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Dedicated to all Children who died from the disease!!!

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Abstract

Research is to see what everybody else has seen and to think what nobody else has thought.
Competent treatment of Kawasaki disease at Children (analysis of literature sources and own research – level of evidence-4) или
Clinical trial (new treatment standards)

Key words: Children, Kawasaki disease, diagnostics, arery aneurysm, Immunoglobulin, Aspirin, Sangviritrin, Imunofan, Alpizarin, treatment, complications, resistance therapy

Introduction

The first descriptions of Kawasaki disease in Russia date back to 1982-1984. Since the mid-1990s, a study of Kawasaki disease was started in Irkutsk (Russia).
More than 130 children with Kawasaki disease were observed, treated, or consulted in Moscow between 2004 and 2012. At the same time, if in 2004-2006 the diagnosis of Kawasaki bolzen was established in isolated cases, in 2009-2011 its frequency was already on average 30 primary cases per year.

In Russia, Kawasaki disease is diagnosed more often, but often at a late date, as a result of which treatment is prescribed late and not adequately.

MUCOCUTANEOUS LYMPHONODULAR disease (KAWASAKI): CURRENT state of the ISSUE in Russia

Epidemiology. Children are more likely to get sick, mainly at the age of a few weeks to 5 years; the ratio of girls to boys is 1.5:1.

In Japan, China and Korea, Kawasaki disease occurs with the highest frequency per year. In recent years, there have been reports of cases of Kawasaki disease in older children and isolated cases-even in adults aged 20-30 years. There were 3 periodic outbreaks of Kawasaki disease in Japan from 1987 to 1996 and an increase in the incidence of the disease between November and February.
Superantigens non-specifically bind antigen-presenting cells (APC) and disrupt the regulation of T-cell activity.

This hypothesis is confirmed by a decrease in the number of AIC after administration of intravenous Immunoglobulin to patients with Kawasaki disease, which most often interrupts the clinical manifestations of the disease. It is recognized that immune activation plays an important role in pathogenesis, which is confirmed by the detection of deposits of immune complexes in affected tissues, increased levels of circulating anti-inflammatory cytokines, and activation of T cells. Kawasaki disease has a multifactorial Genesis of the disease, when an infectious agent leads to clinical manifestations of the disease only only in individuals with a genetic predisposition that occurs from previous vaccination.

This phenomenon is called gene expression, when different nucleotides occur compared to normal ones (author's note). In the pursuit of universal universal vaccination, the disease became a genetic one (author's note).

The study of families in which several people had Kawasaki disease was associated with histocompatibility complex antigens NBA B22, B2212, BW22, as well as with a number of genetic polymorphisms, which is more common in the Asian population (polymorphism of genes encoding calcineurin, prostaglandin Transporter ABCC4). The allergic mechanism in response to environmental factors, home environment, medication, and prolonged illiterate vaccination is also of some importance (author's note).

Primary cause of the disease

This is illiterate vaccination, which in Russia is aggravated by the introduction of more and more new vaccines. In the National calendar, there are 16 vaccinations per child, which is 36 shots, which is dangerous (author's note). The number of vaccines is growing. Under the influence of a large number of vaccine infectious agents, a phenomenon such as gene Expression occurs, when abnormal nucleotides are formed instead of normal nucleotides. Then any disease becomes genetic, and this is doubly dangerous. The author wrote a book-gene Expression (the book requires publication) - (author's note).

Important!!! Official data (official statistics) the incidence of Kawasaki disease in Russia is not!!!

Kawasaki syndrome (the effects of coronavirus) and Kawasaki disease are not the same thing. This is a different kind of pathology.

Statistics in Russia

In Russia, Kawasaki disease is quite common. But there are no official statistics. The prevailing age is 1-15 years. The prevailing gender is women 1.5:1 (Russia differs).

Extremely important-author's analysis of Immunogramms of Children for the years - (1983 - present). This is something that the author observes personally and in different years. All post-vaccination syndromes, as I call them in each clinical case, can be described in this way (author's note).

A characteristic clinical sign of Kawasaki disease in girls and boys is a thickening and reddening of the area at the injection site of BCG.

This symptom is not detected in some countries, since such mass vaccination is not provided in certain States (author's note).
The author revealed that the main agents are (BCG vaccine). Other infections or other vaccine infections may be added. This is called the syndrome of amplification of the infection, when one infection is superimposed on another (author's note). In General, the BCG vaccine does not prevent tuberculosis, but it almost completely kills the child's immune system. There is incomplete phagocytosis, when the body of children can not cope with any disease. Moreover, many countries have long abandoned the use of the BCG vaccine. They do not have this syndrome. This should be heard by the authorities in Russia, medical officials (author's note). In Russia, revaccination from BCG was canceled at 6 years of age, if the reaction to Mantoux or Diaskin test is negative (author's note). But the first vaccination is done immediately in the maternity hospital after birth and gives infection with Koch sticks, but makes phagocytosis insufficient (author's note), when the child's body ceases to resist infection (any).

Conclusion of the pediatric phthisiologist – «the child is infected. Medical withdrawal from BCG for life».
Then postvaccinal BCG syndrome and as a consequence of it – Kawasaki disease will be treated differently than Kawasaki syndrome (author's note).

Schematic Etiotropic Treatment (author's treatment):
Sanguiritrin (from 1 year old) + Imunofan (candles in children), if the cause was tuberculosis vaccination (BCG). It is necessary to make crops from the nose, pharynx, examine sputum, blood, urine, feces.

The drug Sanguiritrin-bactericidal effect on Koch sticks without occurrence resiatance to microflora, reduces CIC (circulating immune complexes) - only take strictly after meals in 30-40 minutes (1/4 tablet diluted in water).

Imunofan can be used from the age of 2. This drug relieves intoxication, so you can not put droppers. You can use earlier than 1-2 years-adjust the dose-1 candle in 2-3 days. Imunofan is a 3-phase drug. Phase 1-3-4 days of treatment-removes intoxication, phase 2-7-8 days-stimulates phagocytosis, phase 3-21 days - correction of immunological parameters - reduction of mutogenic activity, decrease circulating immune complexes, increased concentration of interferon alpha and gamma. Children under 1 year will have to use Immunoglobulin.

Risk Factors or Triggers:

Important!!! In 1982-1983, in Russia, they were vaccinated against mastitis-they were administered to pregnant women, and newborns got sick-exudative catarrhal diathesis, vesiculopustullosis, and the parents of children were sown with Staphylococcus aureus, which required treatment with Immunomodulators (author's note). Vaccinations against mastitis were canceled soon, but many children died from Staphylococcus aureus infection or remain frequently ill as adults with atopic dermatitis (author's note-author's observations). Moreover, dermatitis is often similar to «ace» - looks like Kawasaki disease (see the photo below).

