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

THE SOCIAL PEDIATRIC PROTECTION FUND

Date of Foundation: 30.09.1998
Date and Number Of Registration: #147 9.10. 1998w
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George Chakhunashvili Job of Contact: Chairman of The Board Branches of Fund:
Mtskheta; Kutaisi; Gori.; Abasha.; Batumi.; Sagarejo; Gurjaani; Telavi; Tchiatura; Zugdidi; Territory of Operation:

Georgia (eu) Aim Social Pediatric Protection Fund is to execute programs of social pediatric development and maintain rights and healthcare of Children, Mothers and Adolescents. Fund has great organizational experience, technical equipment and skilled members.

Most of the members are Professors at TSMU, who have clinical and educational experience of 15-20 years and were one of the first, Before the independence, to read lectures about congenital infections, sexually transmitted diseases and prevention of HIV. Fund is also cooperating with physicians, psychologists, Lawyer (who operate in field of social assistance) and Public figures. By the joint forces of all the people above said SPPF is able to hold free medical examinations, juridicial consultations, charity events, informational lectures about healthy way of life, congenital infection, HIV, Social subjects and etc.

Since 1997 more than 93.000 Children and Hundreds of older people have been medically for free in the framework of charity events. Before Independence, The active members of SPPF and their consortium in 1980-1990 examined above 124 000 Children, all over Georgia.

Editor-in-Chief
FUYONG JIAO
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(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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E-mail: 3105089948@qq.com

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.

THE SOCIAL PEDIATRIC PROTECTION FUND

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

№2-4

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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 PEDIATRICS

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ADVANCED ARTICLE

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"THE SOCIAL PEDIATRIC PROTECTION FUND" IS 25 YEARS OLD

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Contact: Prof. George Chakhunashvili
Job of Contact: Chairman of The Board
Branches of Fund: Mtskheta; Kutaisi; Gori.; Abasha.; Batumi.; Sagarejo; Gurjaani; Telavi; Tchiatura; Zugdidi; Territory of Operation: Georgia (eu)

The Foundation for the Protection of Social Pediatrics is 25 years old. During these years, the organization has made an impeccable contribution to the actual implementation of population health prevention, treatment and social assistance. (see completed and ongoing projects).

Aim Social Pediatric Protection Fund is to execute programs of social pediatric development and maintain rights and healthcare of Children, Mothers and Adolescents. Fund has great organizational experience, technical equipment and skilled members. Most of the members are Professors at TSMU, who have clinical and educational experience of 15-20 years and were one of the first, Before the independence, to read lectures about congenital infections, sexually transmitted diseases and prevention of HIV. Fund is also cooperating with physicians, psychologists, Lawyer (who operate in field of social assistance) and Public figures. By the joint forces of all the people above said SPPF is able to hold free medical examinations, juridicial consultations, charity events, informational lectures about healthy way of life, congenital infection, HIV, Social subjects and etc.

Since 1997 more than 93.000 Children and Hundreds of older people have been medically for free in the framework of charity events.

Before Independence, The active members of SPPF and their consortium in 1980-1990 examined above 124 000 Children, all over Georgia.

ACTIVITIES

From 1992 to 1998 was periodically holding humanitarian examinations. From 1998 with the help of Social Pediatrics Protection Fund started charity activities, in which Georgian pediatrists were participating. Activities included: Instrumental and laboratory research of patients in different regions of Georgia, Medical gifts, several funded emergency operations.

07.01.98 – 07.02.99 Tbilisi, - over 9200 children were examined.

23-24.01.99 East Georgia, - over 3500 children were examined.

12-13-14.02.99 Tbilisi, - over 100 children were examined and gifted medicines. Free consultations by professors were held by Mother and Child Diagnostic Centre and other hospitals once a week, consultations in leading pediatric clinics of the city once in a month. In these activities were also participating: 1. Institute of skin and vein 2.Scientific Institute of Parasitology and others.

12-13-14.03.99 expedition in Poti and Abasha (Qedisi, Marani and other), - 950 children were examined and gifted medicines.

29-30. 01-07.08.99 – 4400 children were examined and gifted medicines.

23-24-25.08.99 Khobi and Zugdidi, - Free instrumental and laboratory examinations were funded. Also medicines against louse and itch were given.

04.04.99 - Expedition in Pasanauri – over 400 children were examined.

07.05.99 – Expedition in Lanchkhuti – Free instrumental and laboratory examinations were held and medicines were gifted.

18.05.99 Rustavi, - 250 children were examined and gifted medicines.

22.06.99 Sagarejo, - 250 children were examined and gifted medicines.

13-14.08.99 Chokhatauri, - over 1500 children were examined.

15.08.99 Bakhmaro, - over 2000 children were examined.

16.08.99 Adjara high-mountain regions, - over 750 children were examined.

17.08.99 Tbilisi, – Examinations in Homeless children house.

16.10.99 Dusheti region, - over 200 children were examined and gifted medicines.

2000.

26.02.2000 Gori, - over 500 children were examined. Different medicines were given out.

23.03.2000 Axalgori, - 30 children were examined.

01.04.2000 Marneuli region (Werakvi), - General blood analysis, instrumental examinations – echoscopy, encephalography were done. Over 1500 children were examined.

15.04.2000 Gurjaani, - 1200 children were examined, medicines were given out.

29.04.2000 Rustavi, - 300 children were examined.

05.06.2000 – Children from Avchala colony were examined.

20-28.07.2000 – Children in Tskhneti Orphanage were examined.

21-22-23.07.2000 – Examinations in Abasha and Samtredia region.

7-8.08. 2000, Bakhmaro-Beshumi – 1925 children were examined.

2001.

15.03.2001. Children of employees of Rustavi Nitrogen Factory were examined.

23.06.2001. Children of employees of Rustavi Nitrogen Factory were examined.

14-15-16.09.2001 Baghdati region (Sairme, Witelkhevi, Rokhi, Ochba, Xani, Zegani, Saqraula) – over 2500 children were examined.

2002.

10.03.2002 Axalgori, - 250 children were examined.

20-04.2002 Sighnaghi, - 450 children examined.

23-24-25-26.05.2002 Khulo, - 600 children and 100 adults were examined with the help of Patriarchy.

27-28-29.06.2002 Tbilisi, - 400 children were examined in different Hospitals.

16-17-18-19.07.2002 KodorisKheoba, - 250 children were treated.

3-4-5-6.08.2000 Tusheti (Dikolo, Omalo, Shenaqo) – 200 children were treated.

2003.

05.03.2003 Samtskhe-Javakheti, - 1250 children were examined.

17.04.2003 Werovani, - 450 children were examined.

20.05.2003 Borjomi, - 870 children were examined.

25.06.2003 Mta-Tusheti, - 320 children were examined.

30.07.2003 Bakhmaro, - 630 children were examined.

20.08.2003 Zestaponi, - 210 children were examined.

07.09.2003 Racha, - 170 children were examined.

18.102003 Dmanisi, - 180 children were examined.

2004.

March, April, May – Kaspi, Gurjaani, Telavi, Akhmeta, Lagodekhi, Sighnaghi, Bodbe, Aspindza, Axaltsikhe, Borjomi, Tbilisi, Zestaponi, Kharagauli, Chiatura – over 1728 children were examined. In different regions (Zugdidi, Khulo, Khelvacharui, Qeda, Lanchkhuti, OzurgetiIngiri), SPPF held charity activities with the help of Patriarchy – over 2400 children were examined and medicines were given out.

2005.

Marneuli region – 700 children and 80 adults were examined.

18th of July, Kaspi – 450 children were examined.

8th of October, Mtskheta – 300 children were examined.

14-15-16th of October, Lentekhi – 850 children and 250 adults were examined.

2006.

18th of February –20 Painter Union families were examined.

March – over 100 refugee children were examined.

April – Charity activities were held by ambassadors in Guria.

31th of May – 450 children were examined in Rustavi.

1-2th of June - Open door day in TSMU, 400 children were examined. They were held free consultations and laboratory examinations.

9-10th of June, Kaspi - 300 children were examined.

1th of July, Ckhinvali region – 500 children of war participants were examined. In September-October – 120 children.

In November – over 200 of Journalist's families were examined.

2007.

Marneuli – Free consultations for 100 children. Childrens with Scoliosis were shown. They got espander gifts and were recommended how to treat scoliosis.

Dusheti – 250 children were examined.

Akhalsheni–85 children were held consultations.

9-10th of June, Kaspi – 300 children were examined.

1th of July, Ckhinvali region – 500 children of war participants were examined. In September-October – 120 children.

In November – over 200 of Journalist's families were examined.

2008.

1st of June – Open door day (200 children were examined).

2nd of June – Teddy bear (300 children examined).

14th of June, Akhmeta (QaQucoba) - 450 children were examined and gifted medicines. Also examinations like echoscopy of abdominal cavity and ECG were held.

27th of June – restoration of Georgian Section.

20th of August - STOP RUSSIA (meeting at Igoeti)

1st of September, Tbilisi – STOP RUSSIA (meeting of chain)

4th of October – free consultations and examinations. Painters and artists master classes were held.

6th of December – 110 children were examined in Bergman Clinics with echoscopy of abdominal cavity, ECG and other.

2009.

13.06.2009, Khashuri – 750 children were examined.

26.12.2009, Barisakho – 80 children were examined.

2010.

4th of July – Open door day for family members of war victims (50 children were examined).

10th of July, Karaleti – 200 children were examined and medicines were given out.

4th of November – St. King Tamar orphanage children were examined.

3-4th of December,Tbilisi– 400 sportsmen children were examined.

2011.

1st of June,Tbilisi – 200 children were examined.

24th of December,Tbilisi – 200 children were examined.

2012.

1st of June,Tbilisi – 350 children were examined.

22th of December,Tbilisi – 250 children were examined.

Since 1997 more than 93.000 Children and Hundreds of older people have been medically for free in the framework of charity events.

2013.

1-4.06.2013. Tbilisi, Batumi, Gori, Telavi – 1250 children were examined.

17-21.12.2013. Tbilisi – 350 children were examined.

2014.

1st of June ,Tbilisi – 150 children were examined.

28th of December, Tbilisi – 50 children were examined.

2015.

1st of June, Tbilisi – 350 children were examined.

11.12.2015. Chkorotscu – 1300 children were examined.

2016.

3035 children were examined.

2017.

1305 children were examined.

2018.

200 children were examined.

2019.

250 children were examined.

2020.

95 children were examined.

2021.

55 children were examined.

2022.

250 children were examined.

Since 1997-2012 more than 93.000 Children and Hundreds of older people have been medically for free in the framework of charity events.

Before Independence, The active members of SPPF and their consortium in 1980-1990 examined above 124 000 Children, all over Georgia.

Till today over 228 550 children were examined and thousands of old people. Charity activities continue.

SIMPOSIUMS AND CONFERENCES HELD BY THE SOCIAL PEDIATRIC PROTECTION FUND:

1992. First pediatric cardiology conference – "believe the reality of better future".

01.06.1999. II conference – "Healthy child & peaceful Caucasus".

25.12.1999. III conference – "Today's economic directions in pediatric and its perspective". XXI century Pediatrics should be the start of invalid prophylaxis.

01.06.2000. IV conference – "Child must have right to be protected since embryo".

27.03.2001. Meeting in ombudsman's office – "Under aged criminals, their rights and reality".

01.06.2001. V conference dedicated to Children Protection National Day.

32.03.1999. 01.06.2000. 01.06.2001 "Child treatment in XXI century"

23.04.1999. 01.06.2000 "Child treatment in XXI century" "Orthopedic school"

17.12.1999. Mucoviszidose treatment and diagnostics.

01.06.2000. Young Pediatrists XVII conference.

28.02.2001. Urgent questions of Therapy of respiratory diseases in pediatrics.

01.06.2001. "Child has right to be protected since embryo".

01.06.2001. "Child, adult and family violence".

13.02.2002. "Human genome project".

10.03.2002. Akhalgori, - Presentationof toner drink "Lomisi".

06.11.2002. National Conference: Medical and social problems of people who suffer from mucoviszidose and metabolism disorder.

07.11.2002. "Contemporary aspects of inborn diseases".

04.04.2003. "Urgent pediatric questions" (IX conference).

01.06.2003. Internet conference (X conference) – Social Pediatrics Protection Fund gave out journals and magazines called "Social Pediatrics" (In which is written about social, medical, pedagogic, psychological, religious and other urgent problems).

19.12.2003. Second Georgian Cardiology Congress.

22.10.2004. "Urgent Pediatric questions" dedicated to SPPF president, Victor Moroshkin.

01.06.2004. Second National Internet Conference.

01.06.2005. Urgent Pediatric questions.

09.09.2005. Tbilisi Marriot, - Second National Conference "Healthy child & Peaceful Caucasus".

1st of June, 2006. – SPPF conference. XXIII Congress of Young Pediatrists League.

31.05.2007. III congress of Pediatric Cardiology.

07.12.2007. SPDF XVII conference.

07.10.2008. Conference – "Section of child and adult".

20.12.2008. SPPF and ESMNS second conference.

12.06.2009. SPPF XX conference.

01.06.10. Second conference of Georgian surgeons and XXII conference of Tsalka.

03.12.2010. Conference dedicated to I. Kvachadze 85th anniversary.

01.06.2011. SPPF XXVI conference.

23-24.12.2011. SPPF XXVII conference.

01.06.2012. IV congress of Pediatric Cardiology.SPPF XXVIII conference.

21-22.12.2012. SPPF XXIX conference

1-4.06.2013. SPPF XXX conference

17-21.12.2013. SPPF XXXI conference

1-2.06.2014. SPPF XXXII conference

27-28.12.2014. SPPF XXXIII conference

1-2.06.2015. SPPF XXXIV conference

11.12.2015. SPPF XXXV conference

1.06.2016. SPPF XXXVI conference

9-10.12.2016. SPPF XXXVI conference

01.06.2017. SPPF XXXVIII conference

05.12.2017. SPPF XXXIX conference

01.06.2018. SPPF XL conference

07.12.2018. SPPF XLI conference

01.06.2019. SPPF XLII conference

14.12.2019. SPPF XLIII conference

31.05.2020. SPPF XLIV conference

20.12.2020. SPPF XLV conference

01.06.2021. SPPF XLVI conference

18.12.21. SPPF XLVII conference

01.06.2021. SPPF XLVIII conference

24.12.21. SPPF XLIX conference

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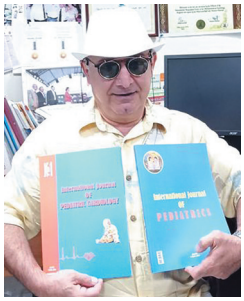
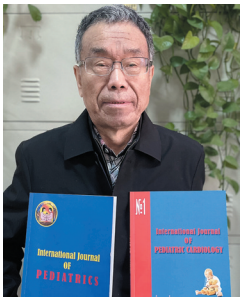


It is most important that for 25 years, the foundation has been publishing the newspaper "Social Pediatrics", the magazines "Social, Ecological and Clinical Pediatrics", "Children's Cardiology", which have played a great educational role in the life of doctors and society; and from 2021, it will be published together with Chinese colleagues. 2 English-language journals "International Jurnal of PEDIATRICS" and "International Jurnal of PEDIATRIC CARDIOLOGY".

(The above can be found at and).



It is important that they are actively read not only in Georgia, but all over the world. According to new data, their number has reached 3000, which is really appreciated.

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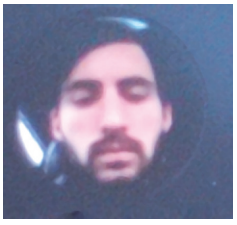
"Social Pediatrics Protection Fund" greatly supports youth in professional growth, both in scientific, as well as clinical and pedagogical directions. Their activity is always summed up in conferences, which are held twice a year - on June 1 on International Children's Day and at the end of the year in December. It is the same this year - 2023. They will contribute to the anniversary L conference of the "Social Pediatric Protection Fund". Good luck to them.

Meetings(G.K. Chakhumnashvili, D.K.CaxunaSvili) with the scientists of the Pauls Stradins Clinical University Hospital, Latvian Centre for Disease Prevention and Control, and Institute of Food Safety, Animal Health and Environment, Riga, Latvia.

2022-2023.
YOUNG GENERATION IN RESEARCH LABS AND ON INTERNATIONAL & LOCAL FORUMS

YOUNG PEDIATRICIANS ASSOCIATION - 2022-2023



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We would like to mention here that with the initiative and direct participation of the “Social Pediatrics Protection Fund”, certificates (of gratitude, praise), greetings, awards - “Golden feather”, “Golden stethoscope”, “Golden lancet” - are given to the worthy every year. „Golden magnifying glass”, “Dedicated doctor”, “Georgia’s recipe of the year”, etc. Meritorious doctors should open “Star” in their clinics.

In this way, the Georgian “Social Pediatrics Protection Fund” has been working fruitfully for 25 years. It continues to work actively and is waiting for partners who will hopefully contact us at and do a lot of good work with them.

May God bless you and wish you many years of creative work.

SUMMARY

“THE SOCIAL PEDIATRIC PROTECTION FUND” IS 25 YEARS OLD

GEORGE S.CHAKHUNASHVILI MD. PhD. DSc. Professor, Academician
(Chairman of the Social Pediatric Protection Fund-Tbilisi, Georgia.)

The Social Pediatrics Protection Fund is 25 years old. During these years, the organization has made an impeccable contribution to the actual implementation of population health prevention, treatment and social assistance..

It is most important that for 25 years, the foundation has been publishing the newspaper "Social Pediatrics", the magazines "Social, Ecological and Clinical Pediatrics", "Children's Cardiology", which have played a great educational role in the life of doctors and society; From 2021, it will be published together with Chinese colleagues,2 English-language journals "International Jurnal of PEDIATRICS" and "International Jurnal of PEDIATRIC CARDIOLOGY".

(The above can be found at www.sppf.info and www.esgns.org).

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and do a lot of good work with them.

May God bless you and wish you many years of creative work.

ORIGINAL ARTICLES AND SCIENTIFIC ACTIVITIES IN PEDIATRICS

CURRENT STATUS OF RESEARCH ON RARE DISEASES IN CHILDREN IN CHINA

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ABSTRACT

Objective: In order to understand and study the diagnosis and treatment status of rare diseases in children across the country. **Method:** The data information retrieved by keywords of rare diseases in children was sorted and analyzed through the Internet, the Internet, official data and other databases. **Result:** Rare diseases are very critical, and have high disability and mortality rates, and 70% of them occur in children, rare diseases are receiving more attention. This paper briefly describes the current status of rare diseases in China in terms of their types, diagnosis, and medication.

Keywords: rare disease, children, status.

INTRODUCTION:

The term "rare disease" is derived from the English word rare disease. In contrast to common diseases, rare diseases are those with relatively low prevalence. According to the World Health Organization (WHO), rare disease is defined as a disease that affects 0.65 to 1 per 1, 000 of the total population. Rare diseases usually affect multiple systems and organs and have a chronic, progressive, and exhaustive course, resulting in disability or life threatening effects.This study is to elaborate on the current status of rare diseases in children 2, 9, 10.

1. Types of rare diseases in China

China is a populous country, according to the latest statistics, the total population of China is 1, 411.78 million, of which 253.38 million are children, accounting for 17.95%.However, with such a large base, because rare diseases are very critical, have high disability and mortality rates, and 70% of them occur in children, rare diseasesare receiving more and more attention. At present, there are 7877 rare diseases included in the world, with data show that there are 121 types of rare diseases identified in China. The investigators investigated and analyzed the distribution of inpatients in tertiary care hospitals as a sample to explore the current status of rare diseases in China.The results showed that 19 of the known rare diseases in China were not included in the rare disease survey list of Beijing Rare Disease Society.Of these, 54, 468 were 102 rare cases, accounting for 0.35% of the hospitalized patients in the same period, the number of the top 10 rarest and least rare cases was 37977, accounting for 0.25% of the hospitalized patients in the same period. The readmission rate of these top 10 rare diseases was as high as 28.42%~64.88%. In terms of age distribution, the proportion of rare diseases among children aged 25-64 years was 45.8%, and the proportion of children aged 0-14 years was 28.6%. 28.6%. These data all reveal that rare disease incidence low number of patients and high recurrence rate1, 10. Wilson's disease (WD) is a rare autosomal recessive disease caused by mutations in the ATP7B gene mutation. The clinical features and mutational analysis of early childhood

WD in China have been rarely described. One researcher retrospectively examined 114 children with WD who were on average 5.9 years old at the time of diagnosis.Eight patients developed acute liver failure at an average age of 9.7 years. 4 of them died. Of the 114 patients, 86.0% were patients were pre-symptomatic at the time of diagnosis. The double allele pathogenic ATP7B mutation was found in all patients.Of the detected of the 60 mutations detected, 10 were novel, including 7missense mutations (p.I566N, p.T704I, p.C980F, p.G1030V, p.A1096Q, p.L1327P and p.L1327P). p.G1030V, p.A1096Q, p.L1327P andp. L1373F), one nonsense mutation (p.K866X), one minor insertion (p.Y44LfsX2) and a minor deletion (p.R1118P). (p.R1118PfsX10), which affected 114 The most frequent mutations were p.R778L, p.P992L and p.I1148T, which affected 27.2%, 25.4% and 20.2%. Patients with p.R778L had a higher incidence of acute liver failure than those without p.R778 L (9.7% vs. 4.8%). This study will help to establish early diagnosis of WD at the genetic level, provide useful information for genetic counseling, and provide clues to the genotype/phenotype correlation of ATP7B mutations2. Hemophilia is a group of bleeding disorders with inherited coagulation disorders.Hemophilia A, or a deficiency of factor VIII (also known as anti-hemophilic globulin, AHG); hemophilia B, a deficiency of factor IX (also known as plasma thromboplastin component, PTC), Hemophilia C, a deficiency of factor D (also known as plasma thromboplastin precursor, PTA). This group of diseases is not not uncommon, with an incidence of 5 to 10/100,000, with hemophilia A is more common.The common feature is a lifetime of minor injuries followed by a tendency to prolonged bleeding. There is no cure for this group of diseases treatment and the medication is expensive. There are many other rare diseases in China, such as spinal muscular atrophy, Fabray's disease, multiple sclerosis, etc. There is no specific medicine or treatment for these rare diseases, the only treatment available is symptomatic treatment to improve the quality of life.

2. Diagnosis of rare diseases

For the diagnosis of rare diseases, because of their incidence is extremely low and awareness is very limited, the high clinical misdiagnosis rate and very difficult to diagnose, which in turn to these patients are difficult to receive timely and effective treatment.And the impact of a wrong diagnosis on a child's parents the impact of an incorrect diagnosis on a parent of a child can be enormous. A study was done on the quality of life of parents caring for children with rare diseases.The results of a study on the quality of life of parents caring for children with rare diseases is severely reduced compared to parents of healthy children3, 9, 10. There are studies that prove that correct and early diagnosis of rare childhood diseases is very important, as it often has fatal consequences for young families. Even with a known disease, in many countries, the there are intolerably long delays in diagnosis. After a long time studies have found that the reason for delayed diagnosis is often not lack of expertise and other resources, but rather a lack of communication between parents, knowledgeable ineffective communication between the celebrity physician and the specialist center. It therefore proposes two promising and feasible approaches: (1)

Strengthen parents' ability to have a dialogue with their physicians, which includes a written information about the diagnostic status in layman's language as an important detail, (2) Establishing binding requirements for centers that specialize in rare and unknown diseases.Many of the observations and considerations made in the field of pediatrics considerations may also be applicable to adults4. For this phenomenon is also one of the reasons why we are desperately searching for a cure for rare diseases major reason.Recently, the International Consortium for Rare Diseases Research researchers have developed methods to enable molecular diagnosis of all rare diseases. The research provides timely molecular confirmation of rare genetic diseases in children and adults, significantly shortening their “diagnostic process”5. Meanwhile, genome sequencing (GS) and exome sequencing (ES) have also been proven to be revolutionary in the diagnosis of rare diseases in pediatrics.Its investigators reviewed genomic technologies associated with aspects of rare pediatric diseases associated with the use of genomic technologies, highlighting the benefits and limitations of ES and GS, the complexity of variant classification, and the importance of genetic counseling, the diagnostic potential of ES and GS in various pediatric multisystem diseases is discussed6. A growing number of studies have also shown that GS can be used in single laboratory workflow to detect an unparalleled of pathogenic abnormalities. Its ability to deliver five inexpensive, rapid and accurate tests to patients with different clinical indications and complex presentations7. These studies, all of which have greatly have greatly improved the diagnosis rate of rare diseases, providing a solid foundation for rapid and effective treatment of children with rare diseases worldwide.

3. Current status of drug therapy for rare diseases

For drugs for rare diseases, also known as orphan drugs.In 2018, one researcher compared orphan drugs in China by how far they have been marketed in compared with orphan drugs in international markets (e.g., the United States) to assess availability. The affordability of orphan drugs was calculated using hospital pharmacy prices and calculated under China's basic medical insurance system for analysis.As of March 16, 2016, the market share of orphan drugs approved in the U.S. reached 39.9% in China. Among them, 93 orphan drugs (54.07%) were included in the national basic medical and work injury insurance drug catalogs, 22 Class A drugs with a high reimbursement rate and 71 Class B drugs with a low reimbursement rate; 79 orphan drugs (45.93%) are not covered by medical insurance or do not have indications for rare diseases. Orphan drugs are unaffordable for the majority of the Chinese population. concluded that the Chinese government could can improve access and availability of orphan drugs through the establishment of incentive policies for orphan drug information sharing and public platforms8. On the latest reports, the China is also paying more attention to the use of drugs for rare diseases. "Hemophilia disease: per capita treatment cost 80-1 million yuan/year, with about 49, 000 patients in China;Spinal muscular atrophy: average treatment cost 700-1.4 million yuan/year, about 30-50, 000 patients in China; Fabray's disease: per capita treatment cost

1-1.29 million yuan/year per person, with about 300 patients in China; Mul-

tiple sclerosis: per capita treatment cost 100, 000-600, 000 yuan/year, about 30, 000 patients in China.These heavy numbers figures would often have brought down a family a decade ago, but now 67% of drugs for rare diseases in China are now covered by medical insurance, greatly reducing the burden of medication on patients. "Every small group should not be should be abandoned," is such a belief that the original price of 700, 000 for Nocinasan sodium injection was reduced to 33, 000 yuan.This undoubtedly shows that the country has not given up on every small group. It gives hope to those children with rare diseases and their families.

4. SUMMARY

For rare diseases, every successful discovery will provide potential diagnostic, preventive and therapeutic opportunities for thus providing precision medicine for that patient population. Therefore, contemporary society should pay attention to this small group of rare diseases, so that rare diseases are not rare and families with rare diseases can be happier.

