J].Skeletal Radiol, 2006, 35 (9) : 629-631.

[5] Xiao Shaoxiong, Xiong Wei, Xia Ping. Kyphoplasty for the treatment of osteoporotic fractures of thoracolumbar spine in elderly patients [J]. Chin J Orthopedics,2009,17 (8) : 22-23.

[6] Gu Xiaohui, Yang Huilin, Zhang Zhiming, et al., Reduction effect of balloon expansion kyphoplasty for spinal compression fractures [J]. Journal of Soochow University Medical Science,2005,25 (5) : 868.

[7] Million R, Hall W, Nilsen KH, et al.Assessment of the progress of the back pain patient[J].Spine, 1982,7 (4) : 204.

[8] Zheng Guangxin, Zhao Xiaoou, Liu Guanglin, et al. Evaluation of low back pain by Oswestry Disability Index [J]. Chin J Sci Sci,2005,15 (4); 242-244.

[9] Bai B, Jazrawj LM, Kummer FJ, et al. The use of mi injectable, biodegradable calcium phosphate honesuhstitute for the prophylactic augmentation of osteoporotic vertebrae and the management of vertebral compression fractures [J]. Spine, 1999, 24:1521-1525.

[10] Schildhauer TA, Bennett AP, Wright TM, et aLIntravertebral body reconstruction with an injectale in situ-setting carbonated apatite: Biomechanical evaluation of a minimally invasive technique[J].0rthop Res, 1999, 17:67-72.

[11] Xu Shaoting, Ge Baofeng, Xu Yinkan. Applied Osteology [M]. 3rd Ed. Beijing: People's Military Medical Publishing House, 2006:593-596.

[12] Li Ninghua, Qu Pinzhong, Zhu Hanmin, et al. Study on the prevalence of primary osteoporosis in middle-aged and elderly people in China [J]. Chin J Orthopaedics, 2001, 21:275-278.

[13] Kareem Khan, Chris Hollis, Tara Murphy,et al.Digital and remote behavioral therapies for treating tic disorders: Recent advances and next steps[J].Frontiers in Psychiatry, 2022, 13:928487

[14] Wang Shoubao, Wang Chun, Lin Jin, et al. Advances in treatment of osteoporotic thoracolumbar compression fractures in the elderly [J]. Journal of Clinical & Experimental Medicine,2010,9 (2): 153-155.

ADVANCES IN THE CO-HOST IMMUNE RESPONSE TO MULTISYSTEM INFLAMMATORY SYNDROME AND KAWASAKI DISEASE IN CHILDREN WITH AI-GUIDED FEATURES

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ABSTRACT/PURPOSE

To explore the role of artificial intelligence in the immune response mechanism of children with multi-system inflammatory syndrome and Kawasaki disease. Methods: To search the domestic and foreign literatures about the immune response mechanism of these two diseases, and analyze the literatures according to the characteristics of artificial intelligence. Results: AI analysis showed that the two kinds of children's syndrome were concentrated in the cytokine storm centered on il-15/IL15RA, which confirmed that the two diseases had the same initial immune pathway, but the differences in immune phenotype, cytokine, cell count and other aspects suggested that KD and MIS-C were two different diseases. Conclusion: It shows the applicability of AI in this research direction, and points out the limitations of the current research scope and samples. The difference between the results of KD and MIS-C research guides the direction of future research. Accurate and comprehensive laboratory indicators and parameters can be applied to artificial intelligence and provide basis for diagnosis and treatment of diseases. As the number of infected people increases, the problem of sample limitation in the current work can also be improved.

Keywords: Artificial Intelligence; Kawasaki Disease; Multi-System Inflammatory Syndrome (MIS-C) Immune Response

Background: Multiple systemic inflammatory syndrome (MISC) caused by SARS-CoV-2 infection has overlapping characteristics with Kawasaki disease, suggesting that vasculitis and possible autoimmune etiology, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a human coronavirus. Coronavirus appeared in December 2019 and spread rapidly around the world, bringing us huge medical and life challenges. In April 2020, children with symptoms similar to incomplete Kawasaki disease (KD) or toxic shock syndrome were reported in the UK, and then similar children were reported in other parts of the world. Jiao Fuyong believes that KD is very similar to coronavirus infectious diseases such as Severe Acute Respiratory Syndrome

(SARS), Middle East Respiratory Syndrome (MERS), 2019 Coronavirus Disease (COVID-19) in terms of epidemiological distribution patterns: it has obvious seasonal characteristics. Combined with a few coronaviruses that can infect humans through cross-species transmission and have symptoms very similar to Kawasaki disease, Kawasaki disease can be regarded as a new manifestation of COVID-19 in children and should be treated [1]. The disease was later defined as coronavirus-associated multisystem inflammatory syndrome in children (MIS-C), which can be fatal in severe cases. Children's multisystem inflammatory syndrome (MIS-C) and Kawasaki disease are highly inflammatory diseases related to infectious diseases, but are they different syndromes or continuous? The characteristics of AI guidance provide new insights for us to understand the co-host immune response of children with multi-system inflammatory syndrome and Kawasaki disease. This article reviews the progress in the study of host immune mechanism of children with multiple system inflammatory syndrome and Kawasaki disease.

FOREIGN RESEARCH STATUS:

The SARS - CoV - 2 pandemic has inspired many research groups to find innovative ways to understand the host's immune response to the virus, of which the proportion of out-of-control is related to death. Through searching multiple (>45000) gene expression datasets of GEO and ArrayExpress, more than 45000 pandemic transcriptome datasets were analyzed, 166 gene signatures were extracted with ACE2 as the "seed" gene, and ViP and severe ViP features were named. Researchers have analyzed 166 genes of H1N1 and H3N2 pandemic infection samples and bacteria and fungi in vitro and in vivo, and found that VIP characteristics are surprisingly conservative. This feature largely enriched genes in the immune system pathway, such as interferon and cytokine signaling pathway. In other words, this feature is widely accepted as a typical host immune response for host defense during any infection. At the same time, 20 gene clusters of 166 genes related to "severity" were found. Through the study of samples of mild and severe diseases during the pandemic of avian influenza (H7N9), IAV (H3N1 and others) and swine influenza (H1N1) viruses, the ViP characteristics of 166 genes and the severity characteristics of 20 genes were similar in the classification of control and mild diseases, but the latter was significantly better in the classification of mild and severe diseases. The 20 gene clusters related to "severity" enrich a completely different set of cell processes, namely DNA damage, stress-induced aging, neutrophil degranulation and cell cycle change. Moreover, severe vip characteristics (sViP) can predict the outcome of COVID-19 patient cohort. The only cytokine/receptor pair in these 166 gene clusters is interleukin 15 (IL15/IL15RA), and cytokine storm (166 genes, including IL15/IL15RA) is induced in a variety of cell types; However, the 20 gene ViP characteristics of disease severity and mortality are most significantly induced in two cell types: (i) known airway epithelial cells that produce il - 15 after virus infection and (ii) known target cells NK cells with physiological and excessive il - 15 response [69,70]. Airway epithelial cells (especially bronchus) constitutively express IL-15 and IL-15RA/B genes. Virus infection and IFNg can induce the effect of its synthesis and secretion of IL-15 [68]. Prolonged and excessive IL-15 stimulation can lead to significant depletion and reduction of NK cells in severe COVID-19 infection cases, and this reduction occurs as early as 6 days after symptoms appear. We conclude that fatal COVID-19 is characterized by a contradictory immune response, that is, inhibiting the function of epithelial cells and NK cells in the context of cytokine storm (excessive immune response) (immunosuppression). Researchers are trying to determine whether SARS-CoV-2 virus can induce ViP characteristics and whether these characteristics can track the treatment response. The first method is to use n - hydroxycytidine, the mother of the prodrug MK4482. We analyzed the lungs of golden Syrian hamsters infected with sars - cov - 2 by RNA sequencing. These hamsters received the drug or carrier control treatment respectively. The ViP signals of 166 and 20 genes were induced in the vector treatment group and effectively suppressed to the level of non-infected control group in the drug treatment group. The second method is to use the sars - cov-2 neutralizing antibody, which binds to the receptor binding domain (RBD-A) of SARS-CoV-2 spike protein in a way that prevents binding with the host ACE2. It has been proved to be effective in preventing infection and weight loss symptoms in the cell-based infected hamster model and in vivo infected hamster model, respectively. There are three key findings: (i) They inhibit 166 and 20 vip signatures, These signatures were induced in infected lungs; (ii) Protect the lungs from immune cell infiltration and alveolar space occlusion; (iii) The expression of IL-15 and IL-15 receptor was significantly lower than that observed in infected lung (Fig. 8i, k). These results verify the calculation method of recognizing ViP signature centered on ACE2. When using antiviral drugs or neutralizing antibodies, the signature is suppressed. The results also show that the reversal of signal and the storm of il - 15 can be used as a reading of therapeutic efficacy. The increase of IL-15 is independently related to mortality. In patients who died and recovered during hospitalization, the level of cytokines is always high. Problems in this study: since the public transcriptome data set of sarscov-2 infection samples is still relatively small, any conclusion drawn from such a small number of samples using any calculation method may lack robustness. The selected calculation method, Boolean analysis, filters some key information. This requires more accurate and specific COVID-19 data set to provide more accurate evidence [2].

Given that children's multi-system inflammatory syndrome (misc) and Kawasaki disease syndrome (KD) have many similar clinical features, PradiptaGhosh et al. used two genetic marker calculation tool packages developed in the context of SARS-CoV-2 infection to compare the two syndromes. Namely, viral pandemic (ViP) and severe ViP signatures, as well as 13 transcript signatures previously proved to be able to diagnose KD. This study confirmed that compared with the healthy control group, the ViP and sViP characteristics in blood and tissue samples of KD patients were up-regulated. Because the diameter of CAA was a predictor of coronary artery sequelae, the development of coronary artery aneurysm

(CAA) was used as a marker of disease severity. It was found that the differential expression of the two ViP characteristics in patients with giant aneurysms and patients without aneurysms could distinguish acute KD patients with giant aneurysms, Since ViP signature represents the host's immune response to different pathogens, the research results show that the up-regulation of ViP signature in KD is consistent with the assumption that KD is triggered by multiple infections, some of which may be viral. When the misc group and acute KD group were compared with the control (subacute KD) samples, the following conclusions were drawn: (i) The host immune response detected by qualitative method using ViP characteristics was similar in KD and MIS-C, and had IL15/IL15RA shared components; (ii) The degree of this host immune response measured quantitatively by ViP signature score is stronger than KD in misc. These findings are consistent with the fact that misc is the host's immune response to SARS-CoV-2 exposure. The research results are also consistent with previous work, that is, the serum level of il - 15 in patients with acute KD is significantly increased, about 10 times as compared with that in subacute KD and normal control group. In order to avoid over-reliance on a group of markers (ViP/sViP), Ghosh et al. subsequently used Kawasaki disease specific gene expression markers, which were previously used to identify Kawasaki disease in children with fever. The study found that KD specific 13 transcript signature could not distinguish misc and KD. In addition, the two non-overlapping signatures, sViP and KD-13, are significantly induced in KD and misc, and are independent of each other. This shows that these two characteristics reflect two fundamentally different and unrelated biological domains in host immune response; Whether their diagnostic/prognostic capabilities have additional benefits remains to be explored. The similarity of KD-13 features and ViP/sViP signatures induced by KD and misc in two independent queues further supports our research. KD and misc are the same in the basic aspects of host immune response. The whole blood transcriptome and cytokine panel reveal the subtle difference between misc and KD. Although the induction of most cytokines in acute KD and misc is not different, there are obvious exceptions. Compared with KD, in misc, TNF α, IFN γ, IL10, IL8 and IL1 β They all increased to a greater extent, but did not reach statistical significance. These findings indicate that the target TNF approved by the fda α And IL1 β The way of treatment may be beneficial to the treatment of misc. IL-1 receptor is expressed in almost all tissues, and its antagonistic effect is blocked by anakinra (the recombinant form of IL-1Ra41) α Or IL-1 β Receptor binding. Similarly, tumor necrosis factor α The chimeric antibody infliximab has been reused in COVID-19. Analysis shows that this drug is expected to be used in the treatment of misc. The researchers tried to understand how similar host cytokine responses triggered two different clinical syndromes, and analyzed the samples of misc and acute KD using cytokine analysis (MSD) and clinical/laboratory parameters. The results showed that: (1) compared with KD, the level of cytokine in patients with misc was higher, the decrease of whole blood cells was more serious, and the host immune response of MISC was significantly higher than that of KD; (2) Misc has the key distinguishing characteristics of thrombocytopenia and low eosinophil count, and both of these characteristics are negatively correlated with serum il-15 and VIP levels. Eosinophilia seems to be a significant common feature between misc and COVID-19, but not KD. These findings are consistent with the fact that KD is known to exhibit higher (rather than lower) eosinophil counts. Thrombocytopenia has been shown to be significantly associated with mortality. Like thrombocytopenia, persistent eosinophilia after admission is associated with the severity and low recovery rate of COVID-19. (3) Misc had impaired cardiac contractility, but KD did not. These two kinds of pediatric syndromes focus on the cytokine storm centered on il-15/il15ra, suggesting that there is a common proximal pathway for immune pathogenesis. However, they differ in other laboratory parameters (platelets, eosinophils) and cardiac phenotype (cardiac function decline, coronary artery dilation). These relevant clinical/laboratory parameters (low PLT and AEC) may be useful indicators of disease severity and prognosis, and can be used to guide hospital treatment and nursing decisions. The current limitation of this experiment is still that the sample size of misc subjects is relatively small. Therefore, the accuracy of analysis can be improved by using the informatics method, that is, Boolean equivalent correlation clustering. This method can identify the basically unchanged (generally conservative) gene expression relationship based on any biological field; Different from some mainstream computing methods (such as differential expression, Bayesian and correlation network analysis, etc.), it can identify the entire spectrum of host immune response, the Boolean equivalence relationship, and mainly identify the potential function-related gene set, and to some extent, it misses some key information. Moreover, due to the small sample size, we cannot obtain the cardiac tissue of KD and misc subjects and determine the possible impact of IL-15/IL15R expression in the heart [3].

Subsequently, Jonathan Y Lam et al. developed a deep learning algorithm called KIDMATCH (Kawasaki disease vs pediatric multi-system inflammatory syndrome), which is based on a two-stage model composed of a precursor neural network and uses the patient's age, five classic clinical signs of Kawasaki disease and 17 laboratory indicators to identify the disease. This is also the first algorithm for diagnosis, which can distinguish misc, kawasaki disease and other similar febrile diseases. However, due to the lack of the gold standard for Kawasaki disease or misc diagnosis, and the limited data of febrile disease and Kawasaki disease used for external verification, the existing algorithms are only optimized for the laboratory test values collected during the initial evaluation. At present, it is not clear how the end user should deal with the patients marked as uncertain, and how it will deal with the data collected at a later point in time. More professional detection methods such as ferritin, troponin, b-type natriuretic peptide or n-terminal b-type natriuretic peptide precursor and d-dimer, as well as anti-SARS-CoV-2 IgG antibody, may be a better solution [4].

The study on the immune mechanism of children with multi-system inflammatory syndrome (misc) and Kawasaki disease (KD) focuses on multiple directions. At present, the study on host im-

munity of misc and kawasaki disease by artificial intelligence has a short time and lacks relevant literature. The number of studies on the pathogenesis of these two diseases was relatively large in the past. Here is a brief introduction:

Marques et al investigated the transcriptional groups of 1596 individuals, including COVID-19 patients, and compared them with the healthy control group, other acute inflammatory states (HLH, children's multi-system inflammatory syndrome, Kawasaki disease) and different respiratory infections (seasonal coronavirus, influenza, bacterial pneumonia). In the study, it was found that a group of neutrophil-related genes reflected a widespread high inflammatory state, and these genes were abnormally regulated at the protein level, which could lead to excessive activation of neutrophils in patients. Studies have shown that severe COVID-19 disease and other acute inflammatory diseases (such as HLH, KD and bacterial pneumonia) have the same characteristics of neutrophil activation. Studies have shown that the accumulation of neutrophils in the inflammatory tissue of COVID-19 patients is the result of the release of pro-inflammatory cytokines and chemokines driven by T cells. The number and dysfunction of neutrophils are related to the outcome of COVID-19. The inhibition of CCR5-CCL4 axis through Leronlima (anti ccr5 monoclonal antibody), or through Tocilizumab (anti il - 6r), Adalimumab (anti tnf- α) Or Anakinra (anti il1r) blocks cytokine signaling pathway, which has been proved to improve severe symptoms of COVID-19 in some cases. In addition, Ruxolitinib is a JAK1/JAK2 inhibitor that acts on jak-dependent chemokines/-cytokines (such as IFN- γ, IL-1 β, IL-6, TNF, G-CSF, CXCL9 and CXCL10), the inhibitor has shown good effect in the treatment of COVID-19, and neutrophil elastase inhibitor has also been suggested to relieve the symptoms of SARS-CoV-2. The limitation of this study is that it did not investigate the effect of different SARS-CoV-2 variants on the transcriptome of COVID-19 patients. Therefore, it is necessary to further study how different variants of SARS-CoV-2 intersect with other highly inflammatory diseases we investigated. At the same time, the influence of age, sex and complications on the common transcriptome characteristics of COVID-19 and other highly inflammatory diseases was not considered [5].

Michael J. Carter's "Peripheral Immunophenotypes of Children with SARS-CoV-2 Infection-Related Multiple System Inflammatory Syndrome" believed that the level of cytokines, including interleukin-1, increased in the acute infection stage of misc β (IL-1 β), IL-6, IL-8, tumor necrosis factor- α, IL-10, IL-17, interferon- γ (IFN- γ) And IL-2 receptor agonists, CRP and ferritin increased, which was the same as that of acute infection stage of Kawasaki disease. However, the increase of fibrinogen, the increase of d - dimer and the decrease of platelets in the acute phase of Misc suggest the procoagulant state, which is not a common feature of Kawasaki disease. The number of neutrophils and monocytes in the misc cohort was not increased, but higher in Kawasaki disease. In Kawasaki disease, CD4 and CD8 counts were higher than those observed in our misc cohort, while the proportion of hla - dr positive CD4+T cells was lower in Kawasaki disease. This study proposes a direction. These differences suggest that misc may be a unique immunopathogenic disease, but it needs to be confirmed by simultaneous immunotyping of Kawasaki disease and multisystem inflammatory syndrome. The limitations of this study are that only HLA-DR is used as a marker of T cell activation, and there is a lack of evaluation of potential genetic susceptibility [6].

Camila Rosat Consiglio et al. found that some genetic variations with medium effect size, such as ITPKC, CD40, FCGR2A and BLK, were related to KD. The inflammatory response of misc has several common characteristics with Kawasaki disease, but it is different from Kawasaki disease in T cell subsets, interleukin (IL) - 17A and biomarkers related to arterial injury. Compared with children with Kawasaki disease, the lymphocyte reduction in children with misc is more obvious. The levels of c-reactive protein (CRP) and ferritin in children with misc are also significantly higher, and the platelet count is also lower. The study evaluated the phenotype of peripheral blood mononuclear cells (PBMC) by flow cytometry. Compared with patients with Kawasaki disease, the naive CD4+T cells and TFH in MISC patients were lower, the central memory subgroup and effective memory subgroup were increased, and the CD57 marker was higher in misc. This indicates that there are some specific differences between the immune cell response of misc patients and Kawasaki disease patients. IL-17A is very important in Kawasaki disease, but IL-17A is significantly reduced in misc patients, which indicates that there are differences in the underlying immunopathology. IL-17A blockers, such as secukinumab, can be considered for use in serious Kawasaki disease patients in future trials. The researchers detected antibodies in plasma samples using human proteome chips, and found many antibodies with differences between MIS-C and Kawasaki disease. The overexpression of EDIL3 autoantibodies was the most obvious in Kawasaki disease patients. CSNK and MAP2K2 family proteins were significantly increased in MIS-C. Autoantibodies may be the pathogenesis of misc and Kawasaki disease. IVIGs can neutralize some immunopathological effects of autoantibodies and be used for the treatment of both diseases[7].

Alice Castaldo published an article on the differentiation of misc and Kawasaki disease by peripheral blood cell immunophenotyping. The white blood cell populations of 46 misc and 28 KD patients were studied by flow cytometry, and compared with 70 age-matched healthy children. The results showed that misc patients had significant lymphopenia, involving B and T, while KD patients showed significant neutropenia and thrombocytosis, which overlapped with previous research results. The granulocyte/lymphocyte ratio is helpful for the diagnosis of misc and KD and has high diagnostic sensitivity, while the multivariate analysis of the number of granulocyte and T lymphocyte is helpful to distinguish these two diseases. The analysis of a group of circulating cells is helpful for early diagnosis and differentiation of these two diseases [8].

DOMESTIC RESEARCH STATUS:

At present, there is no comparison between the two kinds of disease immunity guided by AI features in China. Li Shihua, Li Huimin and others found that HLA-drb1 and HLA-micaA4 are related to KD, and LA-B is considered as the risk allele of severe infection of COVID-19. Autoimmune vasculitis of KD,

KDSS or MISC is caused by HLA, Fc γ Genetic variation of R and/or ADE mediates excessive inflammation of Th17/Treg imbalance The correlation of genetic susceptibility in KD and/or COVID-19 was determined[9].

Conclusion: The above studies confirmed that MIS-C and KD have a common initial immune pathway, but in cytokines (IL-17A increased in Kawasaki disease and significantly decreased in misc patients), T cell subsets (CD4 and CD8 counts in Kawasaki disease were higher than misc,), immunophenotypes (CD57 markers were higher in misc), antibodies (the overexpression of EDIL3 autoantibodies in Kawasaki disease was the most obvious, and CSNK and MAP2K2 family proteins were highly expressed in MIS-C) There are differences in blood coagulation status (fibrinogen increase, d - dimer increase and platelet decrease in acute phase of Misc, not in Kawasaki disease), cell count (neutrophil and platelet increase in KD, and eosinophil count decrease in misc), etc. In view of the difficulties caused by the global pandemic of COVID-19, it is particularly important to use artificial intelligence to help medical researchers lock key molecules and pathways from complex data, study disease mechanisms and carry out drug treatment. The limitations of previous studies include the relatively small sample size and the limited number of public misc data sets that can be independently verified. In the future, strict data research is still needed. In the future, we hope to find more extensive and accurate gene features in existing studies (related to cytokines, cellular immunophenotypes, antibodies, gene susceptibility, etc.), use artificial intelligence algorithms to define and layer diseases from clinical or laboratory parameters, and identify the phenotypes and complications of disease spectrum, including cardiogenic shock (such as MIS-C shock and Kawasaki disease shock syndrome), MAS (cytopenia and coagulation dysfunction related to cytokine storm caused by infection), Kawasaki disease (typical and complete Kawasaki disease phenotype, caused by SARS - CoV-2 or other infectious factors), and provide evidence for the formulation of treatment strategies [10]. In the future, the amount of research data should be further expanded in clinical practice, and the special method of artificial intelligence should be used to diagnose, differential diagnosis and treatment of the above diseases to serve the clinical.

REFERENCE

1. Jiao F. Y. Kawasaki disease: a new manifestation of COVID-19 in children [J]. Chinese Journal of Pediatrics, 20, 22(07):677-67

2. 2. Sahoo D, Katkar GD, Khandelwal S, Behroozikhah M, Claire A, Castillo V,Tindle C, Fuller M, Taheri S, Rogers TF, Beutler N, Ramirez SI, Rawlings SA,Pretorius V, Smith DM, Burton DR, Alexander LEC, Duran J, Crotty S, Dan JM, Das S, Ghosh P. AI-guided discovery of the invariant host response to viral pandemics.EBioMedicine.2021Jun; 68:103390.doi: 10.1016/j.ebiom. Epub 2021 Jun 11. PMID: 34127431; PMCID: PMC8193764.

3. Ghosh P, Katkar GD, Shimizu C, Kim J, Khandelwal S, Tremoulet AH, Kanegaye JT; Pediatric Emergency Medicine Kawasaki Disease Research Group; Bocchini J, Das S, Burns JC, Sahoo D. An Artificial Intelligence-guided signature reveals the shared host immune response in MIS-C and Kawasaki disease. Nat Commun. 2022 May 16; 13(1):2687. doi: 10. 1038/s41467-022-30357-w. Erratum in: Nat Commun. 2022 Aug 11; 13(1):4729. PMID: 35577777; PMCID: PMC9110726.

4. Lam JY, Shimizu C, Tremoulet AH, Bainto E, Roberts SC, Sivilay N, Gardiner MA, Kanegaye JT, Hogan AH, Salazar JC, Mohandas S, Szmuszkovicz JR, Mahanta S,Dionne A, Newburger JW, Ansusinha E, DeBiasi RL, Hao S, Ling XB, Cohen HJ,Nemati S, Burns JC; Pediatric Emergency Medicine Kawasaki Disease Research Group; CHARMS Study Group. A machine-learning algorithm for diagnosis of multisystem inflammatory syndrome in children and Kawasaki disease in the USA: a retrospective model development and validation study. Lancet Digit Health. 2022 Oct; 4(10):e717-e726.doi:10.1016/S2589-7500(22)00149-2.PMID:36150781; PMCID:PMC9507344.

