Kawasaki disease – experience of Pediatric University Hospital, Sofia, Bulgaria, 1993–2014. Part I: clinical manifestations

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Kawasaki disease (KD) is a vasculitis syndrome causing coronaritis in young children. As a result of the vascular damage, coronary lesions (CL), ectasia and aneurysms form in 20%–25% of the untreated children. The assessment of KD is difficult and challenging because of the lack of specific diagnostic or laboratory criteria. This is a retrospective study of 107 patients for a period of 21 years (1993–2014). In the cohort, 30.8% of patients had CL (19.6% had coronary aneurysms and 11.2% had significant coronary dilatations). The number of CL was high compared to that reported in international studies, although 45% of children were treated by modern protocols. In an attempt to analyse the reasons for the high coronary risk, the aim of this study was to investigate the clinical aspects of the disease and to establish the diagnostic problems causing diagnosis delay, which is subsequently related to increased coronary risk. The high incidence of the observed CL was associated with the failure of recognizing the disease, delayed diagnosis and, subsequently, lack of correct treatment. The analysis of the clinical presentation indicated significant correlation of gastrointestinal syndrome with typical and atypical KD. The incidence of the gastrointestinal syndrome correlated with the typical KD symptoms (p = 0.030), suggesting that it could be considered as a further diagnostic criterion.

Introduction

Kawasaki disease (KD) has nearly 40 years of history [1]; however, it still poses many problems that have not yet been resolved. They relate to the etiology, pathogenesis and diagnosis, which remain difficult due to its incomplete, atypical and indolent forms and the lack of diagnostic or laboratory criteria with high sensitivity and specificity. KD presents with symptoms that appear like acute bacterial or viral infection and usually antibiotic treatment is started. KD has a self-limiting course and its acute bacterial or viral infection and usually antibiotic treatment is started. KD has a self-limiting course and therefore untreated – children. The disease has to be recognized clinically up to the 10th day of fever onset and specific treatment with high dose of aspirin and intravenous immunoglobulin infusion (IVIG) has to be started [4]. Such management prevents coronary complications. Timely diagnostic orientation and specific treatment can reduce the risk of CL from 25% to less than 5%. The search for opportunities for early diagnosis of KD, treatment and prevention of the coronary risk combines the efforts of many physicians and scientists. As a whole, the prognosis of KD is considered favourable, but correct diagnosis and proper treatment in time are essential.

The aim of this retrospective study was to present the clinical experience with KD at the Pediatric Rheumatology Clinic at the University Pediatric Hospital Sofia (Bulgaria). Data of 107 patients diagnosed with KD over a period of 21 years (1993–2014) are presented. There have been few reports dealing with the clinical aspects of KD in Bulgaria [5,6].

We discuss the clinical symptomatology in the patients with typical, incomplete and atypical KD presentation and the factors related to the delay of diagnosis that increase the risk of coronary complications, such as: referral time and stage of disease at the time of hospital admission and preliminary diagnosis; clinical manifestations of the acute phase of KD (typical, incomplete or...
atypical) related to the delay of diagnosis; patient’s age at disease onset related to the clinical expression of the disease (complete, incomplete or atypical); patient’s age at disease onset related to the coronary risk.

**Subjects and methods**

**Selection of patients**

This study included 107 children: 65 boys and 42 girls from 2 months to 13 years of age; 76.6% of the patients were younger than 5 years of age. The male-to-female ratio was 1.5:1. Longitudinal follow-up was provided in 38 children, 1.5 to 17 years, after the disease onset (mean 6 years) in patients from 3 to 17 years of age (mean 8.6 years). Echocardiography (ECHO-CG) control was performed in view of cardiac risk and early coronary artery disease. Twelve children were diagnosed with KD for the period of January 2015–February 2017 that were not included in the study. These cases will be included in future analysis that will include a period of 10 years in a cohort of KD patients with cardiac complications.

The present study was approved by the Ethics Committee at the Medical University of Sofia, Bulgaria.

**Diagnostic methods**

The diagnosis of typical, incomplete and atypical course of KD was assessed according to the American Heart Association (AHA) criteria [4]. ECHO-CG was performed by paediatric cardiologists. The accepted Newburger and Takahashi ECHOKG criteria for evaluation of the CL were followed [4].

