NON-CARDIAC SEQUELAE OF KAWASAKI DISEASE. THE SURVEY STUDY OF 90 CASES AND LITERATURE REVIEW

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Abstract:

Introduction and objective

The best-known long-term complications of Kawasaki Disease (KD) are coronary artery aneurysms. However, there are numerous case reports about other unusual chronic complications. These data are only anecdotal, and more systematic observation is missing. We aimed to detect and describe chronic non-cardiac complications of KD.

Material and methods

We surveyed parents of children with KD diagnosed between 2014 and 2019 by phone with the use of standardized questionnaire. Clinical data about the acute phase of the disease, treatment, outcome, and symptoms and signs observed within three months since KD diagnosis were recorded from the caregivers. We recruited children from 3 children's hospitals in Warsaw and a support group on social media.

Results

Ninety children met the inclusion criteria. Parents of 30 children (33%) reported some neurologic sequelae, with persistent irritability being the most common, followed by sleep disturbances, aggression, and chronic fatigue. Seventeen children (19%) suffered either arthralgia or unspecific pain in the upper and lower extremities. In nine children (10%), either atopic or seborrheic dermatitis began shortly after KD. Five children (6%) presented with ophthalmic complications.

Conclusions

Various unspecific complications may emerge after the acute phase of KD. Although correlation does not imply causation, and possible explanations of observed abnormalities are numerous, our data may enhance clinicians' awareness of frequent and poorly understood findings observed after KD in children. It also might help reassure parents that what they observe lies within a range of common and usually transient KD sequelae.

Keywords: immunomodulation, pediatrics, inflammatory disease, extracardiac manifestations.

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Introduction

Kawasaki disease (KD) is a relatively common, acute, febrile, self-limited, systemic vasculitis of unknown etiology occurring most commonly in children under 5 years of age [1]. The disease may involve any medium-sized arteries and any organ or tissue may be affected during the acute, febrile phase. The best-known long-term complications of KD are coronary artery aneurysms (CAAs), which develop in around 4% of children treated with intravenous immunoglobulin (IVIG) [2]. However, there are numerous case reports about other unusual late complications, including e.g., arthritis, myositis, facial nerve palsy, or ptosis [3-5]. These data are only anecdotal, and more systematic observation is missing.

We aimed to identify and report non-cardiac persistent complications of KD.

Material and Methods

Patient's recruitment

In this retrospective cohort study, we surveyed parents of children diagnosed with KD between 2014 and 2019, using a standardized phone questionnaire. We recruited children from three children's hospitals in Warsaw and one social media support group. All phone calls were made between August and November 2019.

The inclusion criteria were:
1) Age <18 years old at the time of KD diagnosis,
2) Diagnosis of classic or incomplete KD per the American Heart Association (AHA) guidelines [2],
3) At least three months since diagnosis.

The initial diagnosis was made by clinicians who treated the child in the acute phase of KD, but we verified it basing on clinical data reported by the caregivers and the patient's medical records.

After obtaining an informed consent, we surveyed the child's caregivers with the use of a standardized questionnaire including multi-choice and open questions. We asked about the signs and symptoms in the acute phase of KD, and any abnormalities observed during convalescence phase. In case of every sign or symptom we asked about its characteristics and total duration. The Bioethical Committee of the Medical University of Warsaw approved the study (AKBE/162/2020).

We considered signs or symptoms to be persistent if they lasted or appeared at the time when fever had already subsided (convalescence phase). Periungual skin desquamation was not involved in the analysis, being a cardinal and well-known late sign of KD.

Statistical Analyses

We presented results as counts and percentages for categorical data and medians and interquartile ranges (IQRs) for continuous data. In addition, we split children into groups regarding classic vs. incomplete KD and IVIG resistance. Data statistical analyses were performed with the use of Excel 2016. Results with p-value <0.05 were considered statistically significant.

Results

We have called the parents of 92 children with KD diagnosis, and 90 met the inclusion criteria. The vast majority, 79 children, were recruited from hospitals, and the rest from the social media group. We summarized the demographic and clinical characteristics of the analyzed group in Table 1.

Most of the children were healthy except KD. Among patients with comorbidities (present before KD diagnosis), two had atopic dermatitis, one had a food allergy, one had allergic rhinitis, one had hypothyroidism, one had autism, and one had drug-resistant epilepsy with mental retardation. Children were admitted to the hospital after a median of three days (IQR 2-5 days) of fever. All but two patients were treated with IVIG. Those two patients presented with an anaphylactic reaction to IVIG: one was not treated with immunomodulatory agents afterward, and the other received infliximab. Among 12 children with IVIG failure, 11 received a second IVIG dose, seven received glucocorticosteroids (GCS), and two received infliximab. Two children had recurrent KD (two episodes each).

