Research

Clinical Characteristics and Outcomes of Kawasaki Disease in Infants Younger than Six Months of Age: Algerian Multicenter Study

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Abstract

Background and Objectives: Kawasaki disease (KD) is one of the most common immune vasculitis in children and the leading cause of acquired heart disease, which predominantly occurs in children under the age of 5 years. However, there are fewer cases of KD in infants younger than 6 months, making diagnosis more challenging. The objective is to characterize the clinical presentation and evolution of KD in infants < 6 months of age as compared to those ≥6 months in western Algeria.

Methods: We retrospectively reviewed the medical records of 62 patients diagnosed with KD in western Algeria followed between January 2018 and January 2023. The data were categorized into 2 groups by age: Group A (<6 months, n=12) and Group B (≥6 months, n=50). We compared differences in laboratory data, clinical presentation, treatment response, and coronary artery outcomes between the two cohorts.

Results: The majority (78%) of infants and children ≥6 months of age were initially diagnosed with KD, as compared to only 33,3% of infants <6 months. Clinical features of KD were more commonly observed in the older cohort: oral changes (90 vs. 75%, P = 0.0023), extremity changes (76 vs. 50 %, P = 0.029), and cervical lymphadenopathy (66 vs. 33.3%, P = 0.0004). Whether treated in the first 10 days of illness or after the 10th day, infants <6 months were at greater risk of developing a coronary artery aneurysm compared to KD patients ≥6 months treated at the same point in the course of illness [≤10 days (55 vs. 8,88 %, P = 0.0001) ; >10 days (66,6 vs. 6,6%, P = 0.046)].

Conclusion: Our data show that despite treatment in the first 10 days of illness, infants <6 months of age have a higher risk of developing a coronary artery aneurysm. Delay in the diagnosis leads to larger coronary artery aneurysms disproportionately in these infants. Thus, suspicion for KD should be high in this vulnerable population.

Keywords: kawasaki disease; below 6 months, Mucocutaneous Lymph Node Syndrome;

Coronary Aneurysm; Immunoglobulins.

Abbreviations

KD: kawasaki disease; CAA : coronary artery abnormalities; IVIG: intravenous immunoglobulin; AHA : american heart association.

Introduction

Kawasaki disease (KD) is a self-limiting acute inflammatory syndrome in children. It preferentially affects children aged 6 months to 5 years, with a male predominance (1). The etiology is unknown, and it has no specific diagnostic test. The diagnosis of KD is essentially clinical and established according to international criteria (AHA 2017). The diagnosis will typically be made in the event of fever lasting ≥ 5 days, associated with at least 4 clinical criteria of adeno-cutaneous-mucous inflammation (figure 1) (1,5). Incomplete KD should be considered in patients with unexplained fever for ≥ 5 days and presenting with 2 or 3 of the clinical features of KD (5-7).

Figure 1 : Diagnostic criteria for KD (according to the recommendations of the AHA 2017) (5) :

Fever lasting ≥ 5 days, associated with at least 4 of the following clinical criteria:
- **conjunctival hyperaemia** acute non-purulent, bilateral ;
- **polymorphic rash** (most often morbilliform, scarlatiniform or urticarial) ;
- **cervical lymphadenopathy**, one of which is more than 1.5 cm ;
- **involvement of the extremities**: erythema, oedema, desquamation (late sign) ;
- **enanthema of the lips and the entire oral cavity:** dry and cracked lips (cheilitis), raspberry tongue (with desquamation of the filiform papillae, giving a shiny red surface), stomatitis, pharyngeal enanthema.(figure: kawasaki disease foundation).

KD is responsible for a vasculitis of the medium-calibre arteries, with a particular tropism for the coronary arteries, which is more frequent in the event of diagnostic and therapeutic delay. KD remains one of the leading causes of acquired heart disease. It can cause coronary artery abnormalities (CAA) in 20-25% of untreated patients, whereas early administration of high-dose intravenous immunoglobulin (IVIG) resolves symptoms of the acute phase of KD, and reduces the risk of cardiac involvement (3).

The peak incidence of KD is from 6 months to 2 years of age. However, there are fewer cases in infants younger than 6 months, making diagnosis difficult. KD patients younger than 6 months are more likely to have an incomplete clinical presentation. Therefore, the diagnosis could be delayed, leading to heart complications that are more common than in older children (8).