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KALEIDOSCOPE OF INTERESTING WORKS

RULES OF INFORMATION TRANSFER, BIOMEDICINE AND BIOINFORMATICS

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"Even brilliant ideas need precise testing" My experience

SUMMARY

In this paper we are trying to discuss and unify the knowledge about biomedicine, bioinformatics, quantum information and physical approaches of information processing in connection with energy and mass of information carriers, main actors in info-dynamic process. This suggest intriguing equivalence relations for translating between biomedicine and bioinformatics for whose details we refer to connection and overlapping of computer science and physics.

INTRODUCTION

Last achievements of Informatics – Computer Science, which studies the structure of representation and transformation of information by machines, as well as quantum physics and modern mathematical approaches are shown that information (information

particles "bits – qubits", and information field) has the properties of quantum matter [1, 2].

At the same time the well-known definition of Biomedicine looks like that it is a system in which medical doctors treat symptoms and diseases using drugs, radiation, or surgery. It also called allopathic medicine, conventional medicine, mainstream medicine, orthodox medicine, and Western medicine [3].

There is a concern that biomedicine is very little focused in its research and practice because biomedicine is guided by a logic that requires all meaningful data to be, in principle, and it is a part of medicine which always be beyond the reach of its scientific capabilities. For instant, to recognize the placebo effect as being psychoactive, as opposed to biochemical, would violate foundational premises that postulate the primacy of the body to the exclusion of mind. Western medicine is often referred to as one of humankind's most outstanding contemporary achievements. At the same time there is a more evident tension more than in the distinctions made between the science of medicine and the art of medicine. (The art of medicine-a euphemistic way of saying that successes cannot be explained in biomedical terms-starts where the science of medicine begins to show its limitations) [4].

On the other hand the field of bioinformation studies provide situated analyses of bioinformation journeys across different domains of biosystems. As huge amounts of data relating to biological processes are collected, aggregated, traded and exchanged, infrastructural systems and machine learners produce real consequences as they turn indeterminate data into actionable decisions for states, companies, scientific researchers and consumers. Bioinformation accrues multiple values as it transverses multiple registers and domains, and as it is transformed from bodies to becoming a subject of analysis tied to particular social relations, promises, desires and futures. It harnesses the anthropological sensibility for situated, fine-grained, ethnographically grounded analysis to develop an interdisciplinary dialogue on the conceptual, political, social and ethical dimensions posed by bioinformation.

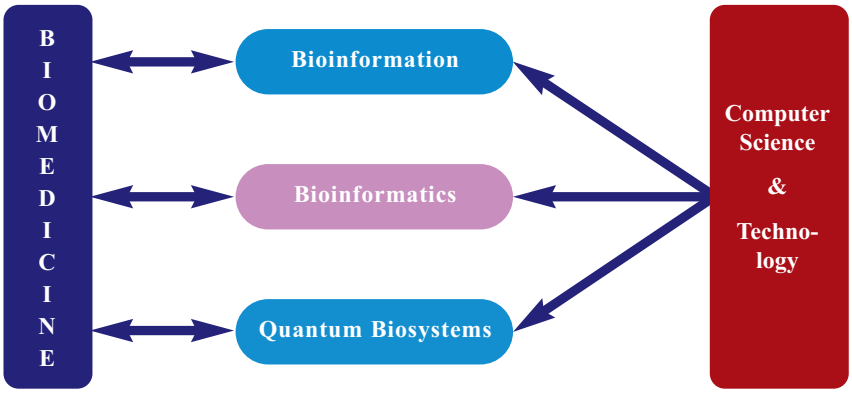

Fig.1. Scheme of interconnection of Biomedicine and its domains with Computer Science & Technology

Another direction of recently merged disciplines of biomedicine and information science and technology is bioinformatics, which is the application of tools of computation and analysis to the capture and interpretation of biological data [5]. (Fig.1).

Bioinformatics is essential for management of data in modern biology and medicine. Analysis of genome sequence data, particularly the analysis of the hu-

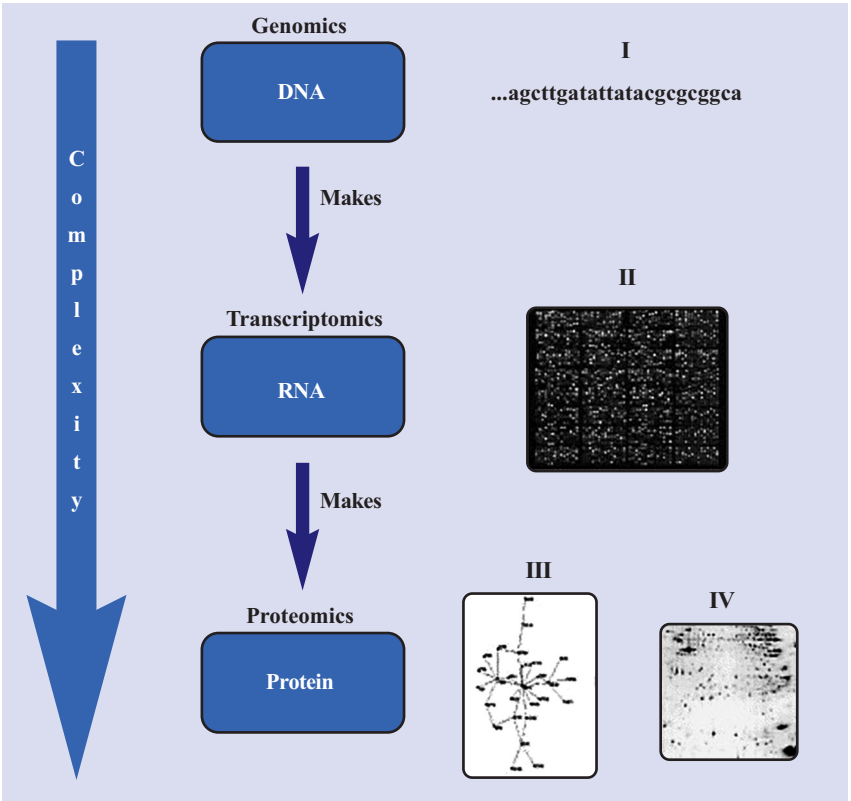

Fig. 2. Schematic diagram representing complexity of genomic data processing. Analysis and interpretation of biological data considers information at every level from the genome (total genetic content) to the proteome (total protein content) and transcriptome (total messenger RNA content) of the cell. The images numbered I-IV to the right of the diagram represent relevant examples of DNA (image I is base pair nucleotides); RNA (image II is a microarray showing levels of gene expression); and protein (image III is a structure of a single protein; image IV is a two dimensional gel electrophoresis showing separation of all proteins of a - spot corresponds to a different protein chain) [5].

man genome project, is one of the main achievements of bioinformatics to date. Prospects in the field of bioinformatics include its future contribution to functional understanding of the human genome, leading to enhanced discovery of drug targets and individualized therapy. Bioinformatics has also been referred to as 'computational biology. However, strictly speaking, computational biology deals mainly with modeling of biological systems. The main components of bioinformatics are the development of software tools and algorithms and the analysis and interpretation of biological data by using a variety of software tools and particular algorithms (Fig.2).

In this direction it seems to be very important to analyze the nanoscale biological systems in connection and using last achievements of computer science and technology. Today we divide the computer science and technology to two parts "Classical" and "Quantum", and we also divide it to theory of information and information technology. Thus we have Information theory and quantum information theory, and accordingly – information technology and quantum information technology. All this it is not enough correct because naturally we have theory of information, which includes the newton mechanics based approaches and quantum mechanics based ones. Above mentioned definition is clear If we call Newton's mechanics "classical" and Schroedinger's mechanics "quantum". In reality information as phenomena is based on probability and relativity, and we should say that non quantum approach to information is the rather weak because it is based on the rough estimations that probability of any action is 0 or 1[6-8].

TRANSMISSION OF INFORMATION

One of the most important part of information science and technology is information movement which can be described as data transfer via communication channels [9]. Transmission of information package, which contains the group of bits/qubits can be done by any known carriers, in the modern times by any known particles and relevant waves transferring the energy. So information transfer is the energy transfer and for this it is necessary to have field and particle. In the modern telecommunication we are using mainly the electrons and photons for information energy transfer. In the future for organization of information-communication process we can use not only magnetons (magnetic particles of magnetic field) but also gravitons (particles of gravity) and others [10].

According to above mentioned information could be measured in electron-volts (1eV=1.60218-19 Joule) or in another energy units. By mass–energy equivalence, the electron-volt is also a unit of mass. It is common in particle physics, where units of mass and energy are often interchanged, to express mass in units of eV/c2.

At the same time following existing definition: Matter is anything that has mass and takes up space. The amount of space an object takes up is its volume. Emotions, thoughts, and ideas are more examples of things that are not matter. They take up no space and do not have mass" [11]. But if we look deeper even those phenomena are based on information (energy) flow and exchange between different parts of brain. So they also are information-communication processes. So it is clear that information is also matter.

The way to these solutions includes the R. Clausius observation that: "The energy the universe is constant the entropy of the universe tends toward a maximum"; C. Shannon's definitions of amount of information as logarithm of a probability of its occurrence from a given source over a given channel thus measuring in 'bits', which has become a household term. Actually, this notion fits with the physics tradition via one transformation. The total entropy of two independent systems is the sum of their individual entropies, while the total probability is the product of the individual probabilities.

While the preceding tandem view seems to highlight the dynamic processes, it equally well forces us to think more about the details of representation of information. It is symptomatic that I. Kolmogorov complexity can be viewed as a theory of string entropy, with random strings as systems in thermodynamic equilibrium. This suggest intriguing equivalence relations for translating between complexity theory and physics, for whose details we refer to connection and overlapping of computer science, and physics and information process is the relation between information field structure and information portions –bits motion[12]. The solution of this problem is lying in unification of the theory of information, computation, dynamic logics of epistemic update in one side, and spintronics, moletronics, memtronics, nanotronics – novel physical approaches for information processing on the other, looking to bits as a real particles together with information field - main actors in info-dynamical processes.

We can examine the real process of information transfer by looking at the current main carrier of information – light particle, photon its behavior and properties.

The term photon was coined by Gilbert Lewis in 1926, though the concept of light in the form of discrete particles had been around for centuries and had been formalized in Newton's construction of the science of optics. The early Greeks were the first to propose that energy is composed of particles. However, later experiments suggested that energy behaved more like waves than particles. In the 1860s, the physicist James Clerk Maxwell discovered that light was a form of electromagnetic waves. In 1900, Max Plank, a German physicist, suggested that light was made up of particles [13].

Under the photon theory of light, a photon is a discrete bundle (or quantum) of electromagnetic (or light) energy. Photons are always in motion and, in a vacuum, have a constant speed of light to all observers, at the vacuum speed of light (more commonly just called the speed of light) of c = 2.998 x 108 m/s. According to this theory photons have zero mass and carry energy and momentum, which are also related to the frequency ν and wavelength λ of the

electromagnetic wave by E = hν and p = h/λ.

Light has properties of both a wave and a particle. Just one of the effects of this wave-particle duality is that photons, though treated as particles, can be calculated to have frequency, wavelength, amplitude, and other properties inherent in wave mechanics.

Photons are electrically neutral and are one of the rare particles that are identical to their antiparticle, the antiphoton. Photons are spin-1 particles (making them bosons), with a spin axis that is parallel to the direction of travel (either forward or backward, depending on whether it's a "left-hand" or "right-hand" photon). This feature is what allows for polarization of light.

In both these cases, the information is communicated at or below the speed of light, in keeping with Einstein's axiom that nothing in the Universe can go faster.

Quantum mechanics allows for a third way to coordinate information. When two particles are quantum mechanically 'entangled' with each other, measuring the properties of one will instantly tell you something about the other. In other words, quantum theory allows two particles to organize themselves at apparently faster-than-light speeds.

Einstein called such behaviour "spooky action at a distance", because he found it deeply unsettling. He and other physicists clung to the idea that there might be some other way for the particles to communicate with each other at or near the speed of light [14, 15].

Albert Einstein claims that the speed of light is the "traffic law of the universe" or, otherwise put, that nothing can travel faster than light. Of course, humanity's dream of time travel has long relied on the hope that Einstein was wrong. We got a glimmer of hope back in the last century when scientists found superluminal (faster-than-light) propagation of optical pulses in some specific medium. Unfortunately, this was later revealed to be a visual effect, and the photons involved couldn't actually transmit information. Einstein's theory rests on two postulates, one of which is that electromagnetic radiation travels at the same speed. Light particles - photons have no mass, so a consequence is that no particle with mass can move at a velocity greater than light. These neutrinos have a tiny, but non-zero, mass and hence should not be able to travel faster than the speed of light [16].

There are two other experiments that shoot neutrinos over long distances that may have something to say about this result. One experiment is in the U.S., and the beam goes from Fermilab, near Chicago, to a detector called MINOS in northern Minnesota. The other shoots a neutrino beam across Japan to an experiment in a mine called Super-Kamiokande. The energies of the neutrinos in these experiments are much lower than the CERN beam, but they may have something to say very soon [17-19].

Since then, there has been a debate surrounding whether or not a single photon might actually be able to travel faster than the speed of light.

Few years ago researchers at the Joint Quantum Institute (JQI), a collaboration of the National Institute of Standards and Technology and the University of Maryland at College Park, can speed up photons to seemingly faster-than-light speeds through a stack of materials by adding a single, strategically placed layer. A single photon travels through alternating layers of low and high refractive index material more slowly or quickly depending upon the order of the layers. A strategically placed additional layer can dramatically reduce photon transit time. At the boundaries between layers, the photon creates waves interfering with each other, affecting its transit time. This experimental demonstration confirms intriguing quantum-physics predictions that light's transit time through complex multilayered materials not depend on thickness, as it does for simple structures but rather on the order in which the layers are stacked [20]. Strictly speaking, light always achieves its maximum speed in a vacuum or empty space, and slows down appreciably when it travels through a material substance. The same is correct for light traveling through a stack of dielectric materials and even nanostructures, which are electrically insulating and can be used to create highly reflective systems that are often used as optical coatings on mirrors or fiber optics or photovoltaic elements [21].

The rule that nothing can travel faster than the speed of light still is one of the most fundamental laws of nature. But since this speed limit has only been experimentally demonstrated for information carried by large groups of photons, physicists have recently speculated as to whether single photons and the information carried by them may be able to exceed the speed of light [22-25].

This experiment, conducted by a team at the Hong Kong University of Science and Technology and led by Professor Shengwang Du, measured the ultimate speed of a photon using controllable waveforms and published their study on the ultimate speed of a single photon in Journal of Physical Review Letters. The results have implications for the maximum speed of information transmission by confirming that single photons obey causality; that is, an effect cannot occur before its cause. They reported the direct observation of optical precursors of heralded single photons with step- and square-modulated wave packets passing through cold atoms. Using electromagnetically induced transparency and the slow-light effect, the single-photon precursor was separated, which always travels at the speed of light in vacuum, from its delayed main wave packet. In the two-level superluminal medium, experimental results suggest that the causality holds for a single photon [26].

It had been measured several properties of photons, such as phase, when they arrived at their havens and found that they did indeed have a spooky awareness of each other's behaviour (Fig.3).

On the basis of their measurements, it had been concluded that if the photons had communicated, they must have done so at least 100, 000 times faster than the speed of light - something nearly all physicists thought would be impossible. It was found that, as the fastest part of a single photon, the precursor wave front always travels at

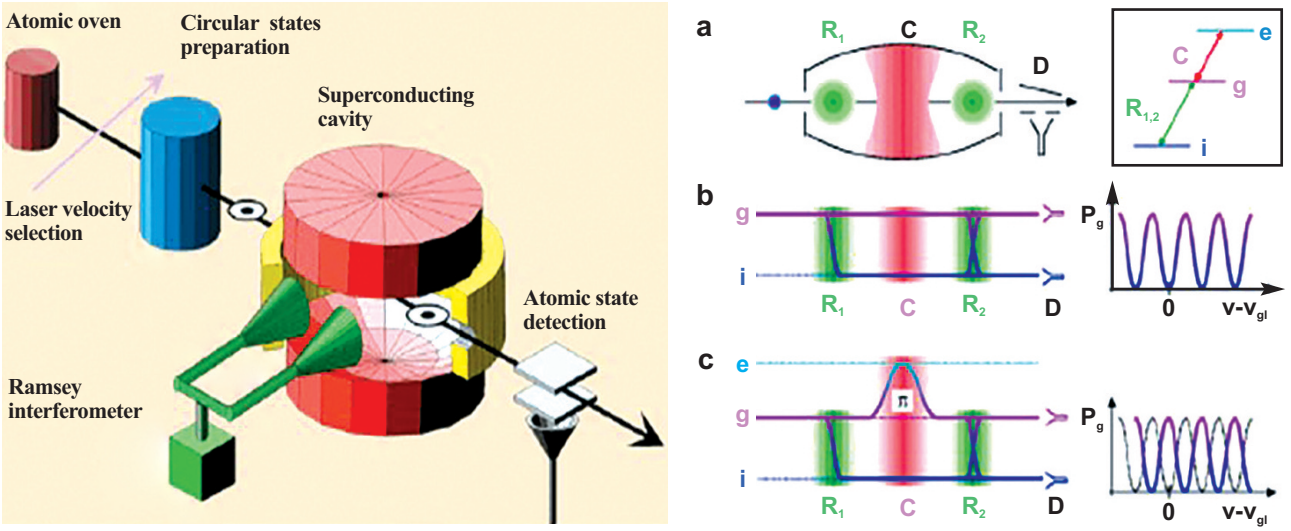

Fig.3. Single photon detection experimental setup and some measurement results [27,28].

the speed of light in vacuum. The main wave packet of the single photon travels no faster than the speed of light in vacuum in any dispersive medium, and can be delayed up to 500 nanoseconds in a slow light medium. By showing that single photons cannot travel faster than the speed of light, last experimental results bring a closure to the debate on the true speed of information carried by a single photon. That indicates, in turn, that time travel is not possible, and that decades of beloved science fiction may not be entirely based on fact.

At the same time it is necessary to underline that in quantum field theory forces are mediated by virtual particles. Because of the Heisenberg uncertainty principle these virtual particles are allowed to go faster than light [29].

Is all above mentioned strongly correct? More less. For today it is more. It is absolutely clear that speed of photons, which are particles of making a light cannot be higher than speed of light and information they are transferring also has the same speed. On the other hand the speed of information which might be transferred by the other particles/waves could travel by the higher/lower speed depending of its carrier.

CONCLUSION

One good example of overlapping the methods and tools of Biomedicine, Physics and Computer Science is usage of the effect of resonance spectroscopy of pathogenic bioparticles. The possibility of vibration always exists wherever there is periodic and repeated movement of a particle about a position of equilibrium or balance. This process is also natural for nano-sized bioparticles of enveloped, positive-strand RNA viruses which infect amphibians, birds, and mammals and now known as coronaviruses. Last studies in this direction aimed to explore nanobiospectroscopy research and technology built a theoretical, computer modelling and experimental basis for development of methods and tools of identification of characteristic vibrational frequency of viruses and then their resonance therapy [30-32]. Spectroscopic methods have the characteristic of providing fast results and reliable information related to the composition of the samples. It has been shown that multivariate analysis techniques are of great importance to analyze spectroscopic data, providing the potential to identify and classify biological samples. We do hope that with advancement in this field of study methods of light therapy of different diseases using EM field characteristics and resonant wave ranges based on computer simulation of nanobioparticles characterization will be widely implemented, and possibility of determination of resonant (own) frequencies of entire system of molecules including virions will be a key point for that.

It is a well-known fact that the yogis of ancient times practiced meditational techniques to get rid of diseases and stay healthy. Meditations induce the positive vibrations which are known to kill many of the harmful microorganisms which get into our body. Recent frontiers in technology are exploring the possibility of using external excitations to vibrate a virus to its death.

We are looking forward for development in the near future the new approaches and methods for investigation of information flow in the human body and nearby as well as in the different biomolecular systems using quantum transport phenomenon and relevant tools.

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DIFFERENT

ASSOCIATIONBETWEEN CYTOMEGALOVIRUS (CMV) BURDEN DURING EARLY CHILDHOOD AND HEARING LOSS

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ABSTRACT

Objective. This study was designed to determine the seroprevalence of CMV among preschool children with hearing loss. **Material and Methods.** A case-control study has been performed in Tbilisi, Digomi - Inclusive Education-Centre for children with hearing loss. The cohort of 15 children with SNHL was studied for HCMV specific IgG and IgM antibodies concentration in the blood. The control group formed 30 healthy children of the same age without any complains about hearing. They were tested on TORCH infection for screening. The serum samples from all subjects were analyzed by enzyme-linked immunosorbent assay (ELISA). Comparison of study and control groups has been performed by chi-square method with Yates correction and Fisher's exact test. **Results.** CMV specific IgG antibodies were positive in 14 (93, 3%) of 15 patients with hearing loss and 14 (46.7%) of 30 children from control group. The difference between groups was statistically significant. **Conclusion.** Thus, the children with nongenetic sensorineural hearing loss has been shown to correlate with higher prevalence of systemic CMV burden than the children without hearing problems. So, the early identification the children with CMV burden in early stages of development, as they are in increased risk for development the SNHL, is very important for early intervention and better outcome.

Key words: CMV infection, children, hearing loss, HCMV specific IgG and IgM antibodies, CMV burden.

INTRODUCTION.

Human cytomegalovirus (HCMV) is a species-specific member of the beta herpes virus family. Cytomegalovirus (CMV) is found universally throughout all geographic locations and socioeconomic groups, and infects between 50 to 85% in of adults in USA by the age of 40. According to other publications the seropositivity rate in the adult population is 60 to 100% [12, 13]. This high rate possibly is due to the transmission of the virus through close interpersonal contact, breastfeeding, sexual contact, and spread among children. CMV is also the virus most frequently transmitted to a developing child before birth. The congenital transmission of HCMV is possible even when maternal immunity is present. CMV has been observed in infants born to mothers who were seropositive before pregnancy [3, 5]. Vertical transmission occurs in around 30% of cases, but the fetus is not always affected.

Approximately 14% of the CMV infections are diagnosed at birth (symptomatic), while the remaining 86% are asymptomatic [12]. Although HCMV infection in healthy children and adults usually is asymptomatic, it is the leading cause of nongenetic sensorineural hearing loss (a type of hearing loss that is caused by deficits in the vestibulocochlear nerve, in the inner ear, or in the central processing centers of the brain) in developed countries [1, 5, 8, 15]. Approximately 10% of cases develop cytomegalic inclusion diseases, with a 20–30% mortality rate [1]. Up to age 2, 10–15% of asymptomatic children develop neurological sequelae [2, 7], such as sensorineural hearing loss, mental retardation, motor deficits, seizures and chorioretinitis.

The incidence of congenitally acquired HCMV in newborns ranges from 0.5 to 2.2% in developed countries [5, 6, 8, 11], but this could be an underestimation, since reliable and national-level estimates are not available [8]. Up to 22% of neonates with hearing impairment are infected with HCMV [3, 4, 14].

The first report on the association between HCMV infection and hearing impairment dates from 1964 [10]. Since then, considerable efforts have been made to clarify the exact mechanism of causing hearing loss, but until now this question has not been resolved. Congenital cytomegalovirus (CMV) infection is a cause of sensorineural hearing loss (SNHL) in children, but the mag-

nitude of its contribution is uncertain. Quantifying the impact of congenital CMV infection requires an evidence-based assessment using a standard case definition of hearing loss [8].

The pathogenesis of congenital CMV infection and the mechanisms of SNHL in children with this intrauterine infection have not been defined. The presence of microcephaly, seizures, abnormal tone, or chorioretinitis in the newborn period has been shown to predict cognitive and motor deficits. However, evidence of central nervous system involvement at birth in children with clinically apparent or symptomatic congenital CMV infection does not predict SNHL [4]. The amount of systemic CMV burden has been shown to correlate with the risk of CMV disease in immunocompromised hosts, including patients with acquired immunodeficiency syndrome and allograft recipients. In addition, a reduction in viral load with antiviral therapy has been used effectively both to prevent and treat CMV disease in immunocompromised individuals [6, 9, 16]

Auditory disability has pernicious effects on the development of speech and on the total development of the child. The age of onset of a child's hearing impairment and the age at which the hearing impairment is diagnosed are crucial parameters for the further development of the child [2, 18]. Intensive auditive stimulation of the cerebral cortex before the age of 6 months leads to significantly higher language abilities of the disabled children compared to those of children who do not receive a hearing aid until the age of 7 to 18 months [1, 5, 17]. For this reason, early detection of hearing problems, universal screening for hearing impairment in babies is very important, and this is one of the aims of the Joint Committee on Infant Hearing (JCIH) and the American Academy of Pediatrics. The JCIH guidelines strongly suggest screening before the age of 1 month, with audiological confirmation by 3 months of age in infants who fail the screening test and the initiation of intervention before the age of 6 months [10]. So, the identification the children at increased risk for SNHL in early stages of development, revealing the factors promoting development of hearing problems in infancy will be crucial for early intervention and better outcome.

There are several publications about congenital CMV-related complications for neonates in Georgia, but there are no data about long term health consequences in children who are infected, but without symptoms at birth. The relationship between the virus burden and outcome in children with asymptomatic congenital CMV infection has not been defined.

This study was undertaken to determine the seroprevalence of CMV among preschool children with hearing loss.

MATERIAL AND METHODS.

A case-control study has been performed in Tbilisi, Digomi - Inclusive Education Centre for children with hearing loss. The study group included 15 children at age 3-6 years: 8 female and 7 male with different degrees of hearing loss. The control group formed 30 healthy children the same age without any complains about hearing. They were tested on TORCH infection for screening.

Detection of CMV specific IgG amd IgM antibodies was performed for evaluating the CMV infection status and /or immunity to CMV. The serum samples from all subjects were analyzed by enzyme-linked immunosorbent assay (ELISA).

Statistics. Comparison of study and control groups has been performed by chi-square method with Yates correction and Fisher's exact test.

RESULTS.

CMV specific IgG antibodies were positive in 14 (93, 3%) of 15 patients with hearing loss and 14 (46.7%) of 30 children from control group. CMV specific IgM antibodies were detected only in 1 patient from the study group and in none from the control. The difference between groups was statistically significant (Chi-square with Yates correction = 7.39, p=0.0066, Fisher's exact method p= 0.0029). So, a possible association between the presence of HCMV and confirmed hearing impair-

Table1. Parameters of children with hearing loss according to the presence of clinical findings at birth and the results of serologic investigation.