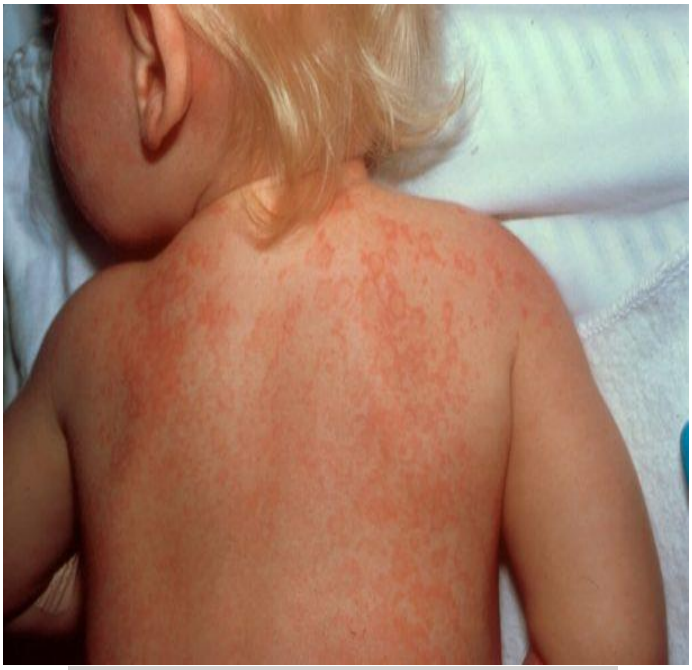
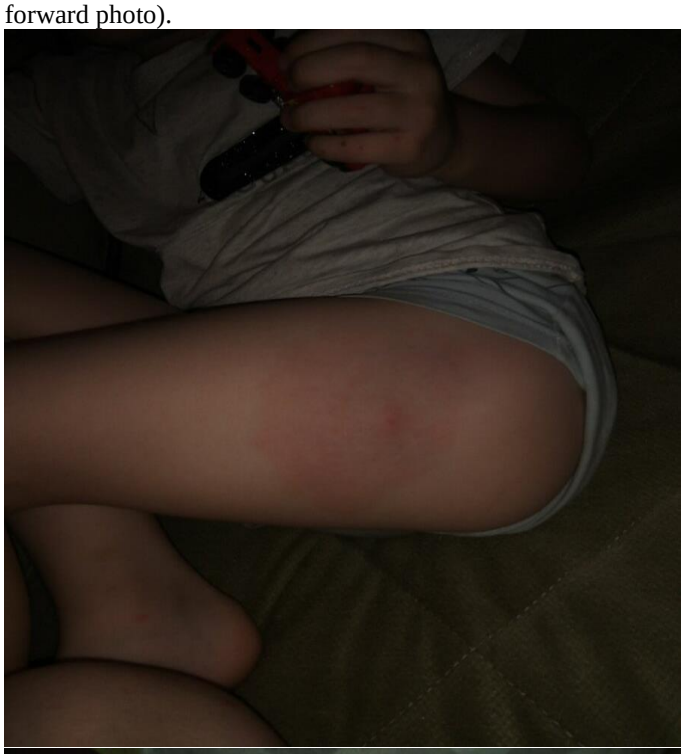
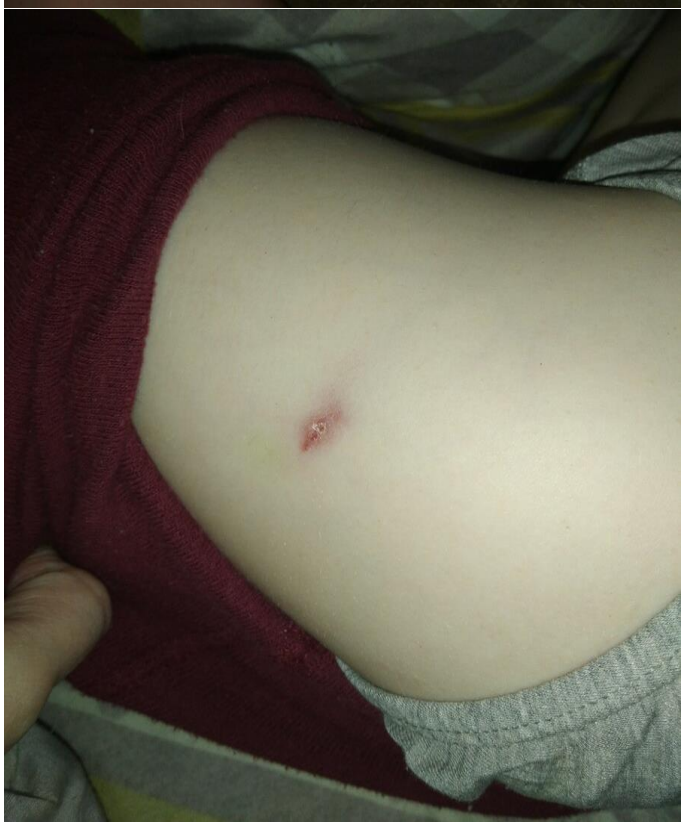


Figure: Rash in Kawasaki disease (Russian Child).

The vaccines tested on children in Volgograd have indeed already been approved and are now in direct sales!!!
Biorhythms of Kawasaki disease-this disease is characterized by seasonality.
The greatest number of cases of exacerbations of the disease are registered in March-April, as well as at the end of the year - December. This seasonality has led experts to believe that the disease is infectious in nature.
Mechanism of disease development (pathogenesis)
Very important!!! Kawasaki disease is caused by the BCG vaccine and other vaccines that are triggers (author's note).
The author calls Kawasaki disease postvaccinal syndromes of various origins (author's note). The author puts an equal sign between these terms (author's note).
There is a syndrome of increased infection, as a result of the occurrence of Kawasaki disease (observations from 1983 to the present).
BCG + Staphylococcus aureus = vasculitis + atopic dermatitis (usually in boys).
BCG + vaccine against mastitis (1983) = vasculitis + exudative-catarrhal diathesis, vesiculopustules (usually in newborn boys).
BCG + Ureaplasma (parvum) = vasculitis + abdominal syndrome ("acute abdomen") in girls with ejection of eggs (hyperovulation), in children under 1 year – Kawasaki disease.
BCG + other vaccinations = vasculitis + angina, spinal muscular atrophy (SMA) in infants and children under 5 years of age, endometritis in young women, multiple sclerosis in young women, amyotrophic lateral sclerosis (ALS) in young men, infectious cancers in children and adults.
DPT (AKDS in Russia) vaccinations were made against the background of existing vaccines-polio, BCG, hepatitis B.
By the evening, we had a temperature of 39, which did not get off. On the feet of children (2 boys 5 and 6 years old – brothers-weather) abscess (see photo below).