**Statistical analysis**

The clinical and patient data are expressed as median values ± range or mean values with standard deviation (±SD). The distribution of quantitative variables was evaluated using Kolmogorov–Smirnov and Shapiro–Wilk tests. For comparison of different groups, the unpaired T-test or Mann–Whitney U-test was applied when appropriate. Results were regarded statistically significant when \( p < 0.05 \).

**Results and discussion**

**Assessment of patients with KD during the period of study**

The first report about four patients with KD in Bulgaria was in 1984 [6]. In the following years, KD became more recognizable and more patients began to be referred to the Pediatric Rheumatology Clinic (Figure 1). Such a trend is observed in many countries where similar studies have been conducted [7].

**Age groups and their relation to the clinical expression of KD and coronary risk**

The age group typical of KD is between 1 and 4 years of age and 70%–85% of the patients are between 6 months and 5 years [7,8]. However, there are many cases with incomplete and atypical forms of the disease in patients under the age of 6 months and older than 8 years of age [9,10]. In our cohort, the youngest patient is 2 months old and the oldest one is 13 years old. The patients in the typical age group (1–4 years) are 61.7%. We observed a significant number of children beyond the typical KD age group. Sixteen children (15%) were younger than 1 year and 25 patients (23.3%) were over 5 years of age with 7 of them (6.5%) over 8 years of age.

The statistical analysis did not reveal any significant differences in the clinical expression of KD (typical vs. incomplete and atypical) in the various age groups (\( p =

![Figure 1](image-url). The number of hospitalized patients has increased significantly through the years of the study (\( p = 0.001 \)).
Patients over 5 years of age expressed more often the incomplete and atypical form (57.1%), compared to 42.9% with typical KD. The age group of less than 1 year and over 8 years of age. It is very likely that the diagnosis of KD was not suspected in the children beyond the usual age groups, where incomplete and atypical clinical expression is more common. There was some delay in the diagnosis, no adequate treatment and increased risk for CL, similar to previous reports [11,12].

Table 1. Age groups and coronary lesions (CL): coronary aneurysms (CA) and significant dilatations (SD).

| Age groups         | CA  | SD  | % CL |
|--------------------|-----|-----|------|
| <1 year (2–12 months) n = 16 | 3   | 3   | 37.5%|
| 1–4 years n = 66 | 11  | 7   | 27.2%|
| 5–8 years n = 18 | 2   | 2   | 33.3%|
| >8 years (8–13 years) n = 7 | 3 (One child with a giant 5 mm aneurysm combined with four multiple aneurysms, and two children with 6 mm saccular aneurysms of both coronary arteries) | none | 42% |

Note: CA, coronary aneurysms; SD, significant dilatations; % CL, coronary lesions.

More CL were observed in the non-typical age groups (Table 1). The highest incidence of CL was detected in children less than 1 year and over 8 years of age. It is very likely that the diagnosis of KD was not suspected in the children beyond the usual age groups, where incomplete and atypical clinical expression is more common. There was some delay in the diagnosis, no adequate treatment and increased risk for CL, similar to previous reports [11,12].

Preliminary diagnosis, KD and co-infections

Patients with KD were usually referred to the Pediatric Rheumatology Clinic with a fever-rash syndrome, fever of unknown origin, suspicion of Still’s disease or other forms of juvenile idiopathic arthritis.

Preliminary diagnosis of infectious disease (including diarrhoea and hepatitis) was made in 59.8% of the patients: scarlet fever in 17.8%, sepsis in 7.5%, viral or other bacterial infections in 26.2%. Meningitis was discussed because of the restlessness and high fever. Diarrhoea, mild hepatitis and urinary tract infection are part of the non-specific symptoms of KD, but misled to other diagnoses. Allergic rash after antibiotic treatment was suspected in 4.7% of the patients.

Children with KD often have co-infections, most commonly streptococcal tonsillitis, viral infection, pneumonia or gastroenteritis. According to Benseler et al. [13], co-infections are recorded in 1/3 of the cases.