Findings	Children with hearing loss (n=15)	Control group children (n=30)
Age	**From 3 to 6 years**	**From 3-6 years**
Sex:		
Male	**7**	**15**
Female	**8**	**15**
When was diagnosed first impairment in hearing	**1-3 years**	**-**
Prematurity	**3**	**8**
Race	**Georgian**	**Gerogian**
Family history for hearing loss	**None**	**None**
Maternal health state during pregnancy:		
Viral infection (measles)	**1**	**3 (upper respiratory tract infection)**
Children health status (congenital):		
Congenital heart disease	**1**	
Autistic spectrum disorder	**1**	**Healthy**
Cerebral palsy	**1**	
Epilepsy	**1**	
Use of antibiotics	**8**	
Consultations:		**18**
Oculist (visual impairment)	**1**	**-**
Audiologist (different degrees of hearing impairment)	**15**	**-**
Psychologist (impaired cognitive development because of hearing problem)	**15**	**-**
Serology:		
IgG +	**14**	**14**
IgM +	**1**	**-**

ment for the different groups was confirmed statistically.

Table 1 shows the number of infants in each group according to the presence or absence of CMV specific IgG and IgM antibodies in the blood. Based on the results the number of infants in group 1 that are HCMV positive (93, 3 %) with hearing loss is two times higher than that of the HCMV-positive samples in the control group (46, 7%).

DISCUSSION.

In this study, we evaluated the children with and without hearing impairments from infancy and studied the content of HCMV specific IgG and IgM antibodies in the blood. The results imply that it may be possible to identify children with asymptomatic congenital CMV infection at increased risk for SNHL by measuring virus burden during infancy. If confirmed in future studies of congenital CMV infection with larger sample sizes, early identification of children who are at risk for SNHL will greatly improve the counseling provided to the parents of infected neonates. Because most children with congenital CMV infection develop normally without any sequelae, the ability to identify children at risk for SNHL in early life can lead to a better use of resources by targeting these children for closer monitoring and intervention. Finally, early identification of at-risk children will be crucial for the evaluation of future antiviral therapies to prevent or reduce the incidence of CMV-related hearing loss.

The children with asymptomatic congenital CMV infection with higher amounts of infectious CMV in urine and CMV DNA in PB during early infancy are more likely to have SNHL [4]. The demonstration that the risk of hearing loss increases when subjects are grouped according to increasing virus burden breakpoints suggests the role of virus burden and viral replication in the pathogenesis of congenital CMV infection. The exact role of virus burden in the pathogenesis of SNHL (in particular, delayed onset hearing loss, progressive hearing loss, or both) will need to be defined in future prospective studies that include a larger number of children with congenital CMV infection with sufficient follow-up [3, 4].

Thus, the children with nongenetic sensorineural hearing loss has been shown to correlate with higher prevalence of systemic CMV burden than the children without hearing problems. So, the early identification the children with CMV burden in early stages of development, as they are in increased risk for development the SNHL, is very important for early intervention and better outcome.

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CONGENITAL INFECTION AS A REASON OF SENSORINEURAL HEARING-LOSS IN CHILDREN

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(ABSTRACT)

The rate of cytomegalovirus, CMV, bearing has been estimated in children suffering from inborn or newborn types of sensorineural hearing loss of hard-to-severe degrees. The test group com-prised 15 hearing-loss children of 3-6 years of age. The control group included accidentally se-lected 30 healthy children of the same ages without any hearing complains. In both groups CMV-specific IgG antibodies were determined in blood via the enzyme-linked immunosorbent assay, ELISA. The excessive amount of IgG antibodies was found in 14 out of 15 children with sen-sorineural hearing loss that being estimated objectively, via computer registration of auditory brainstem responses, ABRs, and in 14 out of 30 children with normal hearing, that being also proved objectively, via specialized screening procedure. The intergroup difference in CMV bearing rates, 93.3% and 46.7%, respectively, has been proved to be statistically significant (p=0.007). CMV bearing happens thus twice as much in sensorineural hearing-loss than in nor-mally-hearing children. Early detection of hearing loss and early assessment of CMV bearing seem essential for an immediate start and, therefore, for a batter chance of positive outcomes of specific treatment/rehabilitation means.

Key words: CMV infection; hearing impaired children; CMV-specific antibodies; CMV bearing.

Cytomegalovirus, CMV, [10, 11] is stated among the most prevalent aetiological agents of congenital infectious diseases [10, 11]. CMV is one of the common causes of mental retardation and various disabilities including hearing loss.

According to some authors [5, 6, 8, 9] 0.2-2.4% of newborns are infected with CMV. In 85% of them the disease is asymptomatic. Although in 10-17% of infested infants sensorineural, considerably progressive hearing loss is developed later [1, 5, 8, 14] . There are serious disorders in 10-15% of prenatally infected infantsAmong them we should emphasize the retardation of growth and development, low birth weight, microcephalism, jaundice, hepatosplenomegalia, anemia, thrombocytopenia, in most infected patients there are additional neurological abnormalities in adulthood. [2, 7].

CMV is one of the types among eight human herpes virus species-human herpes virus 5, HHV 5. After invading into the blood CMV replicates in monocytes and lymphocytes [5, 11].CMV reduces cellular immunity selectively and exceptionally. CMV is able to “get shelter in lymphocytes”. Consequently, for specific antibodies as well as for interferon CMV becomes unapproachable and safe from their blocking action. For this reason CMV silent carriage includes mostly long term period, sometimes the whole life.

CMVdetection and course mostly depends on mother’s immune status [4, 5]. If a mother gets ill during the first period of pregnancy, CMV transmission risk to a fetus equals 40% that is rather high due to undevelopment of immunity mechanisms [6, 7, 14]. In these conditions pathology is observed in 65% of infested patients even during infant period. Due to blocking mechanisms of more or less developed immunity when the already infected woman becomes pregnant CMV invasion probability reduces and equals 0.5-1.5%.

Manifestative CMV infection is observed in 10% of infested newborns during prenatal period [10]. Retardations of prenatal growth, hepatosplenomegalia, hematological disorders such as thrombocytopenia, dermal abnormalities such as petechia and purpura, are typical symptoms of manifestative CMV. Central and/or peripheral neurological disorders dominate in all cases, such as microcephalia, ventriculomegaly, brain atrophy, chorioretinitis, hearing loss, intracerebral calcificates that are verified via computer tomography and suggest about the involvement of brain periventricular region in pathological process, and later they are considered as antecedents of progressive neurological-congenital disorders. Among the reasons of mental retardations congenital CMV infection rate and severity is less than Down's disease alone [2, 7].

Asymptotic CMV infection is particularly observed in those infants whose mothers already have developed immunity against CMV [4].At the moment of birth these kinds of newborns look clinically healthy, although later they may have retardations in growth. Later on the neurological disorder risk

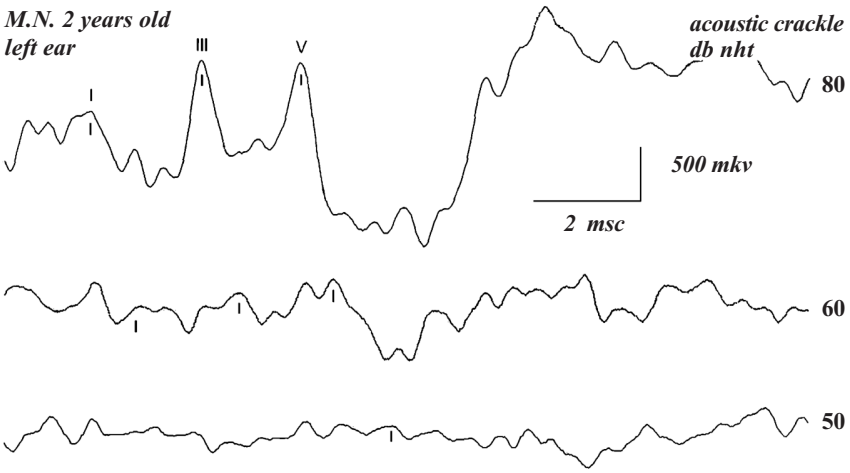

Fig 1. in CMV bearing children different intensity acoustic crackle (80,60,50 db nht normal hearing threshold registered auditory brain stem responses. At high intensity in auditory brain stem responses the three main components are differentiated – waves I, III, V (pointed with verticals), threshold –only wave V. When sound intensity decreases auditory brain stem responses reduces, pick latent periods prolongs.

also increases in them. Exactly these groups are characterized by sensorineural hearing loss tending to process progress. Unilateral of bilateral hearing loss is observed in 15% of CMV infected children. It should be emphasized that newborn hearing screening might not be able to indentify audiology disorders – first signs of hearing deficiency occur some months or years after the birth.

CMV related hearing loss mechanisms are not completely determined [1]. In manifeststive forms of the pathology, when the signs of congenital infection, such as microcephalia, seizure syndrome, chorioenteritis, muscle hypotony, are manifested in newborns, neurological-motor-congenital retardations are farther expected. Sensorineural hearing deficiency is also frequently associated with them. There must be considered the evidence, according to which hearing loss rate is proportional to CMV concentration in urine in individuals who bears congenital asymptotic CMV. The works published about this item [12, 13] suggest that the factors that can help to predict hearing loss in CMV infection are not known up to now. Thus, close hearing monitoring during symptomatic as well as asymptotic CMV disease is recommended at least during the first years of life.

Hearing plays a dominant role in the development of correct speech and generally in the normal development of a child. Child's age is critical at the moment of hearing loss, start time of rehabilitation is also essential. For the development of speech function of a child with hearing loss hearing-speech stimulation of cerebral cortex has much better result before 6 month age than in those children whose hearing deficiency was not defined before the age of 7-18 months and audio stimulation of cortex was not conducted by the appropriate rehabilitation procedures [11, 12]. Consequently, newborn audio screening and medical-rehabilitation measures in case of hearing loss has a principal value in order to develop normal speech.

In the present paper CMV bearing was defined in sensorineural hearing loss children during prenatal and early postnatal period. CMV carriage evidence in hearing loss children were analyzed by collation with the identical evidence of peers with normal hearing.

The main (test) group includes 15 children at the age of 3-6, - there were 8 girls and seven boys who were brought in the National Center of Audiology for consultation. At the beginning, in order to determine functional status of middle ear, every child underwent standard timpanometry. In every case impedancometric evidence proved a normal function of middle ear. Later hearing was screeningly tested in every child via the procedure based on the registration of otoacoustic emission. Each test was completed with fail indication on the screen of screening equipment, suggesting hearing disorder. On the next stage of the investigation hearing dysfunction was objectively estimated via computer registration method of auditory brainstem response. In the process of objective audiometry a child was placed in acoustically attenuated and electrically isolated box. Thresholds for auditory brain stem responses to tones with monaural stimulation were determined at 0.5, 1 and 2 kHz frequencies that are in main speech spectrum line. Stimulation rhythm was 11 sec. In isolated cases in averaged carves the identification was complicated. In order to eliminate difficulties and present individual peculiarities auditory brain stem response configuration and content before the test via tones or in the process of test auditory brain stem responses were recorded under monaural and binaural stimulation (fig 1).

Fig 1. in CMV bearing children different intensity acoustic crackle (80, 60, 50 db nht normal hearing threshold registered auditory brain stem responses. At high intensity in auditory brain stem responses the three main components are differentiated –waves I, III, V (pointed with verticals), threshold –only wave V. When sound intensity decreases auditory brain stem responses reduces, pick latent periods prolongs.

In comparison with tone stimuli, auditory brain stem responses better respond to crepitation, rarely cause inaudibility and consequently make interpretation of records of tones easy. In order to receive auditory brain stem responses, the active, reference and grounding electrodes were fixed on vertex, stimulated and non-stimulated lobe of the ear respectively. Bioelectric activity obtained on the scalp was enhancing in 50-2000 HZ frequency line. Averaging (summation) of the following periods of stimuli was conducted via specialized computer system (eclipse). sempletion (quantization) step was 25 mcsec, epoch (analyzing time) was 12 msec, averaging (summation) number -2000. In case of suspicious configuration carve averaged records cross summated in computer. hence, averaging number in isolated cases was 4000, 6000, 8000. In most investigated children, in particular under 5 years, computer audiometry was conducted under conditions of

sleep induced by diazepam injection in muscles.

In all the 15 children of the main group detectable hearing loss detected via objective audiometry (fig 2). In absolute majority of tested children perception thresholds at test frequencies equaled 60-90 db. Thus, in every individuals of the group III or IV frequency that is severe or the most severe hearing loss detected. In most tested children hearing thresholds were regularly increasing from low frequency, 0.5 kHz, to high frequency, 1 or 2 KhZ, therefore audiometric carves had the oscillation characterized for sensorineural hearing deficiency that is they had sloping configuration. In audiograms of left and right ears inclination angle was equal and for each following frequency was approximately 5 db. (fig 2). In most tested hearing threshold indicators also coincided with each other. Inreaural intensity difference in isolated individuals usually was within the scope of 5, 10, 15 db. By total data Inreaural intensity difference at the three test frequency was only 1-3 db rank. (fig 2), at the same time at the three difference was statistically unreliable. Taking into account coincidence mean indicators of hearing loss at isolated frequencies were calculated towards the both ears. At 0.5, 1 and 2 Khz frequencies, that were used for the registration of auditory brain stem responses mean indicators of auditory threshold and appropriate standard deviations in test group were 71.2±16.1, 75.6±10.4 da 80.6±10.5 db respectively. According to the total of both ears as well as separately left and right ears (fig 2) standard deviations gad the higher values at low frequency, 0.5Khz, that at high frequencies, 1 and 2 KhZ . In its turn standard deviation indicators were equal. Variability coefficient (V) of auditory threshold by standard deviation (SD) and mean ( ) indicators was calculated as follows: V% = 100SD : . By total data of both ears, at 0.2, 1 and 2 KhZ frequencies variability coefficient was 22.7%, 13.8% and 13.1% respectively.

Thus it was realized, that in unhealthy children with hearing loss variability of hearing threshold indicators is higher at 0.5 KhZ, than 1 and 2 KhZ frequencies, whereas at 1 and 2 KhZ frequencies it is equal.

Except hearing-speech manifestative disorders in test group children, some dysfunctions of sight system were also observed. Psychological investigation in all the children except audio-visual system disorders, showed some retardations of mental processes, and generally of mental development.

The control group comprised accidentally selected 30 healthy children of 3-6 ages without any hearing complains- there were 15 girls and 15 boys. According to thorough inquiry and direct survey none of the group members had any hearing-speech deficiency. Hearing screening test of the children completed with indication of "pass" on the monitor. That is the result was positive. Consequently in each individuals of the control group normal function of hearing was also proved objectively.

In both groups CMV-specific IgG antibodies were determined in blood via the enzyme-linked immunosorbent assay, ELISA. The excessive amount of IgG antibodies was found in 14 out of 15 children, that is in 93.3%, and in 14 out of 30 children with normal hearing, that is in 46.7% . Thus, it was realized that CMV bearing happens twice as much in sensorineural hearing-loss than in normally-hearing children. The intergroup statistical difference ($p=0.007$, Fisher test) significantly exceeded threshold indicator of reliability ($p\leq0.05$). Consequently, CMV bearing indicator in the group of children with hearing loss exceeded by high statistical reliability the corresponding indicator in normally-hearing children.

Thus, according to our study, CMV infection is a significant risk factor of sensorineural hearing loss in children. In detection of hearing loss by audioscreening and/or computer audiometry in early age via specific methods, in particular via LgG antibody titre, determination of CMV bearing is not recommended. . Early detection of hearing loss and early assessment of CMV bearing seem essential for an immediate start and, therefore, for a better chance of positive outcomes of specific treatment/rehabilitation means.

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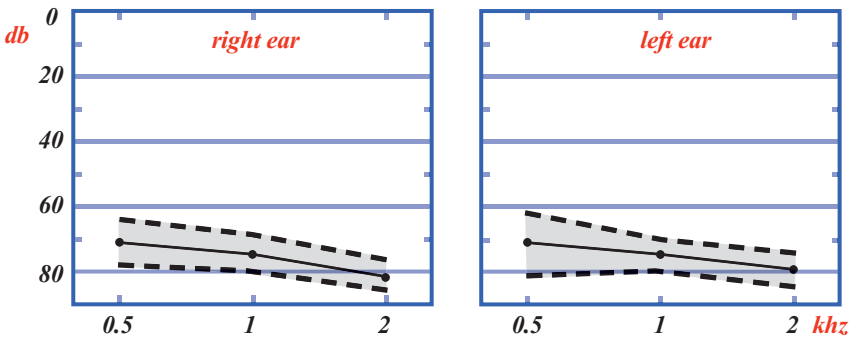

Fig 2. in CMV bearing children at 0.5, 1.2 KhZ frequencies mean indicators of hearing threshold (continuous line) determined by registration method of auditory brain stem responses with positive and negative standard deviations (spline line above and below mean indicators respectively). In order to detect common distribution of hearing thresholds positive and negative standard deviations carves are interconnected with slanting lines.

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A CLINICAL STUDY OF 78 CHILDREN WITH AUTISM

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(ABSTRACT)

Autism, also known as Autism, is a type of pervasive developmental disorder that occurs before the age of 3 and usually manifests in the first or second years of life. The diagnosis of autism falls under one category of mental development disorders. Its incidence is increasing year by year, and there is no specific treatment [1]. This study selected 78 cases of autistic children in Shenmu City Hospital for research and analysis, according to the clinical manifestations, and related laboratory research, examination results, music therapy, comprehensive therapy, intervention methods and their efficacy to analyze and study, suggesting that clinical research on autism should be strengthened.

Key words: Children autism clinical research.

1. INTRODUCTION

Autism is a disease that seriously affects children's physical and mental health, and brings serious burden to society and family. It is estimated that there are 35 million people in the world, 40% of whom are children. The incidence rate of autism spectrum disorders in China is 1:100, and the total number of people has reached 10 million, of which more than 2 million are children aged 0-14. In recent years, scholars have tended to call it Autism Spectnum Disorder (ASD), also known

as Autism spectrum Disorder. Social communication and communication disorders are the core defects of children with autism, and one of the important conditions for children to establish contact with the outside world. As children with autism cannot express themselves properly, they lack basic survival skills and social skills, which have a great impact on their daily life, learning and future work [2]. However, combined with previous studies, most scholars focus on the etiology, occurrence mechanism and communication behavior of autism. In order to improve the research and progress of childhood autism, we conducted clinical analysis and study on 78 children with autism who received outpatient treatment, diagnosis and treatment in Shenmu Hospital from 2017 to 2022.

1.2 RESEARCH BACKGROUND

In recent years, the prevalence of autism has increased year by year, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, published by the American Psychiatric Association in 2013.

According to the Diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, DSM-5, the incidence of autism is 16.8% . 2]. In March 2014, The Centers for Disease Control and Prevention (CDC) reported that The incidence of autism was 1:68; October 2014. The incidence rate of autism spectrum disorders in China is 1:100, and the total number of people has reached 10 million, including more than 2 million children aged 0-14. Children with autism lack social skills such as non-eye contact, inability to recognize other people's emotions, and inability to tolerate changes in the environment. They are unable to communicate and interact with others, develop normal attachment relationships with their parents, and develop good friendships with their peers. Based on this, researchers take autistic children as research objects to improve their social communication disorders as the main research objective. American famous psychoscientist Richard. Mr Cahnner first identified autism as a very rare mental disorder, with an incidence of about 0.04% at the time, and it is still rising. Several studies in Asia, Europe and North America have shown that the prevalence of autism ranges from 1% to 2% on average. The rehabilitation training and education of autism, as well as a series of impacts on society have been gradually paid attention to [3]. Mainly reflected in social communication barriers, poor communication, lack of interest and rigid behaviors. Specific performance is: can not use appropriate words, expressions or movements to express their thoughts correctly. The incidence of autism has been rising and has become a global problem.

Shenmu city is located in the northwest of Shaanxi, with a total land area of 7635 square kilometers. It is the largest county and city in Shaanxi Province with a long history and ancient culture. There were people living in Shenmu city four or five thousand years ago, and Shenmu County was established in the sixth year of yuan Dynasty (1269). Surrounded by the Mu Us Desert, with cold, dry climate and less rain, the city has considerable light and heat resources. It is one of the areas with many sunshine and strong radiation in Shaanxi Province, with an average annual sunshine of 2716 hours, annual average temperature of 9.2ºC and annual average rainfall of 410.3 mm. Its annual economic income is one of the top 100 counties in China, with a GDP of 184.8 billion yuan last year. The city has a population of 571, 900, of which 55.66% are males and 44.34% are females. In the age structure, 22.06% are 0-14 years old, 65.28% are 15-59 years old, 12.66% are over 60 years old, and 8.52% are over 65 years old. The annual population out-birth rate was 11.67 per thousand, the mortality rate was 6.97 per thousand, the natural growth rate was 4.70 per thousand, and the urbanization rate was 70.39 percent. Data on the incidence of children with autism are not well documented [4].

2. GENERAL INFORMATION

Age and Sex

There were 59 males and 14 females, the male to female ratio was 59:14, and 4 cases were 0-3 years old, accounting for 5.5%. 55 patients aged 4-7 years, accounting for 12 patients aged 8-14 years, accounting for 75.3%; There were 30 cases of autism (41.1%), 40 cases of autism spectrum disorder (54.8%), 35 cases of rural area (47.9%) and 38 cases of urban area (51.1%).

3. RESEARCH METHODS

(1) Literature review method: A retrospective study was conducted on 73 cases of children treated in the outpatient department of Shenmu Hospital. Qualified pediatricians and specialist nurses performed medical examinations on 43 cases of children, including cranial NUCLEAR magnetic CT, oral motor function assessment, intelligent development assessment and ABR examination. Finally, statistical analysis was conducted. Through searching domestic and foreign literature research on autism, the theory and methods used in previous research were summarized, thus laying a solid foundation for the development of this study.

(2) Statistical analysis: The general status, sociodemographic characteristics, behavior and clinical manifestations, health status, examination and living environment of 78 children with autism were described by descriptive statistical analysis, and the adoption rate/composition ratio of counting data were described.

4. RESEARCH TOOLS

(1). General information of children with autism: this part mainly includes demographic information, social and economic status of the respondents and health status of the patients, such as name, gender, age and other information.

(2). Physical condition assessment: Head CT, the mouth movement function assessment, smart developmental assessment, childhood autism rating scale, the scale for assessment of autistic children parents, repetitive stereotyped behavior rating scale (total number/total score), ABR inspection (dBnHL), GESELL children's developmental diagnosis table (DQ/DA), children's scale, children with autism ABC scale autism And S-M Infant-Junior High School Social Life Ability Scale (crude score/standard score).

5. RESULTS

43 cases were compared before and after treatment. As shown in Fig.

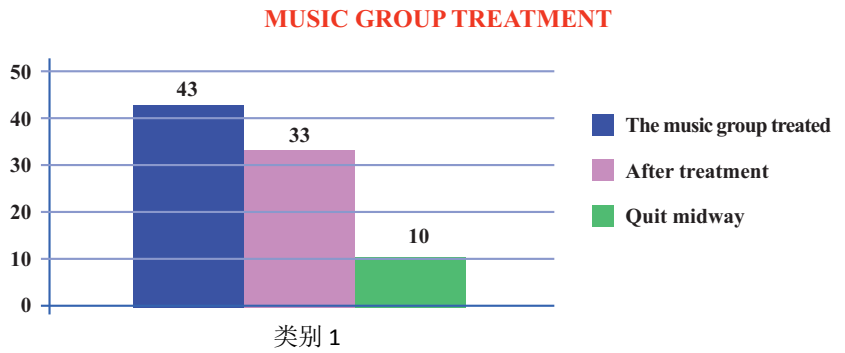

Fig. 1. The music group treated 43 cases, 33 cases after treatment, 10 cases quit midway

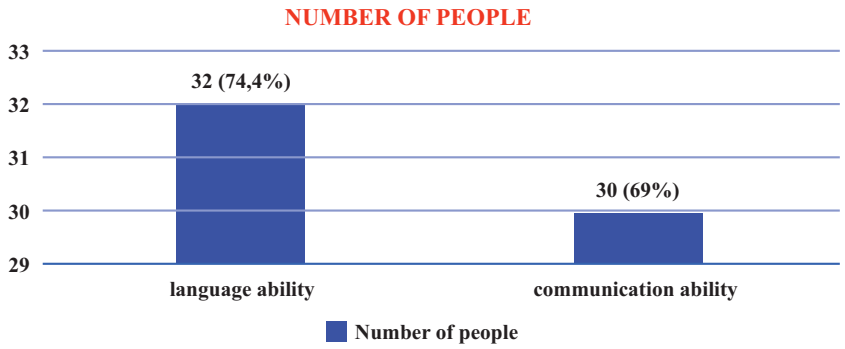

Fig. 2. Comparison of 43 cases before and after treatment showed that 32 cases (74.4%) had improved their language ability significantly, and 30 cases (69%) had improved their communication ability significantly

Table. 1

Test results of 45 autistic children

Project	Head CT	Assessment of the oral motor function	Intelligent development evaluation
Participate in the inspection	14 (100.00%)	3 (100.00 %)	35 (100.00%)
The result is abnormal	6 (42.86%)	3 (100.00%)	31 (88.57%)

1 in the music group, 43 cases were treated, 33 cases were treated after treatment, and 10 cases were quit midway. Fig. 2: Comparison of the effects of 43 cases before and after treatment showed that 32 cases (74.4%) had significantly improved their language ability, and 30 cases (69%) had significantly improved their communication ability.

As shown in Table 1, the physical condition of the participating children was evaluated, among which 14 autistic children underwent head CT examination, 3 autistic children underwent oral motor function evaluation, and 35 autistic children underwent intelligent development evaluation. Children with autism rating Scale, children with autism parents rating Scale and repetitive behavior evaluation were used. 0-6 years old mental development test, ABR test, child psychology scale, etc.

6. DISCUSSION

Autism is a serious disease that affects children's physical and mental health, and its onset is insidious, and it is not easy to be detected and noticed in the early stage. Autism can significantly affect personality development, employment opportunities and social interactions. The long-term course of asD depends on the individual presentation of each patient. There is no specific treatment for autism, and only supportive treatment can be given in individual symptomatic areas.

The main manifestation of autism is communication disorder, including the following two aspects: (1) Non-verbal communication disorder, children with this disorder often cry or scream to express their discomfort or need. Lack of corresponding facial expression, rarely nod, shake head, wave hands and other movements to express their will. (2) Speech communication disorder, children with this disorder have obvious difficulties in speech communication, including: impaired language comprehension to varying degrees; speech development is delayed or not developed, there are also some children before 2-3 years old had expressive speech, but later gradually reduced, or even completely disappeared; abnormal speech form and content: children often have imitation speech, stereotyped and repeated speech, grammatical structure, common errors in personal pronouns, intonation, speed, rhythm, stress and other abnormalities; impaired speech use ability: although some children can recite children's songs and advertising words, they seldom communicate with words, and will not put forward topics, maintain topics or only rely on stereotyped and repeated phrases to talk, entangling in the same topic.

Folding is a pattern of narrow interest and rigid repetition. Children with this disorder are less interested in toys and games, and more interested in objects that are not usually toys, such as wheels or bottle caps, which are round and swivel. Some children also develop attachment to inanimate objects such as plastic bottles and sticks. Children's behavior is often very rigid, such as: often do things in the same way or play with toys, items in a fixed position, go out to the same route, eat only a few kinds of food for a long time. And the regular occurrence of stereotypical repetitive movements and strange and strange behavior, such as repeated jumping, staring hands in front of the eyes, flapping or tiptoe walking.

