ATYPICAL KAWASAKI DISEASE

Kawasaki disease is an acute vasculitis which occurs primarily in children under the age of 5. The etiology of the disease is still unknown. Diagnostic criteria for Kawasaki disease are fever and at least four of the five additional clinical signs. Incomplete Kawasaki disease should be taken into consideration in case of all children with unexplained fever for more than 5 days, associated with 2 or 3 of the main clinical findings of Kawasaki disease. The diagnosis of incomplete Kawasaki disease is based on echocardiographic findings indicating the involvement of the coronary arteries. Cardiac complications, mostly coronary artery aneurysms, can occur in 20% to 25% of untreated patients and in 4% of treated patients. Case Report. In this report we present a case of atypical Kawasaki disease in a 3.5-month-old infant. As soon as the diagnosis was made, the patient received high doses of intravenous immunoglobulin, with the initial introduction of ibuprofen, then aspirin with a good clinical response. Due to the presence of aneurysm of coronary arteries, further therapy involved aspirin and clopidogrel over the following 3 months, and then only aspirin for 2 years. There was a gradual regression of the changes in the coronary blood vessels to the normalization of the echocardiographic findings after 2 years. Conclusion. Kawasaki disease is the second most common vasculitis of childhood, so it should be included in the differential diagnosis for any child with a prolonged unexplained fever. Atypical Kawasaki disease should be taken into consideration in cases when not all clinical criteria are present but coronary abnormalities are documented. Keywords: Mucocutaneous Lymph Node Syndrome; Infant; Child, Preschool; Signs and Symptoms; Fever of Unknown Origin; Vasculitis; Coronary Vessel Anomalies; Immunoglobulins, Intravenous; Aspirin; Diagnosis; Treatment Outcome

Introduction

Kawasaki disease (KD) was first reported by Tomasaku Kawasaki in a four-year-old child (Red Cross Hospital in Tokyo, Japan, January 1961) [1]. This disease is an acute vasculitis in children with the mortality rate of 0.1-2%. The incidence among Asian children is significantly higher than in children from other regions, 134-135 per 100,000 children under 5 years of age, but this disease occurs throughout the world and in all ethnic groups [2–4]. KD occurs primarily in young children, with 80% of patients under the age of 4, and with the peak incidence occurring at 9 to 11 months of age. The illness is extremely rare in infants younger than 3 months of age, while the youngest reported patient in the literature is a 2-week-old neonate [5]. The disease is more common in male children, the ratio between boys and girls being 1.7:1 [1].
Abbreviations:
KD – Kawasaki disease
IVIG – intravenous immunoglobulin
MI – myocardial ischemia
ESR – erythrocyte sedimentation rate
CRP – C-reactive protein
HDL – high-density lipoprotein
GGT – gamma-glutamyl transferase

The etiology of the disease is unknown, but clinical and epidemiological presentation suggests an infectious origin. However, a particular virus or bacteria has not been implicated. There are circumstantial data supporting the role of certain bacterial toxins (e.g. staphylococcal toxic shock toxin, streptococcal erythrogenic toxin), viruses (Epstein-Barr virus, parvovirus, human immunodeficiency virus (HIV)-2) or ubiquitous microorganisms that cause clinically manifested disease in genetically predisposed individuals. Considering the fact that the disease is more common in children of Asian origin, it is likely that genetic factors play a role as well [2, 6, 7]. This theory is corroborated by the fact that the disease is more common in twins and siblings of affected patients than in general population, and is more common in children whose parents had the illness in their childhood [6]. Kawasaki disease consists of generalized systemic vasculitis, affecting predominantly medium-sized vessels [1]. Coronary arteries are most frequently affected, but the process may occur in other extraparenchymal muscular arteries such as celiac, mesenteric, femoral, iliac, renal, axillary and brachial artery [6].

The diagnosis is based on the recognition of characteristic clinical signs [1]. It is important to realize that often not all of the symptoms are present at the same time, so it is necessary to repeat clinical examinations in order to make the diagnosis [7]. Diagnostic criteria for KD are fever and at least four of the five additional clinical signs. Fever within KD can last from 5 to 25 days, usually reaches 40°C and is unresponsive to antibiotics and minimally responsive to antipyretics. Other clinical signs are: 1. bilateral bulbar conjunctival injections not accompanied by suppuration, usually without involvement of the limbus, often accompanied by photophobia; 2. changes in the mucosa of the oropharynx (bright red, swollen lips with vertical cracking and bleeding, red oropharynx, strawberry tongue); 3. changes in the peripheral extremities (erythema of the palms and soles, which is often accompanied by painful, brawny edema of the dorsa of the hands or the feet in the acute phase, followed by desquamation of the fingers which begins at the periangual region); 4. polymorphous rash, usually diffuse maculopapular, although it can be scarlatinitiform, multiformal, urticarial, rarely micropustular, but never bullous or vesicular; 5. cervical lymphadenopathy (more than 1 lymph node exceeding 1.5 cm in diameter), without suppuration, usually unilateral, with involvement of the front cervical lymph nodes [1, 6, 7].