5. Schimke LF, Marques AHC, Baiocchi GC, de Souza Prado CA, Fonseca DLM, Freire PP, Rodrigues Plaça D, Salerno Filgueiras I, Coelho Salgado R, Jansen-Marques G,Rocha Oliveira AE, Peron JPS, Cabral-Miranda G, Barbuto JAM, Camara NOS, Calich VLG, Ochs HD, Condino-Neto A, Overmyer KA, Coon JJ, Balnis J, Jaitovich A, Schulte-Schrepping J, Ulas T, Schultze JL, Nakaya HI, Jurisica I, Cabral-Marques O. Severe COVID-19 Shares a Common Neutrophil Activation Signature with Other Acute Inflammatory States. Cells. 2022 Mar 1; 11(5):847. doi:10. 3390/cells11050847. PMID: 35269470; PMCID: PMC8909161.

6. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, Acors S, Graham C, Timms E, Kenny J, Neil S, Malim MH, Tibby SM, Shankar-Hari M. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med. 2020 Nov; 26(11):1701-1707. doi: 10. 1038/-s41591-020-1054-6. Epub 2020 Aug 18. PMID: 32812012.

7. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, Tan Z, Zicari S, Ruggiero A, Pascucci GR, Santilli V, Campbell T, Bryceson Y, Eriksson D, Wang J, Marchesi A, Lakshmikanth T, Campana A, Villani A, Rossi P; CACTUS Study Team; Landegren N, Palma P, Brodin P. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell. 2020 Nov 12; 183(4):968-981. e7. doi: 10. 1016/j. cell. 2020. 09. 016. Epub 2020 Sep 6. PMID: 32966765; PMCID: PMC7474869.

8. Castaldo A, D'Anna C, Gelzo M, Giannattasio A, Maglione M, Muzzica S, Raia M, Scalia G, Tripodi L, Castaldo G, Tipo V, Grieco D, Grieco M. Immunophenotyping of peripheral blood cells allows to discriminate MIS-C and Kawasaki disease. Transl Med Commun. 2022; 7(1):22. doi: 10. 1186/s41231-022-00128-2. Epub 2022 Sep 4. MID: 36093039; PMCID: PMC9440857.

9. Chen MR, Kuo HC, Lee YJ, Chi H, Li SC, Lee HC, Yang KD. Phenotype, Susceptibility, Autoimmunity, and Immunotherapy Between Kawasaki Disease andCoronavirus Disease-19 Associated Multisystem Inflammatory Syndrome in Children. Front Immunol. 2021 Feb 26; 12:632890. doi: 10. 3389/fimmu. 2021. 632890. Erratum in: Front Immunol. 2021 Aug 05; 12:722582. PMID: 33732254; PMCID: PMC7959769.

10. Tsoukas P, Yeung RSM. Kawasaki disease and MIS-C share a host immune response. Nat Rev Rheumatol. 2022 Oct; 18(10):555-556. doi:10.1038-/s41584-022-00820-5. PMID: 360086-14; PMCID: PMC9406247.

WHAT LESIONS CAN CAUSE CORONARY ARTERY DAMAGE IN CHILDREN?

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ABSTRACT

Coronary artery lesions (CAL) are not uncommon in pediatrics, but their causes are complex, such as congenital coronary artery disease, atherosclerosis, infectious diseases, and rheumatic immune diseases, which can lead to CAL. This review systematically evaluates multiple potential causes of childhood CAL and related pathogenesis, in order to broaden clinical diagnosis and avoid misdiagnosis and underdiagnosis. The main pathogenesis of CAL is an innate immunity imbalance due to exposure of genetically susceptible people to various infections and/or environmental factors. Kawasaki disease is not the only cause of CAL, and pediatricians need to better understand the immunological mechanisms of the CAL to suspect and diagnose. In addition, attach great importance to rheumatic immune diseases and cardiovascular diseases secondary to CAL.

Keywords: Kawasaki disease, dyslipidemia, underdiagnosis, coronary artery injury

INTRODUCTION

The etiological mechanism of coronary artery lesions (CAL) coronary artery dilatation disease is not completely clear, and its pathological manifestations are mainly the destruction of the middle layer of the coronary artery vessel wall structure and the degradation of elastic fibers. Possible causes include atherosclerosis, autoimmune or inflammatory reactions, vascular infectious diseases, and overexpression of gene susceptibility [1]. The disease is prevalent in patients with autoimmune diseases or Kawasaki disease in childhood, in men with dyslipidemia, in men with hypertension, in men who are long-term smokers, and can be triggered by infections with autoimmune abnormalities and emotional agitation. A variety of childhood rheumatic immune diseases can lead to coronary artery lesions (CAL). By understanding the immunological pathogenesis of the disease and broadening the diagnosis and differentiation of the disease, we can help improve the diagnosis and treatment of CAL-related rheumatologic diseases.

MAIN ETIOLOGY

1. Atherosclerosis: coronary artery dilatation disease is a variant of obstructive coronary artery disease.

2. Autoimmune or inflammatory response: Coronary artery dilatation disease in children and adolescents is usually a complication of Kawasaki disease, and connective tissue diseases, systemic arteritis and Marfan syndrome can lead to coronary artery dilatation disease.

3. Vascular infectious diseases: infections such as fungal or septic emboli, syphilis, etc. can damage coronary vessels and lead to coronary artery dilation.

4. The etiology of simple coronary artery dilation disease is unknown and may be related to genetic susceptibility (e.g., specific HLA class II genotype, matrix metalloproteinase gene variants), angiotensin-converting enzyme overexpression, etc.

5. Coronary arteriovenous fistula.

6. Hereditary family cluster nesting hypercholesterolemia.

The predisposing factors

1. Infection and autoimmune abnormalities: infection may directly or indirectly damage coronary arteries by stimulating autoimmune reactions.

2. Emotional excitement or after strenuous activity can trigger the disease, appearing chest pain and discomfort.

3. In addition, smoking, high blood pressure, cocaine use, etc. may trigger this disease.

KAWASAKI DISEASE

Kawasaki disease is an infection-induced systemic inflammatory disease in children, in which vasculitis is the main feature, mainly involving small and medium-sized arteries [2]. Clinical manifestations include fever, rash, congestion of the conjunctiva of the eye and oral mucosa, palmoplantar erythema, hard edema of the finger (toe) ends and enlarged cervical lymph nodes, etc. A few children may even have Kawasaki disease shock syndrome (KDSS) or macrophage activation syndrome (MAS). The disease usually has a good prognosis, with most temporary changes in CAL and long-term complications mainly related to the degree of coronary artery involvement. Coronary artery dilatation to an internal diameter<8 mm and a Z value<10 often results in gradual recovery, whereas giant coronary aneurysms (maximum internal diameter ≥8 mm) are highly susceptible to myocardial infarction, arrhythmia, or sudden death due to coronary occlusion [3-4].

The exact etiology of Kawasaki disease has not been elucidated. It has been found that Kawasaki disease may be associated with infection by different pathogens and genetic susceptibility. The pathology of Kawasaki disease shows inflammatory cells infiltrating the vascular tissue and destroying the luminal endothelium, elastic fiber layer and middle smooth muscle cells, which eventually leads to luminal dilation and

aneurysm formation [5]. Inflammatory cells infiltrating the arterial vasculature include neutrophils, T cells (especially CD8+ T cells), eosinophils, plasma cells (especially IgA-secreting plasma cells), and macrophages [6]. Early in the course of the disease, mainly neutrophils infiltrate the arterial wall, and after 2 weeks, monocytes and CD8+ T cells predominate [7]. Thus, Kawasaki disease may be a systemic inflammatory disease with a predominantly innate immune disorder due to exposure of genetically susceptible individuals to various infections and/or environmental triggers.

MULTISYSTEM INFLAMMATORY SYNDROME (MIS) IN CHILDREN

Since April 2020 several countries have reported the clinical features of cohorts of childhood MIS cases, which occur mostly in previously healthy children and adolescents with a clinical presentation similar to KDSS, presenting with systemic multisystem damage and evidence of novel coronavirus pneumonia (COVID-19). The World Health Organization defines MIS in children [8] as (1) Age <19 years. (2) Fever ≥3 d. (3) Evidence of multisystem injury (≥2): (i) rash, bilateral nonpurulent conjunctivitis, or skin mucosal symptoms; (ii) hypotension or shock; (iii) cardiovascular dysfunction, pericarditis, valvulitis, or CAL; (iv) coagulation abnormalities; and (v) acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain). (4) Elevated inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein, or calcitoninogen. (5) Inflammation due to infection by other pathogens is excluded. (6) Evidence related to COVID-19.

Cardiac involvement is a common manifestation of MIS in children, with 32% of patients having a left ventricular ejection fraction of less than 55% and 11% of them having an ejection fraction of less than 30%. 23% of patients have myocarditis. 23.4% of patients with KD-like symptoms have coronary artery dilatation/aneurysm [9]. 93% of coronary artery aneurysms are mild and 7% are moderate [10]. 40% to 50% of children with MIS meet the diagnostic criteria for Kawasaki disease or incomplete Kawasaki disease, which is very similar to KDSS. The key differences between childhood MIS and Kawasaki disease include a predominantly non-Hispanic black, Hispanic, or Latino population for childhood MIS, mostly in children aged 6-15 years [11]; more prominent gastrointestinal symptoms (especially abdominal pain), more significant elevation of inflammatory markers, lower absolute lymphocyte and platelet counts, and evidence of COVID-19 associated with childhood MIS [12-14].

The climb in the number of cases of childhood MIS occurred several weeks after the peak of COVID-19 community onset, and studies have shown persistent monocyte activation, elevated levels of anti-severe acute respiratory syndrome coronavirus IgG antibodies, enhanced CD8+ T cell activation, and elevated levels of inflammatory cytokines, interleukin (IL), gamma interferon, and tumor necrosis factor TNF and ferritin levels are significantly elevated, among others [11,15-16]. Therefore, MIS in children is an inflammatory cytokine storm disease caused by abnormal immune response induced after viral infection.

MULTIPLE AORTITIS (TAKAYASU ARTERITIS, TA)

TA is a chronic nonspecific inflammatory disease of large and medium-sized vessels, mainly involving the aorta and its major branches, but also the pulmonary and coronary arteries [17]. TA often has nonspecific systemic symptoms in its early stages, such as fever, rash, and malaise; while symptoms such as ischemic limb pain and/or cyanosis, dizziness, and hypertension due to arterial stenosis, occlusion, or dilation are not evident in infants and children [17-18]. The disease is similar to Kawasaki disease and may be characterized by abnormal inflammatory indicators, such as elevated levels of acute phase reactants, anemia, leukocytosis and/or thrombocytosis; histopathology shows a predominantly cytotoxic lymphocyte infiltration in the arterial tissue, especially γδ T cells; other inflammatory cells include histiocytes, macrophages and plasma cells [19]. These cells cause vascular damage by releasing large amounts of the cytolytic protein perforin, which disrupts the vascular elastic membrane and mesothelial muscle layer, leading to aneurysmal dilatation [19-20]. The incidence of TA CAL is 10%-30%, which manifests as focal or diffuse inflammation, dilation, stenosis or occlusion [21], and Kawasaki disease unresponsive to IVIG treatment should be distinguished from this disease.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (JIA)

Systemic JIA is a systemic auto-inflammatory disease [22], which may have no early manifestations of arthritis, but more prominent extra-articular manifestations, including daily intermittent fever (fever peak ≥38.5 °C), pale red maculopapular rash, enlarged liver and spleen lymph nodes, and plasmacytitis, and is easily complicated by MAS [23]. Laboratory features of systemic JIA include increased white blood cell count, elevated granulocyte count and ratio, thrombocytosis, anemia, increased erythrocyte sedimentation rate, and elevated C-reactive protein and serum ferritin, while being negative for autoantibodies [24]. Several papers have reported the finding of coronary artery dilation on cardiac ultrasonography in children with systemic JIA [25-26], which is easily misdiagnosed as Kawasaki disease or incomplete Kawasaki disease similar to Kawasaki disease, and the immunopathogenesis of systemic JIA in individuals with a certain genetic background, in which the innate immune system is dysregulated and overactivated by various promotive factors, producing large amounts of inflammatory cytokines (IL-1, IL- 6 and IL-10, IL-17, IL-21, etc.) and pro-inflammatory proteins (S100-A8, S100-A9 and S100A-12), which in turn lead to systemic multisystemic inflammation and even complications of MAS [27-28]. Given that systemic JIA does not respond to IVIG therapy, children with IVIG non-reactive Kawasaki disease need to be differentiated from systemic JIA, even if coronary artery dilatation is present.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

SLE in children is a chronic recurrent autoimmune disease that presents with multisystemic multi-organ involvement, positive signature autoantibodies, and decreased complement [29-30]. Children with SLE are at significantly higher risk of CAL than the healthy population, and systemic inflammation is an independent risk factor for CAL [31]. Children with SLE have larger coronary artery diameters than healthy children, and a small number of children with SLE can be complicated by coronary arteri-

tis and/or coronary artery dilation, which may be diagnosed early as Kawasaki disease or incomplete Kawasaki disease. It has been suggested that coronary arteritis may be a more common clinical feature of childhood SLE than currently recognized, and early recognition and management would be beneficial in improving long-term cardiovascular outcomes in children with SLE [32-33].

PRIMARY IMMUNODEFICIENCY DISEASES (PID)

Some primary immunodeficiency diseases may also involve coronary arteries, including autosomal dominant hyperimmunoglobulin E syndrome (AD-HIE), which is caused by a subtractive variant of the STAT3 gene [34-35]; and X-linked lymphoproliferative disease (X-linked HIE), which is caused by a variant of the XIAP gene; and partially monogenic auto-inflammatory disease (AID) [36]. AD-HIE coronary artery involvement can manifest as atherosclerosis, tortuosity, dilatation and local aneurysms [35]. XLP-2 often presents as EBV-associated fulminant infectious mononucleosis and hemophagocytic syndrome (HSP), which can lead to Kawasaki disease-like CAL, and the underlying mechanism may be related to excessive activation of CD8+ T cells and inflammatory cytokine storm in EBV infection [37]. AID often presents as recurrent or persistent inflammation of unknown origin, and the clinical features of the exacerbation phase are similar to those of Kawasaki diseases, such as fever, rash, serositis, arthritis, aseptic meningitis, conjunctivitis and uveitis, among which hyper IgD syndrome caused by MVK gene variants can present with coronary artery dilation [36], which is easily misdiagnosed as Kawasaki disease or incomplete Kawasaki disease in early stages, and recurrent Kawasaki disease should be distinguished from AID in particular.

CHRONIC ACTIVE EPSTEIN-BARR VIRUS (CAEBV) INFECTION

CAEBV infection is a rare, life-threatening lymphoproliferative disorder that manifests as persistent infectious mononucleosis-like syndrome, EBV viremia, or EBV-associated phagocytic syndrome [38]. Untreated T-cell CAEBV-infected patients often develop systemic organ lesions due to T-cell infiltration of tissues, phagocytic lymphocytosis, hepatic failure, and CAL [39]. The incidence of coronary artery dilation in CAEBV is approximately 8.5% [40], with some early misdiagnosis as incomplete Kawasaki disease. The mechanism by which CAL occurs in CAEBV may be related to abnormal secretion of inflammatory factors (e.g. tumor necrosis factor α, IL-16 and IL-10), and T-cell immune imbalance [41]. In children with persistent fever, hepatosplenomegaly, and abnormal liver enzymes with coronary artery dilatation, especially those without the typical clinical manifestations of Kawasaki disease, care needs to be taken to differentiate from CAEBV.

CONCLUSION

The pathogenesis of CAL is based on focal or diffuse inflammation leading to destruction of the intima and mesostructure of the coronary vessel wall, degradation of elastic fibers followed by coronary artery dilatation, stenosis or occlusion; as well as immunological mechanisms of over-activation of innate immunity and/or imbalance of adaptive immunity in the presence of infection or other causative factors in individuals with specific genetic backgrounds, followed by acute or chronic inflammatory injury are jointly involved. CAL due to Kawasaki disease is most common in pediatrics, and timely treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of CAL from 25% to approximately 4% [42]. However, CAL is not a unique manifestation of Kawasaki disease, and a variety of childhood rheumatic-immune diseases can lead to coronary artery involvement. Therefore, clinicians should deeply understand the pathogenesis of the disease, be alert to CAL secondary to rheumatic immune diseases and cardiovascular diseases, broaden the diagnosis and differentiation of the disease in all aspects, actively manage coronary complications through multidisciplinary cooperation, and further improve the diagnosis and treatment of CAL lesions in children caused by related diseases.

REFERENCE

[1] Islam A-K-M-Monwarul,Majumder A-A-S. Coronary artery disease in Bangladesh: a review.[J]. Indian heart journal, 2013, (4): 424-35.

[2] Mccrindle Brian-W,Rowley Anne-H,Newburger Jane-W, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.[J]. Circulation, 2017, (17): e927-e999.

[3] Taichi Kato,Masaru Miura,Tohru Kobayashi, et al. Analysis of Coronary Arterial Aneurysm Regression in Patients With Kawasaki Disease by Aneurysm Severity: Factors Associated With Regression.[J]. Journal of the American Heart Association, 2023, 12(3): e022417.

[4] Mccrindle Brian-W,Manlhiot Cedric,Newburger Jane-W, et al. Medium-Term Complications Associated With Coronary Artery Aneurysms After Kawasaki Disease: A Study From the International Kawasaki Disease Registry.[J]. Journal of the American Heart Association, 2020, (15): e016440.

[5] Orenstein Jan-Marc,Shulman Stanford-T, Fox Linda-M, et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study.[J]. PloS one, 2012, (6): e38998.

[6] Kei Takahashi,Toshiaki Oharaseki,Yuki Yokouchi, et al. Kawasaki disease: basic and pathological findings.[J]. Clinical and Experimental Nephrology, 2012, 17(5): 690-693.

[7] Sato Wakana,Yokouchi Yuki,Oharaseki Toshiaki, et al. The pathology of Kawasaki disease aortitis: a study of 37 cases.[J]. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology, 2020: 107303.

[8] Yue-Hin Loke,Charles I Berul, Ashraf S Harahsheh. Multisystem inflammatory syndrome in children: Is there a linkage to Kawasaki disease?[J]. Trends in Cardiovascular Medicine, 2020, 30(7): 389-396.

[9] Kaushik Ashlesha,Gupta Sandeep, Sood Mangla, et al. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection.[J]. The Pediatric infectious disease journal, 2020, (11): e340-e346.

[10] Lee Min-Sheng,Liu Yi-Ching, Tsai Ching-Chung, et al. Similarities and Differences Between COVID-19-Related Multisystem Inflammatory Syndrome in Children and Kawasaki Disease.[J]. Frontiers in pediatrics, 2021: 640118.

[11] Cheung Eva-W,Zachariah Philip,Gorelik Mark, et al. Multisystem Inflammatory Syndrome Related to

COVID-19 in Previously Healthy Children and Adolescents in New York City.[J]. JAMA, 2020, (3): 294-296.

[12] Jerin Jose, Elif Seda Selamet Tierney, Ashraf S Harahsheh, et al. COVID-19 Positive Versus Negative Complete Kawasaki Disease: A Study from the International Kawasaki Disease Registry. [J]. Pediatric Cardiology, 2023: 1-9.

[13] Alberto García-Salido, Juan Carlos de Carlos Vicente, Sylvia Belda Hofheinz, et al. Severe manifestations of SARS-CoV-2 in children and adolescents: from COVID-19 pneumonia to multisystem inflammatory syndrome: a multicentre study in pediatric intensive care units in Spain. [J]. Critical Care (london, England), 2020, 24(1): 666.

[14] Elizabeth Whittaker,Alasdair Bamford, Julia Kenny, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2.[J]. Jama, 2020, 324(3): 259-269.

[15] Consiglio Camila-Rosat, Cotugno Nicola, Sardh Fabian, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19.[J]. Cell, 2020, (4): 968-981.e7.

[16] Conor N Gruber,Roosheel S Patel,Rebecca Trachtman, et al. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C).[J]. Cell, 2020, 183(4): 982-995.e14.

[17] Souza Alexandre-Wagner-Silvade, Carvalho Jozélio-Freire-de. Diagnostic and classification criteria of Takayasu arteritis.[J]. Journal of autoimmunity, 2014: 79-83.

[18] Seza Ozen,Angela Pistorio,Silvia M Iusan, et al. EULAR/PRINTO-/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria.[J]. Annals of the Rheumatic Diseases, 2010, 69(5): 798-806.

[19] Aeschlimann Florence-A,Yeung Rae-S-M,Laxer Ronald-M. An Update on Childhood-Onset Takayasu Arteritis.[J]. Frontiers in pediatrics, 2022: 872313.

[20] Podgorska Dominika, Podgorski Rafal, Aebisher David, et al. Takayasu arteritis - epidemiology, pathogenesis, diagnosis and treatment.[J]. Journal of applied biomedicine, 2019, (1): 20.

[21] Aeschlimann Florence-A,Twilt Marinka, Yeung Rae-S-M. Childhood-onset Takayasu Arteritis.[J]. European journal of rheumatology, 2020, (Suppl1): S58-S66.

[22] Ravelli Angelo, Martini Alberto. Juvenile idiopathic arthritis. [J]. Lancet (London, England), 2007, (9563): 767-778.

[23] Erdal Sağ,Berna Uzunoğlu, Fatma Bal, et al. Systemic onset juvenile idiopathic arthritis: a single center experience. [J]. The Turkish Journal of Pediatrics, 2019, 61(6): 852-858.

[24] Kumar Sathish. Systemic Juvenile Idiopathic Arthritis: Diagnosis and Management.[J]. Indian journal of pediatrics, 2016, (4): 322-7.

[25] A Felix, F Delion,B Suzon, et al. Systemic juvenile idiopathic arthritis in French Afro-Caribbean children, a retrospective cohort study. [J]. Pediatric Rheumatology Online Journal, 2022, 20(1): 98.

[26] Arsenaki Elisavet,Georgakopoulos Panagiotis, Mitropoulou Panagiota, et al. Cardiovascular Disease in Juvenile Idiopathic Arthritis.[J]. Current vascular pharmacology, 2020, (6): 580-591.

[27] Saverio La Bella, Marta Rinaldi, Armando Di Ludovico, et al. Genetic Background and Molecular Mechanisms of Juvenile Idiopathic Arthritis.[J]. International Journal of Molecular Sciences, 2023, 24(3).

[28] Yu-Tsan Lin, Chen-Ti Wang, M Eric Gershwin, et al. The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis.[J]. Autoimmunity Reviews, 2011, 10(8): 482-9.

[29] Silva Clovis-A, Avcin Tadej, Brunner Hermine-I. Taxonomy for systemic lupus erythematosus with onset before adulthood.[J]. Arthritis care & research, 2012, (12): 1787-93.

[30] Ohara Asami, Iwata Naomi,Sugiura Shiro, et al. Evaluation of the European League Against Rheumatism/-American College of Rheumatology-2019 classification criteria in patients with childhood-onset systemic lupus erythematosus: a single-center retrospective study.[J]. Clinical rheumatology, 2022, (8): 2483-2489.

[31] Shen C-C,Chung H-T,Huang Y-L, et al. Coronary artery dilation among patients with paediatric-onset systemic lupus erythematosus.[J]. Scandinavian journal of rheumatology, 2012, (6): 458-65.

[32] Sherif M Gamal,Sally S Mohamed, Marwa Tantawy, et al. Lupus-related vasculitis in a cohort of systemic lupus erythematosus patients. [J]. Archives of Rheumatology, 2021, 36(4): 595-692.

[33] Agarwal Arunima, Student Stephanie-Biglarian-Medical, Limstavros Sophia, et al. Pediatric systemic lupus erythematosus presenting with coronary arteritis: A case series and review of the literature.[Z], 2015: 42-7.

[34] Khaled Z Abd-Elmoniem,Nadine Ramos, Saami K Yazdani, et al. Coronary atherosclerosis and dilation in hyper IgE syndrome patients: Depiction by magnetic resonance vessel wall imaging and pathological correlation.[J]. Atherosclerosis, 2017, 258: 20-25.

[35] Alexandra F Freeman,Elizabeth Mannino Avila, Pamela A Shaw, et al. Coronary artery abnormalities in Hyper-IgE syndrome.[J]. Journal of Clinical Immunology, 2011, 31(3): 338-45.

[36] Sandra Hansmann, Elke Lainka, Gerd Horneff, et al. Consensus protocols for the diagnosis and management of the hereditary autoinflammatory syndromes CAPS, TRAPS and MKD/HIDS: a German PRO-KIND initiative.[J]. Pediatric Rheumatology Online Journal, 2020, 18(1): 17.