Other symptoms: about 3/4 of children with this disorder have mental retardation. About 1/3 to 1/4 of the children have epilepsy. Some children with low intelligence can also appear "autistic talent", such as music, calculation, date calculation, mechanical memory and recitation and other out-

standing performance, known as "idiot savant".

It is reported that music therapy is extremely effective to children with autism, for children with autism, music is the best medicine, they can communicate through music and the world better, take music therapy and compose training for autistic children to intervene, can adjust their mental state and behavior, improve the treatment curative effect, improve the function of speech [5-6]. In this paper, 43 children with autism and autism spectrum disorder were analyzed and studied. It was found that the onset age of autism was mostly 1 year old, and the male to female ratio was 6:1 ~ 9:1, which was very consistent with the literature [6]. China has the largest population in the world, with about 300 million children and about 2 million autistic children. Shenmu city ranks the most northern part of Shaanxi Province, with the largest annual economic income in China and a GDP of 184.8 billion yuan last year. The city has a population of 571, 900, with 22.06% of children under the age of 14. The research shows that there is no direct causal relationship between economic development and the occurrence of autism, and more attention should be paid to the occurrence and early detection of autism in economically developed areas, and the symptoms of autism are mainly language and communication disorders. We can also adopt the design and application of a head-mounted display (HMD) immersive virtual reality system to improve and train the emotional and social skills of children with autism spectrum disorders [7, 8, 9, 10].

Autism treatment principles: ① early discovery, early treatment. The earlier the treatment age, the more obvious the improvement degree; ② Promote family participation, so that parents become partners or participants in treatment. Children themselves, child health care doctors, children's parents and teachers, psychologists and society should participate in the treatment process to form a comprehensive treatment team; ③Adhere to the comprehensive treatment training program with non drug therapy as the main, drug therapy as the supplement, and the two mutually promote; ④ The treatment plan should be individualized, structured and systematic. According to the children with different conditions for treatment, and according to the treatment response at any time to adjust the treatment plan; ⑤ treatment, training at the same time to pay attention to the body of children.

SENSORY INTEGRATION TRAINING

Sensory integration training therapy was founded by Ayres in the United States. It was mainly applied to the treatment of adhd and learning disabilities in children at first. As there are common sensory and perceptual abnormalities in children with autism, this method is also widely used in the treatment of children with autism. The therapy, which uses play facilities such as skateboards, swings and balance beams to train children, has been reported and observed to be effective in reducing hyperactivity and increasing language in children with autism. Other therapies similar to sensory integration include auditory integration, music therapy, chiropractic, squeeze therapy, hug therapy, and touch therapy. The efficacy of sensory integration training is controversial abroad and has not been recognized by mainstream medicine.

THE ROLE OF FAMILY IN AUTISM EDUCATION AND TRAINING

Education and training for autism is not solely a medical issue. The socioeconomic status of the family, as well as parental attitudes, environmental or social support and resources, all influence the outcome of a child. With comprehensive education and training, coupled with medication, the prognosis of children with autism can be significantly improved, and a significant proportion of children may gain the ability to live, study and work independently, especially those with Asperger's syndrome and high-functioning autism. In the process of education or training, three principles should be adhered to: (1) tolerance and understanding of children's behavior; (2) correction of abnormal behaviors; (3) the discovery, cultivation and transformation of special abilities. Training should be family-centered, while paying attention to the full use of social resources, set up day training and education institutions, while training children, but also to spread relevant knowledge to parents, autism education and treatment is the main measures. Parents need to accept the facts, overcome the psychological imbalance, and properly handle the relationship between children's education and training and parents' life and work. With love, patience and perseverance, we actively engage in children's education, training and treatment, and establish long-term consultation and cooperation with doctors.

Prognosis: This disorder is a chronic course of disease with poor prognosis. About 2/3 children cannot live independently in adulthood and need lifelong care and maintenance. The prognostic factors included IQ, communicative language at age 5, and education and training. Planned medical and corrective education early and consistently improves outcomes [11].

7. CONCLUSION

Autism can significantly affect personality development, employment opportunities and social interactions. Because children with autism are unable to communicate effectively, they lack essential survival and social skills, which have a significant influence on their everyday lives, education, and future employment prospects. In economically developed places, more emphasis should be paid to the development and early detection of autism, whose symptoms are primarily language and communication difficulties.

CONSENT

As per international standard, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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PSYCHOLOGICAL RESEARCH PROGRESS IN LUNG CANCER PATIENT

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ABSTRACT:

(1) through research, cancer patients provides the theory basis for psychological problems to provide effective nursing measures;(2) by improving the psychological problems of the cancer patients, and improve the family care of enthusiasm, make improving patient's quality of life.Methods by hownet collection in lung cancer patients with psychological problems for the keyword for screening collection of literature.Results according to the literature analysis results showed that age, education level, place of residence, family income and other demographic factors and cancer staging in patients with lung cancer chemotherapy, coping styles and other factors have a certain degree of influence psychological problems.Conclusion patients with different ways lead to varying degrees of psychological problems, with active approach is given priority to, not only reduce the patient's psychological pressure, can also be disease treatment and recovery of the patients with positive effect.

In recent years, with the development of the society, all kinds of disease incidence increased year by year, especially the malignant tumor. Malignant tumor is a large family of diseases collectively, their common characteristic is the body cells lose normal regulation, abnormal unchecked growth and differentiation, and local tissue invasion and migration in the distance. Malignant tumors can happen at any age, any organ of any organization, its pathogenesis and harmful environmental factors, lifestyle, and closely related to genetic easy sensibility. Most of the early detection of cancer could be cured.Common malignant tumor in the world have stomach cancer, breast cancer, non-hodgkin's lymphoma, lung cancer, esophageal cancer and so on, all have a trauma to the human body big and difficult to cure, are a serious threat to people's health. Among them, the lung cancer is originated from the lungs or bronchial mucosa gland malignant tumor, fastest growing morbidity and mortality. Nearly 50 years of many countries have reported lung cancer incidence and death rate were significantly increased.The latest cancer burden data for 2020 released by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) show that lung cancer ranks second in the total number

of new cancers worldwide (11.4% incidence); With 1.8 million deaths due to lung cancer, its mortality rate (18 percent) is far higher than that of other cancer types, ranking first among cancer deaths. China's cancer incidence rate (23.7%) and mortality rate (30.1%) rank first in the world. However, lung cancer rates (17.9 percent) and death rates (23,8 percent) were far higher than those of other cancers. The incidence of lung cancer is also different between genders. According to the Interpretation of the 2020 Global Cancer Statistics Report published by Liu Zongchao [1] et al., it is known that among the statistics of the new cases of male cancer worldwide in 2020, males are most often diagnosed with lung cancer (accounting for 14.3% of the new cases). Lung cancer (8.4 percent) ranked third among new cancer cases among women. Therefore, lung cancer has become one of the malignant diseases threatening human health.

Numerous studies have demonstrated that the incidence of lung cancer is associated with long-term heavy smoking.According to the ministry of health issued "in the report, the harm to smoking, according to China's smoking rates are still higher levels, smoking and secondhand smoke exposed huge threat to people's health has, for many diseases, especially in the pathogenesis of lung cancer because of one of [3]. In addition, chronic obstructive pulmonary disease, such as coal dust exposure, first-degree relatives home family history of lung cancer, genetic factors were the risk factors of lung cancer.Treatment of lung cancer is surgery, radiotherapy and chemotherapy. And chemotherapy is the main treatment, patients with advanced lung cancer in the kill cancer cells but also damage the body's normal cells with itself, toxic and side effect is obvious.Especially some patients need high doses of chemotherapy, the patients with mental and physical damage more apparent [4]. After the lung cancer patients is common in lung cancer as the worst one of malignant tumors, tumor invasion led to patients have difficulty breathing, pain, chest tightness, the symptom such as cough up blood. Lung cancer has a high mortality, treatment costs, treatment, great burden, hide and recurrence rate is higher a series of negative characteristics, physiological and psychological of patients and their family members bring different levels of pressure force, to the patient's quality of life and patients' families bring a certain degree of psychological torture [5].This study on lung cancer patients psychological research progress.

1. DEMOGRAPHIC FACTORS

Many scholars on the issue of psychological studies the lung cancer patients.Xue-jiao Chen [6] and so on postoperative psychological distress in patients with lung cancer study, points out that psychological distress is multiple factors cause unpleasant individual emotional experience, including psychological, social, spiritual, can range from mild weakness, fear, turn into painful, serious psychological problems such as anxiety, the higher incidence of factors, the patients' gender, age, family income, etc.

1.1 RESIDENCE

To live is different, there is a big difference to the influence of disease on the patient.According to jiang a bell [7] later period lung cancer chemotherapy patients in rural areas, such as psychological distress and coping styles of research, said in patients living in the countryside, often because of intractable disease itself and the adverse reaction of chemotherapy and produce a series of psychological problems, may be related to rural patients inner tenacity, relatively conservative, not easily show really think about, and patients with advanced disease of pain pain can also affect the psychological feelings.This type of patients may be: (1) the low income, disease to itself and some economic problems on the family;(2) patients seeking social support, and limited ability to network support and a series of complicated procedures let the victim is helpless and despair;(3) some patients to disease cognition is not clear, think infectious lung cancer, the patients received due to the bad environment around the eyes and cause mental stress; (4) in patients with insufficient understanding of treatment, the medical staff have limited language understanding, increase a patient's own psychological distress; (5) part of disease in patients with refractory appear to yield the mental state, because of the environmental impact can't send inner pressure, the longer it inside the backlog of patients with negative emotions lead to psychological stress, depression, anxiety and other undesirable mood.

1.2 THE AGE

Psychological distress is a kind of multiple factors is given priority to with spiritual crisis, such as emotional crisis performance of psychological barriers, individuals will withstand pain in heart for a long time for its survival quality, disease rehabilitation, etc. A certain degree of influence., according to a survey of residents in our country now cancer death ratio increased year by year, elderly patients often significant psychological distress.Because older elderly patients with lung cancer, poor state of body functions, limited knowledge of diseases and patients and so lead to mental health status of the elderly patients and the prognosis is worse.And because of the high cost of treatment will bring economic poor families larger economic pressure, a series of factors led to the deterioration of the patients pain in heart.

1.3 THE ECONOMY

Lung cancer as a major disease, trauma, a serious threat to the patient's life, lead to mental patients, physiological, social function and a series of negative change, affecting the quality of life.Chen Sijuan [8] psychological distress in patients with lung cancer chemotherapy results showed that lung cancer chemotherapy patients after illness factors such as working condition, the types of health care, disease stage directly affects the degree of psychological distress.Poor economic condition of family because of the high to afford disease treatment costs and increase their psychological burden.Jiang Dandan [9] and other studies have found that patients by from disease and loss of working ability, make domestic economy severely affected, make the not rich family added more burden, resulting in patients who suffer severe psychological phenomenon.

1.4 THE TUMOR STAGING

Some scholars according to the survey, the higher the tumor stage, the higher the severity of the disease, the worse prognosis and survival, the patient's psychological distress and pain, the more intense.

1.5 LEVEL OF EDUCATION

Different education level of patients after view of disease and illness

state of mind has great difference.He Yi [10], etc. Research shows that patients with higher level of education that the strength of its ability to learn, told of the diagnosis of the disease will be the main study, familiar disease related knowledge, by learning to know how to deal with problems associated with disease, and patients with itself also has a certain ability to lessen their negative emotions, to find a way to ease pressure, keep the degree of psychological distress.

2. COPING STYLE

coping style also called coping strategies, is individual during stress should be a means of passion, to keep the psychological balance, is refers to the individual in the face of setbacks and pressure force cognition and behavior, also can be called the coping strategies or coping mechanism.It is the process of psychological stress an important intermediary regulation factors, individual coping style affects the nature of the stress response and strength, and then adjust the relations between the results of the stress and stress.Zhang [11] on the mental health of patients with lung cancer, such as the study also showed that the mental health status of the patients with lung cancer and its age, course and level of education, income and other factors, and put forward the patients in the relationship between coping style and mental health status, among them, the negative coping styles against the patient's physical and mental health;And positive coping styles can alleviate the pressure of the mental work, improve the patient's psychological adaptability.

3 PSYCHOLOGICAL ELASTIC

Resilience refers to the individual in a major trauma through their own psychological adjustment when beginning to restore to the original state, in the social support and mental health, anxiety sensitivity and mental health, social support and coping styles of play a role of intermediary effect.Tiki [12] on lung cancer patients in the study of mental flexibility, points out that psychological elasticity refers to the individual in case of serious psychological trauma through adjusting the ability to return to original state, their psychological elasticity is larger, the stronger the ability to adapt to the outside world, to help patients as soon as possible to adapt to the change of role, to relieve the patients psychological burden.

4. HUMANISTIC CARE

Malignant disease by the patient, rehabilitation, etc., bring great pain patients.Through the research of many scholars, for the treatment of malignant tumor of the clinical nursing concerns from a single and disease control, turned to focus on the patient's physical, psychological and social adaptation ability, etc.Many scholars pointed out that against the evil tumors in patients with psychological intervention treatment.Bai Yunbo [13] in psychological therapy intervention for patients with malignant tumor such as mentioned in the study, the influence of the intervention is the focus of the malignant tumor diseases take effective anxiety, depression, mood change a good strategy, according to the research found that some patients are not clear about their illness cognition, to timely in the process of psychological therapy intervention for patients with a certain degree of health education, reducing to disease in patients with exaggerated to impact their mood swings.TongChunYu [14], such as psychological therapy for patients with advanced lung cancer in the study of personnel request to treatment, and patients after admission will produce more emotions, such as mental tension, anxiety, fear, he put forward and each patient treatment personnel to establish relationships of mutual respect, mutual help, and through the psychological intervention for the treatment of people to alleviate the mood of patients with anxiety depression, to guide the formation of the correct ideological cognition, allow patients to correct understanding of diseases, to strengthen cooperation and nursing personnel.In the doctor-patient relationship, doctor should constantly improve the self theory knowledge reserves and operating ability, want to often communicate with patients, understand the true idea, help patients bear bad mood, improve its adherence to treatment.

5. SUBTOTAL

Above all, lung cancer worldwide as one of the highest morbidity and mortality of malignant tumor, not only poses a great threat to people's health, the psychological, physiological, social function also has a great influence.According to the literature analysis results show that: (1) demographic factors: the smaller the age is higher, the degree of psychological distress and pain in patients with age is smaller, often family, social responsibility, the greater the for their psychological pressure is big; The higher education level, clear understanding of the disease, can cooperate with the treatment of diseases, more conducive to the recovery of disease;The family per capita income is lower, the higher the degree of psychological distress and pain.May be related to low income lead to fewer available social resources, thus unable to obtain adequate treatment;Cancer staging is higher, the higher the severity of the disease, the stronger the patient's confidence in treatment and psychological distress.(2) coping styles: negative coping ways, patient adherence to treatment is not strong, and thus affect the patient treatment and progress of the disease, strengthen the degree of psychological distress in patients with;And positive coping styles significantly improve the patients' adherence to treatment and treatment effect, reduce the patient's psychological stress, compressive ability and make it improved, thus reducing the patient's psychological distress and pain.(3) resilience: patients, the greater the elasticity of its to the outside world to adapt to the more powerful, more can transform their roles for patients, the stronger the acceptance of the disease, can be a good match and the doctor's treatment;(4) the humanistic care: humanistic nursing care can give patients better understand the real thoughts of patients, give patients the most need of help, can help patients more bad mood dredge, improve patient compliance, beneficial to patients with the treatment and prognosis of the disease.

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COVID-19 in Hospitalized Children: A Single-Center Retrospective Study of 604 patients

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Abstract

Introduction: In 2019, a new strain of Coronavirus - Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) emerged first in China, and then it spread worldwide wreaking havoc on numerous countries and numerous lives. In the pediatric population, disease progression is relatively milder, however, it is of vital importance to gather and analyze the existing data.

Methods: We reviewed and gathered data from all the hospitalized patients with Coronavirus Disease 2019 (COVID-19) diagnoses during the period between November 2020 and March 2021. Medical records of 604 children aged between 0-18 years were collected at Children's New Clinic after Irakli Tsitsishvili.

Results: The results showed the importance of Ferritin and D-dimer as inflammatory markers and a direct correlation between high numbers and severity of the disease. D-dimer, however, in comparison to the adult population, is more likely to be predictive of a severe inflammatory process, rather than a thrombotic event.

Conclusion: We can conclude that SARS-COV-2 causes significantly milder disease in children than in adults. However, the infection spreads much quicker among children because of low adherence to recommended protective actions habits and high morbidity can still cause issues since multiple complications can occur during and after COVID-19.

Keywords: MIS-C, AKI, SARS-COV-2, Bilateral Pneumonia, Severe COVID-19, D-Dimer in pediatric COVID-19, Ferritin in pediatric COVID-19, LDH in Pediatric COVID-19.

Introduction

In 2019, a new strain of Coronavirus SARS-COV-2 emerged first in China, and then it spread worldwide wreaking havoc on numerous countries and numerous lives **[1-3]**. Therefore, a pandemic has been declared by WHO **[4]**. In general, COVID-19 cases in pediatric patients have been rather mild compared to the adult population resulting in a lower hospitalization rate and close to zero death rate **[5-8].** Although, it is of vital importance to gather and analyze the existing data from the hospitalized patients to further increase positive outcomes for this population. Thus, we will be reporting clinical, instrumental and laboratory data that have been acquired from 604 patients who tested positive for SARS-COV-2 and were hospitalized in Children's New Clinic After Irakli Tsitsishvili, which is the biggest pediatric COVID center in Georgia.

Methodology

This study will contain a retrospective review of medical records for 604 pediatric patients with ages 0-18 years, who had a laboratory-confirmed diagnosis of COVID-19 and were hospitalized between November 2020 and March 2021. The study was conducted following the Helsinki Declaration, 1975, and Tbilisi State Medical University (TSMU) ethics committee approval (approval by meeting record 9, 13.01.2022). The data was gathered at Children's New Clinic after Irakli Tsitsishvili.

Classification of Severity

The severity of the disease was classified into two groups: severe and non-severe **[9]**. Patients who were considered severe had either one or multiple of these conditions: dyspnea with desaturation ($O_2 < 92$ %), acute respiratory distress (ARD), shock, encephalopathy, acute kidney injury (AKI), problems with coagulation, symptomatic myocardial involvement **[10]**. All the patients who didn't develop these conditions were considered non-severe.

Laboratory Assays

The laboratory assay data were collected in the following fashion: baseline, which was collected and run upon admission of the patient; intermediary, which was collected and run in between discharge and admission; and endline, which was collected and run right before discharge. It should be noted that not all patients were subjected to intermediary and endline examinations, so the data could not be collected for those patients. The main laboratory assays that will be discussed here are Complete Blood Count (CBC), C-Reactive Protein (CRP), Alanine transaminase (ALT), Aspartate transaminase (AST), Ferritin, D-Dimer, Lactate dehydrogenase (LDH), and Procalcitonin (PCT).

Instrumental Examinations

Instrumental examinations, such as ultrasonography (US), radiography, and computed tomography (CT), were also collected from patients who underwent either one of these examinations.

Statistics

Microsoft Excel 2016 was used for basic statistics and the creation of figures specifically for this study.

Study Limitations

The limitations of this study are that it is a retrospective study and it reviews the medical record of only hospitalized patients, which means the data here cannot be used to generalize to the whole population. One more limitation is the period that the study was held, it should not be generalized to every patient since variant-specific properties might apply.

Results

General Cohort Information

During the period between November 2020 and March 2021, 604 patients were hospitalized at Children's New Clinic (CNC). Out of 604, 290 were female and 314 were male. The majority of the patients (462/604, 76.5 %) were 5 years and younger. The most frequent presenting symptoms and signs were fever (450/604, 74.5 %), cough (300/604, 49.7 %), vomiting/nausea (120/604, 19.8 %), diarrhea (100/604, 16.5 %), catarrhal signs (76/604, 12.6 %), dyspnea (50/604, 8.3 %), headache (25/604, 4.1 %), abdominal pain (20/604, 3.3 %), myalgia (6/604, 1 %). No lethal outcome was observed **(Table 1)**.

Hospital Stay Duration

The average hospital stay duration for all patients was 6.6 days. However, the mean hospital stay duration for patients younger than 2 years was 11.8 days. The longest hospital stay was 50 days and the shortest was 1 day. In total 325 (53.7 %) patients stayed five days or less in the hospital, out of the 299 (95.1 %) were considered non-severe, 16 (4.9 %) were severe. In the remaining 279 (46.3 %) children, the hospital stay was more than 5 days. Out of those patients, 213 (76.3 %) were considered to be non-severe, and 66 (23.7 %) were severe.

Severity of Disease

Out of 604 patients, 522 (86.4 %) were considered non-severe and 82 (13.6 %) were considered to be severe. The majority of the severe patients were older than 5 years, therefore, out of 462 children, who were younger than 5 years **(Table 1)**, only 29 (6.2 %) were considered to be severe.

	Number of Patients	Percentage (%)
Age < 5 years	462	76.5 % (462/604)
Age < 2 years	185	30.6 % (185/604)
Pneumonia	33	9.9 % (33/334)
Desaturation among patients with pneumonia	10	30 % (10/33)
Severe	82	13.6 % (82/604)
Pericardial Effusion	7	8.5 % (7/82)
Pleural Effusion	8	9 % (8/82)
Multisystem Inflammatory Syndrome in Children	4	0.6 % (4/604)
Acute Kidney Injury	2	0.3 % (2/604)
Symptomatic Thrombotic Event	0	0
Death	0	0

Instrumental Examinations

Radiographic examination of the chest was performed in 367 patients out of which 33 (8.9 %) patients had abnormal results and 334 (91.1 %) did not present changes. Pathologies, such as bilateral pneumonia (7/367, 1.9 %), pneumonia (23/367, 6.3 %), pneumothorax with pneumonia (3/367, 0.81 %) were detected. The maximum hospital stay duration was 50 days for 1 patient and the minimum stay duration was 3 days for 1 patient as well. 22 patients (67 %) had hospital duration of 14 days or shorter, however, 11 patients (33%) had hospital stay duration longer than 14 days.

7 cases of pericardial effusion were detected by ultrasound (US) examination. Out of those seven patients, 5 were not showing typical signs and symptoms of moderate or severe pericardial effusion, on the other hand, 2 patients had dyspnea, while no lung injury was detected. 1 patient had aggressive disease progression with significantly

elevated CRP (120 mg/L) and White Blood Cells (WBC) (20.2 x 103) levels, although, no clinical signs or symptoms for pericardial effusion were detected. 8 cases of pleural effusion were detected, and most of them were linked to lung injuries.

Laboratory Assays

CBC

Blood samples for CBC were retrieved from all the patients at the baseline, 172 intermediary samples and 376 endline samples were collected. The mean WBC count at the baseline was 7.86 x 103, the mean WBC at intermediary collection was 7.8 x 103 and at the endline 8.09 x 103 **(Figure 1)**. The mean band count was 5.7 % at the baseline, 4.3 % at the intermediary collection, and 2.9 % at the endline. The mean lymphocyte count was 44.5 % at the baseline, 46.11 % at intermediary collection, and 54.3 % at the endline. Patients who stayed at the hospital for more than five days and were considered severe had a mean WBC count of 9.1 x 103 at the baseline, 8.17 x 103 at an intermediary collection, and 7.8 x 103 at the endline. Whilst, their mean band count was 7.6 %, 3.5 %, and 2.3 %, respectively at the baseline, intermediary, and endline.

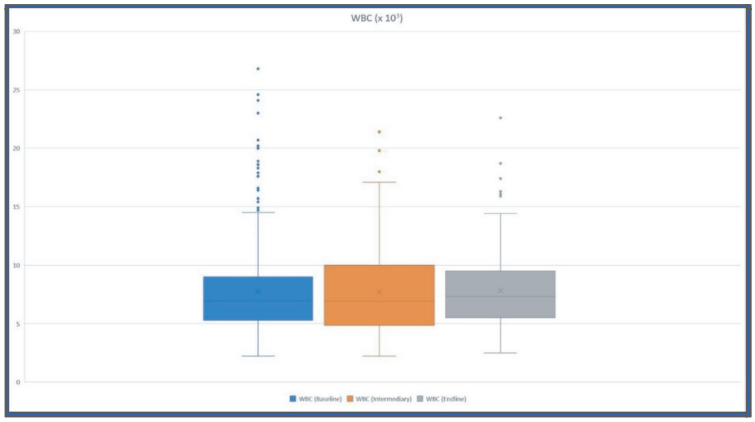

Figure 1: The figure depicts WBC count ranges at the baseline, at an intermediary, and at the endline. The highest values were 26.8 x 103, 21.6 x 103, and 22.6 x 103, respectively at the baseline, intermediary, and at the endline.

CRP

All patients at the baseline were subjected to collecting samples for CRP measurement, 81 at the intermediary and 183 at the endline.

The mean results were as follows, 13.19 mg/L at the baseline, 13.78 mg/L at the intermediary collection, and 7.47 mg/L at the endline **(Figure 2)**. A maximum CRP level of 143 mg/L was detected. At the baseline, CRP level above 50 mg/L was detected in 37 patients, out of which 13 (35 %) were considered severe. CRP level below 50 was detected in 567 patients, out of which only 61 (10.8 %) were considered severe.

In children who had CRP levels above 50 mg/L, 10 (27 %) had pneumonia, and half of them had bilateral lesions of the lung. Whilst, out of the children who had CRP levels below 50 mg/L pneumonia was detected in only 23 (4.01 %) and 4 had bilateral lung injury.

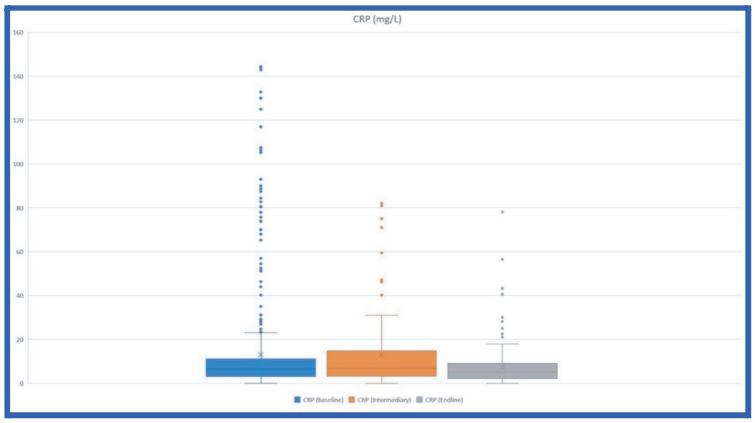

Figure 2: The figure depicts CRP level ranges at the baseline, at an intermediary, and at the endline. The highest values that we detected were 143 mg/L, 80.9 mg/L, and 78.08 mg/L, respectively at the baseline, intermediary, and at the endline.