The least common clinical sign is cervical lymphadenopathy, which is present in only about 50% of children with KD and significantly more often in older children [8]. Younger children with KD tend to be more irritable. Although not included in the diagnostic criteria, gastrointestinal symptoms such as nausea, vomiting and diarrhoea, as well as arthritis and arthralgia, are common in children with KD [9]. In addition, other clinical manifestations may be present in some cases such as aseptic meningitis, facial palsy, ataxia, encephalopathy, hemiplegia, cerebrovascular accident, sensorineural hearing loss, pleural effusion, pulmonary infiltrates, otitis media, acute renal failure, abdominal pain, hepatitis, gallbladder hydrops, pancreatitis, jaundice, swelling of the testicles, urethritis and, very rarely, rhabdomyolysis and hemorrhagic syndrome [1, 3, 4, 6].

Incomplete or atypical KD should be taken into consideration in case of all children with unexplained fever for more than 5 days, associated with 2 or 3 of the main clinical findings of KD [1]. The diagnosis of incomplete KD is based on echocardiographic findings indicating the involvement of the coronary arteries [1, 6]. Ten percent of children with aneurismal changes in coronary vessels fall into this category. Incomplete clinical presentation of KD is very common in infants, especially under the age of 6 months [7]. Two most commonly absent symptoms in atypical cases are cervical lymphadenopathy and polymorphous rash while mucosal changes are nearly always found [3].

Kawasaki disease is usually self-limiting, having a triphasic course, with an average duration of symptoms of approximately 12 days [3, 7]. The acute phase begins with fever, conjunctivitis, oral changes, lymphadenopathy and rash and lasts for almost one to two weeks. The subacute phase is characterized by desquamation of the hands and feet and conjunctivitis may also persist during this phase. The convalescent phase starts when all the clinical signs have resolved and ends when the laboratory abnormalities have returned to normal, usually four to six weeks after the onset of disease [3].

The diagnosis of KD is based on clinical characteristics; there are no confirmatory laboratory tests. However, certain laboratory tests can be used to support the diagnosis, such as elevated erythrocyte sedimentation rate (ESR) (≥40 mm/h) or elevated C-reactive protein level (CRP) (≥3 mg/l), leukocytosis (≥15000/µL) with predominance of granulocytes, normochromic and normocytic anemia, sterile pyuria (≥ 10 leukocytes in the sediment, although suprapubic urine generally does not show piura, which suggests urethritis) and proteinuria. It is expected to find a moderate increase in the levels of transaminases, especially serum alanine aminotransferase >50 U/L (can be found in about 30% of patients due to congestion of the liver), gamma glutamyl transferase (GGT) increase (in almost 70% of patients), mild hyperbilirubinemia (in about 10% of patients), hypoalbuminemia, thrombocytosis >450000/mm3 (an increase in the platelet count is recorded in the second week of illness with a peak in the third week; thrombocytopenia is very rare and is a risk factor for coronary aneurysms), abnormal serum lipid levels, in-
cluding elevated triglyceride levels and low-density lipoprotein (LDL) levels and decreased high-density lipoprotein (HDL) levels, hypernatremia (<135 mEq/L, which is associated with an increased risk of coronary artery aneurysms) and elevated serum IgE levels. Pleocytosis with predominance of mononuclear cells can be detected in the cerebrospinal fluid, as well as in the inflammatory cells in the synovial fluid [1, 6, 7]. Clinical experience suggests that KD is unlikely if acute-phase inflammatory reactants and platelet count are within normal values after seven days of illness [6].

Kawasaki disease, which was initially thought to be a benign, self-limiting febrile illness, is now known to be associated with sudden death in about one percent of the affected children due to acute coronary vasculitis, which leads to thrombus formation in the affected vessels and myocardial infarction [9]. Cardiac complications can occur in 20% to 25% of untreated patients and in 4% of treated patients. The most common cardiac complication seen in KD is coronary artery aneurysm [7]. Changes in blood vessels usually occur 10 days to 4 weeks after the onset of symptoms, but they may occur earlier, while their presence for more than 5 weeks after the onset of fever is uncommon [7, 9]. They tend to resolve in 50% of patients within 5 to 18 months. Expeditious diagnosis is crucial, because treatment with immunoglobulin within the first 10 days of illness significantly reduces the incidence of coronary artery aneurysms [7]. For this reason, it is recommended to perform at least three echocardiograms in children with KD in the first 6 weeks of the disease [10].