[37] Ru-Yue Chen, Xiao-Zhong Li, Qiang Lin, et al. Epstein-Barr virus-related hemophagocytic lymphohistiocytosis complicated with coronary artery dilation and acute renal injury in a boy with a novel X-linked inhibitor of apoptosis protein (XIAP) variant: a case report.[J]. Bmc Pediatrics, 2020, 20(1): 456.

[38] Cohen Jeffrey-I,Jaffe Elaine-S, Dale Janet-K, et al. Characterization and treatment of chronic active Epstein-Barr virus disease: a 28-year experience in the United States.[J]. Blood, 2011, (22): 5835-49.

[39] Quintanilla-martinez Leticia, Swerdlow Steven-H, Tousseyn Thomas, et al. New concepts in EBV-associated B, T, and NK cell lymphoproliferative disorders.[J]. Virchows Archiv : an international journal of pathology, 2022, (1): 227-244.

[40] Kimura Hiroshi, Morishima Tsuneo, Kanegane Hirokazu, et al. Prognostic factors for chronic active Epstein-Barr virus infection.[J]. The Journal of infectious diseases, 2003, (4): 527-33.

[41] Muneuchi Jun,Ohga Shouichi, Ishimura Masataka, et al. Cardiovascular complications associated with chronic active Epstein-Barr virus infection.[Z], 2009: 274-81.

[42] Correction to: Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.[J]. Circulation, 2019, (5): e181-e184.

DIFFERENT

ETIOLOGY AND DIAGNOSTIC CHALLENGES OF RECURRENT FEVER IN PEDIATRIC AGE

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ABSTRACT

Recurrent fevers are defined as three or more febrile episodes in six months, occurring at least seven days apart. Sometimes, it can be the only manifestation of the disease, whereas in some cases it is associated with other organ systems such as gastrointestinal, oropharyngeal, neurologic, musculoskeletal, etc. Recurrent fever is one of the most common conditions among adult and pediatric populations (representing 18%-42% of fevers of unknown origin in adults and 69% of recent pediatric cases), yet it is still not comprehensively understood. The huge variety of etiological factors makes confirming the diagnosis even more complex, especially for children, since along with the already existing difficulty, there is also a communication barrier between a doctor and a patient of pediatric age. This article is mainly focused on the establishment of the etiology and diagnostic challenges of recurrent fever in children. Out of all the divergent origins of recurrent fever, we separated infectious and noninfectious causes, which are further subdivided into autoinflammatory, neoplastic, and immune-mediated etiologies. The main objective of this article is to provide information covering most of the important issues that are necessary for a successful encounter with the case of recurrent fever in the pediatric age and increase awareness about the diversity of its etiological factors.

INTRODUCTION

An increase in body temperature that is defined as a fever depends on a variety of different factors (e.g., the time of day, geographical location, degree of exertion).In general, fever is defined as a temperature > 38°C (100.4°F). Fever is a generalized symptom that can be brought on by both infectious and noninfectious disorders, such as cancer, systemic rheumatic diseases, and adverse treatment reactions. For the diagnosis of uncomplicated infectious causes of fever, history, and physical examination are frequently sufficient (e.g., URI, gastroenteritis). The pretest probability of the differential diagnoses should serve as guidance for laboratory tests and imaging. When treating febrile patients, the major focus should be on treating the underlying cause rather than lowering body temperature using antipyretics. Here, we focus on recurrent fever, which is defined by febrile episodes followed by intervals of normal body temperature. Although recurrent fever is common-representing 18%–42% of fevers of unknown origin in adults and 69% of recent pediatric cases-it is not well defined. This page outlines the infectious and noninfectious factors that contribute to recurrent fever in children.

DISCUSSION

When it comes to establishing the most common etiologies for recurrent fever in the pediatric population, infections are in the first place according to frequency [1]. In 2011 a systematic review of 18 studies was conducted including 1638 children (<18 years of age) that determined the most common causes of recurrent fever in children. 51% of all the cases accounted for infectious etiology (with 59% of bacterial origin). Bacterial causes were further subdivided according to geographical location [2]:

- Developed countries - Bartonellosis, urinary tract infections.
- Developing countries - Brucellosis, tuberculosis, and typhoid fever.

In this section, infections will be discussed in a generalized form and presented in alphabetical order.

- Brucellosis - Due to the infection's latent nature, nonspecific symptoms and indications, and protracted prognosis in the absence of treatment, brucellosis is frequently taken into account in the differential diagnosis of recurrent fever. It is also frequently ruled out as a diagnostic option, especially by doctors who work in cities and could fail to take the disease into account. Clinical signs and symptoms may include hepatosplenomegaly, a modest increase of liver enzymes, lymphocytopenia, osteoarticular complaints, epididymo-orchitis, and persistent fever and fatigue [3]. It's crucial to look into any exposure to cows, goats, other animals, or raw milk between 1-4 weeks before the onset of symptoms [4]. Diagnostic tests should include blood culture, lymph node, and bone marrow biopsy.
- Cat scratch disease - One of the most frequent causes of recurrent fever in children is cat scratch disease (CSD, Bartonella henselae infection) [3]. While solitary lymph node involvement is a common symptom of CSD, hepatosplenic involvement is the distinguishing feature of CSD related to re-

current fever. A preliminary diagnosis can be made with high-resolution abdomen ultrasonography, which shows the many hepatic or splenic filling abnormalities typical of granulomata. A conclusive diagnosis of B. henselae infection can be made using serology or biopsy of lesions in lymph nodes, the liver, or the bone marrow.

- Leptospirosis - Leptospirosis is a widespread zoonotic infection with a global distribution for which humans are incidental hosts, and most infections occur in tropical climates. Clinical signs are vague and may include fever, rigors, myalgias, headache, cough, and gastrointestinal (GI) issues. Leptospirosis is primarily caused by exposure to environmental sources such as animal urine, contaminated soil or water (especially while swimming), or infected animal tissue. Cuts or abrasions in the skin, mucous membranes, or conjunctiva can all serve as entry points. Rarely does the virus spread by aerosols or through consuming food contaminated with urine [3]. Diagnosis can be made with dark field microscopy of urine/blood, serology, and PCR (polymerase chain reaction).
- Mycobacterial - Another significant factor contributing to recurrent fever in children is tuberculosis (TB). In contrast to pulmonary TB, which is typically visible on chest radiography, extrapulmonary TB-also known as diffused TB or TB of the liver, peritoneum, pericardium, or genitourinary tract-is more likely to result in recurrent fever. Children with negative chest radiography and tuberculin skin tests may nonetheless have active disseminated TB illness. Maintaining a high index of suspicion for the illness is necessary, as is obtaining a thorough history of any potential interactions. TB can be diagnosed by culturing the organism from sputum, gastric aspirates, liver, or bone marrow. Choroid tubercles may infrequently be visible under fundoscopic examination. Disseminated infection and recurrent fever can also be brought on by nontuberculous mycobacterial infection, although this is more frequent in children with HIV or other T-cell immunodeficiencies [3].
- Salmonellosis - Salmonella species can be spread through contact with reptiles or animal feces and contaminate a variety of foods, most notably poultry, and eggs. Salmonella species can cause both localized GI illness and typhoidal disease. Typhoid patients frequently have normal pulses or even bradycardia in conjunction with elevated body temperatures. Blood and stool cultures can be used to make the diagnosis, and if the results are initially negative and the fevers continue, they should be repeated. Testing for serology is not advised [3].
- Toxoplasmosis - Another illness that can result in recurrent fever in children is toxoplasmosis. It should be taken into account in children who have eaten game meat or come into contact with soil infected with feline excrement. Although lymphadenopathy of the cervical or supraclavicular region is most frequently present in combination with fevers, this is not always the case. Sometimes, fever can be the only clinical manifestation. A rise in antibody titer can confirm the diagnosis, but because immunoglobulin (Ig)G antibodies to Toxoplasma gondii is common and IgM antibodies can persist for months, a single high antibody titer is insufficient to confirm acute infection. [3]
- Tularemia - The pneumonic or typhoidal types of infection are more likely to result in recurrent fever from tularemia than the glandular forms. Francisella tularensis can be spread through bites, ingestion, or inhalation and is carried by a wide range of animals and insects (including ticks, mosquitoes, lice, fleas, and flies). Children who have a history of animal contact, exposure to dead wild animals (such as rabbits), or intake of rabbit or squirrel meat should be tested for tularemia [3]. To confirm the diagnosis tests should include culture, increased serum transaminases, and creatinine kinase.

Endocarditis should always be suspected in the case of:

- Unexplained prolonged fever, even with a recurrent pattern
- If a new cardiac murmur appears or the features of a preexisting one are modified

A major risk factor of endocarditis in children is a congenital heart defect (CHD).

The most common presenting symptom is prolonged (sometimes recurrent) fever

It should be noted that currently, new categories of children are at risk of infective endocarditis, such as critically ill patients with a normal heart structure and the presence of chronic indwelling catheters and children who have undergone surgical corrections for congenital cardiac disease.

The emergence of these new at-risk groups also has an impact on the etiology of endocarditis; viridans streptococci and Staphylococcus aureus remain the leading causes, but in the last few decades there has been a gradual increase in cases due to Staphylococcus aureus, with a decline in cases caused by streptococci [4].

Borrelia recurrentis is transmitted by a louse vector, while the other relapsing fever borreliae are transmitted by soft tick vectors

Risk factors: poverty, occupational exposure to tick-infested environments, travel history to endemic areas (e.g. African countries)

recurrent fever (due to surface antigenic variation), headache, myalgia, arthralgia, rigors, and nausea

In LBRF, abdominal pain, hepatosplenomegaly, jaundice, renal involvement, central nervous system manifestations, thrombocytopenia, and several bleeding manifestations have been described. Death may occur due to hepatic or cardiac failure, pneumonia, subarachnoid hemorrhage, or splenic rupture

3-10 days incubation → abrupt fever resolved in 3-5 days → rash involving trunk and shoulders → afebrile for 2-7 days [4].

VIRAL DISEASES

The most frequent cause of recurrent fever in children is repeated independent viral infections because of their physiological susceptibility to infections; nonetheless, it is uncommon for a single viral disease to be the cause of several febrile episodes. There have been reports of EBV, Parvovirus B19, HSV1, and HSV2 as the causes of recurrent febrile episodes, which will be discussed in this article [4].

EBV

- The first association of chronic low-grade fever in children, teens, and young adults between 6 and 19 years old is the Epstein-Barr virus (by HHV-4) [4].
- Infectious mononucleosis is an acute condition caused by EBV. The disease is highly contagious and spreads via

bodily secretions, especially saliva. Symptomatic individuals typically first experience fever, which typically lasts 7-10 days and resolves within three weeks, malaise, and fatigue, which is later accompanied by acute pharyngitis, tonsillitis, lymphadenopathy, and/or splenomegaly lasting up to a month. splenic rupture due to splenomegaly and multiple malignancies (e.g., Hodgkin's lymphoma, Burkitt lymphoma) [5, 6].

- Clinical suspicion of IM is confirmed via antibody testing. Monospot test and peripheral smear (lymphocytosis with an increased level of atypical lymphocytes) are used in this disease [6].

PARVOVIRUS B19

- Recurrent parvovirus B19 infection can be the cause of arthralgia and fever. Fatigue, night sweats, headaches, stomachaches, rash, hyperesthesia, swelling of the hands and feet, and erythema nodosum are other concomitant symptoms. Elevated inflammatory markers and moderate anemia are characteristic of this disease. Serologic and PCR assays can be used to exclude this differential [4].

HIV

- Recurrent fevers are typically not caused by HIV infection alone, but febrile diseases frequently develop in AIDS patients as a result of opportunistic infections [8].

FUNGAL DISEASES:

Recurrent fever is rarely caused by a fungus, though histoplasmosis and coccidioidomycosis are potential causes [4].

- Histoplasmosis is caused by exposure to bird or bat droppings. It also should be suspected in immunocompromised patients presenting with unexplained fever although fever associated with histoplasmosis is most commonly prolonged and not recurrent. Hepatosplenomegaly can be a complication of the disease [7].

- Coccidioidomycosis also called valley fever is presented with flu-like illness, meningitis, erythema nodosum, arthralgia, and multiple lesions. Soil/dust exposure in endemic areas (e.g., during windstorms, earthquakes, archeological explorations) is the risk factor, so it is most frequently seen in Southwestern United States, California. Besides history taking, serology tests, X-ray, and sputum culture is done [7].

PARASITIC DISEASES:

From parasitic etiologies, Malaria, and visceral leishmaniasis are mostly seen. In both pathologies, typical fever patterns of recurrent febrile episodes and residence in endemic areas should guide clinical suspicion [4].

- Malaria

- Malaria is an important factor to consider in a child with recurrent fever. Paroxysms of chills, sweating, tiredness, and splenomegaly frequently follow the fever. Although the patient typically has a history of travel to malaria-endemic areas, this is not universal; few cases have been described in people who have never traveled outside of the United States. Malaria infection can occur months after travel and even in persons who have had malaria prophylaxis. Identification of organisms on smears of peripheral blood confirms the diagnosis. Identification of P. knowlesi and P. malariae requires specific PCR-based assays because they are morphologically indistinguishable [4].

- Visceral Leishmaniasis

- If exposure to the sandfly is suspected in patients exhibiting recurrent fever, abdominal discomfort, hepatosplenomegaly, and pancytopenia, the diagnosis of visceral leishmaniasis caused by Leishmania infantum and Leishmania donovani should be taken into consideration. During the first few weeks or months of the illness, intermittent fever is frequent; only a small percentage of patients have the full clinical picture, which includes cachexia and significant hepato-splenomegaly, six months after the sickness initially manifests. Hemophagocytic lymphohistiocytosis may make visceral leishmaniasis more difficult to treat [4].

- The presence of amastigotes in bone marrow or tissue sections is diagnostic. PCR testing on peripheral blood is less sensitive and specific [4].

NONINFECTIOUS CAUSES

1. Periodic Fever Syndromes and Autoinflammatory Disorders

Disease Gene defect and inheritance Age at onset Duration of febrile episode Main associated findings

FMF MEFV; AR First years of life 12-72 h Abdominal pain, thoracic pain, arthritis

HIDS MVK; AR First years of life 3-7 days Abdominal pain, diarrhea, hepatosplenomegaly, lymphadenopathy

TRAPS TNFRSF1A; AD First years of life 1-3 weeks Arthromyalgia, fasciitis, rash, conjunctivitis, and periorbital edema, splenomegaly

AR: Autosomal recessive; AD: Autosomal Dominant; FMF: Familial Mediterranean Fever; HIDS: Hyperimmunoglobulinemia D with periodic fever syndrome; TRAPS: TNF receptor-associated periodic fever syndrome [4]

PFAPA Syndrome and Cyclic Neutropenia

The PFAPA syndrome (Periodic fever, Aphthous stomatitis, Pharyngitis, and Adenitis) and cyclic neutropenia should be considered if the fever is recurring in strictly regular periods. The first episode before age five, a 21–28 day gap between febrile episodes, pharyngitis, stomatitis, and cervical lymphadenopathy are typical characteristics of both diseases. 3-6 days for PFAPA syndrome and 5-7 days for cyclic neutropenia are the lengths of the episodes, respectively. Although PFAPA syndrome is significantly more frequent than cyclic neutropenia, laboratory testing should still be used to rule it out in any questionable cases [4, 9].

After ruling out other potential causes of recurrent fevers in children, PFAPA is diagnosed based on clinical symptoms [9]. Children must be entirely asymptomatic (with normal levels of acute phase reactants) during interval periods. While during attacks, there is a slight increase in erythrocyte sedimentation rate (ESR) and moderate leukocytosis [4, 9].

1. Periodic Fever Syndromes and Autoinflammatory Disorders

Disease	Gene defect and inheritance	Age at onset	Duration of febrile episode	Main associated findings
FMF	MEFV; AR	First years of life	12-72 h	Abdominal pain, thoracic pain, arthritis
HIDS	MVK; AR	First years of life	3-7 days	Abdominal pain, diarrhea, hepatosplenomegaly, lymphadenopathy
TRAPS	TNFRSF1A; AD	First years of life	1-3 weeks	Arthromyalgia, fasciitis, rash, conjunctivitis, and periorbital edema, splenomegaly

Aphthae (shallow ulcers in the pharynx and buccal mucosa that heal without scarring), pharyngitis - characterized by erythematous, swollen tonsils - and cervical adenitis are present in most of the cases; generalized lymphadenopathy or hepatosplenomegaly point to a diagnosis other than PFAPA [2, 11]. Possible but typically minor symptoms include headaches, arthralgia, nausea, and vomiting [9, 11].

On the other hand, a patient with cyclic neutropenia can show signs of recurrent bacterial infections. During the neutropenic period, cellulitis is frequent, especially in the perianal area [4].

The diagnosis of cyclic neutropenia necessitates numerous leukocyte counts, at least 2-3 per week for 4-6 weeks, as neutropenia is not always present at the time of fever. Lower than 500/L neutrophil levels are suggestive. When neutropenia is present, a bone marrow biopsy may confirm the diagnosis [4].

Diagnostic criteria for PFAPA syndrome include the following:

- The onset of disease in early childhood, generally before the age of 5 y
- Regularly recurring abrupt episodes of fever lasting approximately 5 d, associated with constitutional symptoms and both of the following:

- aphthae or pharyngitis (with or without cervical adenitis) in the absence of other signs of respiratory tract infection

- acute inflammatory markers such as leukocytosis or elevated erythrocyte sedimentation rate

- Completely asymptomatic interval periods (generally lasting less than 10 wk) benign long-term course, normal growth parameters, and the distinct absence of sequelae
- Exclusion of cyclic neutropenia by serial neutrophil counts before during and after symptomatic episodes
- Exclusion of other episodic syndromes (FMF, hyper-IgD syndrome, TRAPS, Behçet syndrome) by family history and the absence of typical clinical features and laboratory markers
- Absence of clinical and laboratory evidence for immunodeficiency, autoimmune disease, or chronic infection [9]

AUTOINFLAMMATORY DISORDERS

If fever attacks occur at irregular intervals, an autoinflammatory condition may be suspected. A malfunction in the innate immune system, which results in an exaggerated inflammatory response, is the root cause of autoinflammatory disorders. Autoantibodies are absent in autoinflammatory disorders, in contrast to autoimmune diseases, and there is no evidence of an association between these disorders and HLA class II genes [4].

Monogenic autoinflammatory disorders typically first show symptoms in early childhood, while FMF and TRAPS instances have also been reported in puberty or later. For most autoinflammatory conditions temperatures frequently exceed 39°C. Although symptoms are only occasionally evident during the variable-duration interval between fever episodes, subclinical inflammation may be seen. The differential diagnosis benefits from the triggering causes and related symptoms and indications. Additionally, in some circumstances, ethnicity matters. For example, HIDS is more typical in patients from the Netherlands or Northern Europe, while FMF has a higher prevalence in patients from the Mediterranean or the Middle East [4].

Symptoms of FMF appear between the ages of 2 and 10; 20% of patients are affected before the age of two, and two-thirds are affected before the age of 10 [10, 11]. Fever, abdominal pain, and arthritis are the main signs and symptoms of the condition. The spike in temperature, which lasts between 12 hours and three days and is accompanied by chills, reaches roughly 40°C. Before the fever, abdominal pain may begin suddenly, mimicking appendicitis, and may be accompanied by diarrhea. The condition known as asymmetrical monoarthritis, which affects the ankle, knee, or wrist joint, often goes away in 5 to 14 days. About 25% of patients may have an erysipelas-like rash over the afflicted joint, which could lead to the misdiagnosis of juvenile idiopathic arthritis. The unilateral rash fades away in two to three days. Additionally, possible symptoms include peritoneal abdominal discomfort, pericarditis (1% of the time), and pleuritic chest pain (which may be accompanied by breathing difficulties). 30 to 50 percent of those affected may have splenomegaly. FMF is remarkable in that long-term severe sequelae such as amyloidosis, which is frequently fatal and can lead to end-stage renal disease, can be prevented with the use of colchicine [9, 10, 11].

Nearly one or two people in a million are affected by TRAPS (Tumor necrosis factor receptor-associated periodic syndrome), which tends to affect Caucasians and Asians. With the median age of presentation being around seven years old, it exhibits an autosomal dominant mode of inheritance. The patient's primary symptoms are fever and painful erythema. Every four to six weeks, the fever returns and might persist for five days to three weeks. Infections, physical and mental stress, trauma, and hormonal changes can all cause episodes. Typically, there is a migrating painful erythema/rash that migrates centrifugally from the arms and legs to the body. Lymphocytic infiltrates may be seen during a skin biopsy [11].

Conjunctivitis, periorbital edema, and periorbital pain are examples of ophthalmologic symptoms. Testicular pain, splenomegaly, abdominal pain accompanied by nausea and vomiting, and serositis are less specific but prevalent symptoms. Untreated TRAPS can result in amyloid deposition, similar to familial Mediterranean fever [10, 11, 14].

Due to its pathophysiology and clinical characteristics, systemic juvenile idiopathic arthritis (sJIA) has lately been categorized among non-monogenic autoinflammatory illnesses [4]. Fever can be the first solitary symptom of sJIA for several months. When the temperature rises, it frequently comes with a transitory salmon-pink rash that emerges once or twice every day, generally in the late afternoon or evening. Usually, the patient's body temperature quickly returns to normal, if not drops below normal [4, 12].

With advancing age, attacks become less severe and less frequent. The most severe type of HIDS in infancy, mevalonate aciduria, is characterized by neurological problems, mental impairment, failure to thrive, and a high rate of stillbirth. Episodes of fever, chills, and skin rash are signs of the less severe forms of HIDS, as are painful oral or genital ulcers. The fever starts suddenly and lasts between four and six days. Stress, vaccinations, or diseases may cause a fever. Additionally, the baby might be agitated or violent. Common is prominent generalized lymphadenopathy. Additionally, common observations include arthralgias and petechial rash on the extremities [10, 11, 13].

Even though there have been numerous investigations throughout the last decades, diagnosis of recurrent fever remains challenging.

A complete history of the temperature, duration, symptom-free intervals, existence of any accompanying symptoms, and medication impact on these episodes will be the first step in the workup for these individuals. Additionally, it would look into the family history and potential genetic reasons for periodic fever. After that, the patients would have a thorough examination to search for any symptoms of an autoimmune disease, such as lymph nodes, mouth ulcers, skin rashes, or signs of joint inflammation. Laboratory tests are used to assist in determining the diagnosis. Complete blood count (CBC), CRP, erythrocyte sedimentation rate (ESR), and ferritin would be examples of these [11].

The vast majority of immune-mediated inflammatory conditions are characterized by the course of cycling relapses and remissions. This is the primary reason why they may present with recurrent patterns of fever with variable intervals and duration.

The significance of the early diagnosis of IBD at pediatric age lies in the evidence that a positive correlation exists between the age-at-onset and complicated disease course [15]. Approximately 25% of patients with IBD present before the age of 20 years. Among children with IBD, 4% present before the age of 5 years and 18% before the age of 10 years, with the peak onset in adolescence [16]. Other typical clinical signs to help the diagnosis include GI (abdominal pain/discomfort, diarrhea/constipation, rectal bleeding, nausea/vomiting, perianal disease, mouth ulcers) and extraintestinal (erythema nodosum, pyoderma gangrenosum, arthritis, osteopenia/osteoporosis, primary sclerosing cholangitis, autoimmune hepatitis, episcleritis, uveitis, iritis, nephrolithiasis, pancreatitis, anemia, venous thromboembolism) manifestations [16]. Recurrent fever may even precede the development of typical GI symptoms in weeks or months [4]. In this case, the suspicion can be raised by other associated signs/symptoms such as microcytic hypochromic anemia, and growth retardation [15]. Mouth ulcers mentioned above can also be seen in chronic immune-mediated multisystem vasculitis - Behcet's disease - a less common cause of recurrent fever in children. Even though the prevalence of the disease is increasing in all parts of the world, higher geographical distribution should be noted in Turkey, the Middle East, and Asian countries. Mucocutaneous lesions especially oral ulcers are the earliest and most frequently encountered clinical manifestation followed by ocular, neurologic (e.g. headache, hemiplegia, aseptic meningitis, psychosis), and vascular (venous thrombosis, thrombophlebitis) findings. Enteral symptoms including diarrhea, abdominal pain, vomiting, and bleeding as well as lesions (ulcerations) found throughout the GI tract (sparing rectum) can mimic IBD and must be differentiated based on endoscopy and biopsy. A study of 235 patients with Crohn's disease and intestinal BD revealed that round ulcers, focal single/focal multiple distributions of ulceration, fewer than six ulcers, absence of cobblestone appearance, or aphthous lesions were the most predictive symptoms of BD on colonoscopy in a multivariate analysis [17].