Parents of 44 (49%) children recalled any symptoms and signs which were present after fever of the acute phase of KD subsided. They are summarized in Table 2.

Among neurologic complications, the most frequently reported was irritability. Parents of four children reported that irritability had never resolved, whereas, in the remaining group, irritability lasted for a median of four weeks (IQR 4-18 weeks). In case of sleep disturbances, caregivers of five children reported it had never resolved (one of them was surveyed four months after the disease

Table 1. Demographic and clinical characteristics of children with Kawasaki disease.

Characteristic	All subjects N=90	Typical KD N=73	Atypical KD N=17	IVIG-responsive N=76	IVIG-resistant N=12
Age [years]	2.8 (1.4; 4.3)	2.8 (1.4; 4.5)	2.8 (0.7; 4.2)	3 (1.4; 4.6)	2.2 (1.2; 2.9)
Male gender	49 (54%)	40 (55%)	9 (53%)	40 (53%)	9 (75%)
Comorbidities	7 (8%)	6 (8%)	1 (6%)	5 (7%)	2 (17%)
IVIG timing	6 (3; 8)	6 (5; 7.3)	8.5 (6; 10)	6 (3; 8)	6.5 (5; 7.5)
IVIG resistance	12 (13%)	9 (12%)	3 (18%)	0	12 (100%)
GCS treatment	21 (23%)	16 (22%)	5 (29%)	12 (16%)	7 (58%)
Infliximab	3 (3%)	1 (1%)	2 (12%)	0	2 (17%)
Coronary arteries abnormalities in the acute phase	20 (22%)	15 (21%)	5 (29%)	15 (20%)	5 (42%)
Persistent coronary arteries abnormalities	7 (8%)	3 (4%)	4 (24%)	4 (5%)	3 (25%)

KD = Kawasaki disease, IVIG = intravenous immunoglobulin, GCS = glucocorticosteroids; results are presented as counts and percentages for categorical data and medians and interquartile ranges (IQRs) for continuous data.

Table 2. Symptoms and signs observed in children after Kawasaki disease.

Symptoms and signs	All N=90	Typical KD N=73	Atypical KD N=17	IVIG-responsive N=76	IVIG-resistant N=12
Any neurologic	30 (33%)	25 (34%)	5 (29%)	25 (33%)	4 (33%)
Irritability	16 (18%)	13 (18%)	3 (18%)	14 (18%)	1 (8%)
Sleep disturbances	12 (13%)	9 (12%)	3 (18%)	10 (13%)	1 (8%)
Aggression	10 (11%)	10 (14%)	0	8 (11%)	1 (8%)
Chronic fatigue	10 (11%)	8 (11%)	2 (12%)	9 (12%)	1 (8%)
Anxiety	8 (9%)	7 (10%)	1 (6%)	7 (9%)	1 (8%)
Concentration deficit	7(8%)	7 (10%)	0	6 (8%)	0
Learning difficulties	3 (3%)	3 (4%)	0	3 (4%)	0
Headaches	2 (2%)	2 (3%)	0	2 (3%)	0
Finger numbness	1 (1%)	1 (1%)	0	1 (1%)	0
Hearing impairment	1 (1%)	0	1 (6%)	1 (1%)	0
Psycho-motor delay	2 (2%)	2 (3%)	0	2 (3%)	0
Any limb pain	17 (19%)	13 (18%)	3 (18%)	12 (16%)	4 (33%)
Arthralgia	9 (10%)	9 (12%)	0	6 (8%)	2 (17%)
Joint swelling	4 (4%)	4 (5%)	0	3 (4%)	0
Limping	4 (4%)	3 (4%)	1 (6%)	3 (4%)	1 (8%)
Muscle pain	4 (4%)	3 (4%)	1 (6%)	4 (5%)	0
Any cutaneous	13 (14%)	11 (15%)	2 (12%)	12 (16%)	1 (8%)
Atopic/seborrheic dermatitis	9 (10%)	8 (11%)	1 (6%)	9 (12%)	0
Albinism	1 (1%)	1 (1%)	0	0	1 (8%)
Insect bite allergy	1 (1%)	0	1 (6%)	1 (1%)	0
Any gastrointestinal	9 (10%)	7 (10%)	2 (12%)	8 (11%)	0
Loss of appetite	5 (6%)	4 (5%)	1 (6%)	5 (7%)	0
Abdominal pain	5 (6%)	4 (5%)	1 (6%)	5 (7%)	0
Diarrhea	4 (4%)	3 (4%)	1 (6%)	4 (5%)	0
Constipation	2 (2%)	1	1 (6%)	1 (1%)	0
Celiac disease	1 (1%)	1 (1%)	0	0	0
Any ophthalmic	5 (6%)	5 (7%)	0	4 (5%)	0
Photophobia	4 (4%)	4 (5%)	0	4 (5%)	0
Ptosis	1 (1%)	0	1 (6%)	0	0
Other					
Chest pain	2 (2%)	2 (3%)	0	2 (3%)	0
Growth retardation	2 (2%)	2 (3%)	0	2 (3%)	0
Thyroid gland involvement	2 (2%)	2 (3%)	0	2 (3%)	0
IgA vasculitis	1 (1%)	1 (1%)	0	1 (1%)	0