In this case, the combination is DPT (AKDS in Russia) + polio + hepatitis B against the background of BCG in the hospital (author's note).
Redness around the injection and further development of the abscess.
The abscess was hidden. The wound from the incision was healed for a month, there was wetness and poor healing (Look forward photo).





Junior still has a small hard lump the size of a pea deep in his

leg. Looks like polyarteritis nodosa.
In the early 1970s, it was widely believed that the pathomorphology of Kawasaki disease and nodular polyarteritis is identical.
It has even been suggested that Kawasaki disease is the mildest form of nodular polyarteritis.
Currently, it has been shown that although Kawasaki disease and polyarteritis nodosa belong to the same group of necrotizing vasculitis, morphological changes in Kawasaki disease have some distinctive features:

1.primary damage to the coronary arteries.
2.lower the severity or absence of necrosis fibrinoidnogo
3.pronounced thickening of the intima
4.the nature of cellular infiltration of the vascular wall - the predominance of CD8-positive T-lymphocytes, macrophages and a small number of polymorphonuclear cells, which occurred in this clinical case against the background of vaccination (author's note).

By the way, parents of children could not get records in medical records about complications after vaccinations. The doctor clutched at the medical records, a week later the page with this entry was not there...Official medicine in Russia hides these cases (author's note). If all post-vaccination syndromes are recorded and described, but vaccination should be closed in Russia (author's note).

Clinical example 1. A Boy aged 2 months and 20 days was admitted on the first day of illness (17.10) due to abdominal pain, fever up to 38.8° C with a referral diagnosis of «intussusception? ORVI». Delivered by the car «first aid». Upon admission to the emergency Department based on the results of the surgeon's examination and ultrasound diagnostics of the abdominal organs, surgical pathology is excluded. With a preliminary diagnosis of «acute infectious enteritis», he was hospitalized in the specialized Department.

From the life history: a full-term boy, from the 1st pregnancy, which occurred with the threat of termination in the 1st trimester, delivery on time, double entanglement with the umbilical cord, screamed immediately, weight-3210 g, height-52 cm, vaccinated in the hospital BCG, HBV (these are the root causes of Kawasaki disease). Breastfed to the present. Everyone is healthy at home.

During the examination, attention was drawn to persistent fever up to 38.8° C, anxiety with the preservation of appetite. The skin is pale, there is no rash. The yawn is calm. In the lungs, the breathing is puerile, there is no wheezing. Heart tones are loud and rhythmic. The abdomen is soft, podadut, painless. The stool is yellow, liquefied. Waters. Liver + 2.0, spleen not enlarged.

On the 2nd day (18.10), lethargy increased, skin syndrome joined in the form of a spotty papular rash on the face, behind the ears, in natural folds, on the back, arms, legs. Infusion therapy (Trisol + Prednisone), without effect. In the General analysis of blood - leukocytes up to 10, 0x10/9 l with a shift to the left, platelets-357x10/9 l, ESR-35 mm / h, in the General analysis of urine-leukocyturia - all fields of vision. According to ultrasound examination of the kidneys, mucosal edema and dilatation of the pelvis of the left kidney were noted. Based on the clinical picture and the examination, the diagnosis was "urinary tract infection". Antibacterial (cefurus) and symptomatic therapy was prescribed.

From 3 days on, against the background of persistent fever, the rash increased, sometimes draining, and the rash thickened in the pelvic parts. There was an increase in symptoms of intoxication - lethargy, moodiness, decreased appetite. There are signs of lymphadenopathy-an increase in the cervical group of lymph nodes up to 1.5 cm, more on the right. The stomach is soft, painless, and the liver is + 2.5 cm. Stool 3-4 times a day is yellow, liquid, without pathological impurities. Antihistamines were added to the treatment.

On the 4th day-fever without dynamics, changes in the skin remained, local hyperemia appeared with infiltration in the area of the heels and palms. The phenomenon of scleritis. Lips are bright, dry, slimy, moist, pink, there are no overlays. In order to exclude damage to the cardiovascular system, ECHO-CT was performed, an open oval window, abnormal left ventricular chords, and functional insufficiency of the tricuspid valve were detected.

The Conducted Laboratory Examination Showed:

1.in the General blood test - for 3 days against the background of antibacterial and anti-inflammatory therapy - increasing neutrophilic leukocytosis up to 16, 6X10/9 l, thrombocytosis-527x10/9 l, increased ESR up to 53 mm / hour;
2.in the General analysis of urine-leukocyturia (25-30 in the field of vision), trace proteinuria up to 0.09 g/l);
3.in the biochemical analysis of blood-no pathology was detected, 4. procalcitonin test-negative,
5.fecal analysis for the intestinal group negative.
The conducted instrumental methods of examination made it possible to exclude septic foci of infections:
According to chest radiography, there were no focal or infiltrative shadows. However, clinical changes, lack of positive dynamics against the background of infusion, desensitizing and antibacterial therapy, Kawasaki disease was suspected, which caused the echo-KG to be repeated.
On the 5th day of the disease with Echo-KG (from 22.10)-echo-signs of coronariitis.
Based on the clinical picture (persistent fever, skin and mucosal syndrome, lymphadenopathy, lack of effect from antibacterial therapy) and instrumental data (Echo-KG - signs of coronariitis), it was possible to establish a diagnosis - Kawasaki disease, full form.
According to the data management algorithm, patients were treated with Immunoglobulin (Intratect 2 g / kg) and Aspirin (30 mg/kg/day). Against this background, the temperature returned to normal within 1 day, and the rash disappeared. The child

began to react actively to the environment, and his appetite was restored.

Clinical example 2. A full-term boy, 5 months old, on mixed feeding, was admitted from home in a state of moderate severity with a clinic for acute pyelonephritis (fever, leukocyturia, pyelitis phenomena were diagnosed according to ultrasound diagnostics).

From the medical history, it is known that the boy is from the 2nd pregnancy, which occurred with edema; from 2 urgent deliveries with a weight of 3690 g, height 52 cm. The adaptation period was uneventful, breastfed, not ill, and gained weight well. He was born with dropsy of the right testicle and was sent for elective surgery. During the last 2 weeks, urine tests showed leukocyturia up to 35-40 in the field of vision, subfebrility up to 37.7° C. A uroseptic (Furagin) was prescribed, and within 5-7 days, urine tests and temperature returned to normal.