Many of the signs and symptoms discussed in the previous paragraph can also be seen in SLE - another etiology of recurrent fever in children. In 10-20% of all SLE cases, the onset is marked in childhood. All the body systems can be affected but reportedly common manifestations are as follows: Hematologic (Anemia, lymphopenia, leukopenia, and/or thrombocytopenia), mucocutaneous (Malar rash, photosensitivity, oral or nasal ulcers, and/or discoid rash), musculoskeletal (Arthritis, arthralgia, and/or serositis), renal abnormalities (Proteinuria, hematuria, and/or casts suggestive of nephritis; nephrotic syndrome; and/or biopsy-proven lupus nephritis). Pulmonary, thromboembolic, cardiac, neuropsychiatric, and gastrointestinal signs/symptoms may also be seen [1]. The diagnostic approach should include detailed history-taking and careful examination of every system, considering epidemiological factors (e.g female sex) and laboratory studies including serology for antinuclear antibodies (ANAs), double-stranded DNA (dsDNA) antibodies, antibodies to the extractable nuclear antigens (ENAs), and antiphospholipid antibodies (aPLs) [1]. More specific cutaneous findings are characteristic of juvenile dermatomyositis including Gottron papules, shawl sign, and typical pattern of symmetrical proximal muscle weakness. More rarely the condition may be accompanied by interstitial lung disease, cardiac conduction abnormalities, and localized or generalized edema.

Granulomatous diseases leading to chronic inflammation may present with recurrent fever associated with multiple organ system nonspecific signs/symptoms. Intermittent high fever and arthritis accompanied by other extra-articular manifestations can be seen in Juvenile idiopathic arthritis. Children typically are less than 4 years of age and may also present with rash (pink macular eruptions), fatigue, myalgia, and irritability. Anterior uveitis is less common [18].

Neoplasms and other conditions:

NEOPLASMS

Although neoplasms are most commonly present with a prolonged fever they should always be considered and adequately ruled out in the management of recurrent fevers in children. Thus far only lymphoma, juvenile myelomonocytic leukemia, and atrial myxoma have been reported to cause recurrent fever in children. The two most common neoplastic conditions presenting with complaints of recurrent fever are Lymphomas and leukemias [1].

ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA

Acute Lymphoblastic leukemia and Lymphoblastic lymphoma are the two most common neoplastic conditions associated with recurrent fever. These tumors account for approximately one-third of all childhood malignancies and are the most common forms of cancer in children with Approximately 2500 to 3500 new cases of ALL/LBL diagnosed in children each year in the United States. The peak incidence of ALL/LBL occurs between the ages of two to five years being more common among boys than girls [19].

Common presenting findings associated with ALL/LBL are nonspecific and may be difficult to distinguish from ordinary, self-limited diseases of childhood. Most commonly seen symptoms include: palpable liver, palpable spleen, pallor, fever, or bruising, however approximately 6 percent of children are asymptomatic on presentation.

Acute lymphoblastic leukemia as well as Lymphoblastic leukemia is a malignancy of B or T lymphoblasts charac-

terized by uncontrolled proliferation of abnormal, immature lymphocytes and their progenitors [19]. Due to damage to the lineage of white blood cells (WBC), these patients are at a much higher risk of infections, therefore infections are commonly the cause of recurrent fever episodes in Pediatric patients.

ALL/LBL are also characterized by constitutional B-symptoms: fever, night sweats, and unintentional weight loss caused by increased inflammatory markers such as IL-6 [19]. The spikes in fever are periodic with variable intervals and occur in intervals of days to weeks. These episodic fevers fail to respond to any appropriate medication. Therefore unresponsive drenching fevers, together with unexplained weight loss should always prompt evaluation for leukemia.

Diagnosis: The diagnosis of ALL/LBL requires characteristic morphology and a diagnostic immunophenotype of cells from peripheral blood, bone marrow, lymph node, and/or other involved tissue [19].

Morphology of peripheral blood or Bone marrow is a commonly used diagnostic tool, however, lymphoblastic morphology can be indistinguishable from other malignant or non-malignant causes with similar presentation.

The more specific diagnostic tool is immunophenotyping which allows for the exclusion of other similar conditions by focusing on B and T-cell lineage and the CD-markers such as CD19, CD79a, and CD22.

DIFFERENTIALS.

The presenting signs and symptoms of ALL/LBL are often nonspecific and morphology alone is not diagnostic, so it is important to consider a wide range of malignant and nonmalignant conditions in the differential diagnosis. The condition most commonly confused with ALL/LBLB is Burkitt's lymphoma, an aggressive B-cell lymphoma that can present with similar symptoms, although they develop over a shorter period. BL can have substantial clinical and morphologic overlap with ALL/LBL. The histology of BL typically reveals highly proliferative monomorphic medium-sized cells with basophilic cytoplasm (often with a "starry sky" appearance) that are generally larger than ALL/LBL lymphoblasts [19]. BL is diagnosed based on morphology, immunophenotype, and cytogenetic/molecular characteristics. BL is recognized from ALL/LBL by the translocation involving chromosome 8 and/or MYC rearrangement as well as the distinctive mature germinal center B cell immunophenotype.

ATRIAL MYXOMA

Atrial myxoma is The most frequent primary heart.Although they are mostly seen between the fourth and sixth decades of life, they can also rarely be present in Pediatric patients.

More than 75% of myxomas are thought to originate in the left atrium, either at the mitral annulus or the fossa ovalis border of the interatrial septum. 20% of myxomas are thought to start in the right atrium, and 5% stem from both the atria and the ventricle [20].

Smooth, villous, or friable surface subtypes of tumors are the most commonly seen. When compared to smooth myxomas, which are often larger and have a more obstructive appearance, villous and friable myxomas are more frequently linked to embolic events. Atrial myxomas also lead to the development of cytokines and growth factors leading to constitutional symptoms such as episodic fevers, malaise, anorexia, and weight loss [20].

Diagnosis is usually established through echocardiography, which can characterize the location size and also the attachment of the tumor. Transesophageal echocardiography is preferred to the Transthoracic counterpart, due to better visualization of chambers as well as possible obstruction due to tumor location [20].

Others: Other rare and commonly misdiagnosed conditions can also lead to the development of fever in pediatric patients. Such conditions are: Fabry disease, Sweet syndrome, Kikuchi disease, and Erdheim-Chester

SWEET SYNDROME

Sweet syndrome also known as febrile neutrophilic dermatosis is a rare condition, characterized by the acute onset of dermatologic complications such as tender plaques or nodules usually on the back and upper extremities, as well as constitutional symptoms of fever, headaches, arthralgias, and ophthalmic manifestations(ulcerative keratitis).

The condition is non-infectious, however, the dermatologic symptoms of plaques are caused by neutrophil deposition of the epidermis and dermis leading to local inflammation [21]. Systemic inflammation in this case usually is the cause of fever in patients.

Although usually idiopathic, Sweet syndrome has an identifiable correlation with myeloproliferative disorders (myelodysplasia, acute myelogenous leukemia, chronic myelogenous leukemia, and multiple myeloma).

Neutrophilic dermatosis also can be seen in Post-infectious patients, such as those with HIV, viral Hepatitis, and tuberculosis [21].

A more common condition that is well-known to physicians is the Drug-induced Sweet syndrome, caused by several antibiotics (TMP-SMX, nitrofurantoin, norfloxacin), anti-hypertensives (hydralazine and loop diuretics), anti-epileptic (carbamazepine, diazepam) and antipsychotic (clozapine) medications. In these rare causes of Sweet syndrome, the symptoms go away, with the discontinuation of the drugs [21].

Diagnosis is done based on the history of acute onset tenderness, painful plaques or nodules, and neutrophilic infiltrate in the dermis without vasculitis. Clinical diagnostic criteria include fever >38C, elevated white cell count with neutrophil predominance and elevated inflammatory markers and positive response to corticosteroids.

Laboratory diagnosis is made based on Blood work focusing on inflammatory markers and white blood cell count, as well as biopsy findings of skin infiltration by neutrophils.

Treatment of Sweet syndrome usually involves Corticosteroid treatment, with oral prednisolone as well as topical steroids in the areas of plaques.

FABRY DISEASE

Another rare cause of fever in pediatric patients is a lysosomal storage disease called Fabry disease. In this genetic condition, there is the absence of the lysosomal enzyme alpha-galactosidase, which helps in the breakdown of lipids called globotriaosylceramide or GL3 [22]. The buildup of the fat causes an array of symptoms such as episodes of pain, especially in the hands and feet, high fevers, clusters of small, dark red spots on the skin called angiokeratomas, a decreased ability to sweat (hypohidrosis), cloudiness of the front part of the eye (corneal opacity), and hearing loss. Systemic manifestations affecting renal, CNS, and cardiac systems are seen in more advanced cases of this disease

and are less frequently seen in pediatric patients [22]. Fabry disease is a genetic condition associated with and has an X-linked recessive inheritance, hence most cases are seen in males.

KIKUCHI-FUJIMOTO DISEASE

Kikuchi disease also called Kikuchi histiocytic necrotizing lymphadenitis

Is an extremely rare condition affecting young women with a very high prevalence in Japan and other Asian countries. It is rare in pediatric patients but has significant importance due to its symptomatic as well as histologic resemblance with other more commonly seen conditions such as systemic lupus erythematosus (SLE).

Kikuchi disease has an unknown etiology however it is suspected to be a post-infectious reaction that mimics SLE due to virus-transformed lymphocytes.

From the available literature common infections that have led to Kikuchi disease development have been EBV, human herpesvirus 6, human herpesvirus 8, human immunodeficiency virus (HIV), parvovirus B19, paramyxoviruses, parainfluenza virus, and Toxoplasma [3].

Symptoms of Kikuchi disease are usually Benign and resolve on their own. These include Fever, cervical Lymphadenopathy, and leukopenia. Other less commonly seen symptoms include Rash and Organomegaly [3].

Diagnosis for Kikuchi's disease is done through thorough history-taking and exclusion of other possible causes for a patient's complaints. Blood work frequently shows leukopenia as well as thrombocytopenia. Liver enzymes can also be abnormally increased in some patients.

Since many physicians including pediatricians are unfamiliar with this disease. Many patients have been falsely treated for Lupus as well as Leukemias in the past, significantly worsening their condition.

In older patients, a fine-needle Biopsy of the lymph nodes is the preferred method of diagnosis.

In Pediatric patients, diagnosis can be made based on a scoring system, which is based on Criteria of history of illness, temperature, maximum lymph node size, and serum B2 microglobulin.

No effective treatment has been established for Kikuchi's disease. Signs and symptoms usually resolve within one to four months. In persistent cases treatment with Glucocorticoids has been attempted with limited information on their efficacy [3].

REFERENCES

1. Palazzi, Debra. “Fever of Unknown Origin in Children: Evaluation”. UpToDate, 2023

2. Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. World J Pediatr. 2011 Feb; 7(1):5-10. doi: 10.1007/s12519-011-0240-5. Epub 2010 Dec 30. PMID: 21191771.

3. Palazzi, Debra. “Fever of Unknown Origin in Children: Etiology”. UpToDate, 2022

4. Torreggiani S, Filocamo G, Esposito S. Recurrent Fever in Children. Int J Mol Sci. 2016 Mar 25; 17(4):448. doi: 10.3390/ijms17040448. PMID: 27023528; PMCID: PMC4848904.

5. González Saldaña N, Monroy Colín VA, Piña Ruiz G, Juárez Olguín H. Clinical and laboratory characteristics of infectious mononucleosis by Epstein-Barr virus in Mexican children.. BMC research notes. 2012; 5: p.361. doi: 10.1186/1756-0500-5-361

6. Dowd JB, Palermo T, Brite J, McDade TW, Aiello A. Seroprevalence of Epstein-Barr Virus Infection in U.S. Children Ages 6-19, 2003-2010. PLoS ONE. 2013; 8(5): p.e64921. doi: 10.1371/journal.pone.0064921

7. Thompson G, Brown J, Benedict K, Park B. Coccidioidomycosis: epidemiology. Clinical Epidemiology. 2013: p.185. doi: 10.2147/clep.s34434

8. Rubén E Quirós-Tejeira, Morven S Edwards & Elizabeth B Rand (2022). Overview of hepatitis A virus infection in children.

9. 9. Soon, G. S., & Laxer, R. M. (2017). Approach to recurrent fever in childhood. Canadian Family Physician, 63(10), 756-762. https://doi.org/https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5638471/

10. Long, S. S. (2005). Distinguishing Among Prolonged, Recurrent, and Periodic Fever Syndromes: Approach of a Pediatric Infectious Diseases Subspecialist. Pediatric Clinics of North America, 52(3), 811-835. https://doi.org/-10.1016/j.pcl.2005.02.007

11. Espin Diaz, P. C., Singh, K., Kher, P., Avanthika, C., Jhaveri, S., Saad, Y., & Ghosh, S. (2022). Periodic Fever in Children: Etiology and Diagnostic Challenges. Cureus, 14(7). https://doi.org-/10.7759/cureus.27239

12. Hofer, M., Mahlaoui, N., & Prieur, A. (2006). A child with a systemic febrile illness – differential diagnosis and management. Best Practice & Research Clinical Rheumatology, 20(4), 627-640. https://doi.org/10.1016/j.berh.2006.04.001

13. Tripathi, S. V., & Leslie, K. S. (2013). Autoinflammatory Diseases in Dermatology: CAPS, TRAPS, HIDS, FMF, Blau, CANDLE. Dermatologic Clinics, 31(3), 387-404. https://doi.org-/10.1016/j.det.2013.04.005

14. Cudrici, C., Deuitch, N., & Aksentijevich, I. (2020). Revisiting TNF Receptor-Associated Periodic Syndrome (TRAPS): Current Perspectives. International Journal of Molecular Sciences, 21(9).

15. Oliveira, S. B., & Monteiro, I. M. (2017). Diagnosis and management of inflammatory bowel disease in children. BMJ (Clinical research ed.), 357, j2083. https://doi.org/10.1136/bmj.j2083

16. Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. JAMA Pediatr. 2015; 169(11):1053–1060. doi:10.1001/-jamapediatrics.2015.1982

17. Yıldız, M., Köker, O., Adrovic, A., Şahin, S., Barut, K., & Kasapçopur, Ö. (2019). Pediatric Behçet's disease - clinical aspects and current concepts. European journal of rheumatology, 7(Suppl 1), 1–10. Advance online publication. https://doi.org/10.5152/eurjrheum.2019.19121

18. Hardal, C., Erguven, M., & Saglam, Z. A. (2017). Systemic juvenile idiopathic arthritis as a fever of unknown origin. Northern clinics of Istanbul, 4(1), 81–84. https://doi.org/10.14744/-nci.2016.07769

19. Horton, Terzah. “Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children”. UpToDate, 2022

20. Nguyen T, Vaidya Y. Atrial Myxoma. [Updated 2022 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.-gov/books/NBK556040/

21. Vashisht P, Goyal A, Hearth Holmes MP. Sweet Syndrome. [Updated 2022 Sep 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431050/

22. Graziani F, Ruggio A, Iaconelli A, Verrecchia E, Morrone A, Antuzzi D, Crea F, Manna R. Anderson-Fabry's Disease: A Rare but Treatable Case of Fever of Unknown Origin. Eur J Case Rep Intern Med. 2017 Jul 3; 4(7):000645. doi: 10.12890/2017_000645. PMID: 30755957; PMCID: PMC6346910.

ADAPTIVE CAPABILITIES OF THE BODY OF ADOLESCENTS IN RELATION TO NUTRITIONAL STATUS IN THE CONDITIONS OF TURKMENISTAN

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A special category of the population with a high-risk group are students whose period of final maturation of the body coincides with the period of intensive training. In the modern period, studying at a higher educational institution is characterized by a variety of forms and methods of teaching, high intensity of classes, and the introduction of new technical means [8]. Informational and emotional stresses accompanying training impose certain requirements on the state of health of students. The change of work and rest, sleep and nutrition, the breaking of the school stereotype, the inability to independently allocate their time, the lack of constant and systematic adult control causes students psychoemotional discomfort, which can negatively affect the adaptive capabilities of the young organism [1, 5, 7].

The purpose of the work – identification of adaptive capabilities of the cardiovascular system of adolescents, taking into account the nutritional status. In 2022 year under observation were 500 students of the 1st and 2nd courses of the State Medical University of Turkmenistan, 217 of them were boys and 283 girls.

The state of human health under the influence of actual nutrition is designated by the term "nutritional status". The assessment of nutritional status is based on the indicators of growth, body weight and mass-growth index, metabolism, functional state of individual body systems. Body weight is the most informative criterion for matching the energy and biological value of the diet to the needs of the body. As a differentiated indicator characterizing the level of energy usefulness of daily diets, students were determined by the body mass index (BMI), which is the ratio of body weight (kg) to height squared (m^2) [9]. BMI values in the range of 18.5-24.9 kg/m2 indicate energy sufficiency of nutrition, below 18.5 kg/m2 – low caloric content of diets predisposing to the development of hypotrophy, above 24.9 kg/m^2 – excessive energy value of diets, leading to an increase in body weight, over 30 kg/m^2 - the development of obesity.

The assessment of the adaptive capabilities of the circulatory system was carried out by calculating the index of functional changes (IFC) in points [2]. As an indicator characterizing the state of the functional reserve of the cardiovascular system, the coefficient of efficiency of blood circulation (CEBC) was used, measured in conventional units [6]. CEBC values of more than 2600 conventional units reflect a decrease in the functional reserve and the occurrence of fatigue of the cardiovascular system. Given that the functional state of the cardiovascular system and the level of adaptation depend on the regulatory influence of the autonomic nervous system, the examined students were determined by the Kerdo vegetative index (KVI) [4].

According to the results obtained, out of the total number of students examined, 24% of girls and 7% of boys had low body weight, 67% of girls and 72% of boys had a normal weight-height coefficient. Overweight was noted in 7% of girls and 19% of boys. The incidence of obesity among girls was 2%, among boys - 3%.

Anthropometric indicators (body weight, body mass index) significantly increase with the growth of the energy value of diets, reaching maximum values in students with high-calorie nutrition (table).

Hemodynamic parameters (systolic and diastolic pressure) significantly increase with body weight and in obesity reach almost the same values in boys and girls. The heart rate of students as the Quetelet index increases does not undergo significant changes.

A significant increase in the index of functional changes is determined as the Quetelet index increases. With overweight and obesity in students, the absolute values of the index of functional changes exceed the normative value of 2.1 points, which indicates the transition of the functional state of the cardiovascular system from the physiological norm (satisfactory adaptation) to the state of tension of adaptive mechanisms [3].

The coefficient of efficiency of blood circulation in girls and boys exceeds the standard value (2600 conventional units) with a tendency to increase even more as the Quetelet index increases. With overweight and obesity, the absolute values of the coefficient of efficiency of blood circulation in girls and boys are set at the level of 3300 conventional units, which indicates a weakening of the reserve capacity of the cardiovascular system of students, regardless of gender.

Using the Kerdo vegetative index, was revealed a higher activity of sympathetic-tonic affects in girls at all values of the mass-height coefficient. The negative correlation between the Kerdo vegetative index and the Quetelet index indicates that as body weight increases, the activity of sympathetic-tonic affects decreases, and the influence of the parasympathetic division increases (diagram).

A direct correlation was found between systolic and diastolic pressure, peripheral vascular resistance, an index of functional changes and an inverse relationship between minute and systolic volume of blood circulation from body mass index. Such an ambiguous dependence of hemodynamic parameters on the mass-height coefficient indicates that with a significant

increase in body weight in students with overweight and obesity against the background of an increase in peripheral vascular resistance, systolic and diastolic pressure significantly increase, while the minute volume of blood circulation decreases, mainly, due to the weakening of the strength of heart contractions, which indicates a tense level of functioning of the circulatory system, which causes a decrease in the adaptive capabilities of the circulatory system of a young organism (diagram).

Thus, from the above data it follows that the functional state of the body of students is determined by the degree of energy sufficiency of food rations. With excess calorie intake, 9% of girls and 21% of boys are in a state of tension of adaptive mechanisms, in which, in order to maintain the balance of the body with the external environment, it is necessary to mobilize additional functional reserves, due to which their ability to adapt to various influences, including the training load, reduced. Thus, they are under our close attention, explanatory work is carried out with them on the basics of a healthy diet, diets are individually considered in order to correct their eating behavior.

Table. Anthropometric and hemodynamic parameters in adolescents (M±m)

Indicators	Quetelet index (kg/m²)			
	<18.5	18.5-24.9	25.0-29.9	>30
age, years	17.26±0,20	17.32±0,05	17.48±0.10	17.25±0.26
	17.31±0.07	17.21±0.04	17.27±0.14	17.38±0.48
body weight, kg	56.41±1.02	66.85±0.51*	83.35±1.10*	99.50±4.41*
	47.24±0.41	56.21±0.42*	72.90±1.30*	89.80±0.48*
body length, cm	178.53±1.50	175.64±0.48	176.60±1.03	175.17±1.90
	165.54±0.62	163.01±0.42	165.19±1.38	165.00±3.84
Quetelet index, kg/m²	17.65±0.17	21.64±0.13*	26.69±0.19*	32.35±0.77*
	17.26±0.12	21.16±0.12*	26.77±0.27*	33.00±1.68*
Heart rate, beats/min	81.27±1.01	80.30±0.53	79.05±0.94	83.00±2.34
	85.60±0.84	82.71±0.56*	83.90±1.71	83.00±2.52
ABPs, mmNg	114.67±1.67	115.38±0.59	118.62±1.68	125.00±5.00
	96.12±1.22	103.76±0.79*	110.95±2.59*	126.00±5.99*
ABPd, mmHg	73.67±1.79	75.35±0.51	79.75±1.52*	85.00±5.00
	63.06±0.72	66.76±0.57*	73.33±1.86*	86.00±5.99*
PP, mmHg	41.0±0.72	40.03±0.32	38.87±0.75	40.00±0.01
	33.06±0.70	37.00±0.52*	37.62±1.00	40.00±0.01*
SPd mmHg	87.33±0.26	88.69±0.53	92.71±1.17*	98.33±5.00
	74.08±0.85	79.10±0.61	85.87±2.09	99.33±5.99
SV, ml	65.17±1.40	63.54±0.36	60.27±0.79*	57.62±2.98
	67.50±0.42	67.11±0.42	63.50±0.92*	56.97±3.51
MVB, l/min	5.29±0.17	5.10±0.04	4.76±0.08*	4.77±0.24
	5.78±0.07	5.55±0.05	5.33±0.14	4.71±0.27*
PVR, din/cm	1346.58±58.88	1411.27±16.87	1584.37±43.81*	1690.40±175.11
	1041.77±24.49	1170.16±19.30*	1314.47±58.25*	1733.79±210.92
IFC, points	1.98±0.04	2.11±0.01*	2.31±0.03*	2.65±0.13*
	1.71±0.02	1.93±0.01*	2.22±0.05*	2.68±0.14*
CEBC, conv.unit	3336.33±96.12	3212.44±32.69	3073.50±69.51	3320.00±94.07*
	2820.75±61.58	3047.71±43.23*	3156.43±107.20	3320.00±100.89
KVI, %	8.93±3.01	5.47±0.92	-1.44±1.82	-2.58±5.92
	25.63±1.37	18.34±1.00*	11.82±2.93*	-3.70±7.02

Note: *in the numerator - indicators for boys, in the denominator - for girls.*
** P< 0.05 - significance of differences*

LITERATURE

1. Аминова О.С., Уварова Ю.Е., Тятенкова Н.Н. Оценка фактического питания и пищевого статуса студентов //В мире научных открытий. – 2017. – Т. 9, № 1. – С. 66-67.

2. Баевский Р.М., Берсенева А.П. Оценка адаптационных возможностей организма и риск развития заболеваний. - М., 1997.- 235 с.

3. Баевский Р.М. Проблема здоровья и нормы: точка зрения физиолога //Клиническая медицина. - 2000.- № 4.- С. 59-64.

4. Вегетативные расстройства: клиника, лечение, диагностика /Под ред. А.М. Вейна. - М., 2000. - 752 с.

5. Волкова Л.Ю. Нарушение структуры питания как фактор риска формирования избыточной массы тела и ожирения у детей и подростков //Материалы Международного конгресса “Питание и здоровье” - М., 2013. – С. 21-22.

6. Домрачев А.А. Состояние АЦП-типа темперамента и некоторых параметров сердечно-сосудистой системы в условиях продолжительного рабочего дня //Сибирский медицинский журнал. - 2006. - № 4. - С. 30-34.

7. Шабанова Т.Л. Исследование нарушений пищевого поведения у лиц юношеско-студенческого возраста //Международный журнал прикладных и фундаментальных исследований. - 2017. - № 9. - С.91-95.

8. Шеметова Е.В.. Фоминых И.Л. Рациональное питание и учеба в ВУЗе //Азимут научных исследований; педагогика и психология. 2018. - № 2(23). – С. 315-318.

9. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: World Health Organization, 2000.