KD = Kawasaki disease, IVIG = intravenous immunoglobulin; results are presented as counts and percentages.

onset). The remaining children's median duration of sleep disturbances was 16 weeks (IQR 8-22 weeks). Parents of four children acknowledged that they persisted in being more aggressive since the KD diagnosis – in all those cases, over one year had passed since then. In the remaining group, aggression lasted for a median of four weeks (IQR 4-12 weeks). Chronic fatigue had never resolved in two children, and in the remaining group lasted for a median of 24 weeks (IQR 20-24 weeks). In one boy with recurrent KD, autism symptoms and epilepsy developed after the first episode, worsening after the second episode. Family history was positive for epilepsy in this case. Moreover, two infant boys diagnosed with KD, at the age of five and seven months regressed in neurologic development (loss of head control in one and loss of sitting and crawling in the other), but both recovered within 2-3 months. In one 1.5-year-old girl, parents reported poor motor coordination for eight weeks after KD. Altogether

parents of six children (7%) reported that some neurologic complications persisted.

About 19% of all children suffered from limb pain. Among children whose parents reported arthralgia, in one case it referred to the wrist, in one – the hip, and the rest had painful knees or ankles. Knees and ankles' involvement was symmetrical in all cases. Parents noticed a limited range of motion in two children with swollen and painful joints. Since the KD diagnosis, two girls had had recurrent arthralgia, concomitant with infections. In the remaining children, limb pain lasted for a median of eight weeks (IQR 4-24 weeks).

Complications affecting the skin developed in 14% of patients. In the majority, atopic dermatitis had been diagnosed. Parents usually reported symptoms of the itchy, dry, rough skin in the remaining group. Parents observed exacerbation following KD diagnosis in two boys formerly diagnosed with atopic dermatitis. Among patients with new-onset atopic dermatitis, in two cases, it persisted, and in the remaining group, it lasted for a median of 24 weeks (IQR 24-24 weeks). In two children, caregivers recalled hair problems – loss of hair in one and weak, breakable hair in the other.

Parents of nine children after KD diagnosis recalled gastrointestinal complications. Among five children with abdominal pain, four continued to have recurrent stomachache episodes, and in one, it resolved after about 12 weeks. Poor appetite never resolved in one patient, and in the remaining children, it lasted for four to 24 weeks. In two children, the parents declared that diarrhea never resolved. In two others, it had been recurring for six months and three years, respectively. In two children, constipation lasted for four and 12 weeks, respectively. One girl was diagnosed with celiac disease at the time of KD diagnosis, with no symptoms or signs suggestive of celiac disease in her personal or family history. Among all children with any gastrointestinal signs and symptoms, one had transient growth retardation, and the rest had no complications in terms of somatic development.

Five children (6%) presented with ophthalmic complications. Two children had photophobia and eye fatigue for 16 weeks and one year, respectively. In one girl, ptosis developed after KD treatment and resolved spontaneously after eight weeks.

Parents of two children reported that they had had chest pain and fatigue, presenting on effort ever since KD diagnosis. Neither of them had any cardiovascular complications. Parents of two girls (1.6 and 5.1 years old) recalled that they had had growth retardation since KD diagnosis, one for ca. 6 months and the other for ca. 12 months. The first one was treated with pulsed methylprednisolone for three days in the acute phase of KD. The other one did not receive GCS but presented with chronic episodes of diarrhea and abdominal pain.