In our study, group A beta-haemolytic streptococci were isolated (throat swab) in three children with KD. These children later formed CL because of the delay in diagnosis. Increased anti-streptolysin O titers were found in the acute phase of the disease in four patients with a typical KD course. The diagnosis was also delayed in two children with concomitant viral infections (adenovirus and parainfluenza). The diagnosis of KD was confirmed by detection of CL. Concomitant infections in children with KD are considered the main reason for misleading diagnosis and treatment delay [14].

KD phase at referral time, hospital admission and coronary changes

KD has three main phases: acute, febrile (10 ± 2 days), subacute (30 days) and convalescent (6–8 weeks). Treatment with IVIG and a high dose of aspirin has to be performed in the acute or early subacute phase until the fever persists: the optimal time for infusion is the 7th–8th day of fever [13,15,16]. A chronic, lifelong phase of the disease is observed in patients with cardiac complications and their follow-up continues according to the guidelines for long-term management of patients with KD [17].

During the acute phase, 39.3% of the patients were admitted to hospital, which is a smaller number of patients compared to those admitted in later stages of the disease. The admissions during the subacute phase were 54.2% and 6.5% during the convalescent phase. The analysis indicated that late hospitalization significantly (p = 0.020) increases the coronary risk.

The CL in patients admitted to hospital in the acute febrile phase were 21.2% but those in patients who were hospitalized later were significantly more, 78.8% (p = 0.020). Eighteen children out of 21 with aneurysms came with already formed ones and 6 children out of 12 had significant dilatations by the time of hospitalization. One consequence of late hospitalization is the increased risk of CL, because of the failure to give the IVIG infusion at the right time. The lack of treatment with IVIG and aspirin in the acute phase of KD (up to the 10th day of fever) increases the risk of CL [16,18]. Our data showed a reduction in the referral delay in recent years, from 12 to 5 days from the disease onset, which allows proper treatment with IVIG infusion (Figure 2).

Clinical expression of Kawasaki disease (typical, incomplete and atypical), delay of diagnosis and coronary complications

The acute phase of KD can take a typical, incomplete or atypical course. The diagnostic symptoms in the typical and incomplete KD are identical and differ only by the
number of symptoms. Atypical KD presents with symptoms other than the classical AHA criteria and is a real diagnostic challenge.

Most of the monitored patients had a typical KD (62.6%; \( n = 67 \)), but many showed an incomplete (19.6%; \( n = 21 \)) or atypical (17.8%; \( n = 19 \)) course of the disease. According to some studies, incomplete and atypical cases account for 20%–33%, [11,14] while others estimate them at 10%–45% [19].

Significant dilatations and aneurysms are more commonly seen in patients with incomplete or atypical presentation than in patients with typical KD. In some studies [15], patients with incomplete and atypical KD are reported to reach up to 60% of the patients with coronary involvement. In our study cohort, 33 patients (30.8%) had CL (significant dilatation and coronary aneurysms); 21 children (19.6%) had coronary aneurysms and 12 children (11.2%) had significant dilatations. Of the patients with CL, 51.5% had an incomplete and atypical course of the disease. The monitored patients with atypical KD had significantly higher coronary risk (\( p < 0.010 \)) compared to those with typical and incomplete KD (Figure 3). This is because, in atypical cases, the diagnostic orientation is most difficult and takes time.

The delay in the diagnosis in the patients with typical KD was four days on average, whereas that in patients with incomplete and atypical KD, it was 11 days. This is crucial for the IVIG treatment, because the optimal time for it to be started is between 7 and 10 days from the disease onset. Since the diagnosis of incomplete and atypical KD was significantly delayed compared to that of the typical KD (\( p < 0.001 \)), the right time for the IVIG infusion was missed (Figure 4).

**Clinical symptoms of patients with typical KD**

AHA comments that the classical criteria of typical KD do not have 100% sensitivity and specificity, and only patients with the battery of standard criteria and proved coronary aneurysms have the definite diagnosis [16]. Children who do not meet these criteria may have incomplete or atypical expression of the disease. On the other hand, patients who meet the standard criteria could have another disease [20]. In their early studies, Burns et al. [1] found that 46% of the referred children, initially diagnosed as KD meeting the classical criteria, were subsequently given another diagnosis.