The boy was hospitalized in the infant Department after 2 weeks with complaints of a repeated rise in temperature to 38.5-39.0° C with a guiding diagnosis-acute pyelonephritis.

At admission, the condition is of moderate severity, subfebrile temperature. Active, Moody, appetite preserved. The skin is pale pink, clean. There was no edema. Posterior cervical lymph nodes are palpated up to 0.5-1.0 cm, dense, painless. Yawn pink. In the lungs, breathing is carried out in all departments, clean. Heart sounds are loud, rhythmic, and there is a slight systolic murmur. The stomach is soft and painless; the liver is + 1.5 cm. A chair and a diuresis without features. Ultrasound examination revealed pyelitis, leukocytosis up to 15.6 x 10/9 l; ESR - 19 mm/h; CRP up to 28.6 mg/l. Antibiotic therapy with Ampicillin (Ampicillin + Sulbactam) was prescribed. The mechanism of action is to block the replication of peptidoglycan in the bacterial cell wall. In case of overdose, it can give convulsions (author's note).

On the 2nd day of inpatient treatment, the temperature again rose to 38.2° C; the stool was liquefied; elements of a spotty papular rash appeared, including a zone of hyperemia in the BCG area up To 2 cm in diameter.
By the 3rd day of hospitalization, catarrhal phenomena (cough, runny nose), moderate pharyngeal hyperemia, rash became brighter, on the hands and feet with infiltration, injection of sclera vessels. These changes were considered manifestations of a toxic-allergic reaction to Ampicid (this is an Allergy to Ampicillin), and the antibiotic was changed to Amikacin (an aminoglycoside antibiotic), and antihistamine and hormone therapy was added.

On the 5th day of therapy, the temperature tended to decrease, the rash manifestations somewhat faded, catarrhal phenomena persisted, the liver + 3 cm, blood tests showed leukocytosis and ESR; no pathology was detected on Echocardiography.
The child was examined for viral infections-Epstein-Barr, CMV, enterovirus, Yersinia - received a negative result, IDM for herpes simplex virus-positive (Alpizarin is needed from 3 years old – author's note). For diseases caused by Herpes zoster (shingles) and Varicella zoster (chickenpox) - within 5-21 days. In case of relapses, repeated courses of treatment with the drug are carried out. To prevent relapses of herpesvirus infections, the drug is prescribed one month after the end of treatment for 10-14 days.

The maximum daily dose of the drug for children from 3 to 12 years is 300 mg (3 tablets); for children over 12 years of age and adults-800 mg (8 tablets).

An Echocardiography study was performed on the 2nd and 7th days, only the presence of an open oval window and an abnormal left ventricular chord was noted.

By the 8th day, the child had subfebrile fever, inflammatory changes in the blood (neutrophilic leukocytosis up to 39x10/9 l, ESR up to 22 mm/h; thrombocytosis up to 950x10/9 l).

On the 9th day-the rash decreased, there was a large-plate peeling of the fingers and toes. Given the symptom complex of the disease and impact on outcome of therapy, it was impossible to exclude during the acute phase of Kawasaki disease on the basis of which repeated the Echo and found the change: minor swelling of the walls of the coronary arteries - coronaries.

He was diagnosed with Kawasaki disease and treated with Immunoglobulins and Aspirin.

Against the background of the therapy, the condition stabilized, became more active, the appetite was restored, and steadily began to add weight. The symptoms of intoxication disappeared. The temperature dropped. The skin is pale pink, clean; some elements of large-plate peeling. Zev is calm. No shortness of breath. In the lungs, the breath is puerile, clear. Heart sounds are sonorous, the rhythm is correct, heart rate is up to 120 per minute. The stomach is soft and painless. Liver 1.0-1.5 cm. Yellow stool, no special diuresis. In the neurological status - without pathology. He was discharged home under the supervision of a cardiologist.

But the author offers a new method of treatment – Etiotropic treatment.

Examples of diagnoses (author, 2020)

1.Kawasaki Disease, the full form of bacterial Genesis (BCG vaccine + genetic pathology-hereditary thrombophilia). Mutations in one allele of the methylenetetrahydrofolate reductase gene (heterozygous inheritance) and in one allele of the PAI-1 gene (heterozygous inheritance). Hemochromatosis. Antibodies to chickenpox (catamnesis from childhood). Dilated cardiomyopathy syndrome. Left and right coronary artery aneurysms. Chronic heart failure (CHF) 11a, functional class (FC) II according to Ross.

2.Kawasaki Disease, not a complete form of viral Genesis (herpes simplex on the background of BCG). Occlusion of the right coronary artery. HSN I, FC I by NYHA.

Treatment will vary for different infections (author's note).
This suggests that any treatment should be personalized (author's note).

The Aspirin + Immunoglobin regimen doesn't always work.
In 1 case-the dose of Fraxiparin will be higher, folic acid, Exjade, Alpizarin is prescribed.
In the 2nd case, Imunofan in cancer, Sangviritrin - with 1-2 years.
Alpizarin has antiviral activity against viruses: Herpes simplex type 1 and 2, Herpes zoster, Varicella zoster, cytomegaloviruses.
The inhibitory effect of the drug on the reproduction of the virus is especially evident in the early stages of its development. Alpizarin has immunostimulating properties in relation to cellular and humoral immunity, the ability to induce the production of gamma interferon in blood cells (interferon inducer).
Alpizarin inhibits the growth of gram-negative (Escherichia coli) and gram-positive (Staphylococcus aureus, Mycobacterium tuberculosis) bacteria, fungi (Microsporum canis) and pathogenic protozoa (Entamoeba histolytica, Trichomonas vaginalis). The mechanism of action of the drug is based on the ability to suppress the activity of bacterial nuclease. Alpizarin has a moderate anti-inflammatory effect.

Tetrahydroxyglucopyranosylxanthene (Alpizarin) is largely bound to blood proteins (90-70%), so the effect of the drug is slow.
There are isolated cases of pathology in adults.

There was such a significant adult patient in 2008-25 years old, A., male.

PCR analysis for thrombophilia revealed mutations in one allele of the methylenetetrahydrofolate reductase gene (heterozygous inheritance) and in one allele of the PAI-1 gene (heterozygous inheritance).

The ELISA study found: herpes virus type 6 (anti-IgG), Epstein - Barr virus (NA-a-IgG and VCA-a-UDM), Varicella-Zoster virus (VZV-a-IgM and VZV-a-IgG).
As can be seen, in adults, other combinations of viruses are the causes of Kawasaki disease (author's note).