Two children developed thyroid-related complications. One developed symptomatic hypothyroidism with significant weight gain and high thyroid-stimulating hormone levels. The other one developed anti-thyroid peroxidase antibodies, which were negative before KD. One girl developed typical purpura of IgA vasculitis on the 10th day of KD (after IVIG administration and fever resolution), with concomitant arthralgia and positive occult blood in stool sample – the girl received GCS, and symptoms resolved within one week.

Discussion

We present systematic and comprehensive observations concerning late symptoms and signs following KD in children observed by their caregivers. Half of the parents reported some late sequelae in their children, with neurologic disturbances and limb pain being the most prevalent.

Neurologic symptoms and signs

Neurologic sequelae were the most frequently reported in our group. There are several papers concerning neurologic complications of KD in the literature, although conclusions are inconsistent. Children after KD presented with neurodevelopmental disorders, including epilepsy, intellectual disability, autism spectrum disorders, Tourette syndrome, and attention deficit hyperactivity disorder more frequently than the general population [6]. In addition, some degree of hearing loss was observed in up to 36% of patients after KD [7]. Facial nerve palsy, not noted in our cohort, is another neurologic complication reported in the case series [5,8].

On the other hand, some symptoms and signs within this category (e.g., behavioral abnormalities, sleep disturbances) could be explained by stress due to prolonged hospitalization and invasive medical procedures. However, Carlton-Conway et al. found that KD patients had more common behavioral complications than children hospitalized for other diseases [9]. Interestingly, Baker et al. analyzed children's physical and psychosocial well-being after KD using The Child Health Questionnaire. They found that children with prior KD and without giant CAA did not differ in general health from other children in the population. However, their parents expressed lower general health perceptions than parents in the United States population sample [10]. This observation may reflect the influence of acute severe disease in a child on long-term parental perceptions. Thus, it is difficult to determine which of the neurologic sequelae reported by parents are objective complications of the disease and medical procedures and which are subjective parental concerns.

Limb and chest pain

Limb pain was the second most common symptom observed by parents in their children after KD. Limb pain can be due to both arthritis and myositis, which are difficult to differentiate, as most children in our group were too young to describe their complaints precisely. Arthritis is a well-known complication of KD, reduced from 30% to 2-7.5% after the introduction of IVIG into treatment [3]. The case series have also reported myositis complicating KD [4]. The self-limiting character of limb pain in both our cohort and the literature data is reassuring.

Skin problems

Most children with skin issues after KD presented with atopic dermatitis. This observation is consistent with

a paper by Brosius et al., who found atopic dermatitis to be more prevalent in children with KD than in healthy controls [11]. Psoriasiform eruptions have also been reported to flare after the acute phase of KD [12]. We have not found any literature about hair problems, albinism, or insect-bite allergy in patients after KD.

Gastrointestinal complications

Gastrointestinal complications reported by parents of children with KD are challenging to interpret. Multiple medications administered in those patients, including antibiotics, typically induce some gastrointestinal sequelae. Moreover, diarrhea, constipation, and abdominal pain are frequent and unspecific symptoms in young children. Thus, chronic symptoms in this category should be interpreted with caution. Lack of persistent influence of abdominal issues on children's somatic development in our cohort is reassuring. On the other hand, Italian authors revealed a higher prevalence of celiac disease (5.5%) in children after KD [13]. Thus, monitoring for celiac disease in children after KD, mainly when gastrointestinal symptoms persist, should be considered.

Ophthalmic complications

There are a few case reports of ophthalmic complications of KD, including retinitis, uveitis, and keratitis [8,14,15]. In one case report, photophobia and blurred vision developed three weeks after KD and was diagnosed as crystalline-like keratopathy and interpreted as a complication of IVIG administration [16]. Ptosis after KD may be a part of facial nerve palsy presentation. However, ptosis cases unrelated to oculomotor nerve injury as a complication of KD were also reported [17]. Ophthalmic complications were likewise self-limiting in our cohort.

Other

A few case reports of IgA vasculitis concomitant with KD have been reported [18]. We have not found publications regarding growth retardation or hypothyroidism as KD complications.

Limitations

Our study has some potential limitations:

1. Its retrospective nature could have resulted in biased information from parents, particularly those who recalled observations a few years back.
2. No control group.
3. Despite a relatively large sample size, subgroups were too small for reliable statistical analysis. The patients' population was homogenous and did not include ethnic minorities.

Conclusions

Various unspecific late complications may emerge after acute phase of KD. Although possible explanations of observed abnormalities are numerous, our data may enhance clinicians' insight into frequent and poorly understood findings observed after KD in children.

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