The clinical examination of our patient cohort with typical KD revealed oropharyngeal mucosal changes in all the cases; exanthema, in 98.5%; changes in extremities including periungual desquamation, in 88.1%; conjunctivitis, in 85.1%; cervical lymphadenomegaly, in 68.7%. Gastrointestinal (GI) symptoms were present in 27% of the patients. They are not part of the AHA criteria but are observed quite often and described in one-third of KD patients [21]. They confirm the pathogenetic role of antigen penetration through the mucosa of KD.
patients [6]. The observed incidence of GI syndrome in our patients was shown to correspond with the typical KD symptoms \( p = 0.030 \), suggesting that it could be considered as part of all diagnostic criteria.

Most of the children with typical KD had five (50.7%) or six (44.8%) classical symptoms. The classical symptoms in patients with typical KD were compared with those in the patients with atypical and incomplete KD course (Figure 5). The principal KD symptoms were also observed in the incomplete and atypical KD, but less frequently. GI symptoms remain more apparent in incomplete/atypical KD, even though they are frequently observed in the typical KD.

**Clinical symptoms in incomplete KD**

Children with incomplete KD were diagnosed according to AHA basic and supportive laboratory criteria [4]. Most commonly, our patients presented with oropharyngeal syndrome (63%), rash (59.3%) and changes in the extremities (59.3%), less frequently with conjunctivitis (44.4%) and lymphadenopathy (22.2%). The patients had three or four AHA criteria. Two children had lymphadenomegaly as the leading sign (mediastinal and generalized) and the diagnosis was delayed. They subsequently formed CL. Lymphadenomegaly as a leading symptom of KD has been reported by Waggoner-Fountain et al. [22] and later by Scully et al. [23].

**Clinical symptoms in atypical KD**

The diagnosis of atypical KD is most difficult because of the non-specific symptoms which differ from the classical KD symptoms or other criteria for vasculitis syndromes [8]. In atypical forms, KD presents as a true multisystem disease (Figure 6).

![Figure 4](image4.png)

**Figure 4.** Diagnosis delay (in days) related to the clinical expression of KD.

![Figure 5](image5.png)

**Figure 5.** Comparison of the incidence of specific symptoms in patients with typical and incomplete/atypical KD.

![Figure 6](image6.png)

**Figure 6.** Clinical symptoms in patients with atypical KD. Note: ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase.
In our patient cohort, the GI syndrome was present in 68.4% of the patients with atypical KD, in 40.7% of incomplete KD cases and 26.9% of typical KD cases. Hydrops of gallbladder was found in 30% of the patients with atypical KD. Some children were referred to gastroenterologists because of elevated liver enzymes and direct hyperbilirubinemia. Because of the observed jaundice, Majumdar and Wagner [24] proposed KD to be included in the differential diagnosis of fever-jaundice syndrome in children.

The common reason for referral to a rheumatologist was arthritis, but the soft tissue swelling of the hands and feet was confused with arthritis by non-specialists in 40% of patients (Figure 6). In a study of 414 patients, Gong et al. [25] observed real arthritis in only 7.5% of the cases.

In our study, the presence of myocarditis, neurological, respiratory and renal syndrome was about 10% each. These patients were severely ill and some of them required intensive care treatment.

The non-specific symptoms in patients with atypical KD were compared with the same symptoms in the patients with typical and incomplete KD course (Figure 7). The presence of some atypical symptoms along with the typical KD is remarkable, especially of arthritis and pericardial effusion.

Conclusions

The diagnosis of KD is challenging and difficult, with a high index of suspicion, because of the lack of specific clinical and laboratory criteria and the presence of incomplete and atypical presentations. The high incidence of CL is associated with the failure to recognize the disease on time, resulting in delay of adequate treatment. In our study cohort, 33 patients (30.8%) had CL (significant dilatation and coronary aneurysms): 21 children (19.6%) had coronary aneurysms and 12 children (11.2%) had significant dilatations. There is a high risk of coronary complications in the age groups beyond the ones typical of the disease and the patients with incomplete/atypical forms. KD is becoming more recognizable in recent years, which shortens the treatment delay. The observed correlation of gastrointestinal syndrome with typical and atypical KD suggests that it could be considered for inclusion in the differential diagnostic considerations of the disease. Further studies on larger cohorts are needed to support this recommendation.

Disclosure statement

No potential conflict of interest was reported by the authors.

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