Since the etiology is unknown, pharmacological therapy is non-specific and directed towards modulation of the inflammatory response and inhibition of platelet activation with the aim of preventing coronary artery aneurysms [11]. Treatment should begin with intravenous immunoglobulin (IVIG) and high doses of aspirin as soon as the diagnosis is made. The recommended dose of IVIG is 2 g/kg given as a one-time infusion during an 8- to 12-hour period. It is recommended to start this therapy within the first 10 days of the illness. The exact mechanism of IVIG’s action is unknown, but it appears to have generalized anti-inflammatory activity [7]. In addition to prevention of coronary artery aneurysms, normalization of lipid profiles and improvement of cardiac contractility seem to be other effects. The patient should also be given aspirin for its antiinflammatory and antiplatelet activity. In addition to aspirin, other antiplatelet drugs can be used such as clopidogrel and inhibitors of the platelet glycoprotein IIb/IIIa receptor [1, 11]. For treatment of IVIG-resistant patients, a variety of therapies has been tried including repeated dose of IVIG, high-dose pulse methylprednisolone, cyclophosphamide or methotrexate, but there is no established guideline for the choice of treatment. One possibility is the use of infliximab, a monoclonal antibody against tumor necrosis factor alpha (TNF-alpha), as well as plasmapheresis [12].

The overall prognosis for patients with KD depends on the severity of coronary artery involvement as a risk factor for myocardial ischemia (MI). Patients with aneurysms larger than 8 mm are at the highest risk for MI. Aneurysms that are 8 mm or smaller tend to regress over time, and those that are 6 mm or smaller tend to resolve completely. Patients without any cardiovascular abnormalities tend to do well, and are generally asymptomatic at their long-term follow-up examination [7].

Case Report

The patient is a 3.5-month-old female infant, who developed the symptoms of fever (39.2 °C axillary), cough and diarrhea, followed by redness of the skin on the trunk next day. Ambulatory oral antibiotic therapy (amoxicillin) was introduced. However, the child was hospitalized the same day because of the recurrence of fever. On admission to hospital, the child had clinical signs of disease in the form of rose-colored exanthema on the trunk, dry and intensely red lips, extreme hyperemia of the mucosa of the oropharynx, bilateral suboccipital and submandibular lymph nodes palpable to 0.5 cm. The laboratory analysis showed a high level of CRP (96 mg/l), elevated ESR (48 mm/1h), leukocytes within normal ranges, prolonged activated partial thromboplastin time (APTT) (37.7 sec), elevated level of GGT (2.04 ukat/l) and increased titters of specific IgM antibodies for Adenovirus and Epstein Barr virus. Antinuclear, antimitochondrial, antiparietal, anti-smooth muscle antibodies, serum immunoglobulin, C3 and C4 complement components were within normal ranges. Urine analysis showed proteinuria and sterile pyuria (25-30 leukocytes in the sediment, uriculit negative). Bacteriological culture of blood, cerebrospinal fluid and stool were negative. Staphylococcus aureus was isolated from the nasal swab, while the throat swab showed Candida albicans in large numbers. Ultrasound of the neck pointed to the enlargement of lymph nodes along the sternocleidomastoid muscle, of approximately 12.5 mm in diameter. Echocardiography detected a previously diagnosed heart defect (atrial septal defect and stenosis arteriae pulmonalis) with suspected aberrant coronary blood vessel. The child was examined by an otorhinolaryngologist three times to exclude focal point in the otorhinolaryngeal region.

As soon as the patient was hospitalized, parenteral antibiotic therapy (cefazidime) was introduced with antipyretic for a suspected systemic infection. Despite the applied therapy, the child had daily 4 to 5 episodes of high fever (39.4 °C). Initially present macular rash decreased gradually, while the redness of the lips and buccal mucosa maintained, with the appearance of strawberry tongue and conjunctival injection. In the further course, diarrhea started with 5-7 watery stools. On the 7th day of hospitalization another parenteral antibiotic (amikacin) was introduced. Since the febrility continued with persistent clinical findings and an increase in the level of acute-phase inflammatory reactants (CRP 96 mg/l, ESR
significant number of these children may have a serious fevers in childhood have no apparent cause. A specific IgM antibodies for some virus were elevated, indicating the actual viral infection. A possible infectious agent swab detected Staphylococcus aureus, while the bacteriological cultures taken were negative, nasal is often mentioned as well [13, 15]. In our case, all occurrence of the disease. A genetic component may have an impact on the occurrence of aneurysm of the coronary arteries. Two g/kg dose of IVIG and meta-analyzes, clearly reduces the risk of occurrence of aneurysm of the coronary arteries and to prevent coronary thrombosis [6]. Treatment using a high dose of IVIG is important for the diagnosis, KD can be characterized by the presence of clinical manifestations of other organ systems [7]. Our patient had three of the five criteria, which is a characteristic of atypical manifestations of KD. Exanthema on the trunk and severe oropharyngeal mucosal hyperemia were present at the very beginning of the disease, while in the further course bulbar hyperemia appeared.