Important!!! Since vaccinations also include bacteria (not just viruses), you can treat them with antibiotics (author's note) if the root cause is BCG (Koch's bacterium). It is necessary to do a microbiological analysis-seeding of urine, sputum, blood, the contents of the nasal and pharyngeal mucosa (author's note).

This clinical case demonstrates a rare disease in adults - Kawasaki disease, an atypical form that occurs with heart damage:
Aneurysmal dilation of the coronary arteries and the development of acute large-focal myocardial infarction with the formation of a left ventricular SAC aneurysm. Pathology of the heart developed against the background of hereditary thrombophilia. This case indicates that it is possible to detect Kawasaki disease in vivo, which is important for a practicing therapist. It is obvious that the therapists have not seen this pathology and do not know it (author's note).

Immediately changed the treatment

In PCR analysis for thrombophilia, the detection of mutations in one allele of the methylenetetrahydrofolate reductase gene and in one allele of the RA1-1 gene indicated the development of the disease against the background of hereditary pathology, which worsened the prognosis of the disease and required the combined use of Aspirin and high doses of Fraxiparin, and then a higher dose of Warfarin together with folic acid.

The dose of Fraxiparin was increased to 0.6 ml 2 times a day due to the obtained research results. Folic acid 5 mg, Warfarin with a gradual increase in the dose to 8.75 mg, and hemoexfusions of 150-200 ml per week for three weeks were added to the treatment. From 24.04 to 5.05, the patient received treatment with Crestor 20 mg once a day, which was canceled with an increase in transaminase levels compared to the initial one.
The expression of certain cytokines and biomarkers of inflammation is significantly increased in patients resistant to therapy and patients with coronary artery lesions:

1.granulocyte colony stimulating factor (G-CSF)
2.Interleukin-6
3.soluble tumor necrosis factor receptors of type 1 and 2 (sTNFR1, sTNFR2)
4.true polycythemia protein
5.PVR-1 (Pulmonary Vascular Resistance, pulmonary vascular resistance). These studies should be included in the diagnostic standards for patients (author's note).
Important!!! A combined increase in sTNFR1 and PVR-1 was associated with the development of IGVV resistance and coronary artery disease.
Important!!! Patients with Kawasaki disease and resistance to therapy in the early stages of the disease showed increased levels of PVR-1, as well as G-CSF (Granulocyte-macrophage colony - stimulating factor – polypeptide cytokine-responsible for the formation of white blood cells).

Treatment in the acute period of the disease

It is aimed at modulating the immune response and inhibiting platelet activation to prevent the formation of coronary aneurysms and their thrombosis.

Currently, the treatment regimen for the acute period of Kawasaki disease is generally accepted in the world:
A combination of Immunoglobulin for intravenous administration in a high course dose (2 g per 1 kg of body weight in a single infusion) and Acetylsalicylic acid (Aspirin).

Important!!! Treatment with antibiotics is not effective!!!

The use of IGVV in the treatment of a patient with Kawasaki disease leads to a rapid (1-2 days after administration) decrease in body temperature, improvement of well-being and reduction of the period of normalization of laboratory indicators of inflammatory activity; significantly reduces the risk of coronary artery aneurysms. IGVV is prescribed in the first 7-10 days of the disease, until coronary artery aneurysms begin to form. IGVV is prescribed after the 10th day-for children who have not been diagnosed before, if they continue to have unmotivated fever or coronary aneurysms are detected, and indicators of systemic inflammation (increased ESR or C-reactive protein concentration) remain.
The use of IGVV in the first 7-10 days of the disease reduces the risk of damage to the coronary arteries by 5 or more times.
It is the time elapsed from the onset of the disease to the introduction of IGVV that is critical for preventing damage to the coronary arteries.
It was shown that in the group of patients who received IGVV in the first 7 days, aneurysms formed in 6% of patients; in the group who received the same therapy from the 8th to the 10th days of the disease-in 27%; after the 10th day-in 36%.
Our own data confirm the high dependence of the frequency and severity of coronary artery damage on the timing of treatment initiation:

Small coronary aneurysms were formed in 16.7% of children who received igvv on day 6-7 from the onset of the disease; in patients who received IGVV on day 8-10, the number of patients with aneurysms was 22.3% (in 16.7%-small, in 5.6%-medium - sized aneurysms); in patients who received IGVV after day 10, aneurysms formed in 53.4% of cases (in 26.7% - small, in 17.8%-medium - sized, in 8.9% - giant aneurysms).
Timely diagnosis and adequate therapy are the key to achieving optimal results in children with Kawasaki disease.

Discussion on Drugs of Choice for Kawasaki Disease

The drug of choice at the beginning of treatment is intravenous administration of Immunoglobulin in combination with Aspirin, which reduces the likelihood of coronary artery aneurysms from 20 to 4%, provided that treatment is started in the first 10 days of the disease. If there is no response to intravenous Immunoglobulin therapy, glucocorticoids may be prescribed.

Pharmacological Range of Action of Aspirin

Aspirin has been used for many years to treat Kawasaki disease. The drug has an anti-inflammatory (in large doses) and antiplatelet (in small doses) effect.

In the acute stage of the disease, Aspirin is prescribed in a dosage of 80-100 mg/kg of body weight per day in 4 doses, in combination with intravenous administration of gamma globulin. In the absence of fever for 48-72 hours, the dose of Aspirin is reduced to achieve only an antiplatelet effect (3-5 mg/kg of body weight per day.

Aspirin in small doses is prescribed until the level of markers of acute inflammation (ESR, platelet count) is normalized, if no coronary artery aneurysms were detected during Echocardiography within 6-8 weeks from the onset of the disease.

Aspirin is not able to reduce the incidence of coronary artery abnormalities. There are 3 critical stages of aneurysm formation. At the first stage, the introduction of the extract led to massive activation of T cells. Activation of the immune system was accompanied by the production of TNF a (second stage), which is a mandatory participant in coronary artery disease in mice. It should be noted that patients with Kawasaki disease also showed an increase in the level of TNF a.

At the third stage, TNF a triggered a cascade mechanism of activation of pathological biochemical reactions, one of the components of which is activation of the expression of the matrix metalloproteinase 9 (MMP 9) gene in vascular smooth muscle cells.

Prolonged expression and activation of MMP 9 in smooth muscle cells leads to the destruction of elastin, which is a key point in the formation of an aneurysm.

Aspirin in therapeutic concentrations of 0.1-0.25 mg / ml (corresponds to high doses of Aspirin in children), is not able to inhibit any of the three stages of aneurysm development, but also leads to an increase in the production of TNF a!!!
Aspirin can only be used as an anti-pyretic and antiplatelet agent, which does not require the appointment of high doses of the drug!!!