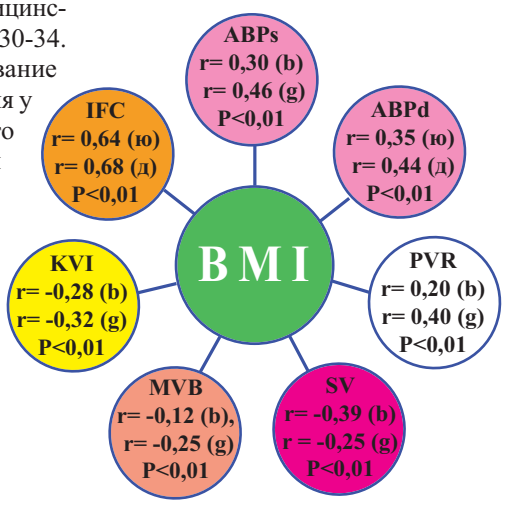

Diagram. Correlation dependence of hemodynamic parameters on body mass index in adolescents (n=500)

PRACTICING PHYSICIANS

GUIDELINE

CHINESE EXPERT CONSENSUS ON INTRAVENOUS IMMUNOGLOBULIN, ASPIRIN, AND GLUCOCORTICOIDS IN THE TREATMENT OF KAWASAKI DISEASE

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ABSTRACT

Kawasaki disease (KD) is an acute vasculitis with unknown etiology usually occurring in children aged younger than 5 years. It is one of the most common acquired heart diseases in children and can cause serious complications, such as coronary injury. Currently, intravenous immunoglobulin (IVIG) combined with oral aspirin is considered the most effective treatment in acute stage KD, and the first-line treatment to prevent cardiovascular complications. Nonetheless, glucocorticoids (GC) are used mainly for KD patients with confirmed or a high risk of coronary artery aneurysm (CAA) and no response to immunoglobulins. Although consensus guidelines on the diagnosis and treatment of KD are present in different countries, inconsistencies regarding the mechanism, optimal timing, and dosage of medications for KD persist in the literature. This article summarizes three consensuses formulated in China regarding KD and the use of IVIG, aspirin, and GC treatments.

INTRODUCTION

Kawasaki disease, also known as cutaneous mucosal lymph node syndrome, is a common febrile disorder in children, commonly seen in children under the age of 5. The main pathological feature is systemic vasculitis, and the clinical features include terminal changes in the extremities, bilateral bulbar conjunctival congestion, lip, and oral changes, and non-purulent enlargement of the cervical lymph nodes in addition to fever. KD is mainly complicated by damage to the cardiovascular system, such as coronary artery dilation and thrombosis In addition, KD can also cause multi-system complications such as pulmonary nodules, arthritis, hepatitis, urethritis, and Kawasaki disease shock syndrome (KDSS), etc[1, 2].

The prevalence of KD varies widely among countries, and the prevalence of KD is 10-30 times higher in East Asian countries, including Japan, Korea, and China than in the United States or Europe, and the prevalence is increasing year by year [3].In 2015, the prevalence of KD among children under 5 years old was 19.1 per 100, 000 in the United States and 19.6 per 100, 000 in Canada in 2014 [4]. The countries of Japan, Korea, and China have the highest KD prevalence rates in the world (more than 50 per 100 000 children under 5 years old) and are increasing gradually[5-7]. Japan is reported to have the highest KD mortality rate in the world, estimated at approximately 264 per 100, 000 deaths in children under 5 years old; the recurrence rate of KD is 3.5%, the mortality rate is less than 2%, and 17.0% of children develop resistance to IVIG [7]. In China, the incidence of KD is on the rise, with a prevalence of approximately 7.06-55.1 per 100, 000 children under 5 years old[8, 9], and in Taiwan was 82.8 per 100, 000 in 2010 [10]. Hong Kong has the highest prevalence of KD in China (74 per 100, 000 among children under 5 years old) [11].

Epidemiological studies in some regions of China have shown that the incidence of KD combined with coronary artery lesion (CAL) is as high as 15.9% and the incidence of combined CAA is 1.8% [12]. Standardized treatment with IVIG can reduce the risk of CAL occurrence from 15-20% to 3%-5% [13, 14]. Medications are currently the main treatment options for KD and its complications. The preferred treatment option IVIG combined with aspirin has been widely used, and GC is used as a complementary treatment for IVIG non-response KD and KD with CAA.

Current studies suggest that KD may be involved with pathogenic infections, environmental factors, immune dysregulation, and genetic predisposition, but definitive conclusions are still deficient. Therefore, individualized treatment for different causes is particularly important [15, 16]. Studies on the dosage, duration, and timing of drug treatment for KD have been inconsistently reported in many countries.

METHODS

The KD Treatment Centre of Shaanxi Province, China, the Shaanxi Clinical Medical Research Centre for Paediatric Internal Diseases, the Children's Hospital of Shaanxi Provincial People's Hospital, the Pediatric Capacity Building Committee of the National Research Society for Maternal and Child Health, and the General Paediatrics (General Practice) Group of the Paediatricians Branch of the Chinese Medical Association, formed the KD Expert Group in 2021, including more than 100 scholars. They discussed the mechanism, treatment dose, course, optimal timing, and safety of IVIG, aspirin, and GC for KD through several online video conferences, and finally formed three consensuses [17-19]. All of the consensuses were published in the Chinese Journal of Zhongguo Dang Dai Er Ke Za Zhi. The consensuses aim to provide a basis for the standardized clinical management of KD in China, ultimately achieving effective prevention of complications and sequelae in children with KD and reducing the risk of cardiovascular events and death in children with KD [20, 21].

These consensuses apply for children under 18 years old with all types of initial and retreatment KD, except those with a history of allergy to IVIG, GC, or aspirin, or with drug contraindications [17]. The use population included all pediatric rheumatologists and pediatric cardiologists and all general practitioners. All these consensuses have been registered on the International Practice Guideline Registrable Platform (http://www.guidelines-registry.cn) under the registration numbers IPGRP-2021CN183, IPGRP-2021CN183, and IPGRP-2021CN321, respectively.

English databases for consensus search include UpToDate, BMJ Clinical Evidence, National Guideline Clearinghouse, Joanna Briggs Institute Library, Cochrane Library, and PubMed, Cochrane library PubMed, etc.; Chinese databases include China Biomedical Literature Service, China Knowledge Network, Wanfang database, etc. All literature searches ended on February 28, 2022. Nearly 200 papers were finally included, including 7 guidelines, 9 expert consensus and standards, 2 BMJ Best Practice, 12 UpToDate, 41 Meta-analyses and systematic reviews, 18 randomized controlled trials, and 102 observational studies.

The consensus was formed after many discussions based on the current research progress and relevant research data on the use of KD in children and referring to the diagnosis and treatment guidelines and experience of KD in var-

ious countries. The principles of consensus are as follows:

(1) Participation of professionals from multiple centers, including pediatric specialty physicians, pediatric cardiovascular physicians, and experts in the field of evidence-based medicine.

(2) With the guidance of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) manual, the recommendation level of a certain clinical problem in this consensus is determined according to the credibility level of the literature or data (guideline recommendation intensity is shown in Table 1, grade quality of evidence and strength of recommendation are shown in Table 2)[22, 23].

1. CHINESE EXPERT CONSENSUS ON IVIG FOR KD [17]

1.1 MECHANISM OF IVIG FOR THE TREATMENT OF KD

The main objectives of treatment in the acute phase of KD are to control and terminate the inflammatory response, reduce the incidence of CAA, and prevent coronary thrombosis[24].IVIG is an immunoglobulin preparation isolated from the blood of healthy people, of which immunoglobulin G is the most abundant immunoglobulin, accounting for more than 95%. Immunoglobulin G (IgG)molecules are hydrolyzed to obtain crystalline fragments, which can bind with harmful complement components in the body, block their deposition in the target tissues, avoid immune damage, and can also bind with crystalline fragment receptors to activate the intrinsic immune regulation immune function [25, 26]. Although the therapeutic regimen of IVIG applied to Kawasaki disease has been gradually refined and matured, its specific mechanism has not been elucidated in detail, and it is currently believed that IVIG treatment of Kawasaki disease may be through the following pathways:

(1) Modulates macrophage activity by inhibiting autoantibodies that bind to crystalline fragment receptors; inhibits endothelial cell activation, adhesion molecule expression, and secretion of soluble mediators; neutralizes antibodies to cytokines, chemokines, and activated complement proteins that activate inhibitory crystalline fragment receptor receptors on macrophages; and blocks the transport of adhesion molecules critical for inflammatory cells to vascular endothelial cells; produces anti-liposomes to reduce inflammation and attenuate endothelial cell injury [27].

(2) Immunoglobulins stimulate an adaptive immune response that can bind to bacteria or viruses and their toxins, and interact with unique type determinant clusters on pathogenic autoantibodies (and autoantibody-producing B cells), allowing direct neutralization of pathogens and thus their clearance; IVIG may also affect the number and function of regulatory T cells that help control inflammation [28].

(3) IVIG can also bind to the crystalline fragment receptors, which are not directly involved in the regulation of immune cell activation but act as a protective receptor by preventing the catabolism of immunoglobulins.

(4) Human immunoglobulin has a regulatory effect on lymphocytes and mononuclear macrophages. Multiple types of antibodies in human immunoglobulin can provide passive immunity to the body in a short period and enhance the immune status of the body. Analysis of serum cytokine levels in children with Kawasaki disease after IVIG treatment showed that the levels of interferon-γ and interleukin-10 decreased rapidly, on the contrary, IVIG treatment could enhance the expression of regulatory T cell transcription factor FoxP3. In IVIG, IgG monomer accounts for more than 95%, the remainder is dimeric or multimer IgG. High-dose IVIG is often effective in the treatment of KD, suggesting that IgG dimers or multimers have a better anti-inflammatory effect. The specific mechanism is still unclear, but it is speculated that the dimer structure of IgG enhances the binding ability of crystalline fragments to their receptors, thus effectively inhibiting the activation of innate immune cells and reducing autoimmune damage [29].

1.2 EXPERT CONSENSUS ON THE USE OF IVIG IN KAWASAKI DISEASE [17]

Recommendations on the best time to use IVIG:

The best time is 5-10 days after the onset of the disease, preferably within 7 days. (1A)

Use within 5 days of onset may lead to an increased incidence of IVIG resistance; it should still be applied promptly in severe cases, such as combined hypertension, shock, myocarditis with hemodynamic instability, and paralytic intestinal obstruction. (1A)

IVIG treatment is still required in children with an onset of more than 10 days, excluding persistent fever due to other causes, with elevated erythrocyte sedimentation rate or C-reactive protein, or with elevated inflammatory markers and CAL. (2B)

Recommendations on dosage and rate of IVIG application:

A single dose of IVIG (2 g/kg) is usually administered intravenously over 12-24 hours. The recommended initial infusion rate is 0.01 mL/(kg.min) [5% IVIG 30 mg/(kg.h)] for 15 to 30 min, increasing to 0.02 mL/(kg.min), then to 0.04 mL/(kg.min) if well tolerated, and finally to a maximum rate of 0.08 mL/(kg.min) (1B).

Recommendations on IVIG applications:

Complete Kawasaki disease, incomplete Kawasaki disease, recurrent Kawasaki disease: IVIG at a dose of 2g/kg administered as a single intravenous infusion over 12 to 24h, together with oral aspirin. (1A)

Non-responsive Kawasaki disease (IVIG-resistant Kawasaki disease): Early reapplication of IVIG at a dose of 2g/kg in a single intravenous infusion over 12 to24h is recommended. For patients who still have a fever, glucocorticoids can be combined with IVIG. (1B)

Recommendations on the safety of using IVIG:

Infants and children with fluid restriction need to avoid low concentration preparations. (1A)

Infants and children with cardiovascular disease should be careful to avoid IVIG with high sodium content. (1B)

Formulations using maltose or glucose as stabilizers are not recommended for patients with diabetes and renal impairment risks. (2A)

Amino acid-containing preparations need to be used with caution in patients with specific genetic metabolic abnormalities. (1B)

Possible adverse effects during the use of IVIG reactions and recommendations for countermeasures:

Headache is a common adverse reaction, usually occurring during or 2 to 3 days after infusion, and mild cases can be treated with NSAIDs for pain relief. (1A)

Transient asymptomatic neutropenia after IVIG treatment usually occurs 2 to 4 days after infusion and recovers within 2 weeks, generally, no treatment is needed, but some scholars believe that it can be prevented by glucocorticoids. (2B)

IgG subclass deficiency and hyper-IgM syndrome are not contraindications to IVIG. Anti-IgA antibodies can be detected in patients who have had severe allergic reactions and IgG replacement therapy should be applied with caution if the anti-IgA antibody titer is high (greater than 1 in 1000) (2A).

Renal impairment is firstly manifested by elevated blood urea nitrogen or creatinine, followed by oliguria and renal failure, which peaks 5 to 7 days after high-dose infusion. In patients with existing renal impairment, IVIG should be infused slowly, and hydrated appropriately, and IVIG products containing sucrose should be avoided. (1B)

The estimated incidence of thrombotic events ranges from 1% to 16.9%. Risk factors for thrombosis include first high dose IVIG, previous or current thrombosis, previous atherosclerotic disease, hyperviscosity syndrome, hereditary hypercoagulable state, and rapid infusion rate. Measures such as pre-hydration of IVIG, at a rate of less than 50 mg/(kg. h), use of hypotonic IVIG products (3% to 6%), and prophylactic use of aspirin or low molecular weight heparin can be used to reduce the incidence of thrombosis in high-risk patients. Patients who already have thrombotic complications need to receive antithrombotic therapy. (1B)

2. CHINESE EXPERT CONSENSUS ON ASPIRIN FOR KD [19]

2.1 MECHANISM OF ASPIRIN FOR THE TREATMENT OF KD

Aspirin can act on the hypothalamic thermoregulation center and cause peripheral vascular dilation, increasing skin blood flow, sweating, heat dissipation, and other cooling effects in children. In addition, Aspirin can cause the acetylation of serine at position 530 of a polypeptide chain, the active site of cytochrome-1 in children, to completely inactivate cytochrome-1, block the conversion of arachidonic acid to thromboxane A2, and achieve the effect of antiplatelet aggregation, to effectively avoid embolism in children and affect blood pressure circulation. Therefore, Aspirin in the treatment of KD children will play a role in antipyretic analgesia and the prevention of thrombosis [16, 30].

2.2 EXPERT CONSENSUS RECOMMENDATIONS FOR ASPIRIN APPLICATION IN KD [19].

Recommendations on dosage forms of aspirin:

Aspirin has an irritating effect on the gastric mucosa and gastrointestinal reactions such as nausea and vomiting are often seen, therefore enteric tablets or enteric capsules should be used for long-term use. (1A)

Generally, drops and syrups are preferred for infants, while solutions, syrups, suspensions, and effervescent can be used for preschool children aged 2 to 5 years. In addition, enteric tablets and capsules must be swallowed whole and are not suitable for use in younger children. Effervescent tablets can be dissolved into a liquid to facilitate accurate dosing and are easy for children to take, making them a suitable dosage form for children, but there are problems with storage and wastage when dispensing, which need to be further explored. (1B)

Recommendations on the dosage and course of treatment of aspirin in the treatment of KD:

Children in the acute phase of KD should be given aspirin 30-50 mg/(kg-d) orally in 2 to 3 divided doses until the fever subsides 48 to 72 h or until 3-5 mg/(kg.d) after 14 days of onset, with maintenance doses. Continue orally for 6-8 weeks, or until coronary artery normalization in children with CAL[31-34].(1A)

Children with KD in the acute phase should receive oral aspirin 3-5 mg/kg.d for 6 to 8 weeks, or until coronary artery normalization in children with CAL.(1A)

Children with undiagnosed KD and atypical KD before IVIG can usually be given oral aspirin 3-5 mg/kg.d for 6 to 8 weeks at an early stage, or until coronary artery normalization in children with CAL.(2B)

Recommendations for the use of aspirin in KDSS :

In the treatment of KDSS, the application of aspirin follows the dose and usage of conventional aspirin in the treatment of KD.

Due to the low prevalence of KDSS, reports on KDSS are still case reports, and reviews on the subject have focused on early identification of KDSS by altered inflammatory markers and exploring how to manage IVIG non-response. The American Heart Association's 2017 consensus on KD diagnosis and management also does not suggest whether the dosage of Aspirin in children with KDSS needs to be adjusted. Therefore, we believe that the decisive factor in the occurrence of CAL in children with KDSS is the timely correction of hypoproteinemia and correction of shock and that the application of Asp is sufficient in accordance with the dosage and usage of conventional Aspirin used in the treatment of KD.

Adverse effects of aspirin in the treatment of KD and preventive measures:

Possible adverse reactions in children with KD treated with aspirin include rhinorrhoea, gastrointestinal bleeding, peptic ulcers, subcutaneous hemorrhage, intracranial hemorrhage, black stools, asthma, liver, and renal failure, rash, loss of appetite, nausea, vomiting, Reye's syndrome, tinnitus, hearing loss, and toxic epidermal necrolysis relaxation/-skin-mucosa-eye syndrome. Although the incidence of these adverse reactions is low, aspirin dose reduction or discontinuation is required if these adverse reactions occur during KD treatment [35]. Hepatic impairment following aspirin therapy has been reported to be closely related to the dose used. It is recommended to add gastric mucosal protective agents during oral aspirin therapy and to review regularly to try to minimize adverse effects to improve the prognosis of children with KD.

Precautions for aspirin use:

Contraindication: allergy to aspirin, active bleeding, liver, and kidney failure, digestive ulcer and frequent recurrence, hemophilia, other coagulation disorders, etc.

Caution: abnormal liver function, minor bleeding of subcutaneous mucosa,

transient nosebleed, asthma, glucose-6-phosphate dehydrogenase deficiency, Reay's syndrome, genetic metabolic diseases similar to Reay's syndrome, ASP-related rash, gastrointestinal diseases, etc.

Other precautions: If liver transaminase increases in KD subacute stage or recovery stage, the aspirin dose should be reduced and/or discontinued. As KD acute stage often appears persistent high fever, clinical use of ibuprofen is possible to reduce fever. The combination of ibuprofen counteracts the irreversible platelet inhibition induced by aspirin and therefore ibuprofen should be avoided in children with CAL and acetaminophen should be used to reduce fever [36]. During the KD recovery period, it is still recommended that children taking low doses of aspirin can be inoculated, but the relevant clinical symptoms need to be strictly observed [37].

3. CHINESE EXPERT CONSENSUS ON GC FOR KD [15]

3.1 MECHANISM OF ASPRIN FOR THE TREATMENT OF KD

Vascular endothelial injury is a key link in the pathogenesis of KD. Neutrophils, CD8+ T lymphocytes, and mononuclear macrophages accumulate in the coronary artery mesothelium during the acute phase of KD, causing vascular endothelial injury is a key link in the pathogenesis of KD. Disruption of the vascular barrier releases cytokines and adhesion molecules that diffuse into the vessel wall, leading to vessel wall edema, elastic fiber fracture, and destruction of the elastic layer, causing vascular remodeling leading to coronary artery dilation or CAA.GC can reduce the transcription of inflammatory mediators and decrease the level of fever and inflammation in KD patients, thus reducing the incidence of coronary artery damage and future cardiovascular sequelae [38, 39].

3.2 INDICATIONS FOR GC APPLICATION FOR KD INCLUDE THE FOLLOWING :

IVIG unresponsive KD remedial therapy; Children with combined CAA or peripheral hemangioma with persistently elevated inflammatory markers; KDSS; KD combined with macrophage activation syndrome(MAS); Children at high risk of IVIG unresponsiveness, including those with an age of onset less than 0.5 years, high levels of inflammatory markers, and a Kobayashi warning score greater than or equal to 5, or children with high-risk KD as judged by the IVIG high-risk warning score at each hospital [40, 41].

3.3 DIFFERENT KINDS AND METHODS OF GC ARE APPLIED TO KD

Recommendation: The type of GC treatment for KD patients was high-dose methylprednisolone intravenous injection followed by oral prednisone sequential therapy [38]. (1A)

3.4 DOSE AND COURSE OF GC APPLIED TO KD

3.4.1 IVIG non-responsive KD

Kobayashi score suggests first-line treatment for children with IVIG non-responsive KD or persistently elevated inflammatory markers combined with CAA or peripheral vascular tumorsflammatory index.

Recommendation: Prednisone 1-2 mg/(kg.d), taken in the morning, with a total dose of less than 60 mg per day or methylprednisolone 1-2 mg/(kg.d), intravenously, once or twice a day, reduced after body temperature and c-reactive protein were normal, and then gradually reduced within 15 days, 1-2 mg/(kg.d), for 5 days; 0.5-1mg /(kg.d) for 5 days; 0.25-0.5 mg/(kg.d) for 5 days[43-47]. (1A)

3.4.2 Second-line treatment of IVIG non-responsive KD

Optional second dose of IVIG plus prednisone (or methylprednisolone).

Recommendation: Prednisone 1-2 mg/(kg.d), taken in the morning, with a total dose of less than 60 mg per day or methylprednisolone 1-2 mg/(kg.d), intravenously, once or twice a day, reduced after body temperature and c-reactive protein were normal, and then gradually reduced within 15 days, 1-2 mg/(kg.d), for 5 days; 0.5-1mg /(kg.d) for 5 days; 0.25-0.5 mg/(kg.d) for 5 days [43-48].(1A)

3.4.3 First-line treatment of KDSS

Recommendation: Methylprednisolone 10-30 mg/(kg.d) for 1 to 3 d with 2 to 3 h of each intravenous infusion. Heparin anticoagulation 10 U/(kg.d) of heparin concurrently 2 h before the start of methylprednisolone] for 24 h is recommended, or low-molecular heparin anticoagulation with coagulation, echocardiography, and blood pressure monitoring [49-52]. (2A)

3.4. 4 First-line treatment of KD combined with MAS

Recommendation: Methylprednisolone 10-30 mg/(kg.d) for 3 d, with each IV infusion for 2-3 h. Sequential prednisone orally [1-2 mg/(kg.d)] until complete control and remission of MAS with gradual dose reduction and discontinuation [53-55]. (2A)

GC is not recommended as routine first-line therapy for KD.GC alone is unsafe and contraindicated as a first-line treatment for KD, as studies have shown that GC alone used as an initial treatment for KD can significantly increase the incidence of coronary artery damage [39, 56].

4. PREVENTION OF ADVERSE REACTIONS

During treatment with GC in children with KD, special attention should be paid to the prevention of Cushing's syndrome, infection, thrombosis, osteoporosis, aseptic necrosis of the femoral head, diabetes mellitus, hypertension, hormonal glaucoma, cataract, bradycardia, secondary adrenocortical insufficiency and growth retardation. For the prevention and treatment of osteoporosis, it is recommended to supplement vitamin D 600-800 U/d and calcium 1000-1200 mg/d during the application of GC. Various infections, such as tuberculosis, fungus, and chickenpox, should be fully excluded before high-dose methylprednisolone shock therapy, and blood pressure and blood glucose should be closely observed and tested to detect any of the above complications in time and deal with them actively. While applying CC, strive to minimize the adverse effects to improve the prognosis of children with KD.

5. MATTERS NEEDING ATTENTION

(1) Contraindicated: hypersensitivity to GC drugs, epilepsy, fractures, un-

controlled infections (e.g. chickenpox, fungal infections), active tuberculosis, etc.

(2) Caution: Cushing's syndrome, myasthenia gravis, hypertension, diabetes mellitus, intestinal disease or chronic malnutrition, infectious diseases, etc. must be combined with effective antibiotics.

(3) Other precautions: Prevent cross-allergy, those who are allergic to one GC drug may also be allergic to other GCs. When using GC, adopt low sodium, high potassium, high protein diet, supplement calcium, and vitamin D, and add drugs to prevent peptic ulcer and bleeding and other adverse reactions. If there is an infection, antibiotics should be applied at the same time to prevent the spread and aggravation of the infection. The interaction between GC and other drugs should be noted, for example, excessive potassium loss can be caused when GC is combined with potassium-removing diuretics (e.g., thiazide or tab diuretics), and the incidence of gastrointestinal bleeding and ulcers increases when GC is combined with NSAIDs [38, 46, 57-59].

CONCLUSION

After more than thirty years of clinical validation, concerning half a century of research results on KD, and combined with the treatment experience of hundreds of pediatric KD clinicians and experts in China, these consensuses standardize the use of IVIG, Aspirin, and GC in pediatric KD medication, which has important clinical significance in effectively reducing the incidence of complications in all systems of KD and preventing cardiovascular sequelae caused by KD. The limitations of consensuses include relatively few high-quality randomized controlled studies, fewer and more foreign references, and insufficient consideration of ethnic differences. Because the pathogenesis of KD is not fully understood, the medication for KD is constantly updated and researched. It is necessary to continuously update the consensus of KD medication according to the latest international studies, and supplement the dosage and regimen of other complications in various medications for myocarditis, acute inflammatory response syndrome, MAS, and other diseases.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Jiao Fuyong developed the concept for the paper. Ren Shuying prepared the first draft of the manuscript. Deng Fangming, Du Zhongdong, Yang Xiaodong, Xie Lijian, Wang Hong contributed to discussions of content, literature search, and critical review of the manuscript.