Most epidemiological data for patients with KD < 6 months are from regions outside Algeria (2, 6, 8-11). It is not known whether the clinical presentation and results are similar in infants under 6 months in the Algerian population. In the United States, despite early treatment with IVIG within the first 10 days of illness, up to 43.4% of infants younger than 6 months develop CAA (3). Most of the epidemiological data for patients with KD < 6 month of age are from regions outside of Algeria (2, 6, 8-11). It is unknown whether the clinical presentation and outcomes are similar in infants under 6 months in the Algerian population.

Thus, this study aims to characterize the clinical presentation and outcomes of KD in Algerian infants under 6 months of age with those of older patients (> 6 months).

Methods

We retrospectively evaluated 12 infants < 6 months and 50 infants and children ≥ 6 months with KD (typical or incomplete) diagnosed, treated and followed up in the pediatric departments of the 3 major University Hospitals in the western Algerian region (CHU Oran, CHU Tlemcen and CHU Sidi Bel-Abbes) between January 1, 2018, to December 31, 2022.

We compared the differences in clinical presentation, biological data, treatment response and CAA results between the two cohorts. The data were categorized into 2 groups by age: Group A (<6 months, n=12) and Group B (≥6 months, n=50).

The diagnosis of complete KD was retained according with the American Heart Association (AHA) guidelines (5) (figure 1). Incomplete KD was defined per the AHA guidelines as fever and fewer than 4 of the KD clinical criteria with either supportive laboratory or an echocardiographic abnormality.

Patients suspected of having KD but who did not meet the diagnostic criteria or who had not had IVIG administration after diagnosis were excluded from this study. Also, in the context of the COVID-19 pandemic, children with a diagnosis of Kawasaki-Like or multisystem inflammatory syndrome in children (MIS-C = Multi-system inflammatory syndrome in children or PIMS = Pediatric inflammatory multisystem syndrome) were excluded from the study.

Day 1 of illness is defined as the first day of fever. Information on the treatment, including treatment with IVIG, intravenous corticosteroid therapy or antibiotics, was collected.

Coronary measurements were related to body surface area and expressed as a Z-score to assess baseline coronary risk and allow comparison over time.

Aneurysms are classified according to the measurement of their internal diameter in echocardiography and normalized according to the Z-score (which expresses the deviation from the normalized mean value, in standard deviation, according to the body surface area).

The Z-score was calculated using the Dallaire and Dahdah formula (7). Z-score max is defined as the highest Z-score of coronary arteries during the first 6 weeks of illness. Measurements were made by echocardiography at the time of diagnosis and up to 8 weeks after the onset of fever.

CAA were classified (on echocardiography) as normal (Z-score < 2.5), dilated (Z-score ≥ 2.5 to ≤ 4), aneurysmal (Z-score > 4 to ≤ 10), or giant aneurysm (Z-score > 10) according to the 2017 AHA KD Guidelines (3, 7) (figure 2). Patients with Z-scores but without verified height and weight or sick day were excluded from the study.

Aspirin (50 mg/kg/day) and IVIG (2 g/kg) were administered during the acute phase of the illness. After obtaining apyrexia, the dose of aspirin was reduced to 5 mg/kg/day and maintained for 6 to 8 weeks. If the patient had CAA, aspirin administration was continued until the patient no longer showed evidence of coronary changes. If the patient had recurrent or persistent fever for ≥ 36 hours after IVIG administration, a second dose of IVIG was administered (16,17). Furthermore, methylprednisolone was intravenously administered if the patient had recurrent or persistent fever even after the second IVIG administration (18,19).