Aspirin is involved in the formation of aggregates of aspirin-labile proteins including immunoglobulins (Kamyshnikov V. S., 2003).

The Association of polypeptide chains into larger aggregates is called a Quaternary structure. The formation of randomly formed aggregates is an error that leads to the appearance of functionally inactive proteins, so cells provide mechanisms for their rapid degradation and decomposition into individual amino acids.

Back in 1997, R. W. Carrel et al. it was proposed to call diseases in the pathogenesis of which the key link is a violation of the tertiary structure of the protein, "conformational diseases". The

list of diseases that can be attributed to this group is constantly expanding. The number of proteins that can lose their conformational stability and form pathogenic aggregates (and, consequently, diseases caused by this process) is constantly increasing.... When considering the consequences of conformational changes in proteins, it becomes obvious that in almost all cases, the development of the disease is associated with the accumulation of protein aggregates. Pathogenic effects of aggregates can be direct or indirect (V. N. Sakharov, P. F. Litvitsky, 2005).

Proteins of the acute phase of inflammation are subject to conformational transitions:

1.serum amyloid protein A
2.alpha1-antitrypsin
3.lysozyme
4.immunoglobulins.
Most of the incorrectly folded, denatured, and other abnormal proteins also are degraded rapidly in the cytosol. They usually break down in a few minutes, while normal copies of the same proteins are preserved. ...

Abnormal proteins, and proteins that are genetically programmed for rapid replacement, are eventually destroyed in the cytosol by the same proteolytic mechanism.

The role of Aspirin and NSAIDs in the etiology of human suffering is underestimated. Hypodiagnostics of hypersensitivity to ASA and NSAIDs in the practice of various specialists is an urgent problem, since it not only contributes to the persistence and progression of respiratory tract inflammation, but also poses a real threat to the lives of patients when they are prescribed Aspirin and NSAIDs due to any pathology.

Any medication taken for a long time and a lot will lead to complications. Aspirin is an excellent medicine that can quickly eliminate the beginning cold with hypothermia and use as an antiplatelet, but for the acute period of Covid. It should be thoroughly crushed and washed down, consumed after a small snack with a hot drink. The drug has been tested for a hundred years. Naturally, someone may have an intolerance, etc. Everything is individual.
Aspirin is not recommended for Covid-19.
It is necessary to be very careful with Kawasaki syndrome in children. Dangerous development of Reye's syndrome (or Reye). Especially against the background of vaccination against flu, chickenpox and coronavirus (author's note).

Intravenous Immunoglobulin

The introduction of Immunoglobulin has a General anti-inflammatory effect, stops fever and reduces the concentration of inflammatory markers in the blood. The effectiveness of intravenous Immunoglobulin in reducing the risk of coronary artery abnormalities has been repeatedly described.

A study conducted by A. S. Lau et al. (2009) showed that the administration of intravenous Immunoglobulin in high doses inhibits the activation of lymphocytes and reduces the production of TNF a, but does not prevent the production of activated proteases by it. Low concentrations of Immunoglobulin do not completely prevent the synthesis of TNF and, accordingly, do not prevent further production of MMP 9 and its damaging effect on elastin.

Intravenous Immunoglobulin at a dose of 2 g / kg of body weight should be administered to the patient within 12 hours after diagnosis. For maximum effect, the diagnosis should be established as early as possible, within 7-10 days from the onset of the disease. It is shown that 5% of children have minimal transient lesions of the coronary arteries, and 1% have large aneurysms, even with timely (in the first 10 days of the disease) treatment - the introduction of Immunoglobulin. If the patient does not respond to the initial therapy with intravenous Immunoglobulin, the drug administration in the same dose is repeated for 36-48 hours after the first infusion.

You need to look for other drugs to treat Kawasaki disease.
The author found such a drug (Imunofan). Imunofan-3-4 days works as a detoxicant, then as a phagocytosis stimulator (7-10 days), and then as an Immunomodulator (author's note). It can be used to treat coronavirus and to treat Kawasaki disease.
Management of patients with Kawasaki disease and coronary artery disease
Treatment should include antiplatelet therapy with Aspirin, possibly in combination with Dipyridamole or Clopidogrel, anticoagulants (Warfarin or low-molecular-weight Heparin), or a combination of antiplatelet and anticoagulant therapy with Warfarin in combination with Aspirin.

In asymptomatic forms of Kawasaki disease with small lesions of the coronary arteries, low-dose Aspirin therapy should be prolonged. The combination of Aspirin with other drugs that have a similar effect (Dipyridamole-the drug stimulates the production of endogenous Immunoglobulin) or Clopidogrel is used to increase the volume of arterial damage or with a persistent increase in platelet count (>1 million cells mm3).
A combination of Aspirin with intravenous infusions of Heparin is prescribed for large or rapidly increasing aneurysms.
For patients with giant aneurysms, it is considered most appropriate to prescribe low doses of Aspirin in combination with Warfarin until the values of the international normalized ratio (INR) are equal to 2.0-2.5 (MNO in Russia). Cases of coronary artery thrombosis in children with Kawasaki disease are quite rare.

Some studies report more or less successful treatment of coronary artery thrombosis in children of different ages using Streptokinase, Urokinase, and tissue plasminogen activation factor. The use of glycoprotein II A/III B inhibitors (Abacximab) may be promising in antithrombotic therapy of

children with Kawasaki disease.

Patients who have suffered from Kawasaki disease may experience aneurysms, calcification and stenosis of the coronary arteries, as well as heart valve failure due to the development of heart failure.

Drug Route of administration Dosage

Aspirin per os Antiplatelet dose 3-5 mg per day

Clopidogrel per os From 1 mg / kg per day to a maximum (for adults) of 75 mg per day

Dipyridamole per os 2-6 mg / kg per day in 3 doses

Unfractionated heparin intravenous loading dose: 50 U/kg, infusion: 20 U/kg. The maintenance dose for achieving a therapeutic effect is determined by the plasma level of Heparin equal to 0.35-0.7; by the activity of the XA anti-factor or by the APTT (60-85 sec).

Low-molecular-weight Heparin-subcutaneously Newborns: Treatment: 3 mg / kg per day, in 2 injections prevention: 1.5 mg / kg per day, in 2 injections Children and adolescents: Treatment: 2 mg / kg per day, in 2 injections prevention: 1 mg / kg per day, in 2 injections the Maintenance dose to achieve a therapeutic effect is determined by the activity of the XA anti-factor equal to 0.5-1.0 U / ml.

Abcximab Intravenously bolus: 0.25 mg / kg Infusion: 0.125 mg / kg per minute for 12 hours.

Streptokinase Intravenously bolus: 1000-4000 U / kg for 30 min Infusion: 1000-1500 U/kg per hour.