Liver Function Tests (ALT, AST)

Sample for AST and ALT measurement was taken from 538 patients at the baseline, 38 at an intermediary, and 27 at the endline. Mean

values for AST were 38.2 IU/L, 41.9 IU/L, and 44 IU/L, respectively at the baseline, intermediary, and endline. Whereas, the mean values for ALT were 25.1 IU/L, 30.9 IU/L, and 32.16 IU/L **(Figure 3)**.

AST was 100 IU/L or higher in 14 patients. Their average hospital stay duration was 20 days (50 max., 3 min.). Out of the 9 (9/14, 64 %) were considered to be severe, 4 (4/14, 29 %) had pneumonia with a single case (1/4, 25%) of confirmed bilateral lung injury. At the same time, the number of severe patients, among those who had AST < 100 IU/L, was 74 (74/524, 14.1%) and 27 (27/524, 5.1 %) had pneumonia with 7 cases (7/27, 26 %) of the confirmed bilateral lesion.

ALT was 100 IU/L or higher in 9 patients. Their average hospital stay duration was 29 days (50 max., 9 min.). Out of these children, 8 (8/9, 89 %) were considered to be severe, and 4 (4/9, 44 %) had pneumonia with a single (1 /4, 25 %) bilateral lesion to the lungs. Among those, who had ALT < 100 IU/L, only 62 (62/538, 11.5 %) were considered to be severe, 26 (26/438, 4.8 %) had pneumonia with 7 cases (7/26, 27 %) of bilateral lung injury.

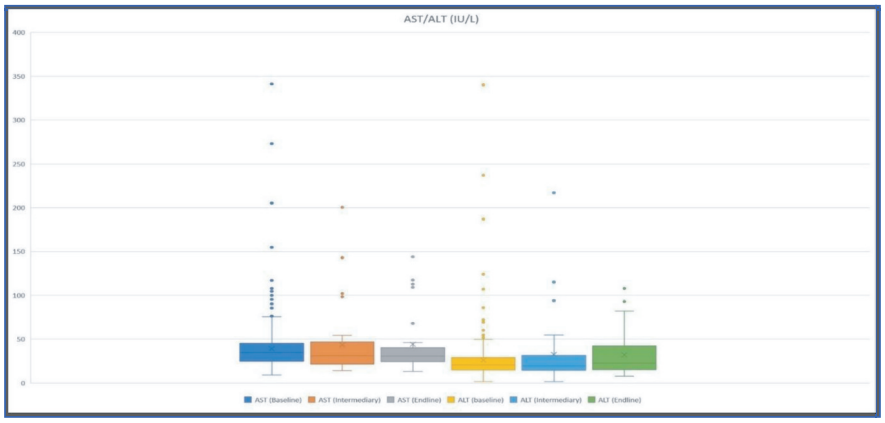

Figure 3: The figure demonstrates ranges of AST and ALT levels at the baseline, at an intermediary, and at the endline. The highest values for AST were 341 IU/L, 200.5 IU/L, and 144 IU/L, whilst for ALT 340.1 IU/L, 217 IU/L, and 107.8 IU/L, respectively at the baseline, intermediary, and at the endline.

Ferritin

Ferritin levels were measured in 182 children at the baseline, 45 children at an intermediary, and 53 at the endline. Mean values were 158 ng/ml, 181 ng/ml, and 161 ng/ml, respectively at the baseline, intermediary, and ending **(Figure 4)**.

Patients who had ferritin values of 500 ng/ml and higher at the baseline had a mean hospital stay duration of 11 days (max. 35, min. 2). 23 patients had such ferritin values, out of which 14 (61 %) were considered to be severe and 9 (39 %) were non-severe. 4 (4/24, 17%) had pneumonia and all of them had bilateral lesions.

On the other hand, 158 patients had ferritin values lower than 500 ng/ml at the baseline. Their mean hospital stay duration was 3 days (max. 5, min. 1). 27 (27/158, 17 %) were considered to be severe, 131 (131/158, 83 %) were non-severe. 13 (13/158, 8 %) had pneumonia and only 3 out of 13 had bilateral lung injury.

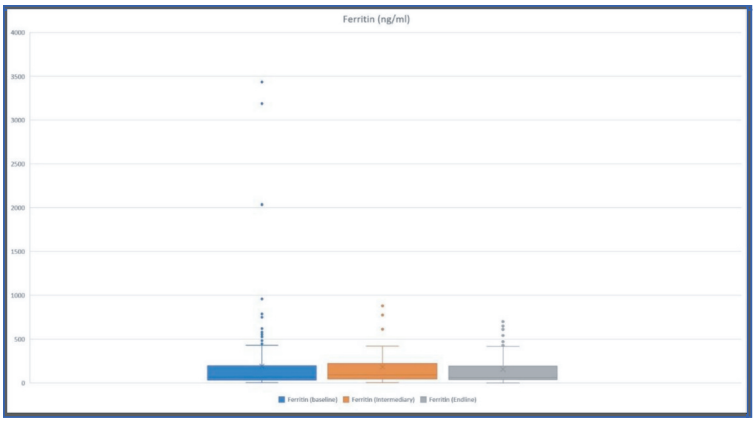

Figure 4: The figure shows ranges of ferritin levels at the baseline, at an intermediary, and at the endline. The highest values for ferritin were 3434 ng/ml, 879 ng/ml, and 650 ng/ml, respectively at the baseline, intermediary, and at the endline.

D-Dimer

D-Dimer was measured at the baseline in 125 children, 61 at an intermediary, and 70 at the endline. Mean values were 1.99 mcg/ml, 5.92 mcg/ml, and 1.64 mcg/ml, respectively at the baseline, intermediary, and ending **(Figure 5)**.

Among the patients who had hospital stays more than 5 days, the mean D-Dimer value at the baseline was 2.41 mcg/ml, whilst those who stayed 5 days or less had a mean value of 1.57 mcg/ml.

In those patients who were considered to be severe and had their D-Dimer measured mean was 5.4 mcg/ml.

We also detected those 8 patients had D-dimer levels above 2 mcg/ml (13.78 mcg/ml, 18.03 mcg/ml, 2.01 mcg/ml, 2.3 mcg/ml, 2.4 mcg/ml, 3.17 mcg/ml, 3.3 mcg/ml, 4.13 mcg/ml), and were considered non-severe plus there was a serious discrepancy between these results and other laboratory results together with the clinical course of the disease. Therefore, the results were re-run and all of these patients had their D-dimer results lower than 0.5 mcg/ml.

There were also patients, whose clinical course and other laboratory results corresponded with the high D-Dimer levels. For example, one patient, whose D-Dimer was 20.5 mcg/ml, LDH was as high as 7696 U/L, serum creatinine was 2.17 mg/dl, and had a severe course of the disease with AKI and Multisystem Inflammatory Syndrome in Children (MIS-C). Another example was a patient who had D-Dimer 35.2 mcg/ml, ferritin as high as 3434 ng/ml with progressive kidney function deterioration, and in the end diagnosis of MIS-C was considered. There also were 5 patients whose D-dimer levels were also skyrocketing (1.85mcg/ml, 1.9 mcg/ml, 10.7 mcg/ml, 14.6 mcg/ml, 17.85 mcg/ml), all of them had signs for respiratory failure, and radiologically 3 of them had bilateral lung lesions. 2 patients with hypovolemic shock had significantly elevated D-Dimer levels (10.7 mcg/ml, 2.6 mcg/ml).

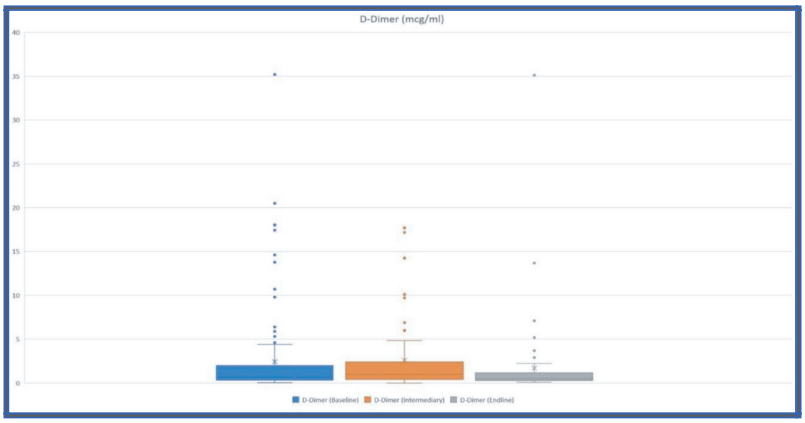

Figure 5: The figure presents ranges of D-Dimer level at the baseline, at intermediary, and at the endline. The highest values were 35.2 mcg/ml, 17.17 mcg/ml, and 35.1 mcg/ml, respectively at the baseline, intermediary, and at the endline.

LDH

LDH levels were measured in 151 patients at the baseline, in 13 patients at an intermediary, and in 15 patients at the endline. Mean values that were received were 498 U/L, 804.6 U/L, and 354.6 U/L, respectively at the baseline, intermediary, and ending **(Figure 6)**.

We detected two instances when LDH levels were higher than 1500 U/L at the baseline. Both of them had MIS-C.

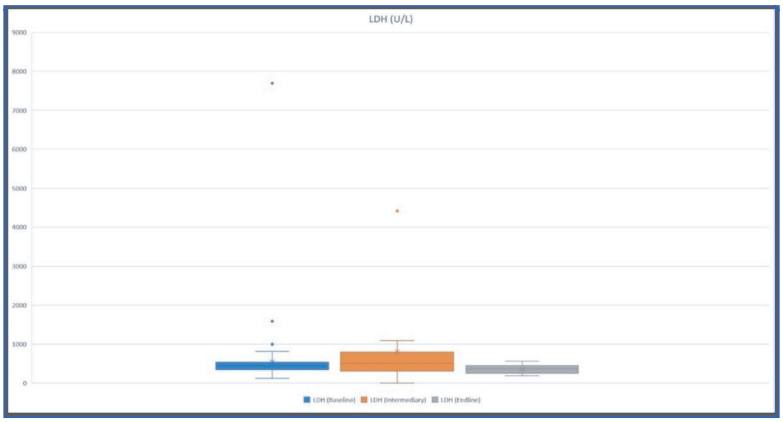

Figure 6: The figure shows ranges of LDH levels at the baseline, at an intermediary, and at the endline. The highest values were 7696 U/L, 4414 U/L, and 354.6 mcg/ml, respectively, at the baseline, intermediary, and at the endline.

Discussion

In this single-center retrospective study, we tried to analyze the vast amount of information that has been gathered at the Children's New Clinic after Irakli Tsitsishvili. Since the pandemic is still ravaging Georgia, we will continue to monitor and try to detect variant-specific characteristics of COVID-19.

The current data about the severity of SARS-COV-2-induced disease suggests that the clinical course is much milder in children than in adults, the data that we gathered are also suggestive of that **[11-16]**.

Information that was gathered suggests that children who were younger than 2 years had a longer hospital stay duration (6.6 days vs 11.8 days). Since the majority of the patients, who were considered to be severe were 5 years and older, we took a deeper look at the medical records for those below 2 years of age. A thorough analysis of their medical history showed us that inability of the caregiver to follow instructions for symptomatic treatment at home (mainly, adequate hydration) and the high risk of severe dehydration, hypovolemia was the reason for their prolonged hospital stay.

Radiographic data suggest that in the pediatric population lung involvement is significantly lower when compared to the adult population. As per our results, 33 cases of lung injury were confirmed out of 367 patients, which is 8.9 %. Whilst, in adults this number is drastically different and higher - it ranges anywhere between 47 % - 100 % **[17-21]**.

Pericardial effusion was detected by ultrasonography in 7 patients, out of which 2 children had dyspnea when no lung injury was observed. Whilst it is already a well-established fact that myocardial, pericardial, and coronary artery involvement is quite frequent in MIS-C **[22-24]** our data together with other publications might be suggestive of the fact that mild pericardial involvement with or without myocardial involvement might be more frequent than currently detected and might even be found in patients who did not develop MIS-C **[25,26]**.

We detected 4 patients with suggestive clinical and laboratory data who were considered to have MIS-C according to CDC criteria **[27]**. 2 of them had AKI, diarrhea, fever, gastrointestinal involvement (elevated AST/ALT) hypoalbuminemia, low platelet count, increased inflammatory markers (Ferritin, LDH, D-Dimer, Procalcitonin (PCT)), effusion was found in peritoneal, pericardial and pleural cavities, serum creatinine was increased in one patient (2.17 mg/dl), which had oliguria and hypertension, the other patients had progressively increased serum creatinine levels (last documented > 4 mg/dl), which eventually developed anuria and was transferred to a hospital with the capability of hemodialysis. 1 patient had a fever, vomiting, seizures, hypovolemia, and increased inflammatory markers (CRP, PCT, D-Dimer). The fourth one had a fever, vomiting, mucocutaneous involvement, effusion of the hip and knee joint, and significantly elevated inflammatory markers (CRP, D-Dimer, PCT). Blood cultures were negative for all of them. The minimum hospital stay was 15 days, maximum of 35.

CRP was highly predictive of severe disease when levels were above 50 mg/dl at the baseline, as opposed to levels below 50 mg/dl. Our data showed that in those children who had values > 50 mg/dl, 35 % (13/37) were considered severe and 27 % (10/37) had lung injuries, whilst 50 % (5/10) had bilateral injuries. Percentages were drastically different from those who had values below 50 mg/dl, 10.8 % (61/567) were severe, 4% (23/567) had pneumonia, and 17 % (4/23) had bilateral injuries to the lung. According to this data and other published data CRP can be a good tool in the assessment of the disease progression and suspecting serious complications such as MIS-C **[28-30].**

Increased AST and ALT levels equal to 100 IU/L and higher were highly predictive of severe disease according to the data. In the case of AST, children who had values > 100 IU/L had almost four times the chance of severe disease (64 % vs 14 %) and more than five times the chance of pneumonia (29 % vs 5 %). In the case of ALT, patients who had values > 100 IU/L had almost eight times the chance of severe disease (89 % vs 12 %) and almost ten times the chance of developing pneumonia (44 % vs 4.8 %). Similar findings have been found in other studies, reporting that levels below 100 IU/L were mostly detected in non-severe patients, however, values above that were frequently found in severe patients as well as in MIS-C cases **[31-33]**.

Ferritin levels were also quite useful in predicting serious complications or severe disease if the levels were 500 ng/ml or higher. These levels were also clearly associated with longer mean hospital stay duration (11 days vs 3 days). The number of severe patients in this group of children was as high as 61 % (14/23), while in those who had < 500 ng/ml, this number was 17 % (27/158). There was also a significant difference in the rate of pneumonia (17 % vs 8 %), all of the patients (4/4) who had ferritin levels of 500 ng/ml or higher had bilateral lung lesions, while in the other group – 23 % (3/13) had bilateral injuries. These data are also following other articles that have shown - ferritin levels can be an important marker of severe disease both in the pediatric and adult population, although, in most of these reports the pediatric population with high ferritin levels tends to have hyperinflammatory processes, which was not the case in the data that we are reporting **[34-38]**.

Our findings of D-Dimer indicated that if high levels (>2 mcg/ml) are detected and there are no other signs of a serious infection, it would be wiser not to panic, observe the patient and/or redo the testing to make sure that the received results are correct. On the other hand, the data suggest if there are signs of serious infection, complication, or other changes in inflammatory markers such as extremely high ferritin, or LDH, it should be taken into account so that we do not miss severe lung injury, AKI, MIS-C, etc. A thorough review of the medical records for the patients who had high D-Dimer suggested that in the pediatric population this was a sign of either a severe course of the disease or hyperinflammatory process rather than being

prognostic of a hypercoagulative state, the latter is also suggested and reported by multiple authors as well **[39-41]**.

We found that LDH was higher than 1500 U/L in two cases and both patients were considered severe, both of them had clinical and laboratory signs suggestive of MIS-C.

According to our data **(Table 1)** and other reported data, we can underline that severity of the disease among the pediatric population is significantly milder, although, it does not mean that either the caregiver or service provider should neglect the possible serious complications or severe course of the disease. Therefore, it would be wise to advise parents to vaccinate those, for whom the vaccine use has already been approved.

Conclusion

In the end, we can conclude that SARS-COV-2 causes significantly milder disease in children than in adults. However, the infection spreads quicker among children and high morbidity can still cause issues since multiple complications can occur during and after COVID-19. Also, it must be noted that high D-Dimer in this population should alert a pediatrician, if the clinical progression is also serious, to the possibility of a hyperinflammatory state as well as severe disease.

Author Contributions

All authors are responsible for the work described in this paper. All authors were involved in at least one of the following: [conception, design of work or acquisition, analysis, interpretation of data] and [drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content]. All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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A TECHNIQUE FOR IRRADIATING THE STERNUM USING PLASMA STREAMS FOR THE TREATMENT OF STRESS ULCERS CAUSED BY TRAUMA AND ACUTE ILLNESS

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ABSTRACT:

Diagnosis and treatment of formidable complication of critical conditions such as acute bleeding from stress gastroduodenal ulcers is still a rather complicated and difficult task.

We studied data on 560 critically ill patients on mechanical ventilation, of which in 42 cases bleeding from stress ulcers was revealed. The activity of bleeding from a stress ulcer and the assessment of the degree of hemostasis were determined according to the Forrest classification generally accepted in the world practice. Conservative treatment was carried out according to the generally accepted method. All patients received standard treatment aimed at stopping bleeding.

In order to eliminate one of the etiological factors of bleeding from stress ulcers (a decrease in the barrier function of the gastric and duodenal mucosa), we proposed and for the first time applied plasma therapy to the sternum to stimulate stem cell differentiation. It was found that this leads to the stabilization of microcirculation and an improvement in trophism in the gastroduodenal zone, which reduces the factors of aggression leading to the occurrence of stress ulcers.

With a hemostimulating purpose, 37 patients with stress ulcer bleeding were irradiated with a plasma stream of the sternum. Relapse of bleeding did not occur, after 5-6 procedures of plasma stimulation of stem cells, the pallor of the mucosa practically disappeared, erosive and ulcerative defects significantly decreased in size, and in some cases practically disappeared.

Key words: stress conditions, ulcer bleeding, plasma therapy.

THE ACTUALITY OF THE PROBLEM.

In conditions caused by acute diseases of various organs, severe injuries and after surgical interventions, acute stress ulcers and erosions of the gastrointestinal tract are frequent complications. Stressful situations for the body in these cases are shock, collapse, oxygen starvation of body tissues, acute liver and kidney failure. When several of these factors are combined, the risk of stress ulcers increases dramatically (1; 3; 7; 14).

In this case, the mechanism for the development of an ulcer is considered to be a violation of the interaction of factors of aggression and factors of protection of the mucous membrane of the stomach or duode-

num, when the factors of aggression begin to prevail over the factors of protection. The mechanism of ulcer development includes the release of stress hormones glucocorticoids and catecholamines into the blood, which stimulate the release of hydrochloric acid, reduce the production of gastric mucus, and contribute to the disruption of blood microcirculation in the wall of the stomach and duodenum (4; 9; 10; 13).

Because of microcirculation disorders, hemorrhages occur in the mucous membrane. Hemorrhages can be small or large. Then, in the place of hemorrhage in conditions of reduced protection of the mucosa, the destruction of the surface layer of the mucosa occurs - erosions form. Erosions gradually deepen and, reaching the muscular layer of the stomach or duodenum, turn into an ulcer. The main danger of stress ulcers is the possibility of massive bleeding from them. Diagnosis of these mucosal changes is very difficult and is often diagnosed late, or not detected at all in vivo. (2; 5; 6; 12).

MATERIALS AND METHODS.

We analyzed 560 case histories of patients treated in our medical centers from 2012 to 2022 about acute diseases of various organs, severe injuries and after abdominal surgery. Stress erosive and ulcerative changes in the gastric and duodenal mucosa were detected in 160 (28.5%) patients, bleeding from stress ulcers was observed in 42 (7.5%) patients, of which 22 were men and 20 were women. Age of the patients was 32-92 years. Most often, patients were in the age group of 60-70 years.

Among the patients, 34% had an acute cerebrovascular accident, 26% had a postoperative condition, 23% had acute respiratory failure of various origins, 12% had a critical condition due to sepsis, and 5% had other pathological conditions.

In the clinical picture, the greatest attention was paid to hemodynamic parameters, such as arterial blood pressure, the presence of tachycardia, the appearance of the so-called “coffee grounds” in the discharge from the stomach through the probe, the presence of liquid black stools - “melena”. An absolute sign of bleeding in the stomach or intestines was hematemesis or tarry stools. Laboratory blood tests revealed a decrease in hemoglobin, hematocrit, a decrease in the number of red blood cells. These indicators were important in a dynamic study, since their informative value in a single study was small. Also, special attention was paid to an important feature - a decrease in the volume of circulating blood. In 70%, there was a decrease in hemoglobin below 90 g/l, however, it should be noted that hemoglobin below 60 g/l occurred only in 12.5%. The number of erythrocytes is above 2.5 * 1012 units, was in 23% of patients, below 2.5 * 1012 units, in 55%, below 2.0 * 1012 units, in another 22% of patients.

When assessing the condition the authors took into account the anamnesis, data from clinical and special research methods (blood pressure, pulse, hemoglobin level, degree of change in hematocrit, erythrocytes, volume of circulating blood, indicators of the blood coagulation system). When determining the general condition of gastrointestinal bleeding, 4 degrees of its severity were distinguished in patients.

At the first degree of severity, the condition of the patients was relatively satisfactory, there was pallor of the skin, the maximum blood pressure remained at the level of normal values or decreased (but not lower than 100 mm Hg), the pulse increased slightly, the volume of circulating blood decreased by 10-15%, the coagulating activity of the blood increased, which is explained by a protective reaction.

The second degree of severity was defined as a state of moderate severity, pallor of the skin was noted, tachycardia developed, respiration became more frequent, and the maximum arterial pressure dropped to 80 mm Hg., hemoglobin - up to 50% of the norm, decreased volume of circulating blood by 20-25% and blood clotting.

The third degree indicated a serious condition: pallor of the skin, swelling of the face, blood pressure below 50 mm Hg., the number of red blood cells 2.0 * 1012 units. and less, hemoglobin fell to 25% of the norm, and volume of circulating blood to 60% of the normal value, blood hypocoagulation developed, and residual nitrogen increased.

The fourth degree of severity was characterized by a terminal state, from which the patient can be brought out only by resuscitation.

All patients underwent gastroduodenoscopy. Bleeding from a stress ulcer was mainly detected 2-3 days after admission to the hospital, in accordance with the time of development of stress ulcers.

All necessary laboratory tests and therapeutic and diagnostic endoscopy were performed during the first two hours of the patient's stay in the clinic. In addition, if necessary, auxiliary methods were used, such as ultrasound of the abdominal organs and X-ray examination.

When determining bleeding activity and assessing the degree of hemostasis, the Forrest classification was followed (8):

Forrest I: - active bleeding.

F-I a - jet, pulsating, arterial bleeding.

F-I b - venous, sluggish, parenchymal bleeding.

Forrest II: signs of ongoing bleeding.

F-II a - visible thrombosed vessel.

F-II b - fixed thrombus or clot.

F-II c - hemorrhagic impregnation of the bottom of the ulcer.

Forrest III: no endoscopic evidence of bleeding.

F-III - clean bottom of the ulcer, the absence of direct visual signs listed above in the presence of melena (no stigma).

With bleeding from stress ulcers, in our observations, arterial bleeding was noted (F - 1 a) - in 10% of cases,

flaccid venous bleeding (F - 1 b) - in 27%, a fixed thrombus or clot (F - 2 b) - in 31 % of cases, hemorrhagic impregnation of the bottom of the ulcer (F - 2 c) in 13% of cases. In 19%, a clean bottom was detected endoscopically, however, melena (F - 3) was noted in patients.

During endoscopy, the source of bleeding, localization of the ulcer, its size, and bleeding activity were determined. Stable hemostasis meant: the absence of fresh blood in the stomach and duodenum, the presence of a tightly fixed white thrombus, and the absence of visible vascular pulsation in the area of the source of bleeding. Under unstable hemostasis: in the bottom of the source of bleeding, thrombosed, pulsating vessels, red or brown blood clots; a loose red clot, the presence of old or fresh blood in the stomach or duodenum.

In almost all cases, the mucosa of the stomach and duodenum was pale with foci of hyperemia in the area of the mucosal defect (the area of the stress ulcer). In the lumen of the stomach there was a large amount of secretory fluid, mucus, liquid blood and blood clots.

Endoscopic diagnosis of the source of bleeding was started with gastroscopy performed with Gif Q-30 endoscopes from Olympus (Japan). In case of a satisfactory condition of the patients, the studies were performed under local anesthesia (Sol. Lidocaini 10% spray), in case of restless behavior of the patients, additional premedication was performed (Sol. Promedoli 2% -l.0; Sol. Atropini 0.1% -0.5; Sol. Relaniumi 0.5% -1.0 i/m).

RESEARCH RESULTS.

In 12 patients, a bleeding stomach ulcer was determined, in 30 - ulcerative bleeding of the duodenum. Gastric ulcer in 6 cases was localized along the lesser curvature in the area of the body of the stomach, in 3 cases on the greater curvature and in 3 cases in the pyloroanthral part of the stomach. The duodenal ulcer in 16 patients was localized on the anterior wall, in 12 - on the posterior wall, in 2 - in the post-bulbous sections, when the endoscopic diagnosis of a bleeding postbulbar ulcer was complicated due to severe deformity and an invisible, blood-covered substrate.

On the 4th-5th day, i.e. with some delay, stress ulcers were detected only in 2 cases. Thus, the sensitivity of endoscopy in the timely determination of the source of bleeding, according to our data, was more than 95%.

Endoscopy allowed not only to establish the source of bleeding, its localization, but in most cases the size of the ulcer. Of the 42 patients, the size of the stress ulcer was determined in 39 cases, of which in 23 cases the ulcer was covered by a blood clot. Thus, the possibility of determining the size of the ulcer was more than 94%.

Endoscopy made it possible in our cases to predict the possibility of recurrent bleeding. Visual endoscopic prognostic criteria for rebleeding were the size of the ulcer, its localization, and belonging to the Forrest class.

All patients received standard treatment aimed at stopping bleeding (endoscopic hemostasis, intramuscular and intravenous hemostatics, regional hypothermia), restoring blood loss and water and electrolyte balance (hemotransfusion, infusion and detoxification therapy). Antiulcer therapy was also carried out with proton pump inhibitors, H-2 blockers, antacids, etc.