In addition to these clinical signs of disease, which are important criteria for the diagnosis, KD can be characterized by the presence of clinical manifestations of other organ systems [7]. Our patient had diarrhea as well. According to the literature, the disease often manifests with less than 4 characteristic criteria in children under 6 months and over 5 years of age, which is beyond the typical age for KD appearance. These children are also at greater risk for making a diagnosis after 12 days from the onset of the disease [14]. All of this was confirmed in the case of our patient.

As far as laboratory analysis is concerned, no single finding is crucial for the diagnosis of KD. However, associated pathological values of certain laboratory parameters can help us to make the diagnosis. In case of KD and related laboratory findings, we expect an increase in the level of acute-phase inflammatory reactants, anemia, thrombocytosis, hypoalbuminemia, hyponatremia, hypertriglyceridemia, a decreased level of HDL with an increased level of transaminases [1, 6, 7]. In our patient, the laboratory analysis revealed an increase in CRP, fibrinogen and procalcitonin level, leukocytosis, thrombocytosis and an increased level of GGT. Urine analyses of patient with KD often show sterile pyuria and proteinuria [6], as observed in our case. Other laboratory tests were within normal ranges.

When KD is diagnosed on the basis of clinical manifestations and laboratory criteria, the therapy should be immediately introduced in order to prevent possible complications [10]. The aim of the therapy in the acute phase is to reduce inflammation in the walls of the coronary arteries and to prevent coronary thrombosis [6]. Treatment using a high dose of IVIG with aspirin, based on randomized controlled trials and meta-analyses, clearly reduces the risk of occurrence of aneurysm of the coronary arteries. Two g/kg of IVIG is the optimal dose, usually given as a single infusion and this regimen is considered to have a greater therapeutic effect in prevention of aneurysm.
comparing to the 4-day regimen (400 mg/kg/day for four consecutive days). Currently, aspirin at a dose of 30–50 mg/kg/day is recommended during the acute phase of the illness. It has not been proved that treatment with higher doses of aspirin is more effective in reducing the incidence of complications. Lower doses are better tolerated in terms of gastrointestinal and other side effects [10].

In case of our patient, the diagnosis was not made at the onset of the disease due to the atypical clinical presentation, and the treatment started at a later phase of the disease, on the 13th day of hospitalization. Our patient had been receiving IVIG for four days in a total dose of 1.8 g/kg with aspirin in a dose of 50 mg/kg/day and the clinical improvement was observed immediately after the introduction of therapy with IVIG and aspirin, and the laboratory parameters returned to the normal values. Cardiac complications can occur in 20% to 25% of untreated patients and in 4% of treated ones. Patients under 1 year of age are more likely to have coronary artery abnormalities [7, 14]. In spite of the applied therapy, some complications appeared in our patient. Echocardiographic monitoring revealed aneurysms of the coronary arteries with the subsequent occurrence of thrombosis on the 13th day of treatment. Long-term therapy for patients who develop coronary artery aneurysms is aimed at preventing myocardial ischemia and myocardial infarction [6]. If aneurysms persist, low doses of aspirin are recommended. Clopidogrel is an alternative therapy that may be taken into consideration [10]. In our case, both aspirin and clopidogrel were initially introduced due to the persistence of aneurysms and in the later course only aspirin was continued leading to gradual regression of the mentioned complications after 2 years.

**Conclusion**

Kawasaki disease is the second most common vasculitis of childhood, so it should be included in the differential diagnosis for any child with a prolonged unexplained fever. Atypical Kawasaki disease should be taken into consideration in cases when not all clinical criteria are present but coronary abnormalities are documented. Making the early diagnosis is the main challenge for the physicians because treatment in the first ten days modifies the prognosis of the disease. As soon as the diagnosis is made, the therapy should start and the patient should be carefully re-evaluated for possible development of complications.

**References**