Plasminogen activation factor intravenously bolus: 1.25 mg / kg Infusion: 0.1-0.5 mg / kg per hour for 6 hours, then re-evaluate the need for drug administration.

Urokinase Intravenous Bolus: 4400 U / kg for 10 min Infusion: 4400 U/kg per hour.

Warfarin per os 0.1 mg / kg per day, daily (0.05-0.34 mg / kg per day; until the INR (MNO in Russia) values are 2.0-2.5.

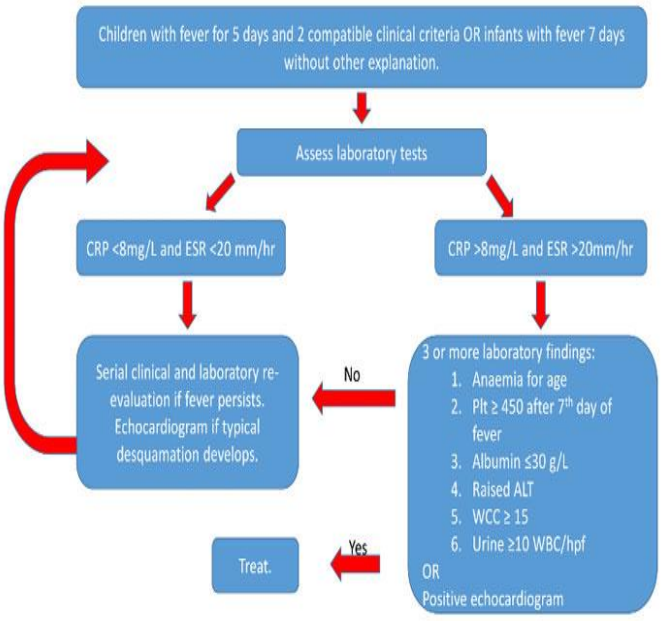


Figure: Vaccination problems in Kawasaki disease

The development of antigenic imprinting may have individuals previously vaccinated against pathogens of infectious diseases, representatives of the families Orthomyxoviridae, Arenaviridae, Retroviridae, Flaviviridae, Parvoviridae and Plasmodiidae, so for developers of vaccines intended to prevent infectious diseases caused by microorganisms - the representatives of these families must be receiving at the stage of preclinical proof of absence of risk of development of the people of this phenomenon. Most likely to develop an antibody - dependent increase in infection in individuals previously vaccinated against infectious diseases, representatives of the families of viruses Orthomyxoviridae, Paramyxoviridae, Rhabdoviridae, Coronaviridae, Retroviridae, Parvoviridae, Filoviridae, Flaviviridae, Togaviridae, Picornaviridae; as well as bacteria-pathogens of streptococcosis, staphylococcosis, tuberculosis and rickettsiae. That is why developers of vaccines, serums, and immunoglobulins intended for the prevention and specific treatment of infectious diseases caused by members of these families should be required to obtain evidence at the stage of their preclinical research that there is no risk of developing this phenomenon in people. This is known to some eminent doctors, such as phthisiatrist M. V. Supotnitsky, who advocated the abolition of the BCG vaccine for children, since it only kills the entire immune system of a newly born child.

The author developed a treatment for BCG vaccine blockers to remove the risk of post-vaccination syndrome from this vaccine. It is necessary to work in the same team of Doctors and Pharmacists. Only then will there be a sense in the treatment of human diseases.

Ricochets on medications

Regression of the aneurysm is accompanied by the preservation of the vascular pathological reaction to Nitroglycerin and Acetylcholine, which indicates the existing endothelial dysfunction. An extremely rare complication of a coronary artery aneurysm is its rupture, which occurs during the first months of the disease.

The disease begins with a high fever, followed by a vesicular rash that resembles an infectious disease.

Platelet activation is the main manifestation of the acute phase of the disease.

It persists in the stages of convalescence and chronization of the disease, which determines the important role of Aspirin in any stage of pain. Low-dose Aspirin is indicated for patients without severe symptoms of the disease when the disease is stabilized. Aspirin, however, does not reduce the incidence of coronary artery aneurysms. When the coronary arteries are involved in the process, a combination of Aspirin with other antiplatelet drugs - Clopidogrel and Dipyridamole-becomes more effective.

With the rapid development of aneurysms, the risk of thrombosis increases significantly, and preference is given to a combination of Heparin and Aspirin.

In patients with giant coronary artery aneurysms, low doses of Aspirin and Warfarin are prescribed with an international normalized ratio (INR) of 2.0 to 2.5.

During the acute phase of the disease, Aspirin is used in a dosage of 80 to 100 mg / kg of weight in combination with intravenous administration of gamma globulin, which can enhance the anti-inflammatory effect. The use of gamma-globulin in the acute phase of the disease can reduce the incidence of coronary artery aneurysms. It is prescribed at a dose of 2 g / kg of weight in the

form of a single infusion. This therapy is performed during the first 7-10 days of the disease, while early treatment does not prevent cardiac complications.
Important!!! About 10% of patients with Kawasaki disease are not sensitive to the use of gamma globulin, as evidenced by the persistence of fever for more than 36 hours after its initial administration.
However, most experts recommend repeated administration of Gamma globulin.
The use of glucocorticoids in Kawasaki disease reduces the duration of fever, but the benefits of reducing the frequency of coronary artery damage have not been proven.