37 patients with stress ulcer bleeding were irradiated by low-temperature plasma flows of the sternum. According to a number of scientific papers of Zv. Kheladze (2008), this leads to the activation of stem cell differentiation, which in turn leads to an improvement in the trophism of the gastric wall and a regulation of the increase in hydrochloric acid caused by stress in patients with critical conditions (11). We used the following technique: treatment of the sternum projection area with plasma rays occurred for 5-10 minutes, in the form of 1 or 2 procedures per day during the first week of the patient's stay in the hospital. The removal of rays from the surface of the sternum was 10-15 cm. The plasma jet was obtained using argon, in the flow of which plasma appeared with a plasma jet temperature of 10000-120000C, which sharply decreased at the skin surface to 40^{0}C.

In the course of work using this technique, not a single complication in the form of recurrent bleeding was noted, and rapid healing of the stress ulcer was noted. It should be noted that after 5-6 procedures of plasma stimulation of stem cells, i.e. on the 10-12th day of treatment, during endoscopic examination of the stomach and duodenum, the pallor of the mucosa practically disappeared, the color became pink, erosive-ulcerative defects significantly decreased in size, in some cases they practically disappeared, signs of scarring were visible. Our data were confirmed by repeated (2-4 times) endoscopic examinations with gastrobiopsy and histological parameters, both at admission and after the treatment.

Thus, the method of irradiating the sternum using a plasma jet, which we used in our work, made it possible to improve the trophism of the gastric mucosa by mobilizing the reserves of the immune system, which led to the healing of ulcerative defects in it.

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NEW PROGRESS IN DIAGNOSIS AND TREATMENT OF MYCOPLASMA PNEUMONIAE PNEUMONIA IN CHILDREN DOMESTIC AND OVERSEAS

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ABSTRACT

Mycoplasma pneumoniae pneumonia is a common disease that threatens the health of children around the world. Mycoplasma pneumoniae caused by the incidence of respiratory infections increased year by year, and the onset of atypical, disease progression, and more complicated with serious complications. Clinical attention should be paid. This paper summarizes the epidemiological characteristics, pathology, imaging features, atypical clinical manifestations and diagnosis and treatment of mycoplasma pneumoniae pneumonia at home and abroad.

Key words: Mycoplasma pneumoniae; pathogenesis; diagnosis and treatment; children

Mycoplasmal pneumonia (MPP), also known as primary atypical pneumonia, is a common disease in children and adolescents aged 3-7 years, accounting for 10% to 20% of the total number of pneumonia, and can rise to 30% in epidemic years [1]. MPP is widely found throughout the world, with a high incidence in densely populated areas such as military, kindergartens and schools [2]. In recent years, according to aetiological investigation, about 12% of community-acquired pneumonia diseases are mycoplasmal pneumonia (MP). Compared with most foreign areas, there is a relatively high incidence of MPP diseases in our country [3]. Studies have shown that about 12.3% of bacteria in community-acquired pneumonia in Asia are MP, while 22% and 26% of MPP diseases are found in the incidence of community-acquired pneumonia in Beijing and Shanghai [4]. MPP can occur at any age and is common-

ly seen in young adults and patients with community-acquired pneumonia [5]. It was previously believed that MPPS were self-limited diseases with slow onset and good therapeutic effect. However, with the increase of antibiotic-resistant strains, the effectiveness of macrolide antibiotics treatment declined, and some cases still progressed to severe (refractory) or fatal pneumonia even after standard treatment, which caused trouble to pediatricians [6]. This article reviews the new progress in diagnosis and treatment of MPP in children.

1. GLOBAL EPIDEMIC STATUS

In 1938 REIMAN discovered that MP was the pathogen that caused "atypical pneumonia". In 1941, EATON found that MP could cause primary atypical pneumonia. Atypical pneumonia accounts for 15%~25% of the total pneumonia patients. MPP accounts for about 50%~70% of atypical pneumonia [7]. MP exists in the natural environment, MP can be transmitted directly between people, it has no cell wall, easy to change the cell structure AND has the function of ARN-AND production of hemolysin. Most MPPS occur in autumn and winter, and are more common between 6 months and 3 years old. Medical experts from Israel and other countries have reported [8] that the rate of SARS is increasing recently, especially in developing countries. Israeli researchers conducted a retrospective study on 416 patients diagnosed with mycoplasma pneumonia in University Medical Center (1000-bed tertiary Medical center) from 2007 to 2012 [9], among which 68(16.3%) patients were admitted to ICU. The mean length of stay in the ICU was 7 days, and the mean length of stay was 11.5. 54.4%(37/68) of ICU patients received mechanical ventilation. Heart damage occurred in 36.8%(25/68) of patients. The ICU hospital mortality rate was 29.4%(20/68). It is suggested that there is an increasing trend of severe MPP patients in recent years.

2. NEW PATHOLOGICAL TRENDS OF MPP

MP belong to soft membrane-like bacteria, including unique life forms including a small genome of 100, 000 base pairs, in any case unable to produce cell walls. MP is the most common pathogenic species infecting humans. MP can lead to atypical pneumonia, showing various forms of pathological damage, such as interstitial pneumonia, bronchiolitis, bronchial wall thickening, edema, arterial obstruction/thrombotic epithelial cells, respiratory cilia, and interstitial cells in lung tissue destroyed by MP [10]. In particular, MP cannot penetrate into cells.

Pathologists in India report that although most cases of mycoplasma pneumonia can be managed in an outpatient setting, complications can occur in the elderly and children leading to multiple organ damage. Their studies have shown [11] that with molecular diagnostic methods and genetic, immune and ultrastructural analysis, new virulence factors of MP have been discovered from the subcellular level. Several additional mechanisms of subsequent toxicity, such as intracellular localization, direct cytotoxicity, and the inflammatory cascade response through toll(TLRs) -like receptor activation leading to inflammatory cytokine mediated tissue damage, play an important role in pathogenesis. The most important of these is the newly discovered virulence of MP-induced community-acquired respiratory distress (CARDS), which is primarily caused by adenosine diphosphate (ADP) riboylation and inflammatory activation resulting in airway inflammation. Germany reported that HapE, a new potential toxic factor produced by MP, is a bifunctional enzyme in which alanine produced by cysteine desulfurase is metabolized to produce pyruvate and hydrogen sulfide, and the activity of purified HapE protease is related to hemolysis in patients caused by MP [12].

3. PATHOGENESIS OF MPP

The intrapulmonary inflammation of MPPS has varying degrees of changes in severity and severity, and can cause multi-system extrapulmonary complications with long course and severe disease, and even cause multi-organ dysfunction syndrome (MODS) or multi-organ failure (MOF), or even death, which has attracted wide attention [13]. So far, the pathogenesis of MPP is still not very clear. At present, the theories of immunological pathogenesis, adsorption of respiratory epithelial cells and direct invasion of MP are mainly favored. Currently, immunological pathogenesis is believed to play an important role in the pathogenesis of MPP, mainly autoimmune and immunosuppression [14]. Autoimmune believes that MP, as an antigen, has common antigens with the body's heart, lung, brain, liver, kidney, smooth muscle, etc. After MP infection, lymphocytes produce autoantibodies. MP often has multi-system extra-pulmonary complications, which may be due to the activation of complement by the immune complex formed by antigens and antibodies, the production of neutrophil chemokines, the attraction of a large number of white blood cells into the lesion site, the release of hydrolytic enzymes in lysozyme, and the proliferation and destructive lesions [15]. The adsorption of respiratory epithelial cells believes that MP infection is transmitted by droplets. When MP is inhaled into the respiratory tract with droplets, it closely adheres to respiratory epithelial cells on the mucosal surface, resulting in the destruction of the mucosal epithelium [16]. This may be caused by MP utilizing neuraminic acid receptors of mucosal epithelium to release a harmful substance which may be hydrogen peroxide. If neuraminic acid receptors were artificially inhibited, MP induced mucosal epithelial damage was greatly reduced. MP has been isolated from the blood of children with MPP, so it is thought that MP may directly invade [17]. MP has also been isolated from chest fluid, middle ear secretion or skin blisters in children [18]. However, the direct causal relationship with the disease has not been completely confirmed and needs further confirmation.

4. NEW CLINICAL CHANGES AND DIVERSITY OF MPP

The most common age for MPP is older children over five years old, but infants can also be infected. It has been reported at home and abroad [19] that MP infection is trending at a younger age. Recently, even newborns and infants of 2 to 3 months have severe MPP. Symptoms and signs: often paroxysmal, intractable and severe pertussis - like spasmodic cough, lasting 1-4 weeks, affecting sleep and activity. The early stage of the disease was mainly dry cough. Late phlegm, sticky, occasionally containing a small amount of blood. The clinical manifestations of infants are not typical, often accompanied by wheezing and shortness of breath. If combined with respiratory syncytial virus (RSV) infection, dyspnea, acute onset and long course of disease. Older children can even trigger asthma. High fever, moderate fever or low fever, headache, general discomfort, sore throat and cough. MPP is characterized by low pulmonary signs, decreased respiratory sounds, wet rales, and inconsistent pulmonary signs and symptoms as well as imaging findings.

On the basis of the general clinical manifestations of MPP (high fever, stubborn and severe cough, few pulmonary signs), severe MPP can be diagnosed if one of the following manifestations: (1) lobular consolidation of one or both lungs with moderate or higher pleural effusion; (2) necrotizing pneumonia; (3) Respiratory function involvement or other organ dysfunction; (4) combined with bronchus obliterans (5) combined with systemic inflammatory response syndrome; (6) Rapid onset, severe symptoms, lung lobar consolidation, poor response to single macrocyclic lipid antibiotic treatment.

5. MPP EXTRAPULMONARY COMPLICATIONS

MP mainly infects respiratory tract, causing pharyngitis, bronchitis, pneumonia, and can also cause many extrapulmonary symptoms. Its pathogenesis is unknown. Mycoplasma has some common antigens with some human tissues, such as heart, lung, liver, brain, kidney, smooth muscle, etc. After infection, autoantibodies of corresponding tissues can be produced, leading to autoimmune damage, lesions of target organs outside the lung, and corresponding symptoms [20~22]. The incidence of extra-pulmonary complications varied from different reports [23], ranging from 25.0% to 39.3%, including nervous system, gastrointestinal tract, cardiovascular system, blood, skin mucosa, kidney features, skeletal system, etc. It has been reported abroad that nervous system damage is the most common extrapulmonary manifestation of MP infection, and cardiovascular and gastrointestinal diseases are more common in China [24]. Extrapulmonary complications may occur before, during, and after MPP, or in patients without respiratory symptoms, suggesting an important role of autoimmune responses [25].

6. MPP DIAGNOSIS

6.1 Serological examination and characteristics

The diagnosis of MP infection is mainly based on MP isolation culture, serological examination and polymerase chain reaction (PCR) and other etiological examinations. Positive MP isolation culture is the gold standard for the diagnosis of MPP, but the operation is complicated, time-consuming and too many negative blood cultures are not conducive to early clinical diagnosis [26]. Detection of MP antibody is currently a commonly used method in clinical practice. IgM is the earliest antibody after MP infection, and MP-igm is a recognized diagnostic test indicator for acute infection of MP. Common detection methods include complement binding test (CFT), gelatin particle condensation test (PLA), condensation set test (CAT) and enzyme-linked immunosorbent assay (ELISA). Combined with bacterial characteristics: often neutrophil and peripheral blood leukocyte total proportion in normal, some patients can increase.

6.2 Imaging examination and characteristics

There is no specific clinical manifestation of MPP, which leads to greater difficulty in etiological diagnosis. Therefore, when detecting MPP, it is necessary to refer to clinical manifestations and laboratory examinations, combined with imaging findings, so as to provide reliable basis for clinical diagnosis. [27] Chest X-ray features: 1, patchy shadow of bronchopneumonia 2, interstitial pneumonia 3, unilateral or bilateral hilum thickening, blurred structure, 4, single or multiple lobes showing uniform and consistent patchy shadow of lobar pneumonia. The above changes can be migratory infiltration, one after another transformation, sometimes a cloud infiltration shadow. Features of chest CT: patchy or large shadows are generally present, among which, Mosaic perfusion signs can be seen in high-resolution CT examination, and unilateral lung transparency is enhanced. A few are accompanied by pleural effusion [5, 28].

6.3 Fiberbronchoscopy

At present, fiberoptic bronchoscopy has become an important means to detect severe and refractory MPP. [29] The main manifestations of severe and refractory MPP under fiberoptic bronchoscopy are bronchial mucosal congestion and edema, poor ventilation of some lung segments, protrusion of small nodule of tube wall mucosa, and inflammatory stenosis of lumen opening. In some children, mucus thrombus can be seen in the bronchus, leading to continuous narrowing of lumen and complete occlusion in severe cases. [30] When bronchoscopy is used, it can be combined with the examination of pulmonary cytophlorage fluid. In this way, not only can the lesion sites of children be observed directly, but also the cytophlorage fluid of children can be retained for cell classification, so that children can be examined repeatedly and the changes of their conditions can be dynamically observed.

7. MPP TREATMENT

7.1 Use antibiotics for treatment

The most prominent feature of MP is the absence of cell wall, and antibi-

otics whose main mechanism is to hinder cell wall synthesis are ineffective against MP, so drugs that interfere with and inhibit bacterial protein synthesis should be selected clinically [31]. Since quinolones, tetracyclines and aminoglycosides can inhibit bone development, tooth staining, ototoxicity and kidney toxicity in children, macrolides are generally used at present, and these drugs are only considered for children with contraindications to macrolides.

Macrolide antibiotics can have a good blocking effect on bacterial protein synthesis in children, and its immune regulation can reduce lung inflammation, prevent epithelial cells and stabilize cell membrane. Macrolides can reduce cytokine secretion and regulate neutrophils. Prevent the production of biofilms [32]. It has the advantages of strong pertinency, high bioavailability, small adverse reactions and complete dosage form. It has a good effect on the treatment of MPP. Therefore, macrolide antibiotics are commonly used in the treatment of MP. At present, the commonly used clinical azithromycin, erythromycin, roxithromycin, clarithromycin and so on. Children with mild and moderate MPP are generally given azithromycin, erythromycin and roxithromycin orally. The Azithromycin with a dose of 10mg/kg and continuous administration is better, while roxithromycin and erythromycin need to be taken for 1-2 weeks. For children with moderate or above levels, anti-infection treatment is often required for 4 weeks. Azithromycin has an obvious after-antibiotic effect, and its effective concentration can be maintained for 10 days. The dosage can be taken for 3 days and then stopped for 4 days, which not only reduces the number of administration and adverse reactions, but also improves the compliance of children. For severe MPP accompanied by mycoplasma, 3 to 5 days of intravenous erythromycin (no more than 7 days) is commonly used in China, followed by oral or intravenous azithromycin, and the total course of treatment is 4-6 weeks of sequential therapy [33, 34], which can simultaneously take into account the balance between blood concentration and intracellular concentration of MP sensitive antibiotics.

However, due to refractory and severe MPP children will develop some resistance to this drug, coupled with the severity of the disease in the children, therefore, clinical treatment should be combined. Among them, rifampicin is a commonly used anti-tuberculosis drug, which is used in combination with macrolide antibiotics, and can jointly act on different stages of protein synthesis in children, thus playing a certain inhibitory effect on MP. Doxycycline belongs to a semi-synthetic tetracycline class of drugs. This drug has similar pharmacological effects to tetracycline, but the incidence of adverse reactions is relatively low. Therefore, doxycycline is clinically used to treat refractory MPPS. However, the drug is only used in children over the age of eight because of adverse effects such as cartilage damage and yellowing of teeth.

7.2 Use glucocorticoid therapy

Adrenocorticosteroids can be used to treat patients with rapid progression of the disease in the acute stage, with severe MPP or atriotasis due to lung disease. This is mainly because glucocorticoid can effectively inhibit the further development of systemic inflammatory response syndrome in the children, relieve trachea and alveolar edema and congestion in the children, improve the ventilation function and ventilation function of the children, and thus effectively improve the state of bronchiole occlusion in the children. It promotes the effective control and absorption of inflammation in children, thereby buying time for anti-infection treatment [35].

In view of the role of humoral and cellular immunity disorders in the pathogenesis of MP infection, immunosuppressants such as glucocorticoids may be used in treatment. Glucocorticoids can block the immunological mechanism, and adrenal glucocorticoids can be added to patients with rapid and severe MPP in acute stage or atatasis, pulmonary interstitial fibrosis, bronchiectasis or extrapulmonary complications due to prolonged lung lesions [36]. A retrospective study of severe MP patients with respiratory failure in ICU [37] found that early combination of sufficient antibiotics and glucocorticoids could rapidly improve the patient's condition. Animal experiments have also shown that macrolide antibiotics alone can effectively reduce MP concentration in lung tissue, while glucocorticoid combined with macrolide can effectively reduce the production of cytokines and inflammatory chemokines, and reduce the inflammatory response in lung tissue [38]. Currently commonly used methods are: hydrocortisone 5 to 10mg/ (kg•d), intravenous drip, or dexamethasone 0.1 to 0.25mg/ (kg•d), intravenous drip, or prednisone 1 to 2mg/ (kg•d), orally divided.

7.3 Use immunomodulators for treatment

Currently, drugs such as gamma globulin and pidomod are mainly used in clinical combination to treat refractory MPP. The mechanism is mainly through activating NK cells, monocyte phagocytosis activity and neutrophilic neutrophil deactivation, which can effectively regulate the non-specific immune function in children and effectively promote lymphocyte proliferation. Thus, the ratio of CD4+ / CD8+ in children is restored to a normal level, the secretion of interleukin-2 and Y-interferon is promoted, and the specific immune function in children is finally regulated to some extent [39]. Clinical research data [40] showed that the treatment of refractory MPP with immune modulators could reduce the number of recurrent episodes and shorten the time of antibiotic use in children.

7.4 Use fiberbronchoscopy for treatment

A common complication of refractory MPP is atatasis. Endoscopic lavage

treatment can not only effectively remove secretions from the mucosa of the lower respiratory tract of children, but also effectively remove harmful pathogenic microorganisms, so as to improve airway obstruction, reduce pathogen damage, and alleviate clinical symptoms and signs of children. Thus, the large shadow of children can be absorbed, especially for the treatment of atelectasis with significant effect [41]. However, some children did not suck sticky secretions when receiving lavage, and it was also found that the bronchial orifice is prone to collapse during aspiration, which may be related to the blockage of the mucus plug in the small airway at the lower end of the bronchial orifice during aspiration. Therefore, local hormone injection and multiple lavage can be performed to achieve good therapeutic effect [42]. Clinical studies [43] have shown that for refractory MPP, the timing of bronchoscopy has a direct impact on the clinical treatment effect.

Therefore, for children with refractory MPP, we should provide them with bronchoscopy as soon as possible to promote the recovery of atelectasis, save their lives and buy time for further treatment.

8. SUMMARY AND OUTLOOK

In recent years, the number of MPP patients has gradually increased, and they are characterized by severe illness, rapid progression, many changes, and difficult diagnosis and treatment. Many patients are complicated with serious complications, which poses challenges to clinical medical staff. Therefore, attention should be paid to atypical pathogen infection and to understand the progress of diagnosis and treatment of MP infection, so as to provide better guidance for clinical treatment and disease control. In conclusion, there is still much to be done about the pathology, pathogenesis and diagnosis of MPP. How to detect and treat as early as possible, how to apply adrenocortical hormone, improve clinical efficacy and reduce adverse reactions need to be solved by large sample and multi-center prospective studies. The immune mechanism of vitamin D, traditional Chinese medicine and antibiotics still needs further study. Therefore, it is necessary to clarify the clinical epidemiological characteristics, pathological mechanism, imaging characteristics, diagnosis and treatment status, as well as research and development status of MPP, so as to ensure that the determination of clinical diagnosis and treatment mode is more reasonable. It also provides some reference value for clinical diagnosis and treatment of MPP diseases.

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STRENGTHEN THE DIAGNOSIS AND TREATMENT OF INCOMPLETE KAWASAKI DISEASE IN CHILDREN

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ABSTRACT:

Although more than 50 years have passed since the investigation of Kawasaki disease (KD) by Professor Tomisaku Kawasaki, there is still a lack ofno specific diagnostic indicators yet for the early stage of KD, the diagnosis of incomplete KD (IKD) poses a particular challenge. Since there is no clear diagnostic criteria for IKD at present, it is easy to be missed or misdiagnosed in clinical, and coronary artery lesion (CAL) is prone to occur. Not good for children's physical and mental health. Therefore, this article mainly summarizes the concept, epidemiological characteristics, diagnosis, treatment, prevention and prognosis of IKD, hoping to help improve the clinical diagnosis and treatmen t of KD in my country and improve the prognosis of children.

Key words: *Incomplete Kawasaki disease, diagnosis, treatment, prevention, children*

Kawasaki disease (KD), also known as cutaneous mucous lymph node syndrome, is an acute, self-limiting small and medium vasculitis with unknown etiology, most commonly seen in infants and young children. Currently, it has become the most common acquired heart disease in children [1]. The disease was first reported by Professor Tomisaku Kawasaki in Japan in 1967. It has since been found in all parts of the world and in all ethnic groups. With the deepening of people's understanding of this disease, more and more cases with atypical manifestations or incomplete KD diagnostic criteria have been reported at home and abroad. Recent studies in Japan showed that incomplete KD accounted for 13. 8% of children with KD [2]. A domestic study found that 19. 4% KD children were atypical or incomplete (atypical or incomplete[3]. The atypical or atypical atypical [3]. (Atypical Kawasaki disease is mainly due to the course of the disease, the clinical manifestations are not as obvious as the typical Kawasaki disease. Incomplete Kawasaki disease refers to those who do not fully meet the diagnostic criteria for Kawasaki disease. Because their clinical symptoms do not fully meet the diagnostic criteria for Kawasaki disease, the name is incomplete Kawasaki disease.) Therefore, it is of great significance to understand the new progress in the diagnosis and treatment of incomplete KD at home and abroad.

1. THE CONCEPT OF INCOMPLETE KD

KD is a febrile disease mainly occurring in children under 5 years of age with small and medium vasculitis as the main lesion. Clinically, the main manifestations are fever lasting more than 5 days, conjunctival congestion of eyeball, diffuse flushing of skin and mucosa, non-suppurative enlargement of cervical lymph nodes, rigid edema of finger (toe) end and membranous peeling around finger (toe)

nail, etc. The main life-threatening symptoms are coronary artery damage, such as coronary artery stenosis, thrombosis, infarction and tumor rupture, etc., which can lead to sudden death of children [4]. The etiology of KD is unknown, but it is believed to be related to immune abnormality and viral infection. The clinical diagnosis of KD mainly relies on clinical features combined with the manifestations of systemic multi-system vasculitis and laboratory examination, which lacks the gold standard and requires the exclusion of other diseases. KD is divided into complete Kawasaki disease (CKD) and incomplete Kawasaki disease (IKD) [5]. The diagnosis of typical KD or CKD is usually not difficult. However, clinically, some children with KD do not meet the current KD diagnostic criteria, their diagnosis and clinical manifestations are different, some symptoms and signs appear late or do not appear, with a certain degree of occult, and with many pediatric infectious or connective tissue disease clinical symptoms overlap, prone to misdiagnosis and missed diagnosis, resulting in cardiac sequelae or death. Therefore, such patients are referred to as IKD at home and abroad [6, 7].

2. EPIDEMIOLOGICAL CHARACTERISTICS OF IKD

Due to the lack of a gold standard for the diagnosis of IKD, reports on the incidence of IKD vary greatly. In relevant domestic studies, the incidence of IKD was 19. 4% [8] and 28. 4% [9], respectively. At the same time, there are also many foreign reports. Sonobe et al. [10] conducted a national survey in Japan, showing that IKD accounted for 16. 1% of all KD, while the relevant survey and research in Japan from 2013 to 2016 was as high as 22%[11]. Relevant domestic studies also confirmed the same upward trend. Some scholars believe that the onset of IKD is related to the season. Domestic studies have reported that the incidence of the disease is mostly in spring and summer [12, 13], while American [14] and Japanese [15] scholars have found that the peak of the incidence is in winter. Considering that seasonal differences in IKD incidence may be related to epidemiological changes of viral infection [16].

In addition, age is also considered by most scholars to be an important factor affecting the onset of IKD. As for the onset age of IKD, compared with children with CKD, IKD children are younger, with a larger proportion of children ≤2 years old and ≥6 years old. In the United States, approximately 75% to 80% of children with IKD are under 5 years of age (median age is 1. 5 years). According to statistics, the ratio of male to female IKD children is 1. 5:1 [17]. Eg. There are reports that The incidence of IKD in 1-year-old children may be > 4 times that of 1-year-old children [18]. Other studies have found that age. IKD accounted for 28% of children aged 6 months, and 85% of them developed coronary artery lesions [19].

3. CLINICAL FEATURES OF IKD

The clinical features of IKD children are fever and high incidence of membranous peeling around finger (toe) nail and blotches in convalescence stage, low incidence of red chapped lip, conjunctival congestion, stiff swelling of hands and feet, swollen lymph nodes of bayberries tongue and neck, and high level of serum C-reactive protein (CRP).