CONSENT TO PUBLISH

The authors affirm that the Chinese Journal of Current Pediatrics provided informed consent for the publication of this paper.

REFERENCES

1. Gorelik M, Chung S A, Ardalan K, Binstadt B A, Friedman K, Hayward Ket, alMustafa R A. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease. Arthritis Care Res (Hoboken). 2022; 4: 538-48.

2. Bayers S, Shulman S T, Paller A S. Kawasaki disease: part II. Complications and treatment. J. Am. Acad. Dermatol. 2013; 4: 511-3, 521-2.

3. Burns, Jane, C., Kobayashi, Tohru, Sajiet, alElfriede. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease A Scientific Statement for Health Professionals From the American Heart Association. Circulation: An Official Journal of the American Heart Association. 2017; 17: E927-99.

4. Kim G B, Park S, Eun L Y, Han J W, Lee S Y, Yoon K Let, alLee K Y. Epidemiology and Clinical Features of Kawasaki Disease in South Korea, 2012-2014. Pediatr. Infect. Dis. J. 2017; 5: 482-5.

5. Manlhiot C, O'Shea S, Bernknopf B, LaBelle M, Chahal N, Dillenburg R Fet, alMcCrindle B W. Epidemiology of Kawasaki Disease in Canada 2004 to 2014: Comparison of Surveillance Using Administrative Data vs Periodic Medical Record Review. Can. J. Cardiol. 2018; 3: 303-9.

6. Huang W C, Huang L M, Chang I S, Chang L Y, Chiang B L, Chen P Jet, alLee C Y. Epidemiologic features of Kawasaki disease in Taiwan, 2003-2006. Pediatrics. 2009; 3: e401-5.

7. Kim G B, Han J W, Park Y W, Song M S, Hong Y M, Cha S Het, al-Park S. Epidemiologic features of Kawasaki disease in South Korea: data from nationwide survey, 2009-2011. Pediatr. Infect. Dis. J. 2014; 1: 24-7.

8. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Yet, alYanagawa H. Descriptive epidemiology of Kawasaki disease in Japan, 2011-2012: from the results of the 22nd nationwide survey. J. Epidemiol. 2015; 3: 239-45.

9. Du ZD, Zhao D, Du J, Zhang Y L, Lin Y, Liu Cet, alZhang T. Epidemiologic study on Kawasaki disease in Beijing from 2000 through 2004. Pediatr. Infect. Dis. J. 2007; 5: 449-51.

10. Ma X J, Yu C Y, Huang M, Chen S B, Huang M R, Huang G Y. Epidemiologic features of Kawasaki disease in Shanghai from 2003 through 2007. Chin Med J (Engl). 2010; 19: 2629-34.

11. Lin M C, Lai M S, Jan S L, Fu Y C. Epidemiologic features of Kawasaki disease in acute stages in Taiwan, 1997-2010: effect of different case definitions in claims data analysis. J. Chin. Med. Assoc. 2015; 2: 121-6.

12. Abstracts of the 10th International Kawasaki Disease Symposium. February 7-10, 2012. Kyoto, Japan. Pediatr. Int. 2012; 38-142.

13. He L, Liu F, Huang G Y, Wu L, Chu C, Lu Y. [Application of selective coronary angiography in children with Kawasaki disease complicated with severe coronary artery lesion]. Zhonghua Er Ke Za Zhi. 2019; 2: 108-12.

14. Newburger J W, Takahashi M, Burns J C, Beiser A S, Chung K J, Duffy C Eet, alEt A. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986; 6: 341-7.

15. Wu M H, Chen H C, Yeh S J, Lin M T, Huang S C, Huang S K. Prevalence and the long-term coronary risks of patients with Kawasaki disease in a general population <40 years: a national database study. Circ Cardiovasc Qual Outcomes. 2012; 4: 566-70.

16. Bressieux-Degueldre S, Schaffner D, Hofer M, Sekarski N, Vanoni F. [Kawasaki disease: an update]. Rev Med Suisse. 2018; 594: 384-9.

17. Zhang R L, Lo H H, Lei C, Ip N, Chen J, Law B Y. Current pharmacological intervention and development of targeting IVIG resistance in Kawasaki disease. Curr. Opin. Pharmacol. 2020; 72-81.

18. Shaanxi Provincial Diagnosis and Treatment Center of Kawasaki Disease. Zhongguo Dang Dai Er Ke Za Zhi. 2021; 9: 867-76.

19. [Pediatric expert consensus on the application of aspirin in Kawasaki disease]. Zhongguo Dang Dai Er Ke Za Zhi. 2022; 6: 597-603.

20. Pediatric expert consensus on the application of glucocorticoids in Kawasaki disease. Zhongguo Dang Dai Er Ke Za Zhi. 2022; 3: 225-31.

21. Suzuki T, Michihata N, Aso S, Yoshikawa T, Saito K, Matsui Het, alYasunaga H. Sodium-containing versus sodium-trace preparations of IVIG for children with Kawasaki disease in the acute phase. Eur. J. Pediatr. 2021; 11: 3279-86.

22. Brozek J L, Akl E A, Alonso-Coello P, Lang D, Jaeschke R, Williams J Wet, alSchunemann H J. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009; 5: 669-77.

23. Brozek J L, Akl E A, Alonso-Coello P, Lang D, Jaeschke R, Williams J Wet, alSchunemann H J. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009; 5: 669-77.

24. Ozen S, Marks S D, Brogan P, Groot N, de Graeff N, Avcin Tet, al-Beresford M W. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. Rheumatology (Oxford). 2019; 9: 1607-16.

25. Imbach P, Barandun S, Baumgartner C, Hirt A, Hofer F, Wagner H P. High-dose intravenous gammaglobulin therapy of refractory, in particular idiopathic thrombocytopenia in childhood. Helv Paediatr Acta. 1981; 1: 81-6.

26. Kane J, Porretta M, Krajden S, Goldhar J, Diena B B. An autochthonous phaeohyphomycotic nail infection in Canada caused by Hendersonula toruloidea. Mycoses. 1990; 1: 37-40.

27. Guo M M, Tseng W N, Ko C H, Pan H M, Hsieh K S, Kuo H C. Th17- and Treg-related cytokine and mRNA expression are associated with acute and resolving Kawasaki disease. Allergy. 2015; 3: 310-8.

28. Rasouli M, Heidari B, Kalani M. Downregulation of Th17 cells and the related cytokines with treatment in Kawasaki disease. Immunol. Lett. 2014; 1 Pt A: 269-75.

29. Teeling J L, Jansen-Hendriks T, Kuijpers T W, de Haas M, van de Winkel J G, Hack C Eet, alBleeker W K. Therapeutic efficacy of intravenous immunoglobulin preparations depends on the immunoglobulin G dimers: studies in experimental immune thrombocytopenia. Blood. 2001; 4: 1095-9.

30. Loomba R S. Comment on the paper by Su et al. entitled 'safety and efficacy of warfarin plus aspirin combination therapy for giant coronary artery aneurysm secondary to kawasaki disease: a meta-analysis'. Cardiology. 2015; 3: 164-5.

31. [The expert consensus on diagnosis and acute-phase treatment of Kawasaki disease]. Zhonghua Er Ke Za Zhi. 2022; 1: 6-13.

32. Fukazawa R, Kobayashi J, Ayusawa M, Hamada H, Miura M, Mitani Yet, alKimura T. JCS/JSCS 2020 Guideline on Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease. Circ. J. 2020; 8: 1348-407.

33. Kobayashi T, Ayusawa M, Suzuki H, Abe J, Ito S, Kato Tet, alTakahashi K. Revision of diagnostic guidelines for Kawasaki disease (6th revised edition). Pediatr. Int. 2020; 10: 1135-8.

34. Michihata N, Matsui H, Fushimi K, Yasunaga H. Guideline-Concordant Treatment of Kawasaki Disease With Immunoglobulin and Aspirin and the Incidence of Coronary Artery Aneurysm. Clin Pediatr (Phila). 2015; 11: 1076-80.

35. Asada D, Taura Y, Itoh H, Tatsumi Y. Acute gastrointestinal hemorrhage in Kawasaki disease occurring before aspirin therapy. Pediatr. Int. 2019; 11: 1177-8.

36. Huang X, Huang P, Zhang L, Xie X, Xia S, Gong Fet, alJin L. Is aspirin necessary in the acute phase of Kawasaki disease? J Paediatr Child Health. 2018; 6: 661-4.

37. Dhanrajani A, Yeung R. Revisiting the role of steroids and aspirin in the management of acute Kawasaki disease. Curr. Opin. Rheumatol. 2017; 5: 547-52.

38. Chang L S, Kuo H C. The role of corticosteroids in the treatment of Kawasaki disease. Expert Rev Anti Infect Ther. 2020; 2: 155-64.

39. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera Tet, alEt A. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet. 1984; 8411: 1055-8.

40. Morishita K A, Goldman R D. Kawasaki disease recognition and treatment. Can. Fam. Physician. 2020; 8: 577-9.

41. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa Met, alMiura M. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Lancet Child Adolesc Health. 2018; 12: 855-62.

42. Shin J, Lee H, Eun L. Verification of Current Risk Scores for Kawasaki Disease in Korean Children. J. Korean Med. Sci. 2017; 12: 1991-6.

43. [Consensus on the application of glucocorticoid from relative experts in pediatric rheumatoid diseases(part 1)]. Zhonghua Er Ke Za Zhi. 2018; 3: 166-73.

44. Friedman K G, Jone P N. Update on the Management of Kawasaki Dis-

ease. Pediatr Clin North Am. 2020; 5: 811-9.

45. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa Met, alMiura M. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Lancet Child Adolesc Health. 2018; 12: 855-62.

46. Wardle A J, Connolly G M, Seager M J, Tulloh R M. Corticosteroids for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2017; D11188.

47. Yu J J. Use of corticosteroids during acute phase of Kawasaki disease. World J Clin Pediatr. 2015; 4: 135-42.

48. Yang Ying, Zhang Jing. A retrospective control study of glucocorticoid, intravenous immunoglobulin and their combination in the treatment of intravenous immunoglobulin non-responsive Kawasaki disease. Chinese Journal of Evidence-Based Pediatrics. 2016; 04: 265-9.

49. Cakan M, Gemici H, Aktay-Ayaz N, Keskindemirci G, Bornaun H, Ikizoglu Tet, alCeliker A. Kawasaki disease shock syndrome: a rare and severe complication of Kawasaki disease. Turk J Pediatr. 2016; 4: 415-8.

50. Jiang D J, Huang P, Zhang L. [The research progress of Kawasaki disease shock syndrome]. Zhonghua Er Ke Za Zhi. 2016; 12: 961-3.

51. Ma L, Zhang Y Y, Yu H G. Clinical Manifestations of Kawasaki Disease Shock Syndrome. Clin Pediatr (Phila). 2018; 4: 428-35.

52. Rassas A, Guizani R, Werdani A, Jammeli N, Mahjoub B. Kawasaki disease shock syndrome complicated by coronary aneurysms: a case report. Pan Afr Med J. 2021; 52.

53. Garcia-Pavon S, Yamazaki-Nakashimada M A, Baez M, Borjas-Aguilar K L, Murata C. Kawasaki Disease Complicated With Macrophage Activation Syndrome: A Systematic Review. J Pediatr Hematol Oncol. 2017; 6: 445-51.

54. Grom A A, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. Nat. Rev. Rheumatol. 2016; 5: 259-68.

55. Han S B, Lee S Y. Macrophage activation syndrome in children with Kawasaki disease: diagnostic and therapeutic approaches. World J. Pediatr. 2020; 6: 566-74.

56. McCrindle B W, Rowley A H, Newburger J W, Burns J C, Bolger A F, Gewitz Met, alPahl E. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation. 2017; 17: e927-99.

57. Caplan A, Fett N, Rosenbach M, Werth V P, Micheletti R G. Prevention and management of glucocorticoid-induced side effects: A comprehensive review: Gastrointestinal and endocrinologic side effects. J. Am. Acad. Dermatol. 2017; 1: 11-6.

58. Oray M, Abu S K, Ebrahimiadib N, Meese H, Foster C S. Long-term side effects of glucocorticoids. Expert Opin. Drug Saf. 2016; 4: 457-65.

59. Ritter A, Burow A, Vallelian F, Schaer D. [Systemic glucocorticoids: diagnosis, prophylaxis and treatment of side effects]. Praxis (Bern 1994). 2014; 17: 987-98, 996.

UPDATE RESEARCH OF KAWASAKI DISEASE

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ABSTRACT:

Kawasaki disease is an acute, self-limited vasculitis of unknown etiology, which mainly occurs in infants and children. The target organs of Kawasaki disease are coronary arteries and other cardiovascular structures. The initial manifestations of Kawasaki disease are high fever, inflammation of skin and mucosa, and enlargement of cervical lymph nodes. About 25% of children who are not treated with intravenous immunoglobulin during the acute phase of the disease will develop coronary artery aneurysms. Nowadays, Kawasaki disease has replaced rheumatic fever as the main cause of acquired heart disease in children in developed countries. However, there is still no specific diagnostic test, echocardiography is still the main diagnostic method of coronary artery involvement in children with Kawasaki disease, and risk stratification assessment is carried out according to Z value to assist in the short-term and long-term diagnosis and treatment of Kawasaki disease. In the aspect of treatment, there are reports on the application of corticosteroids, infliximab, cyclosporine, methotrexate, interleukin receptor blockers and so on.

1 EPIDEMIOLOGY

Kawasaki disease was first reported and named after Fuzuo Kawasaki in 1967. Kawasaki disease is more common in children, 80% of the age is less than five years old, and there are also teenagers. The young age of onset indicates that the susceptibility may be related to the maturity of the immune system [1]. Now we have some knowledge and understanding of Kawasaki disease, and its incidence varies greatly in different populations. Japan has the highest incidence rate, and the number of cases continues to rise. According to the

survey, the incidence rate has reached 264.8 per 100000 children (< 5 years old) [2]. South Korea is also increasing year by year, according to a retrospective epidemiological survey, the incidence rate has reached 217.2 per 100000 children (< 5 years old) [3]. In China, the incidence rate of a 10-year survey in Beijing has reached 55.1 per 100000 children (< 5 years old); the result of a five-year survey in Shanghai is 46.3; in a recent survey in Taiwan, the incidence rate is 82.8 per 100000 children (< 5 years old), ranking third in the world [4] [5] [6]. The United States passive Monitoring and Analysis Management Database shows that the incidence rate is 19 per 100000 children (< 5 years old) and 24.7 per 100000 children (< 5 years old) in California [7]. Among American children in Hawaii and California, the high incidence of children of Asian and Pacific island descent suggests that there may be an important gene contributing to their susceptibility (incidence rates are 210, 50.4 per 100000 children (< 5 years old) respectively) [8] [9]. A genome-related study in Japan also shows that susceptibility to Kawasaki disease may be related to genes [10]. In France, it is 7 per 100000 children (< 5 years old), while in Japan it is 30 times that of France. And Kawasaki disease has obvious seasonality in the northern hemisphere [11].

When people with genetic susceptibility to Kawasaki disease are exposed to an environment where Kawasaki disease triggers may be widely distributed, they cause an immune response if they enter the upper respiratory tract [12]. Some genetically susceptible children will have irreversible coronary artery wall damage. Available records can indicate the accumulation of cases in time and space, but there is still no evidence of human-to-human transmission [13]. It is assumed that potential cases can occur under the following two triggers: 1) replication of infectious pathogens in mucosal epithelial cells of the upper respiratory tract; and 2) widespread distribution of antigens in the environment. Recently, some data support the interesting hypothesis that the triggers of Kawasaki disease are carried by large-scale convective air. Moreover, the seasonal clusters and annual epidemics of Kawasaki disease cases in Japan, Hawaii and southern California are in the northeastern provinces of China [1].

2. PATHOLOGY

Among the pathological changes caused by Kawasaki disease, the most common is to affect the coronary artery, followed by other substantive muscular arteries. A comprehensive review of 32 cases of Kawasaki autopsy and 8 cases of heart transplantation described three points related to the progression of vascular lesions in the arterial wall: necrotizing arteritis, subacute / chronic vasculitis and myofibroblast hyperplasia [14].

1) Acute arteritis is characterized by neutrophil infiltration from the vascular lumen and is associated with extensive necrosis of the vascular walls of coronary arteries and other medium-sized arteries [15]. Neutrophil elastase may also cause some damage to the internal and external elastic membrane of the vascular wall, leading to the formation of aneurysms. Neutrophil elastase inhibitors have been used to block this pathway in Japan [16].

2) subacute vasculitis begins a few weeks after fever, or months and years later, and is closely related to the proliferation of myofibroblasts in the third process [13]. Inflammatory cells mainly infiltrate the lymphatic system and adventitia, and the involvement of CD8+ cytotoxic T lymphocytes has been confirmed, suggesting that anti-T cell therapy may be effective, such as calcineurin inhibitors cyclosporine and tacrolimus [17] [18] [19].

3) the proliferation of myofibroblasts may be the pathological process of myofibroblasts derived from smooth muscle cells mediated by transforming growth factor-β [20] [21]. The polymorphism of transforming growth factor pathway is associated with increased susceptibility to aneurysm inflammation in patients with Kawasaki disease [22]. Myofibroblast proliferation can lead to lumen stenosis and myocardial ischemia. A prominent histological feature of late aneurysms is that layered thrombus is commonly found in calcification-related aneurysms, which can be detected by computed tomography ((CT)) [23]. It should be noted that because the histological description of Kawasaki disease is mainly based on autopsy of individuals with vasculitis complications, it is characterized by severe cardiovascular pathological changes. These data can be used to judge the condition of patients with potential risk of cardiovascular complications.

3. DIAGNOSIS

At present, there is no specific diagnosis of Kawasaki disease. The diagnosis is now based on clinical standards developed by the Japanese Ministry of Health and adopted by the American Heart Association, alongside non-specific laboratory tests that support the diagnosis. Timely diagnosis and treatment is very important, which largely depends on careful medical history collection and thorough physical examination.

3.1 CLINICAL MANIFESTATIONS

The common clinical features of Kawasaki disease are as follows: fever for five days or more, conjunctival congestion in both eyes, red lips, red bayberry tongue, diffuse hyperemia in oral and pharyngeal mucosa, pleomorphic erythema and rash, hard edema of hands and feet, erythema of metatarsus and toes, and membranous peeling at the skin migration of nail bed at fingertip (convalescent stage). Non-suppurative cervical lymph node enlargement was found in the acute stage, often unilateral and > 1.5cm in diameter. [24]

3.1.1 Typical Kawasaki disease

The diagnosis of classical Kawasaki disease is based on fever for more than 5 days and the presence of 4 or more clinical features [24]. Experienced clinicians may make a diagnosis in rare cases where the hands and feet are red and swollen, and the diagnosis takes only 4 days of fever. Fever usually dissipates within 36 hours after the completion of IVIG infusion. If not, the patient is considered to be resistant to IVIG and needs further treatment. In addition, fever that dissipates spontaneously after 7 days cannot be considered evidence that the diagnosis of

Kawasaki disease has been excluded. Kawasaki disease should be considered in infants with long-term fever with unexplained aseptic meningitis or culture-negative shock and ineffective antibiotic treatment of cervical lymphadenitis.[25]

These typical clinical features do not necessarily appear at the same time, and often can not be found early in the process of diagnosis, and some clinical features may be weakened with the delay of time, so it is necessary for clinicians to carefully examine the symptoms and signs of children in order to make an early diagnosis and prevent delays in the disease.

3.1.2 Incomplete Kawasaki disease

For incomplete (atypical) Kawasaki disease, infants or children with long-term fever of unknown causes and children with less than 4 main clinical features need to consider its possibility, if there are relevant laboratory tests and echocardiography, it can be diagnosed as incomplete Kawasaki disease [25]. Although the Z score of left anterior descending branch or right coronary artery branch is not sensitive, it has high specificity for diagnosis [26] [27].

3.2 LABORATORY INSPECTION

(1) the laboratory indicators in the acute and subacute stages of Kawasaki disease have been summarized in the process of continuous accumulation, including the following:

1) the acute phase of Kawasaki disease is characterized by an increase in immature and mature granulocytes, positive cell euchromic anemia, and high protein in the acute phase. 2) Thrombocytopenia may occur in the process of intravascular thrombosis and degradation, which is characterized by a significant increase in the level of D-dimer. 3) Thrombocytopenia may occur in the subacute stage of Kawasaki disease. 4) about 35% of the patients had mild to moderate increase in serum transaminase or γ-glutamyl transpeptidase activity. 5) about 10% of patients have mild hyperbilirubinemia. 6) hypoproteinemia may occur in patients, which is also a serious acute manifestation of correlation. 7) up to 80% of children's urine tests showed the presence of sterile pyuria [28]. 8) some patients may have elevated N-terminal B-type brain natriuretic peptide (NT-BNP), but this only indicates cardiac involvement and does not fully diagnose Kawasaki disease, and its meaningful numerical increment has not been determined [24].

3.3 ECHOCARDIOGRAPHY:

Echocardiography is the main cardiac imaging in acute phase. In North America, echocardiographic measurements of the internal diameter of the proximal coronary artery segment corrected based on body surface area have been standardized [29]. The American Heart Association classifies as: small aneurysms $2.5 \leq Z < 5$; moderate aneurysms $5 \leq Z < 10$; giant aneurysms $Z \geq$ or inner diameter > 8 mm [30]. The Japanese standard is to define the size of an aneurysm according to the size of the lumen: small aneurysms ≤ 4 mm, medium aneurysms > 4 mm and ≤ 8 mm, and giant aneurysms > 8 mm. In children ≥ 5 years old, the size of aneurysms can also be classified by the ratio of their internal diameter to adjacent segments: 1.5 times for small aneurysms, 1.5 times to 4 times for moderate aneurysms, and more than 4 times for giant aneurysms [31] [32].

3.4 DIFFERENTIAL DIAGNOSIS:

Because there are no specific diagnostic criteria, it needs to be distinguished from other diseases with similar clinical manifestations, including EB virus, adenovirus, echo virus, measles, toxic shock syndrome, scarlet fever, idiopathic juvenile arthritis, nodular polyarteritis, Rocky Mountain spotted fever leptospirosis, adolescent mercury poisoning and adverse drug reactions, Stephens-Johnson syndrome, etc. [33] [34] [35].

4. STAGES OF CLINICAL COURSE OF DISEASE

The clinical process of Kawasaki disease is divided into four stages:

(1) Acute phase: this stage will last for 1-2 weeks without treatment. Children usually present with relaxation fever, which can reach as high as 40 □ at the peak of the disease, and show some major symptoms such as cardiac changes, including valvulitis, pericarditis and myocarditis. (2) subacute stage: this stage is about 2 weeks. As the fever recedes, the child is at high risk of sudden death from myocardial infarction.

(3)in the recovery stage, the clinical symptoms basically disappeared and the level of serum reactants returned to normal in the acute stage.

(4) chronic phase: mainly patients with coronary artery involvement who need follow-up treatment. Therefore, we should make diagnosis and timely treatment in the acute phase as soon as possible to reduce inflammation and reduce the risk of coronary artery involvement in the later stage of the disease.

5. EVALUATION OF ACUTE KAWASAKI DISEASE

Clinical laboratory examination can support clinicians' suspicion of Kawasaki disease, but it needs to be combined with symptoms and auxiliary examinations to assist in differential diagnosis and assess the intensity of inflammation. There are no systematic and accurate diagnostic methods for both clinical standards and laboratory characteristics, and clinical standards depend on non-specific symptoms that may not occur, but can be present in many other vasculitis toxin-mediated diseases [33], as mentioned above. It is not possible to rely solely on clinical criteria, because the characteristics of Kawasaki disease do not necessarily occur at the same time. The main clinical manifestations may be accompanied by a variety of symptoms of febrile vasculitis, including arthritis, gastrointestinal discomfort, fatigue and other systematic clinical manifestations, all of which may lead to misdiagnosis and delay treatment [24] [36]. Especially in infants under 6 months of age, clinical symptoms may only find high fever of unknown causes, and most of them are irritable or sleepy [1]. Easily misdiagnosed as upper respiratory tract infection, acute conjunctivitis, skin allergy, lymphadenitis. Other occasional features such as abnormally increased cells in pyuria and cerebrospinal fluid may indicate the

presence of other infections that may delay diagnosis [37]. The diversity of symptoms makes it difficult for clinicians to make a diagnosis. It is necessary to consider the delay of Kawasaki disease in any case and other fever of unknown causes. This also hinders the diagnosis of incomplete Kawasaki disease, which is an important part of patients with Kawasaki disease.

Children less than 1 year old and children over 5 years old are more likely to develop incomplete Kawasaki disease [38] [39]. These patients account for about 25% [40] of Kawasaki disease, and may delay treatment due to a high misdiagnosis rate, resulting in an increased risk of coronary artery complications. A case-control study in Australia has shown that for children with potentially high cardiovascular risk, changes in aortic intima-media thickness are likely to be a sensitive indicator of cardiovascular risk after Kawasaki disease. however, it is not clear whether this change in mid-childhood indicates atherosclerotic burden or cardiovascular risk in adulthood [41].