Clinical Example

Patient A., aged 2 years, was observed in the rheumatology Department for 1.5 years. The boy was born from the 1st pregnancy, which proceeded physiologically, urgent delivery. The birth weight was 3,010 g and the length were 51 cm. In the early period, physical and psychomotor development corresponded to age. Preventive vaccinations were carried out according to the national calendar (the root cause is BCG+ other vaccines). Hereditary history of rheumatic diseases is not burdened.
The boy became ill at the age of 3 months, when on the 2nd day after vaccination with the drug akds (syndrome of increased infection = BCG + akds), the temperature increased to 38.5°C.
Against the background of taking antipyretic drugs (Ibuprofen), daily temperature rises (1 time per day) to febrile numbers persisted. On the 4th day of the disease, the child had a cough, hoarseness of voice, rhinitis phenomena, on the 5th day-injection of the sclera, diarrhea, an uncontrolled increase in temperature. Due to the lack of effect from taking antipyretic drugs, the child was hospitalized in a pediatric hospital at the place of residence, where the diagnosis of intestinal infection was established, antibacterial therapy with Ceftriaxone and symptomatic treatment were performed. On the 2nd day of hospitalization, against the background of persistent fever, the boy had edema of the face, hands, feet; small point, sometimes discharge rash on the limbs, marbling of the skin; catarrhal phenomena persisted. The child's condition was assessed as serious, and the patient was transferred to the intensive care unit, where antibacterial therapy was continued without significant effect. On the 10th day of the disease, the child had a pronounced «stocking» type of peeling of the feet. In the clinical blood analysis, thrombocytosis up to 954x1012/l (norm up to 450), leukocytosis up to 18, 3x109/l (norm up to 11), increased erythrocyte sedimentation rate (ESR) up to 50 mm/h (norm up to 20), serum C-reactive protein (CRP) concentrations up to 43 mg/l (norm up to 5) were noted. On the 20th day of the disease, the child was first suspected of having Kawasaki disease. According to the results of echocardiography (EchoCG), a blood clot was detected in the left coronary artery, and a Doppler scan of the coronary arteries revealed a picture of multiple aneurysms. The child was diagnosed with Kawasaki Syndrome. The course of therapy included a combined intake of human normal Immunoglobulin at a dose of 1.5 g / kg of body weight and Aspirin at a dose of 15 mg / kg per day.
During the next 3 weeks, the child showed weakness, lethargy, the boy was capricious, refused to eat; in blood tests, leukocytosis and thrombocytosis persisted.
Given the severity of the child's condition, as well as the insufficient effect of the treatment, the boy was sent to the children's health Research center for emergency reasons. 6 weeks after the onset of the disease, the patient was admitted to the rheumatology Department to clarify the diagnosis and treatment.

Upon admission: the condition is severe, due to severe weakness, symptoms of intoxication.
On examination: pallor of the skin, small-point and papular rash on the face and trunk, hyperemia of the oral mucosa, injection of sclera, visible swelling of the hands and feet.
According to the results of electrocardiography: the boundaries of relative cardiac dullness are not changed, auscultation heart tones are sonorous, rhythmic, heart rate is 128-152 beats / min, blood pressure is 75/35 mm Hg.for other organs and systems, pathologies were not detected.

In a clinical blood test: thrombocytosis up to 934x1012/l, leukocytosis up to 17, 5x109/l, increased ESR up to 46 mm / h; serum CRP concentrations up to 44 mg/l.
In order to determine antibodies to intestinal and viral infections, the child underwent an enzyme immunoassay, and a bacteriological study of the pharyngeal culture - no data for the infectious process was obtained.

According to EchoCG data: pronounced expansion of the right coronary artery (from 10 to 12 mm), in the left coronary artery-aneurysms from 6 to 7 mm, a blood clot 2x3 mm.
Ophthalmologist diagnosed-bilateral conjunctivitis.
Taking into account the medical history, clinical picture, results of laboratory and instrumental examinations, the child was diagnosed with Kawasaki syndrome, although it is Kawasaki disease (author's note).
Given the duration of the disease (6 weeks), the development of life-threatening complications (coronary artery aneurysms), pathogenetic therapy, according to international protocols for the treatment of Kawasaki syndrome, included the " gold standard»:
10% solution of human normal Immunoglobulin for intravenous administration (IVIG) at a dose of 2 g / kg per course continuously for 8-12 hours and Aspirin at a dose of 80 mg / kg per day for the purpose of anti-inflammatory effect, followed by a decrease to 5 mg / kg per day for the purpose of antithrombotic effect. Heparin therapy at a dose of 300 U / kg per day was also aimed at preventing the development of arterial and venous thrombosis and embolism.
After 1 day of treatment, the child apparently decreased swelling of the feet and hands and appeared to have an appetite.
Echocardiography of the heart showed no negative dynamics.
On day 3 of therapy, the rash was stopped, conjunctivitis significantly decreased, and laboratory indicators of disease activity (ESR and CRP) were normalized.

Conclusion

1.This clinical case demonstrates a rare disease in adults - Kawasaki disease, which occurs with heart damage: aneurysmal expansion of the coronary arteries and the development of acute large-focal myocardial infarction with the formation of a left ventricular SAC aneurysm.
2.Heart Pathology developed against the background of hereditary thrombophilia. This case demonstrates the possibility of detecting Kawasaki disease in vivo, and not only in a child, which is important for a practicing therapist.
3.At the present time, the etiology of the development of Kawasaki disease is precisely established:
4.Infectious agents (usually vaccinated) against the background of the existing genetic predisposition in a particular patient.
5.Destructive-proliferative vasculitis, which is the pathogenetic basis of the pathological process in this pathology, more often affects infants and young children and should be considered as the cause of febrile fever.
6.This acute systemic disease, being a relatively rare pathology, can cause the development of acquired cardiovascular diseases - aneurysms and stenoses of the coronary arteries, especially with late diagnosis and untimely and / or inadequate treatment.
7.Characteristic diagnostic signs allow timely diagnosis and start specific therapy. It is extremely important to prescribe the optimal course of therapy, which will determine the prognosis for a particular patient in the future. This new Immunomodulators (Imunofan in cancer), new antithrombotic without determining INR (MNO in Russia) and others.
8.Among Russian patients with Kawasaki disease, boys predominate (especially in the younger age group); half of the patients are children under 5 years of age, most of the patients belong to the European race.
9.Along with the initial diagnostic symptoms-fever, inflammatory changes in the oral mucosa, transient skin rash, non-purulent cervical lymphadenitis, changes in the skin of the extremities, patients often have hepatosplenomegaly, damage to the urinary system, nervous system, abdominal syndrome, diarrhea, arthritis.
10.Heart Damage is manifested in half of cases by myocardial dysfunction (usually moderate), QT-T shifts on the ECG of the ischemic type, echocardiographic signs of coronaritis (in some patients in combination with coronary dilation), anginal pain or their equivalents, arrhythmias, myopericarditis, or pancarditis. Present – heart murmur, gallop rhythm, thispage.
11.Diagnosis of Kawasaki disease in Russia often occurs only by 3-4 weeks from the onset of fever, which is due to insufficient knowledge of this nosology by pediatricians and infectious diseases specialists, underestimation of clinical and laboratory data.
12.In the population of Russian children, coronary injuries and secondary dilatation of the left ventricle are common (in 90.9% of cases). Rare but dangerous complications of the disease are severe heart failure, myocardial infarction, and sudden death.
13.Treatment with Aspirin and intravenous human Immunoglobulin is accompanied by the disappearance of acute symptoms and laboratory changes in 5-25 days, and with a 5-year catamnesis, all these patients are alive and do not have severe cardiac complications.
14.The use of Imunofan gives detoxification, increases phagocytosis reactions, reduces circulating immune complexes, which is an etiotropic treatment of infections.
15.The use of Imunofan is sparing for children, since it is carried out in candles, droppers are excluded (author's note).

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