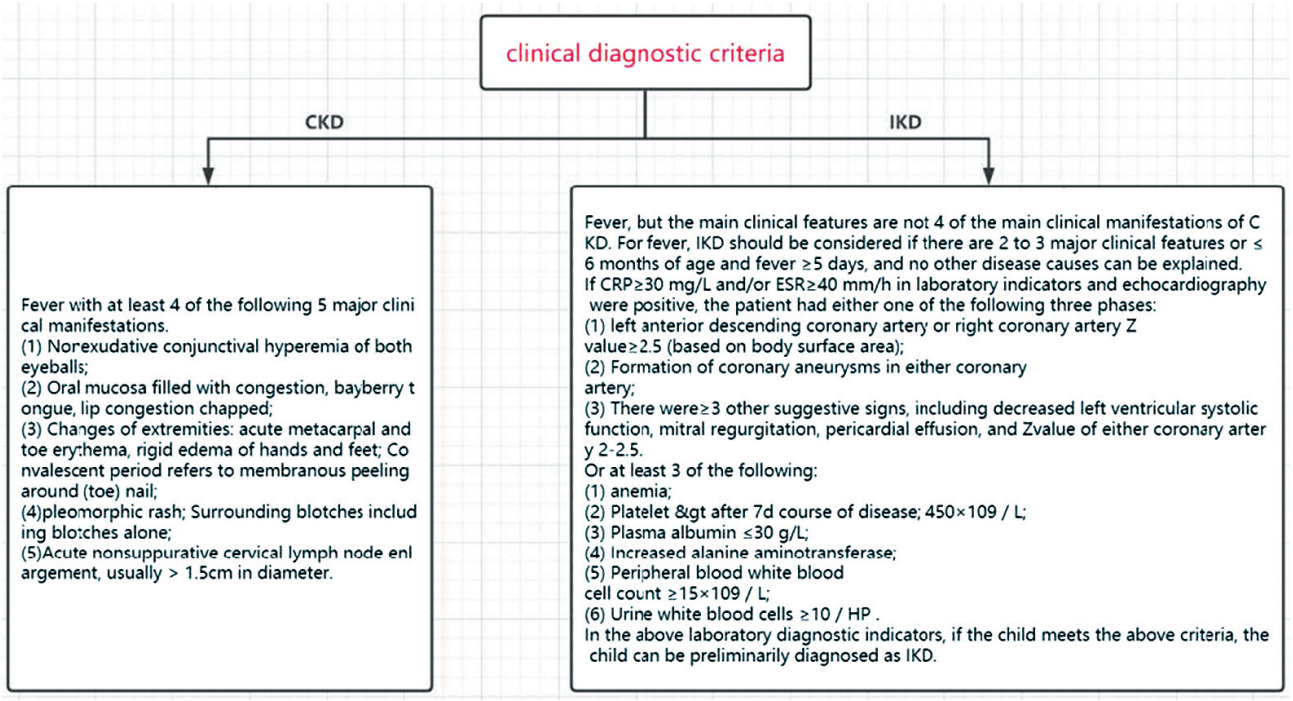
Japanese scholars conducted a comparative study on the frequency of six major symptoms of IKD and CKD [20], and the results showed that the frequency of cervical lymph node swelling in children with IKD was lower, 35%, while the frequency of CKD was 65%. The frequency of other symptoms of IKD were fever 75%, rash 50%, lip changes 65%, extremities 70% and bulbar conjunctival changes 75%. In addition, the probability of redness and swelling around the BCG vaccination site in acute stage of IKD is higher than that of CKD, so it is important to pay attention to children with redness and swelling after BCG injection [21]. Most scholars believe that IKD has a higher probability of coronary artery lesions than CKD[22]. American KD diagnosis and treatment guidelines [23] : < 6 month old baby with unexplained fever. On day 5, even if there is only one typical KD symptom, combined with positive laboratory indicators, cardiac ultrasound should be performed immediately to rule out the possibility of coronary artery disease. Related retrospective studies [24, 25] have found that IKD(18. 4%) has a higher incidence than CKD(14. 2%) in children with coronary artery disease. It is considered that IKD is more likely to occur in infants and children, who are prone to coronary artery disease. Meanwhile, due to the atypical clinical characteristics of IKD, the diagnosis time is often delayed. Thus the disease can not be controlled in time. In addition, a small number of children may have some rare symptoms or exhibit very atypical clinical symptoms.

4. DIAGNOSIS OF IKD

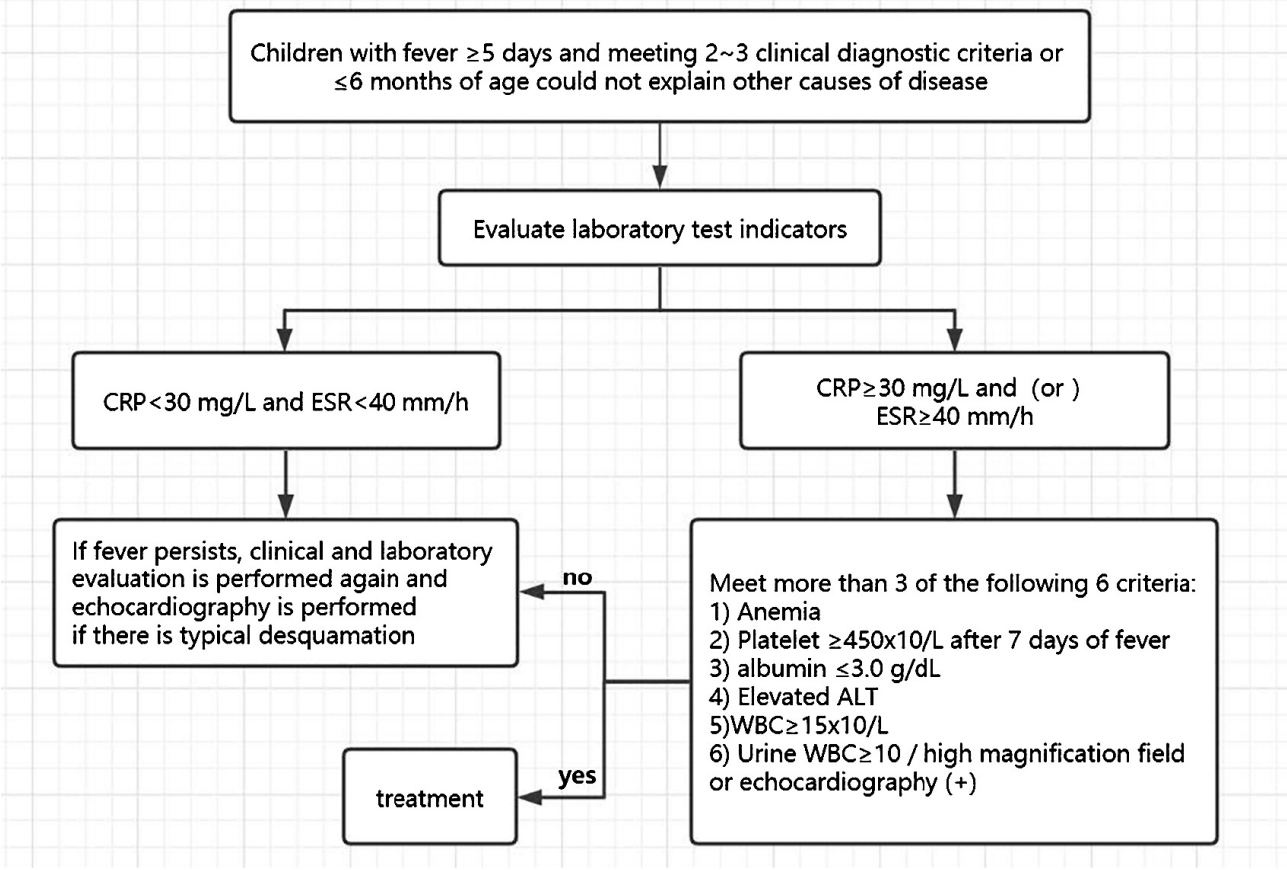
As there is no clear regularity or standard in the occurrence time of clinical manifestations of IKD during the onset of the disease, there are great differences between different children. The clinical manifestations in the early stage of the onset of the disease have not been fully expressed, and it is difficult to make early diagnosis. In the absence of the current diagnostic gold standard, the following clinical diagnostic criteria can be used as reference [23, 26] : **CKD:** Fever with at least 4 of the following 5 major clinical manifestations. (1) Non-exudative conjunctival hyperemia of both eyeballs; (2) Oral mucosa filled with congestion, bayberry tongue, lip congestion chapped; (3) Changes of extremities: acute metacarpal and toe erythema, rigid edema of hands and feet; Convalescent period refers to membranous peeling around (toe) nail; (4) pleomorphic rash; Sur-

rounding blotches including blotches alone; (5) Acute non-suppurative cervical lymph node enlargement, usually > 1. 5cm in diameter.

IKD: Fever, but the main clinical features are not 4 of the main clinical manifestations of CKD. For fever, IKD should be considered if there are 2 to 3 major clinical features or ≤6 months of age and fever ≥5 days, and no other disease causes can be explained. If CRP≥30 mg/L and/or ESR≥40 mm/h in laboratory indicators and echocardiography were positive, the patient had either one of the following three phases: (1) left anterior descending coronary artery or right coronary artery Z value≥2. 5 (based on body surface area); (2) Formation of coronary aneurysms in either coronary artery; (3) There were≥3 other suggestive signs, including decreased left ventricular systolic function, mitral regurgitation, pericardial effusion, and Z-value of either coronary artery 2-2. 5. Or at least 3 of the following: (1) anemia; (2) Platelet &gt after 7d course of disease; 450×109 / L; (3) Plasma albumin ≤30 g/L; (4) Increased alanine aminotransferase; (5) Peripheral blood white blood cell count ≥15×109 / L; (6) Urine white blood cells ≥10 / HP. In the above laboratory diagnostic indicators, if the child meets the above criteria, the child can be preliminarily diagnosed as IKD and given standard treatment. If CRP is < 30 mg/L and/or ESR is < 40 mm/h in the laboratory and fever persists, clinical and laboratory re-evaluation is required, and echocardiographic re-evaluation is required if a membranous peel is typical.



Notes for the diagnosis of IKD: there are few clinical symptoms and signs of IKD. The diagnosis of IKD requires comprehensive judgment by combining laboratory indicators and echocardiography, and sometimes even dynamic observation during the course of the disease. If the child's echocardiography is negative, it is necessary to continue to observe the child's temperature changes, such as children no longer have fever, can be excluded KD; If the fever persists, echocardiography should be reviewed again and KD experts should be consulted to determine the next treatment plan. In children with KD, for children beyond the age of common onset, special attention should be paid to changes in laboratory indicators, including elevated white blood cell count, dominated by neutrophils; Hemoglobin decreased; Increased platelet count; Aseptic pyuria; C-reactive protein increased; Erythrocyte sedimentation rate increased; Liver enzymes increased and total bilirubin increased. Albumin and blood sodium decreased; interleukin (IL) 6, IL-1, tumor necrosis factor-α increased. Some scholars have suggested that the elevation of plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) should be used as a reference for the diagnosis of IKD. However, there is a lack of sufficient confirmatory research support [27]. coronary echocardiography has the important value for the diagnosis of IKD. During the examination, coronary artery damage (CAL) should be carefully observed, and myocardial function, valvular regurgination, and pericardial effusion should be evaluated. The following is a flowchart describing the diagnostic workup.



5. DIFFERENTIAL DIAGNOSIS OF IKD

One of the keys to IKD diagnosis is to exclude other IKD-like diseases. In addition to CKD, diseases that need to be identified with IKD mainly include scarlet fever, rheumatoid arthritis, juvenile idiopathic arthritis, adenovirus infection, Epstein-Barr virus infection, Stevens-Johnson syndrome, drug allergy syndrome, toxic shock syndrome, measles, leptospirosis, etc. [28]. For these diseases, some have specific diagnostic methods, such as measles can be serologically measured measles IgM antibodies; For scarlet fever, group A streptococcus hemolyticus can also be cultured from throat swabs. Sensitivity to antibiotic treatment such as penicillin can also help in the diagnosis of scarlet fever. The characteristics of the history also help in the identification [29]. However, the joint symptoms of children with rheumatoid arthritis are often obvious, and there is no eye-binding membrane congestion, no lip congestion chapped, no rigid edema of hands and feet, and no membranous peeling around the finger (toe) nail [30]. For some diseases, if there is a clear history of medication, be aware of the possibility of drug allergy syndrome. In Steven-Johnson syndrome, mucosal ulceration changes and/or bullous lesions are rare in children with IKD. Toxic shock syndrome often presents significant hypotension and renal dysfunction, which are not usually seen in children with IKD. However, the distinction between IKD and systemic juvenile rheumatoid arthritis is sometimes very difficult, and a definitive diagnosis can be made only when the child presents obvious joint symptoms and fails to treat large doses of IVIG [31]. Viral infection, such as Epstein-Barr virus infection, can also lead to coronary aneurysm and coronary artery dilation [32], and there have been domestic reports of Epstein-Barr virus infection misdiagnosed as KD [33]. However, positive Epstein-Barr virus IgM antibody and elevated xenomeric lymphocytes in peripheral blood contribute to the diagnosis of Epstein-Barr virus infection. It has been reported in foreign literature that it is difficult to distinguish IKD from acute adenovirus infection [34]. Studies have found that ESR in children with IKD can increase significantly compared with adenovirus infection, and the recent rapid detection of adenovirus antigen can rapidly diagnose adenovirus infection, providing a better method for the differentiation from KD [35]. However, this method should be applied with great care, because adenovirus infection can have latent infection, and this latent infection can develop into acute infection during KD acute phase, KD combined with adenovirus infection.

Other issues that need to be noted in the diagnosis of IKD: The main clinical features of IKD do not all present at a single point in time, and some clinical features may subside within a few days, so careful inquiry and examination are required. At the same time, IKD is systemic vasculitis with multi-system damage, and some specific organ damage can be the first symptom. Sometimes, it can be misdiagnosed as other diseases, such as urinary tract infection, suppurative lymphadenitis or mumps, acute abdomen, hepatitis, arthritis, etc.

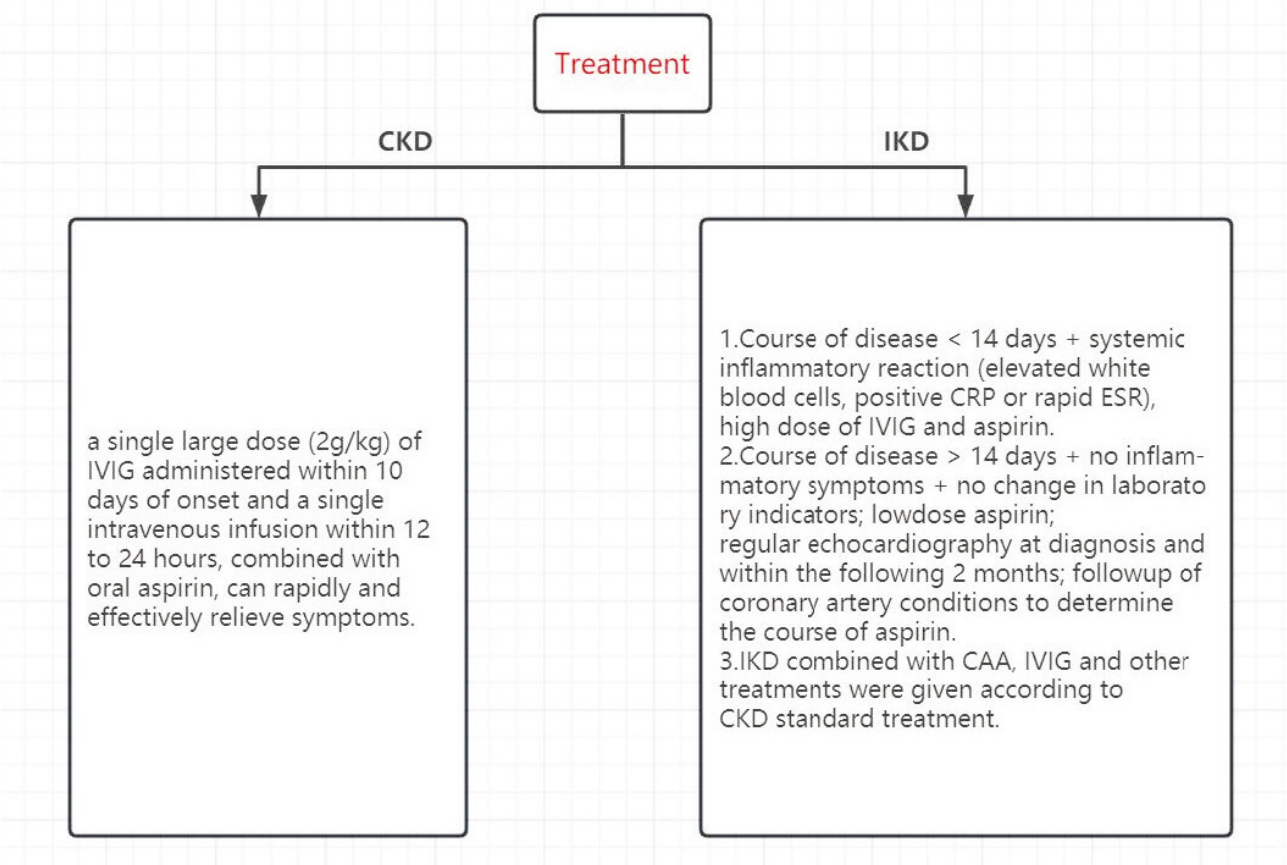
Therefore, careful identification should be made when diagnosing IKD.

6. TREATMENT OF IKD

The principle of holistic treatment of IKD is the same as that of CKD. With KD standard treatment, IVIG should be given in time to reduce the occurrence of CAL [36]. All advocated that a single large dose (2g/kg) of IVIG administered within 10 days of onset and a single intravenous infusion within 12 to 24 hours, combined with oral aspirin, can rapidly and effectively relieve symptoms such as fever and reduce the content of cytokines in the blood. coronary artery aneurysm (CAA) decreased the incidence of CAL and coronary artery aneurysm (CAA). It is worth noting that IKD is easily delayed until 10 days after diagnosis, when there is no acute symptoms such as fever, and it is sometimes difficult to decide whether to take remedial treatment.

It is generally believed that if the child is still within 14 days of the course of the disease, as long as the child still has systemic inflammatory reactions, such as chapped lips, conjunctival congestion, elevated white blood cells, positive CRP or rapid ESR, regardless of whether the child still has fever, large doses of IVIG and aspirin should be given. If the disease has been over 14 days and there are no inflammatory symptoms and no changes in laboratory indicators, only a small dose of aspirin should be given to prevent platelet aggregation and thrombosis, but regular echocardiography should be performed at the time of diagnosis and in the following 2 months to follow up the coronary artery conditions to determine the course of aspirin.

Some children with IKD may develop CAA complications due to delayed treatment or unresponsive IVIG. For children with IKD complicated with CAA, especially huge CAA, preventing thrombosis is an important goal of long-term anticoagulant therapy. In terms of the treatment of IKD, some medical staff have a misunderstanding, believing that IKD is a mild disease and IVIG treatment is often not active enough. However, studies have found that IKD does not represent mild symptoms. On the contrary, some patients may be more prone to cardiovascular sequelae such as CAL. Therefore, it is still necessary to give IVIG and other treatments according to the standard KD treatment regimen.

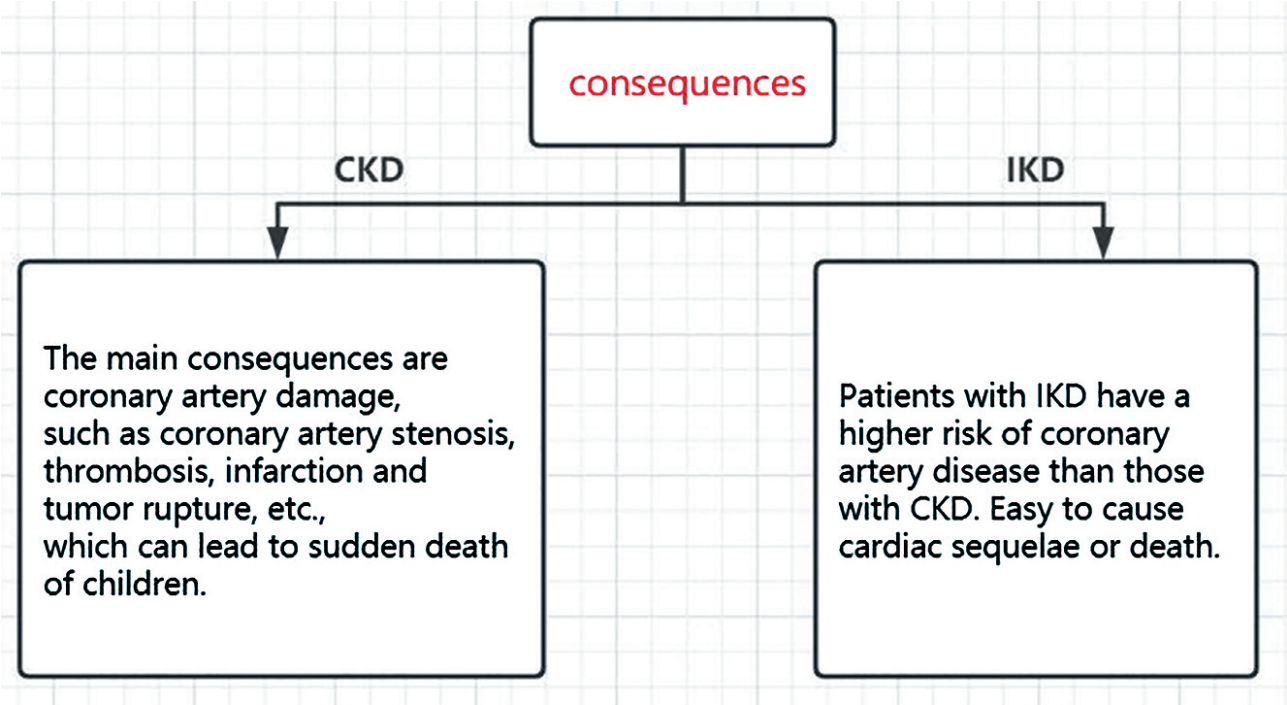


7. PREVENTION OF IKD

Due to the lack of specific laboratory examination of IKD, physicians have insufficient understanding of this disease. Due to inertia of thinking, they tend to tend to common infectious diseases, which are easily considered as acute lymphadenitis, respiratory tract infection, scarlet fever, sepsis, etc. The symptoms of infants and young children are not typical, easy to be confused with severe infections and immune diseases, often systemic use of corticosteroids. With some rare symptoms as the first symptom, it interferes with the early diagnosis. Therefore, the prevention of IKD mainly lies in the early and timely di-

agnosis of the disease and the reduction of the incidence of misdiagnosis.

First of all, the understanding of KD among clinicians should be improved. Clinicians should not only be familiar with the clinical manifestations of CKD, but also the clinical characteristics of IKD, as well as the characteristics of dispersed symptoms of the disease, other complications that may be caused by KD, and the early and specific diagnostic basis, such as inflammatory indicators CRP and platelets. In addition, the medical history of the child should be asked in detail, and a comprehensive and careful physical examination should be conducted, especially for difficult cases, careful examination should be conducted in strict accordance with the examination procedures of various systems, and attention should be paid to minor abnormal symptoms [37]. Secondly, if a child is suspected to be IKD, a comprehensive examination should be carried out on the skin, eyes, hands and feet and lips of the child to detect small changes in physical signs. Laboratory indicators were further evaluated. If the patient has fever for more than 5 days, and has oral mucosal changes, rash and ocular conjunctivitis, the clinical features can be further evaluated to determine whether the patient is IKD. When the fever persists, echocardiography (UCG) may be performed, and a short review is required if the diagnosis is not confirmed. Finally, clinicians should always have KD in mind, and pay attention to patients with persistent high fever, should actively examine, find the cause, and raise vigilance, prohibit (early) abuse of hormones.



8. FOLLOW-UP OF IKD

The purpose of KD follow-up management is to prevent cardiovascular events such as myocardial ischemia, myocardial infarction and sudden death as much as possible. Follow-up management of IKD is the same as KD, which can be referred to the clinical Management Recommendations for KD coronary artery disease (2020 revision) [38]:

(1) Patients without coronary artery dilatation and patients with mild coronary artery dilatation in the acute stage returned to normal within 30 days; Clinical follow-up for 5 years; The duration of follow-up was 1 month, 2~3 months, 6 months, 1 year and 5 years. Echocardiography and electrocardiogram (ECG) were performed during follow-up. ECG exercise was recommended at the last follow-up. (2) Patients with small coronary aneurysms need long-term follow-up; The duration of follow-up was 1 month, 2~3 months, 6 months, 1 year, and then once a year. If the recovery to normal can be once every 2 years; Induced myocardial ischemia was evaluated every 3 to 5 years. Give cardiovascular risk assessment and guidance. Echocardiography was performed during follow-up, and ECG was performed if necessary. If echocardiography shows a return to normal, multislice spiral CT angiography (MSCTA), magnetic resonance coronary angiography (MRCA), and exercise ECG are recommended. (3) Lifelong follow-up of patients with mid-sized CAA; The duration of follow-up was 1 month, 2~3 months, 6 months and 1 year. Once a year thereafter; Induced myocardial ischemia was evaluated every 1-3 years. Give cardiovascular risk assessment and guidance. Echocardiography and ECG were improved during follow-up. Chest radiographs if necessary; Multi-slice spiral CT (MSCTA), magnetic resonance coronary angiography (MRCA) or coronary angiography (CAG) are recommended after 3 months of disease course. If echocardiography shows a return to normal, MSCTA or MRCA or CAG

confirmation is recommended. If noninvasive tests suggest myocardial ischemia, CAG, MSCTA, or MRCA should be performed. (4) Lifelong follow-up of patients with giant CAA; The duration of follow-up was 1 month, 2~3 months, 6 months, 9 months, 1 year, and then every 3~6 months. Induced myocardial ischemia was evaluated every 6 to 12 months. Give cardiovascular risk assessment and guidance. Echocardiography and ECG were improved during follow-up. Chest radiographs if necessary; The course of the disease was about 3 months and the first CAG was performed. In the future, MSCTA or MRCA can be selected according to the situation. If noninvasive tests suggest myocardial ischemia, CAG should be repeated. If the echocardiogram shows a return to normal, confirmation by the CAG, MSCTA, or MRCA is required. (5) CAA with coronary artery stenosis with or without myocardial ischemia: lifetime follow-up, with the same duration and content as for patients with giant CAA. Follow-up plans for both CKD and IKD need to be determined by the person, and various tests should be selected at different follow- up times according to the disease condition, which should not be generalized.

9. OUTLOOK AND SUMMARY

In recent years, substantial progress has been made in the etiology and pathology of the characteristic diseased artery abnormalities of KD, but there is still a lack of specific early diagnostic indicators for KD, especially the diagnosis of IKD is more difficult. As there is no clear diagnostic criteria for IKD at present, it is easy to miss or misdiagnose IKD in pediatric clinical work, which is prone to coronary artery injury. As a result, IKD patients have a higher risk of coronary artery lesions than CKD patients. Although IKD symptoms are atypical, it does not mean that IKD can be ignored. Therefore, in clinical work, on the one hand, doctors should be proficient in the diagnosis, treatment and long-term follow-up management of IKD, which is crucial for the prevention of patients. On the other hand, doctors should also inquire the medical history in detail, comprehensively analyze the condition, perform routine cardiac ultrasound and related auxiliary examinations, diagnose as early as possible, and give reasonable treatment as soon as possible, which is helpful to improve the clinical diagnosis and treatment level of KD and improve the prognosis of children.

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RESEARCH PROGRESS ON THE ROLE OF INFLAMMATION IN KAWASAKI DISEASE

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ABSTRACT:

As the pathogenesis of Kawasaki disease continues to evolve, researchers have proposed a number of hypotheses, from viral infections, genetic and environmental influences, to toxin-mediated autoinflammatory responses. More and more attention has been paid to the role of inflammation in KD pathogenesis. Objective: To explore the role of inflammation in Kawasaki disease and to provide a new idea for the diagnosis and treatment of KD. Methods: A systematic search was conducted from PubMed and CNKI databases (last updated on March 31, 2023) for relevant and qualified articles evaluating the role of inflammation in KD. Results: The research results of the last five years were selected from these articles for meta-analysis. Conclusion: Through comprehensive analysis, we conclude that inflammatory response is the main process of vascular damage in Kawasaki disease, especially the NLRP3 inflammasome plays an important role. However, the etiology and pathogenesis of KD are very complex, and inflammation is only one of the manifestations, the specific details are still not fully understood. In this paper, we will review some of the major concepts and recent views on the role of inflammation in Kawasaki disease.