5.1 CHANGES IN LABORATORY TESTS DURING THE ACUTE PHASE

Including neutropenia, euchromic anemia, and acute high protein, there are also changes in platelets, slightly higher activity of serum transaminase or γ-glutamyl transpeptidase, hypoproteinemia, aseptic pyuria, and so on.

5.2 ECHOCARDIOGRAPHY IS THE MAIN MANIFESTATION OF CARDIAC IMAGING IN ACUTE PHASE.

1) the Japanese standard defines the size of the aneurysm according to the size of the lumen, and it can also be classified by the ratio of the internal diameter to the adjacent segments. The American Heart Association's assessment of coronary artery abnormalities has been described earlier.

2) Echocardiography is an important auxiliary method in abnormal diagnosis. But normal echocardiography does not rule out Kawasaki disease. In addition, normal baseline echocardiography does not rule out the possibility of later development of coronary artery aneurysms in the first week of onset; therefore, echocardiography should be reexamined at 1-2 weeks and 4-6 weeks after treatment. Coronary artery z values > 2 at baseline or with high-risk clinical features (e.g. persistent fever, intravenous gamma globulin resistance) should be examined more frequently [1].

3) two-dimensional and M-mode echocardiography only showed temporary left ventricular dilatation, systolic dysfunction, pericardial effusion and valvular regurgitation (especially mitral regurgitation). Systolic dysfunction on the echocardiographic baseline is a risk factor for coronary artery aneurysms [42]. Kawasaki disease shock syndrome is rare in patients, and warm shock usually occurs with decreased peripheral vascular resistance [43], which can be confused with toxic shock syndrome or sepsis.

6. ACUTE PHASE MANAGEMENT

6.1 INITIAL TREATMENT

The purpose of acute treatment is to minimize systemic and cardiovascular inflammation in order to prevent cardiovascular sequelae. The main method is high-dose IVIG combined with aspirin, fever within 10 days (early) C ball should reduce the incidence of coronary artery disease from 25% to 5% [44] [45].

Although the mechanism of Kawasaki disease is not fully understood, the efficacy of intravenous immunoglobulin (IVIG) as first-line treatment for acute Kawasaki disease has been verified in many prospective multicenter trials. Administration of IVIG within ten days after fever helps to reduce inflammation, but has little effect on preventing coronary artery damage. Aspirin is widely recognized as a therapeutic drug, but there is little evidence of its therapeutic benefits. A retrospective study in Canada showed that low-dose aspirin was no less effective in reducing the risk of coronary artery abnormalities than high-dose aspirin in the case of combined immunoglobulin injection [36]. However, the risk of high-dose aspirin administration, including aspirin toxicity, Wright's syndrome and conductive hearing loss, has led to adjustments in administration practices in some countries, including Japan, where the recommended acute dose has been reduced to 30-50mg/kg/d [46]. Timely treatment is the key to prevent the adverse outcome of coronary artery.

6.2 TREATMENT OF PATIENTS WITH IVIG RESISTANCE

(AHA) of the American Heart Association defines drug-resistant Kawasaki disease as "relapse or persistent fever at least 36 hours after the first injection of IVIG." [25] it is reported that if patients are treated in the first five days of fever, the rate of IVIG resistance is higher, although it is not clear whether early treatment will lead to a worse prognosis, or whether patients with Kawasaki disease have more severe symptoms on the fifth day [47]. Two kinds of IVIG action mechanisms have been established in patients' peripheral blood mononuclear cell related studies in vitro: the first is to stimulate myeloid dendritic cells to secrete IL-10, and make T cells differentiate into regulatory phenotypes through the constant region of immunoglobulin molecule Fc. The second mechanism is to present the treated Fc peptide to a subset of regulatory T cells to amplify and produce IL-10 [49]. Peptide mapping studies have identified the specific Fc region that mediates this amplification [50]. As the effect of gamma globulin on fever and the improvement of skin and mucosal symptoms is very rapid, other mechanisms such as anti-cytokines and anti-idiotypic antibodies, although lack of specific data, may also be important. Most patients with rapid improvement in clinical experience and infusion of gamma globulin will stop fever, but about 10% to 20% of patients will develop recurrent fever and require additional anti-inflammatory treatment [51]. The prognosis of IVIG resistance is poor because intractable fever indicates progressive arteritis, and these patients tend to have a higher risk of developing coronary artery aneurysms.

6.2.1 Second dose of immunoglobulin

Many authorities recommend the use of a second dose of IVIG2g/kg for treatment. Repetitive IVIG has been shown to be safe and effective, but it

has not been proved by sufficient randomized trials. There may be a theoretical advantage when using different IVIG products for initial treatment, as preparations from different donor pools may have different antibody sequences or different quantities and components, as well as other anti-inflammatory factors [52].

6.2.2 Corticosteroids

The use of steroids in the treatment of Kawasaki disease has gone through a tortuous process, which is more reasonable and acceptable because of its wide availability and relatively low price. There is evidence that the use of steroids can improve inflammatory markers, disappear rapidly, and may reduce the incidence of CALS [52]. AHA suggests that a short course of high-dose steroids can be used as a reasonable change in the second intravenous gamma globulin, or as a reasonable treatment after two doses of IVIG are ineffective. AHA's alternative recommendation for drug-resistant KD is to start taking steroids in addition to a second dose of IVIG and aspirin [25]. However, there is no clear evidence of the optimal dose, formulation, duration and duration of corticosteroids. A recent randomized controlled trial in Japan found that prednisolone added to the standard IVIG regimen significantly reduced the incidence of undesirable coronary arteries, but these have not been found outside the Japanese population [53].

6.2.3 Infliximab

Infliximab in patients with IVIG resistance can solve fever and inflammatory markers more quickly, reduce hospitalization days, reduce medical costs, and have better tolerance. In the largest randomized trial of infliximab as an adjuvant primary therapy for IVIG, there was no evidence that infliximab reduced resistance to Kawasaki disease [54]. On the basis of retrospective data, AHA believes that infliximab can replace the second dose IVIG [25].

6.2.4 Cyclosporine

The efficacy of cyclosporine has been shown in some cases, and studies have shown that targeting the calcium signaling pathway may prevent T cells from destroying the coronary artery wall [18] [19]. Small sample studies have shown that cyclosporine has few serious adverse events and is a good choice for patients with drug-resistant Kawasaki disease, but further research is needed [52].

6.2.5 Methotrexate

A retrospective study and evaluation of 10 years' data in South Korea showed that low-dose methotrexate was effective in the treatment of patients with IVIG resistance. The results showed that the clinical symptoms of the patients were improved, the fever disappeared rapidly, the reactants decreased in the acute phase, and no adverse reactions of methotrexate were observed [37]. Therefore, methotrexate may be a candidate treatment for patients with anti-IVIG resistance.

6.2.6 Interleukin receptor blockers

Data indicate that Atto vastatin inhibits the transformation of endothelial cells to mesenchymal cells in children with Kawasaki disease and coronary artery abnormalities in children) and promotes T cell regulation in an interleukin receptor blocker, anabhitin (an acute disease with abnormal coronary artery in infants and children), phase I/Ila trials investigate whether it is effective (pharmacokinetics / safety study in children with Kawasaki disease and coronary artery abnormalities). However, further clinical trials are needed to improve its therapeutic effects and methods.

6.2.7 Cyclophosphamide

Cyclophosphamide, a cytotoxic drug, is often used in combination with corticosteroids to treat other rare cases of refractory severe progressive aneurysms [56].

There are many reports on the use of other drugs, including other biological agents, cytotoxic agents, ulinastatin and plasma exchangers in drug-resistant Kawasaki disease [57]. In the case of severe inflammation, patients with giant aneurysms have a higher risk of coronary artery thrombosis. These drugs are used in refractory patients who fail to treat. However, further research and clinical practice are needed for the treatment of Kawasaki disease.

6.2.8 Percutaneous Coronary intervention in the treatment of Aneurysm

The treatment of aneurysms in the acute phase of Kawasaki disease is an uncertain area. If echocardiography shows coronary artery dilatation or aneurysm diagnosis, pediatric cardiologists should participate in patient care and develop individualized treatment plans. The existence of coronary artery dilatation requires the early participation of pediatric cardiologists, multiple echocardiographic monitoring of the coronary artery, and long-term routine stress and perfusion tests on the heart [58] [59].

In patients with high risk of ischemia, percutaneous coronary intervention is feasible. This includes intracoronary thrombolysis, balloon angioplasty, stent implantation and rotational grinding, and should be performed in patients with symptomatic ischemia, laboratory examinations showing ischemia, or patients with severe stenosis, and in patients with progressive coronary artery ischemia. If angiography detects severe occlusion or endangers collateral blood supply, coronary artery bypass surgery should be performed [57] [59].

7. LONG-TERM ASSESSMENT

AHA stratifies the risk of coronary artery disease according to the risk of coronary artery thrombosis or stenosis / occlusion associated with myocardial ischemia [25], which facilitates long-term prediction and individualized management of patients, including follow-up, diagnostic trials, assessment and management of cardiovascular risk factors, drug therapy, thrombosis prevention, physical activity and reproductive counseling. (1) Coronary artery lumen diameter measured by echocardiography, risk stratification was performed using Z value converted to body surface area correction (class □ a, class B); (2) based on the most severe degree of coronary artery involvement and current coronary artery involvement

(type □ a, grade C). (3) in addition to coronary artery diameter, other clinical features that may increase the risk of long-term myocardial infarction (such as distal terminal aneurysm, number of aneurysms, number of affected coronary artery branches, irregular coronary artery lumen, irregular inner layer of coronary artery wall (calcification, wall fibrosis), coronary artery dysfunction (vasodilation damage, hemodynamic changes), lack of collateral circulation, insufficient blood supply. Premature angiogenesis, premature thrombus regeneration, premature myocardial infarction, ventricular dysfunction) were considered for risk stratification (class □ a, class C). In general, the coronary artery lumen Z score is stable, the lumen is no longer enlarged. If the Z value of the patient is still increasing after the end of the recovery period, coronary artery changes should be evaluated and followed up.

8. CHRONIC PHASE MANAGEMENT

The purpose of chronic phase management is to prevent coronary artery occlusion and myocardial infarction by reducing platelet aggregation and inhibiting thrombosis.

Long-term treatment included antiplatelet aspirin dose of 3-5 mg / kg / day until normal echocardiography was displayed at 6-8 weeks [25]. If the abnormality of the coronary artery cannot be reversed during this period, long-term drug treatment and diagnostic follow-up are involved. Patients with coronary artery involvement need to take aspirin for a long time to fight platelets. In addition, systemic anticoagulation therapy with warfarin or low molecular weight heparin is used in patients with large or multiple large aneurysms. Low molecular weight heparin may be statistically beneficial to reduce coronary artery score and is unlikely to cause severe bleeding, which makes it a feasible choice for children with severe coronary artery involvement [60]. Children with Kawasaki disease and children with acute coronary artery disease should reduce exposure to atherosclerotic risk factors, including obesity, hyperlipidemia and smoking [61]. There is a delay in immunization in children treated with IVIG, as this treatment blocks the acquisition of active immunization by preventing the replication of live viral vaccines [62], so immunization should be postponed appropriately.

8. CLINICAL RESULTS

Possible results of Kawasaki disease include [62]:

(1) no cardiac sequelae;

(2) coronary artery abnormalities, of which about 60% are reversed within one year;

(3) cardiac involvement, including myocarditis, aneurysm thrombosis, cardiac rhythm disorders or myocardial infarction.

(4) recurrence of Kawasaki disease:

Before IVIG was found as a safe and effective treatment in 3% of patients, 20 to 30% of patients progressed to coronary artery dilatation, with a mortality rate of 2% [63] [64]. If IVIG was treated within 10 days of fever, only 3% of children had transient coronary artery relaxation and 1% developed giant aneurysms [65]. The risk factors of cardiovascular sequelae in patients with Kawasaki disease include longer duration of fever before treatment, low serum albumin at admission (< 3g/L), age less than 1 year or more than 5 years old, and IVIG resistance or incomplete Kawasaki disease [62]. During the 5-year period, Shaanxi Provincial people's Hospital classified and analyzed 170 children with Kawasaki disease, and regularly followed up and found that nearly 1/4 were incomplete Kawasaki disease, and about 1/5 had abnormal coronary arteries. Most of the children with giant aneurysms recovered after treatment but often showed persistent abnormalities [66]. For healthy survivors of Kawasaki disease, the long-term effect is to accelerate the development of atherosclerosis. Only a few cadavers have been studied in patients with coronary artery involvement, and there appears to be endothelial dysfunction and coronary artery scarring. Although the contractile force of patients with transient myocarditis is normal during Kawasaki disease, there are histopathological abnormalities during myocardial biopsies [24]. However, the increase in secondary atherosclerosis with intramural fibrotic degeneration indicates an increased risk of atherosclerosis development, which may become apparent as asymptomatic Kawasaki disease patients approach middle age [67] [68].

9. CONCLUSION

Kawasaki disease is a disease with high risk and there is no specific diagnosis. The main features of Kawasaki disease and the rational use of echocardiography are helpful to timely treatment and improve the prognosis of patients, but the diagnosis of incomplete Kawasaki disease is more complicated and accompanied by severe coronary artery disease. If patients with Kawasaki disease have not been diagnosed and treated, coronary artery disease may become an important factor in the morbidity and mortality of heart disease. More and more people in developing countries such as China and India realize that Kawasaki disease may replace rheumatic fever as the most common cause of childhood acquired heart disease, which is of great significance to doctors and cardiologists. it may also affect the health care system in developing countries, so Kawasaki disease is by no means a childhood disease, it has significant public health importance. Especially for developing countries like China and India [69] [70]. In view of the serious consequences of late diagnosis and the rising global incidence of Kawasaki disease, newborns and pediatric clinicians should be prepared to diagnose Kawasaki disease for children with long-term fever.

REFERENCE

[1]. Newburger J W, Takahashi M, Burns J C. Kawasaki disease[J]. Journal of the American College of Cardiology, 2016, 67(14): 1738-1749.

[2]. Makino N, Nakamura Y, Yashiro M, et al. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey[J]. Journal of epidemiology, 2015, 25(3): 239-245.

[3]. Ha S, Seo G H, Kim K Y, et al. Epidemiologic study on Kawasaki disease in Korea, 2007-2014: based on

health insurance review & assessment service claims[J]. Journal of Korean medical science, 2016, 31(9): 1445-1449.

[4]. Du Z D, Zhao D, Du J, et al. Epidemiologic study on Kawasaki disease in Beijing from 2000 through 2004[J]. The Pediatric infectious disease journal, 2007, 26(5): 449-451.

[5]. Ma X, Yu C, Huang M, et al. Epidemiologic features of Kawasaki disease in Shanghai from 2003 through 2007[J]. Chinese medical journal, 2010, 123(19): 2629-2634.

[6]. Huang W C, Huang L M, Chang I S, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003–2006[J]. Pediatrics, 2009, 123(3): e401-e405.

[7]. Uehara R, Belay E D. Epidemiology of kawasaki disease in Asia, Europe, and the United States[J]. Journal of epidemiology, 2012, 22(2): 79-85.

[8]. Callinan L S, Holman R C, Vugia D J, et al. Kawasaki disease hospitalization rate among children younger than 5 years in California, 2003–2010[J]. The Pediatric infectious disease journal, 2014, 33(7): 781-783.

[9]. Holman R C, Christensen K Y, Belay E D, et al. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawai ‘i[J]. Hawaii medical journal, 2010, 69(8): 194.

[10]. Onouchi Y. Genetics of Kawasaki disease[J]. Circulation Journal, 2012, 76(7): 1581-1586.

[11]. Burns J C, Herzog L, Fabri O, et al. Seasonality of Kawasaki disease: a global perspective[J]. PloS one, 2013, 8(9): e74529.

[12]. Rowley A H. Kawasaki disease: novel insights into etiology and genetic susceptibility[J]. Annual review of medicine, 2011, 62: 69-77.

[13]. Kao A S, Getis A, Brodine S, et al. Spatial and temporal clustering of Kawasaki syndrome cases[J]. The Pediatric infectious disease journal, 2008, 27(11): 981.

[14]. Orenstein J M, Shulman S T, Fox L M. Three linked vasculopathic processes characterize Kawasaki disease[J]. a light and transmission electron microscopic study, 2012: 7.

[15]. Takahashi K, Oharaseki T, Naoe S, et al. Neutrophilic involvement in the damage to coronary arteries in acute stage of Kawasaki disease[J]. Pediatrics international, 2005, 47(3): 305-310.

[16]. Kanai T, Ishiwata T, Kobayashi T, et al. Ulinastatin, a urinary trypsin inhibitor, for the initial treatment of patients with Kawasaki disease: a retrospective study[J]. Circulation, 2011: CIRCULATIONAHA. 111.028423.

[17]. Brown T J, Crawford S E, Cornwall M L, et al. CD8 T lymphocytes and macrophages infiltrate coronary artery aneurysms in acute Kawasaki disease[J]. The Journal of infectious diseases, 2001, 184(7): 940-943.

[18]. Suzuki H, Terai M, Hamada H, et al. Cyclosporin A treatment for Kawasaki disease refractory to initial and additional intravenous immunoglobulin[J]. The Pediatric infectious disease journal, 2011, 30(10): 871-876.

[19]. Tremoulet A H, Pancoast P, Franco A, et al. Calcineurin inhibitor treatment of intravenous immunoglobulin–resistant Kawasaki disease[J]. The Journal of pediatrics, 2012, 161(3): 506-512. e1.

[20]. Shimizu C, Oharaseki T, Takahashi K, et al. The role of TGF-β and myofibroblasts in the arteritis of Kawasaki disease[J]. Human pathology, 2013, 44(2): 189-198.

[21]. Lee A M, Shimizu C, Oharaseki T, et al. Role of TGF-β signaling in remodeling of noncoronary artery aneurysms in kawasaki disease[J]. Pediatric and Developmental Pathology, 2015, 18(4): 310-317.

[22]. Shimizu C, Jain S, Davila S, et al. Transforming Growth Factor-β Signaling Pathway in Patients With Kawasaki DiseaseClinical Perspective[J]. Circulation: Genomic and Precision Medicine, 2011, 4(1): 16-25.

[23]. Kahn A M, Budoff M J, Daniels L B, et al. Calcium scoring in patients with a history of Kawasaki disease[J]. JACC: Cardiovascular Imaging, 2012, 5(3): 264-272.

[24]. Newburger J W, Takahashi M, Gerber M A, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association[J]. Circulation, 2004, 110(17): 2747-2771.

[25]. McCrindle B W, Rowley A H, Newburger J W, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association[J]. Circulation, 2017, 135(17): e927-e999.

[26]. Muniz J C G, Dummer K, Gauvreau K, et al. Coronary artery dimensions in febrile children without Kawasaki disease[J]. Circulation: Cardiovascular Imaging, 2013: CIRCIMAGING. 112.000159.

[27]. Bratincsak A, Reddy V D, Purohit P J, et al. Coronary artery dilation in acute Kawasaki disease and acute illnesses associated with Fever[J]. The Pediatric infectious disease journal, 2012, 31(9): 924-926.

[28]. Tremoulet A H, Jain S, Chandrasekar D, et al. Evolution of laboratory values in patients with Kawasaki disease[J]. The Pediatric infectious disease journal, 2011, 30(12): 1022.

[29]. Parameter(z). Pediatric and fetal echo Z-scores. Available at: http://parameterz.blogspot.com. Accessed February 1, 2016.

[30]. Manlhiot C, Millar K, Golding F, et al. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease[J]. Pediatric cardiology, 2010, 31(2): 242-249.

[31]. Kamiya T. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Diagnostic Criteria of Cardiovascular lesions in Kawasaki Disease[J]. http://www. niph. go. jp/wadai/mhlw/1984/s5906011pdf, 1983: 1-10.

[32]. Ogawa S, Akagi T, Baba K, et al. Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease (JCS 2008): Digest Version[J]. Circulation journal: official journal of the Japanese Circulation Society, 2010, 74(9): 1989-2020.

[33]. Weiss P F. Pediatric vasculitis[J]. Pediatric Clinics, 2012, 59(2): 407-423.

[34]. Scuccimarri R. Kawasaki disease[J]. Pediatric Clinics of North America, 2012, 59(2): 425-445.

[35]. J. Newburger. Kawasaki disease[J]. Pediatric Cardiology, chapter 25, pp. 1067–1078, 2010.

[36]. Dallaire F, Fortier-Morissette Z, Blais S, et al. Aspirin dose and prevention of coronary abnormalities in Kawasaki disease[J]. Pediatrics, 2017, 139(6): e20170098.

[37]. Jang H, Kim K Y, Kim D S. Clinical Outcomes of Low-Dose Methotrexate Therapy as a Second-Line Drug for Intravenous Immunoglobulin-Resistant Kawasaki Disease[J]. Yonsei medical journal, 2018, 59(1): 113-118.

[38]. Johnson S R, Goek O N, Singh-Grewal D, et al. Classification criteria in rheumatic diseases: a review of methodologic properties[J]. Arthritis Care & Research, 2007, 57(7): 1119-1133.

[39]. Kentsis A, Shulman A, Ahmed S, et al. Urine proteomics for discovery of improved diagnostic markers of Kawasaki disease[J]. EMBO molecular medicine, 2013, 5(2): 210-220.

[40]. Manlhiot C, Christie E, McCrindle B W, et al. Complete and incomplete Kawasaki disease: two sides of the same coin[J]. European journal of pediatrics, 2012, 171(4): 657-662.

[41]. Chen K Y H, Curtis N, Cheung M, et al. Cardiovascular Risk After Kawasaki Disease-Findings From an Australian Case-Control Study[J]. 2018.

[42]. Printz B F, Sleeper L A, Newburger J W, et al. Noncoronary cardiac abnormalities are associated with coronary artery dilation and with laboratory inflammatory markers in acute Kawasaki disease[J]. Journal of the American College of Cardiology, 2011, 57(1): 86-92.

[43]. Kanegaye J T, Wilder M S, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome[J]. Pediatrics, 2009, 123(5): e783-e789.

[44]. Furusho K, Nakano H, Shinomiya K, et al. High-dose intravenous gammaglobulin for Kawasaki disease[J]. The Lancet, 1984, 324(8411): 1055-1058.

[45]. Newburger J W, Takahashi M, Beiser A S, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome[J]. New England Journal of Medicine, 1991, 324(23): 1633-1639.

[46]. Hsieh K S, Weng K P, Lin C C, et al. Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited[J]. Pediatrics, 2004, 114(6): e689-e693.

[47]. Kuo H C, Yang K D, Chang W C, et al. Kawasaki disease: an update on diagnosis and treatment[J]. Pediatrics & Neonatology, 2012, 53(1): 4-11.

[48]. Burns J C, Song Y, Bujold M, et al. Immune-monitoring in K awasaki disease patients treated with infliximab and intravenous immunoglobulin[J]. Clinical & Experimental Immunology, 2013, 174(3): 337-344.

[49]. Franco A, Touma R, Song Y, et al. Specificity of regulatory T cells that modulate vascular inflammation[J]. Autoimmunity, 2014, 47(2): 95-104.

[50]. Burns J C, Touma R, Song Y, et al. Fine specificities of natural regulatory T cells after IVIG therapy in patients with Kawasaki disease[J]. Autoimmunity, 2015, 48(3): 181-188.

[51]. Hwang J Y, Lee K Y, Rhim J W, et al. Assessment of intravenous immunoglobulin non-responders in Kawasaki disease[J]. Archives of disease in childhood, 2011, 96(11): 1088-1090.

[52]. Phuong L K, Curtis N, Gowdie P, et al. Treatment Options for Resistant Kawasaki Disease[J]. Pediatric Drugs, 2018: 1-22.

[53]. Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial[J]. The Lancet, 2012, 379(9826): 1613-1620.

[54]. Tremoulet A H, Jain S, Jaggi P, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial[J]. The Lancet, 2014, 383(9930): 1731-1738.

[55]. Singh S, Newburger J W, Kuijpers T, et al. Management of Kawasaki disease in resource-limited settings[J]. The Pediatric infectious disease journal, 2015, 34(1): 94-96.

[56]. Wallace C A, French J W, Kahn S J, et al. Initial intravenous gammaglobulin treatment failure in Kawasaki disease[J]. Pediatrics, 2000, 105(6): e78-e78.

[57]. Fukazawa R, Ogawa S. Long-term prognosis of patients with Kawasaki disease: at risk for future atherosclerosis?[J]. Journal of Nippon Medical School, 2009, 76(3): 124-133.

[58]. Pinna G S, Kafetzis D A, Tselkas O I, et al. Kawasaki disease: an overview[J]. Current opinion in infectious diseases, 2008, 21(3): 263-270.

[59]. Ogawa S, Akagi T, Baba K, et al. Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease (JCS 2008): Digest Version[J]. Circulation journal: official journal of the Japanese Circulation Society, 2010, 74(9): 1989-2020.

[60]. Brogan P A, Bose A, Burgner D, et al. Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research[J]. Archives of disease in childhood, 2002, 86(4): 286-290.

[61]. Ogawa S, Akagi T, Baba K, et al. Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease (JCS 2008): Digest Version[J]. Circulation journal: official journal of the Japanese Circulation Society, 2010, 74(9): 1989-2020.

[62]. Jamieson N, Singh-Grewal D. Kawasaki disease: a clinician's update[J]. International journal of pediatrics, 2013, 2013.

[63]. Dajani A S, Taubert K A, Gerber M A, et al. Diagnosis and therapy of Kawasaki disease in children[J]. Circulation, 1993, 87(5): 1776-1780.

[64]. Kato H, Akagi T, Sugimura T, et al. Kawasaki disease[J]. Coronary Artery Disease, 1995, 6(3): 194-206.

[65]. Hsieh K S, Weng K P, Lin C C, et al. Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited[J]. Pediatrics, 2004, 114(6): e689-e693.

[66]. Jiao F, Yan X, Wu X. The Xi'an Experience of Kawasaki Disease–Lessons Learnt over 5 years[J]. The Indian Journal of Pediatrics, 2016, 83(10): 1195-1196.

[67]. Oates-Whitehead R M, Baumer J H, Haines L, et al. Intravenous im-

munoglobulin for the treatment of Kawasaki disease in children[J]. 2003.

[68]. Tobayama H, Takahashi K, Fukunaga H, et al. Analysis of arterial function in adults with a history of Kawasaki disease[J]. Journal of cardiology, 2013, 61(5): 330-335.

[69]. Jiao F, Jindal A K, Pandiarajan V, et al. The emergence of Kawasaki disease in India and China[J]. Global cardiology science & practice, 2017, 2017(3).

[70]. Singh S, Sharma A, Jiao F. Kawasaki disease: issues in diagnosis and treatment-a developing country perspective[J]. The Indian Journal of Pediatrics, 2016, 83(2): 140-145.

[71]. Jiao F, Zhilong Mu, Kaisheng Xie.Be alert to cardiovascular sequela caused by Kawasaki disease.Health News(7) 2021.03.17.

INFORMATION

PROGRESS IN DISTINGUISHING KAWASAKI DISEASE FROM OTHER MULTI-SYSTEM INFLAMMATORY SYNDROMES BY ARTIFICIAL INTELLIGENCE

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ABSTRACT:

Purpose: To explore the role of artificial intelligence in distinguishing Kawasaki disease from other multi-system inflammatory syndromes.

Method : Retrieve relevant articles at home and abroad and apply artificial intelligence for comprehensive analysis.

Result: The clinical application of artificial intelligence has played a time-saving and labor-saving role in the differentiation of Kawasaki disease and other multi-system inflammatory syndromes, suggesting that the application of big data in clinical practice can bring new development opportunities for medical treatment.

Conclusion: Kawasaki disease and other multi-system inflammatory syndromes are similar and overlapping in clinical practice, which is difficult to distinguish and easy to misdiagnose and miss diagnosis. Artificial intelligence is applied to analyze the above disease data, so as to achieve the effect of accurate differentiation, timely diagnosis, symptomatic treatment and reduction of complications.

Key words: Artificial intelligence; Kawasaki disease; Inflammatory syndrome.

1. BACKGROUND

Since December 2019, when the first case of the novel coronavirus (COVID-19) was first reported in Wuhan, China.[1] Later, large outbreaks spread globally, and a new syndrome, multisystemic inflammatory syndrome (MIS), with fever and cytokine release after infection with SARS-COV-2, was initially considered to be an atypical form of Kawasaki disease (KD), as most of its clinical symptoms are similar to Kawasaki disease and may also lead to cardiac complications. The difference is that left ventricular insufficiency and cardiovascular shock, coagulopathy and gastrointestinal involvement are more serious in

this novel syndrome than in Kawasaki disease. MIS can be seen in both adults and children. Here we will only describe the symptoms that occur in children, which we call pediatric multisystem inflammatory syndrome (MIS-C). Kawasaki disease (KD), previously known as cutaneous mucosal lymph node syndrome, was first reported by TamisakuKawasaki Kawasaki in 1974. The disease is a systemic inflammatory disease with medium sized vasculitis and is mainly seen in children under 5 years of age.[2] Artificial intelligence (AI) is a technology that integrates advanced brain cognition, big data, cloud computing and machine learning based on modern medical and biomedical theories.Corresponding studies have shown that the multi-system inflammatory syndrome associated with the SARS-CoV-2 pandemic partially overlaps with Kawasaki disease (KD).[3] Various studies have described and compared cellular changes in patients with MIS-C and Kawasaki disease, and it is now found that leukopenia and lymphocytopenia are more severe in MIS-C. Various studies have described and compared cellular changes in patients with MIS-C and Kawasaki disease, and it is now found that leukopenia and lymphocytopenia are more severe in MIS-C. In patients with MIS-C tested by deep immunoassay, a significant reduction of lymphocytes was found in a short period of time, while T cell involvement was more pronounced. Diagnostic biomarkers identified by immune cell profiles of Kawasaki disease and MIS-C may be helpful for early differentiation and diagnosis of these two diseases.[4] With our current knowledge reserve and medical level, KD and MIS-C cannot be judged quickly and accurately, which may make patients in emergency environment or emergency department unable to receive timely and effective symptomatic treatment. We boldly hypothesized whether some modern technologies, such as artificial intelligence, could be used to distinguish these two diseases quickly and effectively. Therefore, the author searched and read the literature on this aspect and found that there were very few literatures on the use of artificial intelligence to distinguish and study KD and MIS-C. The study is prospective, and it's worth debating whether using AI to distinguish between diseases can be accurate.It will be a cause for celebration for pediatricians if the research proves to be feasible enough to be applied to the clinic.

2. CONTENT

In the "Research on Knowledge Map Construction of Kawasaki Disease" published on September 10, 2018 by Huang Zhisheng et al., the etiology of Kawasaki disease is still not clear, and no specific biological marker can be found to diagnose the disease even after many scholars have done a lot of research. Therefore, it is prospectively proposed that knowledge graph can be an important method in the application of artificial intelligence.The establishment of this map requires the collection of various knowledge resources related to Kawasaki disease, including clinical guidelines, experimental data, drug knowledge base, medical literature, adverse drug reaction knowledge base, etc.[5] The research is advanced in that it uses the knowledge map to unify all resources on Kawasaki disease, saving clinicians a lot of time, but the project requires a lot of manpower and effort in the early stages of operation. We boldly imagined whether MIS-C could be accurately distinguished from Kawasaki disease by incorporating relevant data about it through artificial intelligence technology and comparing it with Kawasaki disease. However, this method only used clinical characteristics to distinguish the two diseases, but only stayed on the surface of the disease without further exploration. "AI-guided discovery of the invariant host response to viral pandemics, " published on June 11, 2021, fills an earlier gap, The first attempt to define host immune response using artificial intelligence is presented. The authors analyzed transcriptome data sets from more than 45, 000 pandemic viruses, using ACE2 as a "seed" gene to extract 166 genetic markers into host cell receptors. The authors found 166 genetic signatures to be surprisingly conserved across all viral pandemics, including COVID-19, with a subset of 20 genes categorizing disease severity, inspiring the naming of ViP and sViP signatures, respectively.[6] In addition, the precise nature of cytokine storms was defined, the IL15 cytokine and its receptor, IL15RA, were identified as invariant components, and a subset of 20 genes with "severe" ViP characteristics, indicating stress-induced aging, transcriptional inhibition, DNA damage, and apoptosis, were also shared among various viral pandemics. The authors and colleagues tested their theory by using BooleanNet algorithm using Boolean equivalent correlation cluster (BECC).[6] The results of this algorithm can play a guiding role in this pandemic.However, each study has its advantages and disadvantages. This algorithm may lead to over-fitting of some data due to traditional analysis, and may lack of repeatability when applied to other data sets. Published May 16, 2022 in Nature Communication as "An artificial intelligence-guided signature reveals the shared host immunein response in MIS-C and Kawasaki disease, an AI-guided approach was proposed to reveal the shared host immune response in Kawasaki disease and multi-system inflammatory syndrome in children.In the context of SARS-CoV-2 infection, the authors developed a computational tool for two genetic signatures to compare the two syndromes, namely ViP and sViP. In addition, there are 13 transcript features that have previously been used to demonstrate the diagnosis of Kawasaki disease.Experiments have demonstrated that KD and MIS-C are in the same continuum of host immune response as COVID-19.Both pediatric syndromes have cytokine storms centered on IL15/IL15RA, suggesting the same proximal pathway of immune pathogenesis.However, there were still differences between ViP and sViP in other laboratory parameters and cardiac phenotypes. In order to further understand the disease analysis, the author et al through the collection of data for comparison, the characteristics of VIP and SVIP induction observation, found that □ gender has no effect on it □ can not predict the treatment response to IVIG □ in the differentiation of responders and non-responders as good performance but the degree of ViP induction characteristics of responders is lower than that of non-responders.Finally, it was proved that the ability of 20 gene sVIP was superior to 166 gene VIP [7]. Notably, the data collected did not seem to mention differences in age, race, region, or history of other diseases prior to or at the time of illness.As for age, the answer is

given in the study of TongT et al. MIS-C is more common in older children and adolescents.[8] Three conclusions were obtained: (1) The host immune response detected qualitatively by ViP features was similar in KD and MIS-C, and shared an IL15/IL15RA component; The degree of the host immune response measured quantitatively by ViP characteristic score was stronger in MIS-C than KD.(3) KD and MIS-C induced KD-13 characteristics to similar degrees in two independent cohorts, further supporting the observation of ViP/sViP characteristics that KD and MIS-C share basic aspects of host immune response with each other.Liu Jiayi and other scholars have detailed and interpreted this document from five aspects, making it easier for readers to understand its content [9]. Pediatric multi-system inflammatory syndrome (MIS-C) and Kawasaki disease are both highly inflammatory diseases associated with infectious diseases. PaulTsoukas et al. conducted a further exploration based on the study of Ghosh et al. to further understand whether they are different syndromes or exist in the continuum [10]. Postinfective severe inflammatory syndromes were stratified into subgroups based on the clinical phenotypes identified next to them in a manner independent of infection triggers.It is concluded that these two syndromes have a common host immune response, suggesting a single spectrum of disease. "A machine-learning algorithm for diagnosis of multisystem inflammatory syndrome in children and Children, " published on October 4, 2022Kawasaki disease in the USA: a retrospective model development and validation study "in which the authors attempt to distinguish KD, MIS-C, and other similar febrile diseases by developing and verifying an AI computational approach. In this literature, the authors et al. developed a deep learning algorithm named KIDMATCH (Kawasaki Disease and Pediatric Multisystem Inflammatory Syndrome) using a retrospective model development and validation study.The algorithm was tested through phase 1 and 2 of internal validation on 1, 517 patients with MIS-C, Kawasaki disease, and other febrile diseases; A further 175 MIS-C patients (from different hospitals) were added for external verification.The results showed that MIS-C patients had higher band counts, lower sodium concentrations, lower platelet counts, higher C-reactive protein, and older age than patients in the other febrile and Kawasaki disease cohorts in the data comparison between the two groups [11].It is worth considering that this deep learning algorithm is only an initial evaluation. If MIS-C advances to the middle and late stages, whether this learning algorithm can still evaluate and classify MIS-C and Kawasaki disease or other febrile diseases.In addition, the number of children involved in the study was not large enough and the study area was not broad enough to see whether there would be a difference. In addition, in sensitivity analysis, Kawasaki disease patients with coronary aneurysm and MIS-C patients with decreased left ventricular ejection fraction were tested as characteristic patient subgroups, and the final models were correctly assigned. Raw eigenvalues were extracted from a random sample of the internal validation of the final model and compared with two experienced pediatric infectious disease clinicians with Kawasaki disease expertise to assign diagnoses based on characteristics.The results showed that the algorithm outperformed the two clinicians. This paper presents a novel approach -- a machine learning model -- for screening patients with MIS-C, Kawasaki disease, or similar febrile diseases. This is the first known application of artificial intelligence to help diagnose MIS-C and distinguish it from Kawasaki disease and other febrile diseases.The advantage of this computing is that the required functionality is universally available in most health care settings.

Several studies have used clinical and laboratory methods to distinguish MIS-C from Kawasaki disease. TongT et al., through a meta-analysis of clinical features, concluded that respiratory and gastrointestinal symptoms of MIS-C were more common than Kawasaki disease [8], [12] possibly due to increased viral load in gastrointestinal tissues. Studies have shown that MIS-C may be a post-infection sequela of COVIN-19, while coronavirus is a non-staged plus strand RNA virus, which can be indicated positive by swabs and stool examination in children.[13] Another study on patients with MIS-C found that gastrointestinal tract involvement was the second most frequently involved organ system after cardiovascular system [14] [15]. A meta-analysis of laboratory features compared to clinical features suggested that MIS-C patients had lower lymphocyte counts, ALT, and ESR levels, higher D-dimer and fibrinogen levels, and higher ferritin levels.Platelet levels in MIS-C were higher than those in Kawasaki disease, but there was no significant difference in neutrophil levels between the two.Analysis of a group of circulating cells may help in early diagnosis and differentiation between the two diseases. These characteristics were also confirmed in the study of AnuradhaRajamanickam et al. [16].But similarity is its own challenge in the clinic and in the laboratory. AngelaChun et al. used AI to distinguish MIS-C from typhoid fever in endemic areas. They established an equation to calculate the "MET" score based on demographic, clinical and laboratory characteristics. The final experimental results showed that only 10 characteristics were enough to distinguish typhoid fever.[17] In addition, both MIS-C and Kawasaki disease can cause cardiac involvement in patients. Laboratory data from MIS-C show elevated CRP, erythrocyte sedimentation rate, and D dimer, but no arteriovenous thrombosis.Whether there is any literature that can support this conclusion, the author has not found. Nowadays, there are many methods to distinguish MIS-C from Kawasaki disease at home and abroad, but most of them are based on the clinical characteristics and laboratory test results of the disease.There are few studies on the shared immune response of MIS-C and KD by artificial intelligence. After reading and thinking about relevant literature, the problem that has been solved so far is that we can temporarily distinguish Kawasaki disease, MIS-C and other febrile diseases by some technologies, but whether this technology is mature enough and when it can be applied in clinic remains to be investigated. In addition, for the pathogenesis of Kawasaki disease and MIS-C, as well as the targeted and effective treatment of MIS-C, we are still unable to accurately answer the question, which requires further in-depth research and a large number of data support. Can we

use AI's technique of distinguishing MIS-C from typhoid to distinguish Kawasaki disease from other multi-system inflammatory syndromes? With the development of science and technology and the gradual application of artificial intelligence in clinical practice, the application of artificial intelligence in disease research and treatment will become a more and more hot topic.The research has obvious feasibility.However, the disadvantage is that the preliminary study may have a long time, which requires a lot of effort, data and experiments to support the research.

3. SUMMARY

In conclusion, Kawasaki disease (KD) and pediatric multisystem inflammatory syndrome (MIS-C) are both autoimmune hyperinflammatory diseases involving multiple organ systems. It is still a difficult and important task to distinguish these diseases by immunophenotype through the method of artificial intelligence.Artificial intelligence algorithm is used to diagnose and discriminate diseases based on patient age, clinical manifestations and laboratory measurements. It can distinguish MIS-C, Kawasaki disease and other similar febrile diseases and effectively guide the diagnosis and treatment of these diseases. Through the research and analysis of these diseases by artificial intelligence, Further exploration of the pathogenesis and sequelae of Kawasaki disease (KD) and pediatric multi-system inflammatory syndrome (MIS-C) may be of great significance to reduce the occurrence of disease complications, reduce the mortality of children and improve the quality of life of children, which is worth further promotion and research in clinical practice.

REFERENCES:

[1] Zhiguan Feng, Yanmin Bao, Yonghong Yang, Yuejie Zheng, Kunling Shen.Severe acute respiratory syndrome coronavirus 2-induced multisystem inflammatory syndrome in children[J].

[2] Feldstein L.R., Tenforde M.W., Friedman K.G., et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA. 2021; 325(11):1074–1087.

[3] Esteve-Sole A, Anton J, Pino-Ramirez RM, Sanchez-Manubens J, Fumadó V, Fortuny C, Rios-Barnes M, Sanchez-de-Toledo J, Girona-Alarcón M, Mosquera JM, Ricart S, Launes C, de Sevilla MF, Jou C, Muñoz-Almagro C, González-Roca E, Vergara A, Carrillo J, Juan M, Cuadras D, Noguera-Julian A, Jordan I, Alsina L. Similarities and differences between the immunopathogenesis of COVID-19-related pediatric multisystem inflammatory syndrome and Kawasaki disease. J Clin Invest. 2021 Mar 15; 131(6):-e144554.

[4] Castaldo A, D'Anna C, Gelzo M, Giannattasio A, Maglione M, Muzzica S, Raia M, Scalia G, Tripodi L, Castaldo G, Tipo V, Grieco D, Grieco M. Immunophenotyping of peripheral blood cells allows to discriminate MIS-C and Kawasaki disease. Transl Med Commun. 2022; 7(1):22.

[5] Huang Zhisheng, Miao Chong, Hu Qing, Liao Mingqun, Liu Guanghua.Research on knowledge map construction of Kawasaki disease [J]. China Digital Medicine, 2018, 13(9):28-31

[6] Sahoo D, Katkar GD, Khandelwal S, Behroozikhah M, Claire A, et al. AI-guided discovery of the invariant host response to viral pandemics. EBioMedicine. 2021 Jun; 68:103390.

[7] Ghosh Pradipta, Katkar Gajanan D, Shimizu Chisato, Kim Jihoon, Khandelwal Soni, Tremoulet Adriana H, Kanegaye John T. An Artificial Intelligence-guided signature reveals the shared host immune response in MIS-C and Kawasaki disease.[J]. Nature communications, 2022, 13(1).

[8] Tong T, Yao X, Lin Z, Tao Y, Xu J, Xu X, Fang Z, Geng Z, Fu S, Wang W, Xie C, Zhang Y, Wang Y, Gong F. Similarities and differences between MIS-C and KD: a systematic review and meta-analysis. Pediatr Rheumatol Online J. 2022 Dec 5; 20(1):112.

[9] Liu Jiayi, Yang Zhaoyu, Wang Jiemin, Jiao Fuyong.Study on the cohost immune Response of children with multisystem inflammatory syndrome and Kawasaki disease by artificial Intelligence-guided signaling [J].Chinese Journal of Pediatrics, 2002, 24(12):1318-1320.

[10] Tsoukas P, Yeung RSM. Kawasaki disease and MIS-C share a host immune response. Nat Rev Rheumatol. 2022 Oct; 18(10):555-556. doi: 10.1038/s41584-022-00820-5. PMID: 36008614; PMCID: PMC9406247.

[11] Lam Jonathan Y, Shimizu Chisato, Tremoulet Adriana H, Bainto Emelia, Roberts Samantha C, Sivilay Nipha, Gardiner Michael A, Kanegaye John T, Hogan Alexander H, Salazar Juan C, Mohandas Sindhu, Szmuszkovicz Jacqueline R, Mahanta Simran, Dionne Audrey, Newburger Jane W, Ansusinha Emily, DeBiasi Roberta L, Hao Shiying, Ling Xuefeng B, Cohen Harvey J, Nemati Shamim, Burns Jane C. A machine-learning algorithm for diagnosis of multisystem inflammatory syndrome in children and Kawasaki disease in the USA: a retrospective model development and validation study[J]. The Lancet Digital Health, 2022, 4(10).

[12] Chang L, Yang HW, Lin TY, Yang KD. Perspective of Immunopathogenesis and Immunotherapies for Kawasaki Disease. Front Pediatr. 2021 Jul 19; 9:697632.

[13] Jiao F.Y. Kawasaki disease: a new manifestation of COVID-19 in children [J].Chinese Journal of Pediatrics, 20, 22(07):677-678.

[14] Lee MS, Liu YC, Tsai CC, Hsu JH, Wu JR. Similarities and Differences Between

COVID-19-Related Multisystem Inflammatory Syndrome in Children and Kawasaki

Disease. Front Pediatr. 2021 Jun 18; 9:640118.

[15] Wessels PA, Bingler MA. A comparison of Kawasaki Disease and multisystem inflammatory syndrome in children. Prog Pediatr Cardiol. 2022 Jun; 65:101516.

[16] Rajamanickam A, Nathella PK, Venkataraman A, Varadarjan P, Kannan S, Pandiarajan AN, Renji RM, Elavarasan E, Thimmaiah A, Sasidaran K, Krishnamoorthy N, Natarajan S, Ramaswamy G, Sundaram B, Putlibai S, Hissar S, Selladurai E, Uma Devi KR, Nutman TB, Babu S. Unique cellular immune signatures of multisystem inflammatory syndrome in children. PLoS Pathog. 2022 Nov 2; 18(11):e1010915.

[17] Angela Chun, MD1; Abraham Bautista, MS2; Chad Weatherly, BS et al. Distinguishing Multisystem Inflammatory Syndrome in Children from Typhus Using Artificial Intelligence PLoS Pathog. 2022 October 21,


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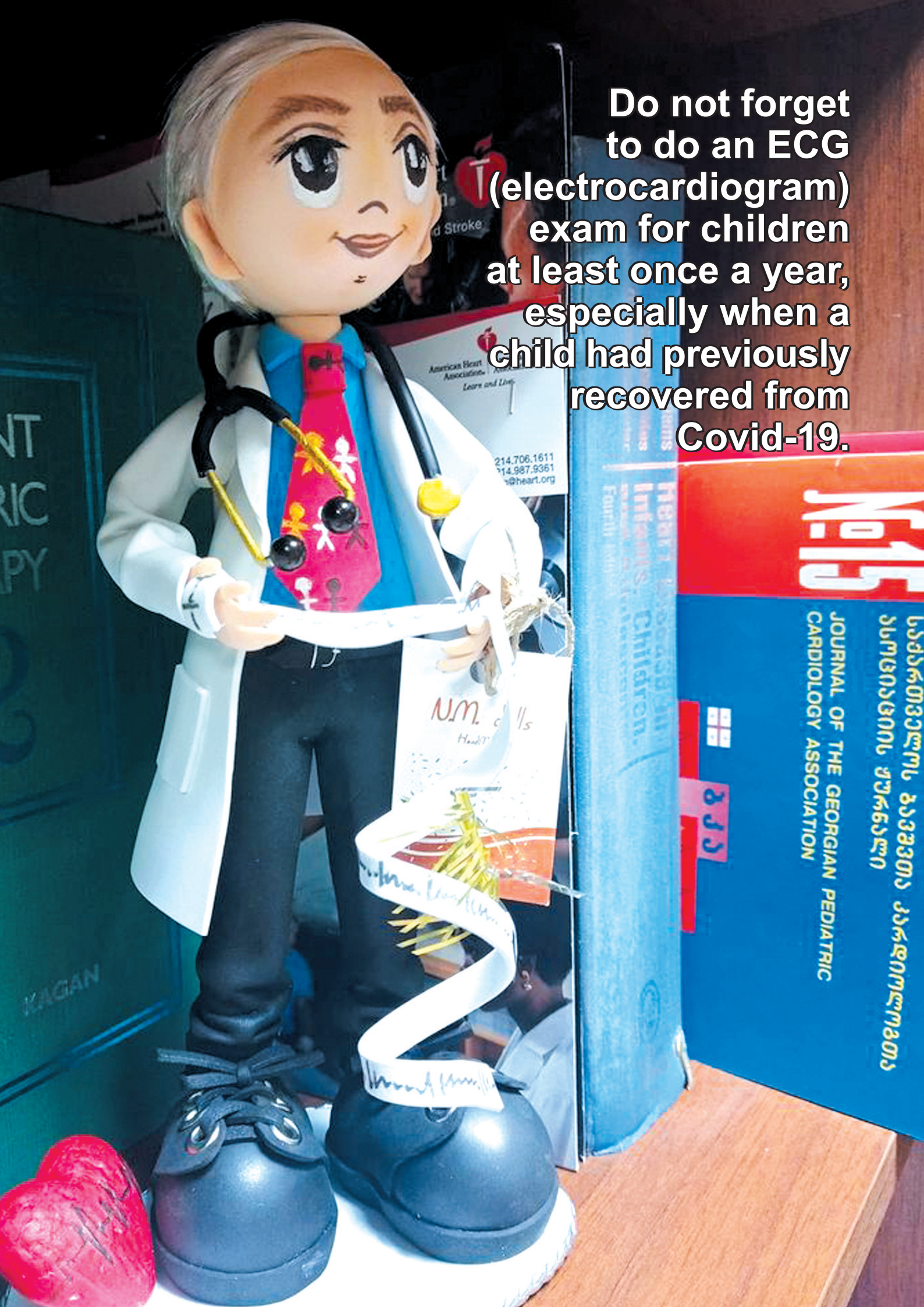
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