Key words: *Inflammation; Inflammatory corpuscles; Kawasaki disease; children*

Kawasakidisease (KD) is a common childhood vasculitis that tends to occur in children under 5 years of age. It is usually acute, self-limited, and highly inflammatory in its early stages, mainly involving coronary arteries, but its pathogenesis has been unknown. In recent years, the incidence of KD has been increasing year by year, which is one of the most common causes of acquired heart disease in children [1] The role of inflammation in Kawasaki disease is summarized from the following aspects:

1. HISTOPATHOLOGY

The initial study of KD inflammation was a histopathological examination of the heart and coronary vessels of deceased patients. Early in the disease, stage I, a large number of mixed inflammatory infiltrates of neutrophils, eosinophils, macrophages, and lymphocytes are seen involving the inner and outer membranes of coronary arteries [2] . In the second stage, coronary aneurysms may develop due to proliferative inflammation of the intima and damage to smooth muscle cells and elastic fibers in the medium. Again, this infiltration is mixed and includes lymphocytes, monocytes, macrophages, plasma cells, and fibroblasts [3].

Generally, M1 macrophages are thought to be pro-inflammatory and may reflect activation of innate immune stimuli. In a study of KD coronary artery disease, a large number of immune inflammatory cells, especially M1 macrophages, were found to be the main phenotype of KD [4] . Abnormal activation of immunoactive cells such as macrophages, monocytes and lymphocytes is the main characteristic of KD. These cells secrete various inflammatory cytokines and chemokines such as IL-1, TNF-α, etc., thereby causing vasculitis of endothelial cells [5] . As a natural barrier between the circulatory system and the vascular wall, vascular endothelial cells play a vital role in maintaining the normal function of blood vessels. Studies have shown that endothelial cell injury, including inflammation and apoptosis, is the main pathological mechanism of KD [6] .

With the deepening of exploration and the support of technology, the study of KD inflammatory response has been upgraded from histopathology to the analysis of whole gene expression profile, such as the mouse model of KD patients in the acute stage, such as LCWE mouse model, and transcription profile analysis, which confirmed the up-regulation of multiple immune pathways. Including intracellular signal transduction, T cell activation, B cell development, etc. [7] , these studies further suggest the role of immune inflammatory response in KD. Here we discuss the role of innate immunity and adaptive immune inflammation in KD.

2. CONGENITAL IMMUNE INFLAMMATORY RESPONSE

2.1. Inflammatory factor

High levels of IL-1β have long been thought to be at the core of KD's acute inflammatory phase [8] .

IL-1β is produced by a variety of immune and non-immune cell types as part of the innate immune response. IL-1β has a variety of pro-inflammatory effects, the most important of which is the direct activation of coronary endothelial cells, resulting in the up-regulation of cell adhesion molecules, and the production of IL-6 and IL-8, both of which are important inflammatory factors [9] .

In addition to IL-1β, cytokines also have TNF-α. Relevant reports have shown that the levels of TNF-α released by macrophages and monocytes in the serum of KD patients are significantly higher, which plays a facilitating role in inducing coronary artery inflammation and promoting the development of coronary artery aneurysms [10] . However, stimulating the production of inflammatory cytokines is achieved by activating inflammasome.

2.2 Inflammatory bodies

Inflammatory bodies are intracellular protein complexes of the innate immune system that respond to pathogen-associated molecular patterns (PAMPS) or DAMPS.

Nod-like receptor protein 3 (NLRP3) activation is the key of inflammatory activation in typical inflammatories. There was a correlation between NLRP3 and tongue-associated speck-like protein, apoptosis-associated speck-like protein, ASC), cysteinyl aspartate-specific proteases-1 (caspase-1) containing cysteine combined to form inflammatory bodies. By regulating caspase-1 activation, Promote the maturation and release of inflammatory factors such as IL-1β and IL-18, and play a pro-inflammatory role [11] . In addition, activation of atypical inflammatories has been reported to be associated with caspase-4 or caspase-5-dependent pyrodeath, which is known to be induced by intracellular lipopolysaccharide (LPS) in Gram-negative bacteria [12, 13] . At the same time, the activation of caspase-4/5 also induced typical NLRP3 inflammasome. mRNA levels of TIFA, NLRP3, CASP1, CASP4, CASP5 and IL1β were significantly increased in acute and convalessive KD patients. Therefore, both NLRP3/ Caspase-1-dependent typical inflammatories and Caspase-4/5-dependent atypical inflammatories are involved in pro-inflammatory immune responses in KD patients at the transcriptional level [14] .

2.3 Activation of NLRP3 inflammasome:

Studies have shown that the NLRP3 inflammasome is a complex composed of three subunits, and activation of the NLRP3 inflammasome requires two signals.

The first signal causes NFB activation, which leads to increased NLRP3 and pro-IL1β levels. Binding of pathogen-associated molecular patterns (PAMP) or damage-associated molecular patterns (DAMP) to pattern recognition receptors (PRRS) results in NFB activation. NFB is a transcription factor that increases NLRP3 and pro-IL1β in cells, which is called priming.

The second signal leads to the assembly of the namesome protein, resulting in the activation of caspase 1, which is called activation. Caspase-1 converts pro-IL1β and pro-IL18 to IL1β and IL18, respectively. It also leads to programmed inflammatory cell death through the formation of pores in the cell membrane, with the end result being the release of inflammatory cytokines and inflammatory cell death through the formation of cell membrane pores. [15]

2.4 Regulation of NLRP3 inflammasome

1. MicroRNAs(miRNAs) are endogenous non-coding RNA molecules responsible for a variety of cellular and metabolic pathways, including cell proliferation, differentiation, and death. miRNAs are also involved in the regulation of inflammatory response and maintenance of immune homeostasis [16] . Recent studies have shown that MicroRNA-223(miR-223) limits the development of cardiovascular diseases by down-regulating NLRP3 inflammasome activity and subsequent IL-1β production. miR-223 may be a potential biomarker for the early diagnosis of KD in humans, and may be promising as a novel therapy for KD in the future[17].

2. Studies at different periods consistently found that ITPKC polymorphism is associated with KD susceptibility, and ITPKC controls NLRP3 activation by regulating calcium ion mobilization. ITPKC is a gene that encodes inositol triphosphate 3-kinase, which converts inositol triphosphate (IP3) to inositol tetraphosphate and terminates the propagation of Ca2+ signaling pathways. Recent studies have shown that reduced function of inositol 3-kinase triphosphate leads to accumulation of IP3 [18] . Increased IP3 leads to increased intracellular Ca2+ and activation of NLRP3. Increased IP3

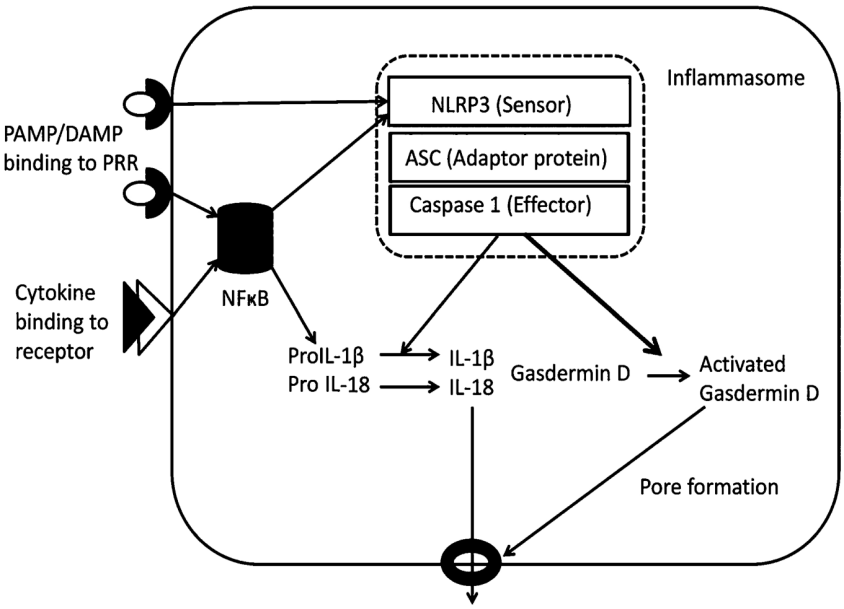

Figure 1. NLRP3 inflammasome activation pathway:

also leads to activation of T cells through Ca2+/NFAT (nuclear factor that activates T cells) pathway [19] .

The role of ITPKC, NLRP3 and cytokines such as IL1β and IL18 in children with acute KD has been investigated. They found that ITPKC was down-regulated and NLRP3 was up-regulated in the children. IL18 levels are elevated and associated with inflammatory markers. IL1β levels were not significantly elevated in children with KD compared to controls, but were higher in IVig-resistant children in their cohort. These studies may indicate that NLRP3 inflammator-driven IL-1β plays an important role in disease development in children with Ivig-resistant KD, and also suggest that in addition to IL-1β, it is also a therapeutic target for KD through the regulation of NLRP3 inflammator-resistant [20] . Management of the water-soluble portion of Candida albicans (CAWS) is a mouse model that causes KD coronary arteritis. This model was used to show that damage to KD vascular inflammation is mediated by NLRP3 activation and IL-1β production, as the control group suggested that NLRP3 deficient mice did not develop vasculitis [21] . In both studies, NLRP3 bodies were found to be involved in KD pathogenesis.

Based on the above studies, it can be seen that the action process of inflammatories in KD is that when the body is subjected to invasion by exogenous pathogenic toxins or stimulation by endogenous danger signals, inflammatories are self-activated and form active substances (caspase-l), which further promote maturation of more downstream pro-inflammatory factors (such as IL-1β and IL-18), thus promoting cellular inflammatory response. Even apoptosis. The production of inflammatory factors can further cause the activation of immune cells such as T cells and NK cells, and the release of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and other inflammatory factors. Such recurrent and even diffuse inflammation leads to the damage of vascular endothelium, which may play a role in KD systemic vascular inflammation and CAL. Although a single mechanism such as inflammasome may not fully explain the pathogenesis of KD, such research will certainly promote the development of new diagnostic markers and therapeutic targets in KD.

3. ADAPTIVE IMMUNE INFLAMMATORY RESPONSE

In addition to the role of innate immune response in generating inflammation in KD, relevant studies have shown that antigen-specific adaptive immune response also occurs in KD patients. For example, both B cells and CD8+T cells have been reported to have oligonclonal amplification in acute KD. Autoantibodies against various myocardial, endothelial, and extracellular matrix proteins have been documented in many studies. The clinical significance of these autoantibodies is unclear.

In a long-term follow-up study, 22% of patients detected autoantibodies several years after diagnosis of KD [22] . However, there is no convincing evidence that KD patients are at higher risk of developing autoimmune diseases later in life.

3.1. B cell activating factor (BAFF) and IgA reactions

1. B cell activating factor is an important cytokine for B cell activation and differentiation. In autoimmune diseases characterized by autoantibody production, BAFF is usually highly expressed and is a target for therapeutic intervention [23, 24] . Children with KD also showed high levels of BAFF and returned to normal after IVIG treatment [25, 26] . The increase in BAFF may be related to the increase in the percentage of antiboy-secreting cells in acute KD, which decreased after treatment [27] .

2. In KD patients, IgA producing plasma cells infiltrate the coronary wall. The frequency of IgA plasma cells is also higher in the upper respiratory tract of KD patients. A recent study has suggested that IgA response in KD may be an important factor in vascular injury. LCWE mouse model is an example of PAMP-induced coronary arteritis, and LCWE-induced KD model was used to demonstrate that adaptive immune response is involved in vascular injury in KD patients. Foreign scholars have proved that vascular inflammation is related to the increase of serum IgA level and IgA+B cells in lymphoid tissue [28] . Deposition of the IgA-C3 immune complex was also noted in the heart and aorta of LCWE-treated mice. In this model, vascular inflammation and damage were IgA dependent, because IgA deficient mice did not develop coronary vasculitis [28] .

3.2. CD8+ T cells

LCWE mouse model experiments suggest that CD8+T cells promote vascular inflammation and injury [29] . The coronary arteries of LCWE-treated mice showed infiltration of CD4+ and CD8+T cells as well as regulatory T cells, dendritic cells, neutrophils, and macrophages. Elimination of CD8+T cells with monoclonal antibody significantly alleviated vasculitis and myocarditis in LCWE-treated mice. The clearance of CD4+T cells and other cells did not have the same effect [29] , indicating that CD8+T cells played a role in KD vasculitis injury.

In conclusion, KD inflammation mainly involves innate immune inflammatory response and adaptive immune inflammatory response, including the involvement of inflammatory cells, inflammatory factors and inflammatory bodies, among which inflammatory bodies play an important role. Early detection of the expression of NLRP3 inflammatory bodies in peripheral blood and intervention therapy may provide new ideas for the diagnosis and treatment of KD. However, how specific inflammatory bodies cause damage to blood vessels in KD patients still needs further study. By exploring the specific pathogenesis of inflammation in Kawasaki disease, we hope to provide new guidance for clinical diagnosis and treatment, so as to reduce the incidence of Kawasaki disease, especially the coronary artery injury.

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HOW TO IDENTIFY TWINS

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ABSTRACT:

In this paper, we have tried to draw your attention to the fact that in the case of both monozygotic and dizygotic twins, the order of birth of an individual twin may be considered as an important factor in the formation of certain characteristics of the organism. Along with this, people have the ability to notice the differences between twins and even identify which twin was born first and which was born for the second time. As for monozygotic twins, you know that it is difficult for even family members to distinguish them from each other, although there are people who stand out from the rest with the ability to recognize a twin. Some people believe that a first-born twin is "older" in appearance than a second-born twin, more purposefulness and activity are felt. Others found differences in head shape and so on. There were those who simply learned to recognize the first-born twin through practice, and they were more likely to make mistakes because of it exists many reasons to be mistaken by this direction. For example, often happens that as a result of caesarean section, the fetus, which was supposed to leave the uterus first, is removed for the second time in a row. At this time, a controversial issue arises - which should be considered as the first born, the baby who was first taken out of the womb or the baby whose position during physiological birth definitely determined its first delivery?!

Question-try to guess which one is the first-born twin and which one is the second?

AND THE CORRECT ANSWE IS

First born *Monozygotic twins* *Second born*

It is a universal conundrum – the capability to correctly differentiate between identical twins. It has been seen however, that those who have been exposed to identical twins for prolonged periods, may it be their children, siblings, or other relatives – they have a higher tendency to correctly distinguish between them.

Our aim was - To understand and identify the differences between the twin siblings in Monozygotic and Dizygotic twins.

Method – A questionnaire was created and distributed among students of our university and family in close association with twins.

Along with their answers, photos of the twins were also provided.

Study A – using the photos, a study was conducted to see how many members of a test group would be able to correctly identify the older twin from the younger twin based of the picture, and if there were any concrete basis for their choices. The members who answered correctly for the first picture were formed a separate test group and were shown a series of pictures of other twin siblings. With this selected group, they were shown 6 more photos of twin siblings. At the same time most of the premise for the assumptions made by the test group was either based on the height, or facial composition (maturity). First born were also identified based on the facial composition differentiated by the fact that older twin have look like they are responsible for taking care of both the twins, however the younger twin takes care of themselves and only them.

Next sample about dizygotic twins and the same question-which one is the first born and which one is the second born?

The first born twin *Dizygotic twins* *The Second born twin*

It was seen that sometimes it was more difficult to identify the older twin among dizygotic twins than monozygotic twins.

Study B – The parents of two pairs of twins were shown a series of photos of twins for identification. The results are

	Correct Answers
Mother of Twin Set 1	5 out of 6
Father of Twin Set 1	4 out of 6
Mother of Twin Set 2	5 out of 6
Father of Twin Set 2	3 out of 6

It was also seen that the member of the group who is a mother to twins were able to identify all the twins correctly. At the same time preparation for birth is the most important moment for twins. Their position in the uterus, which may change throughout pregnancy, determines their birth order. But everything changes when a caesarean section is performed instead of a physiological birth...

It often happens that as a result of caesarean section, the fetus, which was supposed to leave the uterus first, is removed for the second time in a row. At this time, a controversial issue arises - which should be considered as the first born, the baby who was first taken out of the womb or the baby whose position during physiological birth definitely determined its first delivery?!

The observations revealed that external identification signs (height, facial features, facial expressions, etc.) do not correspond to the artificially created order and correspond to the order that we would have in the case of physiological childbirth. But, while researching this issue, we face another problem - regarding the disappearance of qualitative distinguishing features (character, vision, susceptibility to infectious diseases, etc.) in twins born as a result of cesarean section.

The extent of the aforementioned fact and whether it appears in the majority of twins born by caesarean section, the research of this assumption is ongoing. Out of the 30 twins we have seen so far, 21 had similar characteristics. It is too early to get the final result and confirm the hypothesis, however, this fact became the reason for raising the third problem. Why is this happening? What is the reason for the similarity of distinguishing characteristics between twins born by cesarean section for the first time and for the second time? - We think the answer to this is the different role of physiological delivery and caesarean section in the adaptation of the newborn, a brief description of which is as follows: A newborn born by caesarean section is weak, while a baby born by physiological delivery is able to fight and is well adapted to the environment. Leaving the mother's body is the first big test for the fetus, and during this time it learns to overcome obstacles. During physiological childbirth, the fetus is active it is involved in the birth process, and during cesarean section it is removed at once, due to which its adaptive properties are less developed.

At the same time when we looking for differences between first born and second born tween it`s necessary to take into account the discovery of DNA methylation gave us a mechanism to understand how epigenetic phenomena happen in twins. The histone modification can also be used to modulate the expression of a gene - turn it on a little, quite a bite, quite a lot and so on.

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Monozygotic twins born by caesarean section. The twin on the left was delivered first, while the twin on the right would have been born first in the womb in a natural birth.

ABSTRACTS OF INTERESTING ARTICLES PUBLISHED IN VARIOUS JOURNALS

Discover Health Systems

COMPARATIVE ANALYSIS OF A PRIVATE TELEHEALTH CLINIC AND COUNTRY-WIDE COVID-19 PATIENT MANAGEMENT RESULTS

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ABSTRACT:

The first majorly destructive pandemic of the twenty-first century broke out due to the spread of Severe Acute Respiratory Syndrome Coronavirus 2 worldwide. Remote management was put in place to efficiently assess the patients to prevent unnecessary hospitalization and educate the infected on the red flags. This study is a retrospective case control study that will contain a retrospective include analysis of medical records of 13,174 pediatric and adult patients with a laboratory- confirmed diagnosis of Coronavirus Disease and were undergoing remote management at REDMED online clinic in the period of July, 2021 and March, 2022. The retrieved data will be analyzed in specific detail and the hospitalization rate will be compared with country-wide results. The analysis helped us conclude, that there is a statistically significant difference between the country-wide hospitalization rate (16.8% by December 31, 2021 and 15.1% by July, 2022) and hospitalization rate (total mean value—1.8%) recorded at REDMED ($x^2=2123.488$, df=1 $p<0.0001$ and $x^2=1824.761$, df=1, $p<0.0001$). This type of discrepancy requires further investigation. However, we have a reason to believe that direct communication with your doctor through an application might be the reason for being compliant and trusting the service provider. Well- managed and organized telemedicine is an efficient tool to manage Coronavirus or other Infectious Diseases remotely, especially when direct patient-to-doctor audiovisual communication is enabled.

Journal of Medical Case Reports (2023)

RARE PRESENTATION AND RETROGRADE DIAGNOSIS OF TOTAL COLONIC AGANGLIONOSIS IN A FEMALE INFANT: A CASE REPORT

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EKA KVIRKVELIA,
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ABSTRACT:

Background Total colonic aganglionosis is an extremely rarevariant of Hirschsprung's disease, which is predominant in males and can be seen in 1:50,000 live births. The presented case not only depicts a rare case, but also unusual clini- cal, laboratory, and instrumental data.

Case presentation A 2-day-old Caucasian female newborn was transferred to our hospital from maternity. The initial presentation was reverse peristalsis, abdominal distention, and inability to pass stool. Fever had started before the patient was transferred. Hirschsprung's disease was suspected, and tests such as contrast enema and rectal suction biopsy were done. Before

enterostomy, the management of the disease included fluid resuscitation, colonic irrigation, antibiotic administration, enteral feeding, and supportive therapy. During ileostomy operation, no transition zone was visualized and full-thickness biopsy samples were retrieved from the rectum and descending colon. After surgical intervention, status significantly improved-defervescence and weight gain most importantly improved.

Conclusion It is well known that diagnosis of total colonic aganglionosis may be delayed for months or even years since the transition zone may not be visible and rectal suction biopsy, unlike full-thickness biopsy, is not always reliable. It might be more prudent not to be derailed because of negative radiography and rectal suction biopsy. Also, doctors should be more suspicious of the disease if signs and symptoms are starting to be consistent with Hirschsprung-associated enterocolitis, despite biopsy and radiology results.

Keywords Total colonic aganglionosis, Enterocolitis, Hirschsprung disease

Pediatric Cardiology №17 (2023)
(Tbilisi, Georgia)

BASICS OF CHILDREN'S CARDIO-RHEUMATOLOGY

(AGE LIMITS OF CHILDREN AND ADOLESCENTS AND THEIR MOST IMPORTANT ROLE IN CARDIOVASCULAR DISEASES IN MANAGEMENT)

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ABSTRACT:

In the management of cardio-rheumatic diseases in children and adolescents, a complex, detailed analysis of their anamnestic, clinical, laboratory and instrumental data is of the utmost importance, taking into account age norms. We also note that foreign language explanations are deliberately used in the text, so that we did not violate the data of the primary sources, for which we apologize, and the authors We thank you very much.

When discussing individual cardiovascular diseases, you will be convinced that the role of age limits in children and adolescents is very important in the management of diseases.

Pediatric Cardiology №17 (2023)
(Tbilisi, Georgia)

BASICS OF CHILDREN'S CARDIO-RHEUMATOLOGY

(INSPECTION, PERCUSSION, AUSCULTATION-HEART TONES AND MURMURS)

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ABSTRACT:

In the period of modern urbanization, inspection, percussion and auscultation have not lost their role in children's cardio-rheumatology.

That is why the goal of our work was the children's sister

Elevation of diagnostic values of clinical parameters in adolescents.

The work is based on 100, 000 cases of children and adolescents analyzed in the consulting clinical databases of 1981-2023.

Since, in this work, we discussed age groups, the characteristics of blood circulation in children in the pre- and postnatal period, and then the data of inspection, percussion, auscultation (heart tones, murmurs, pericardial friction, etc.) with the clinical values of the age groups during normal and pathological conditions, we considered it useless here. We also discussed congenital heart defects (CHD) in general and what will be of great practical help to clinicians in the complex.

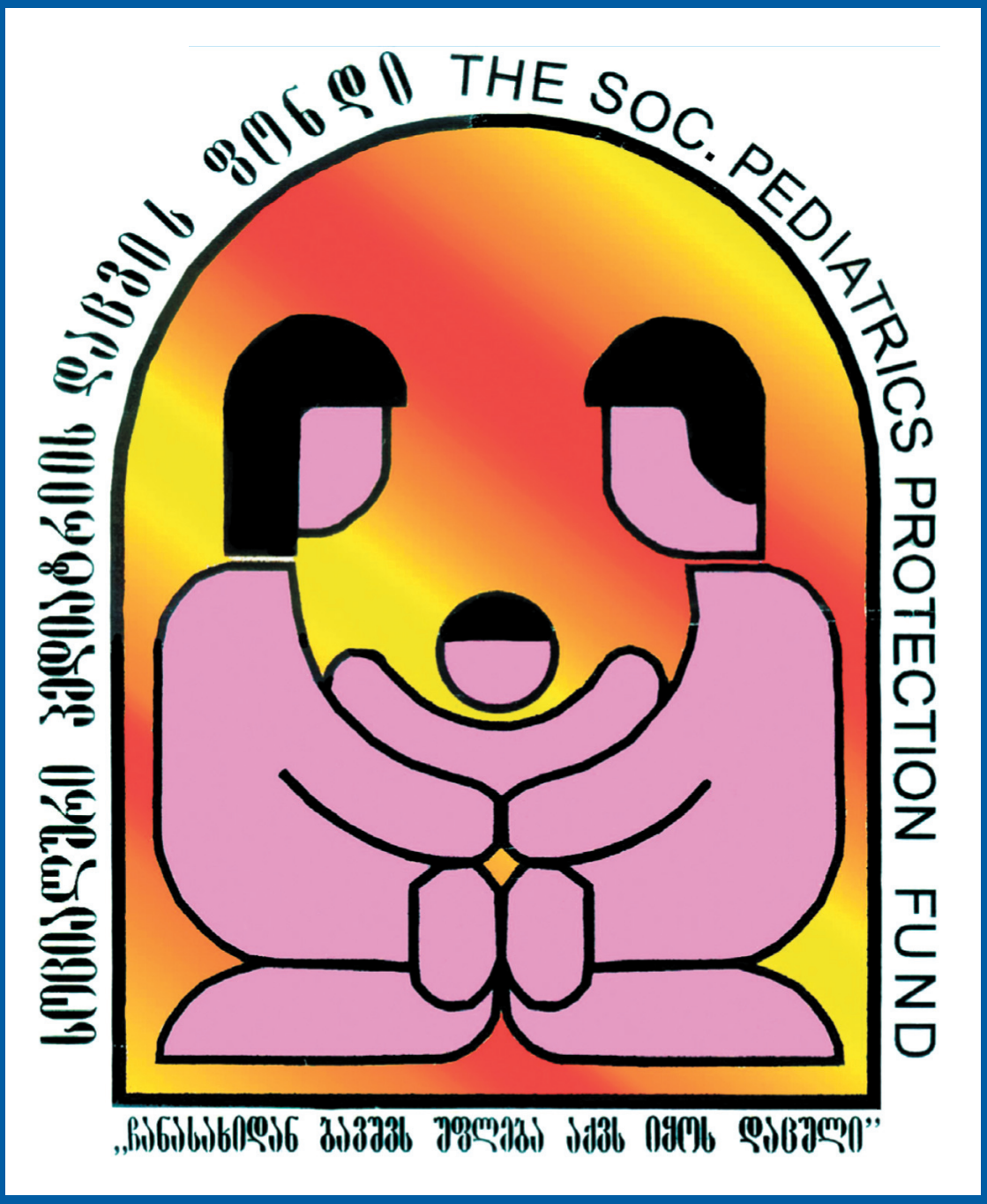
The Belt The Road Five European Countries, Georgia, Mongolia, Israel Academic Exchange

TCM WORLD

European center of traditional Chinese medicine (TCM) in Prague, Czech and xi'an, China

The Belt and Road Medical Communication——Georgian

“The Social Pediatric Protection Fund“ is 25 years old



”Children’s rights must be defended since embryo”