Data collection was done in an Excel spreadsheet. Quantitative variables were described by the mean (± standard deviation and extremes). Qualitative variables were described as frequency and percentage. The comparison of the groups on the qualitative parameters was carried out by the Chi-square test or the Fisher's exact test. For all statistical tests, A p of <0.05 was considered statistically significant. Statistical analyzes were performed using SPSS software (version 20, SPSS Statistics, IBM Corporation) and Epi Info.
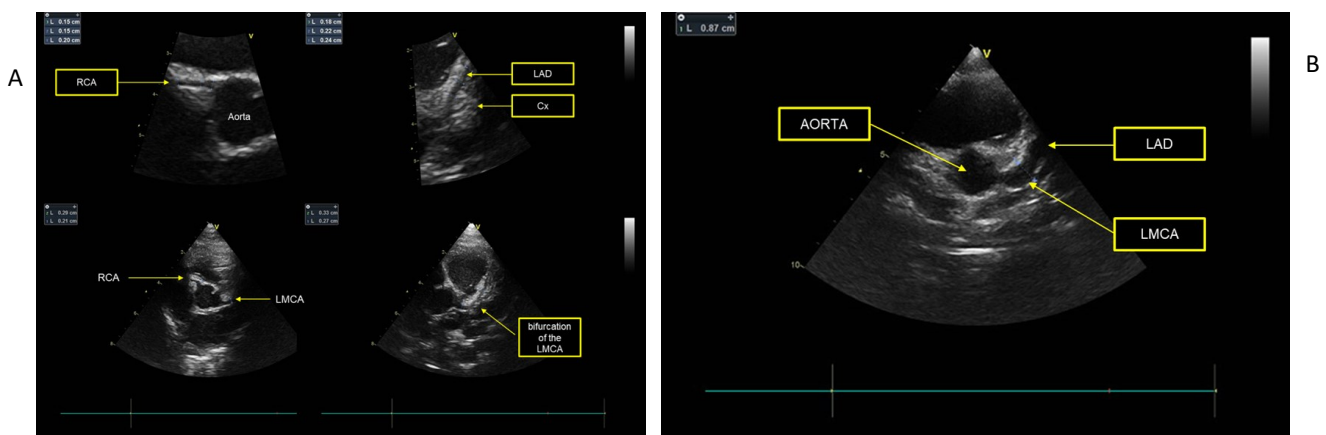

Figure 2: *Coronary arteries in two-dimensional transthoracic echocardiography*
(The left parasternal position, a modified parasternal short axis view of great vessels) :
2A – the right and left coronaries of normal caliber. (Z-score < 2.5).
2B – Aneurysmal dilation of the LMCA and LAD in a 5-month-old infant (giant LAD aneurysm measuring 8.7 mm = + 11 Z-score).
LAD: left anterior descending coronary artery, LMCA: left main coronary artery, CX: circumflex. RCA: right coronary artery.
(figures : Pr Bekkar M.M).

Results

Over a period of five years, we identified a total of 62 patients under the age of 15 with KD followed by 3 Pediatric Departments of the University Hospitals of Oran, Tlemcen and Sidi Bel-Abbes. Demographic and clinical data collected retrospectively are presented in **Table 1.**

Of the 62 patients, 12 (19.3%) were younger than 6 months old (group A). The remaining 50 patients (80.7%) were between 6 months and 12 years old (group B) (**Table 1**). Most patients were male, and there was no gender difference by age cohort (66.6 versus 60%, P = 0.24).

The duration of fever before admission was significantly shorter in group A (4 days) than in group B (7 days) (p=0.0003), and the hospitalization period was longer on average in Group A (8 days) than in Group B (5 days) (p = 0.00018).

Table 1. Comparison of the clinical features and laboratory data of infantile Kawasaki disease patients and older patients.			
Characteristic	**Group A (<6 months old)**	**Group B (≥6 months old)**	*P -value*
Demographic and clinical data :			
Number of patients (%)	**12** (19.35 %)	**50** (80.65 %)	-
Median age (months)	4.0 (3.0 - 5.0)	36.0 (15 - 60.0)	<0.0002
Sex (male), N (%)	8 (66.6%)	30 (60%)	0.24
Fever duration before admission (days)	4.0 (3.0 - 8.0)	7.0 (5.0 - 10)	0.0003
Total hospitalization period (days)	8.0 (6.0 - 10.0)	5.0 (4.0 - 7.0)	<0.00018
Laboratory data :			
WBC (x10^3)	19.5 (14.6 - 24.8)	14.2 (11.2 - 19.4)	<0.0001
Neutrophils (%)	65.2 ± 13.4	69.2 ± 15.2	0.022
Hémoglobin (g/dl)	10.2 ± 1.4	11.1 ± 0.7	<0.05
Platelet count (x10^3)	452 (308 - 547)	405 (288 - 515)	0.44
ESR (mm/hr)	62 (21 - 92)	68 (22 - 120)	0.50
CRP (mg/l)	55 (32 - 92)	42 (29 - 58)	0.22
AST (IU/L)	24.0 (16.0 - 32.2)	42.0 (24.0 - 87.0)	0.00027
ALT (IU/L)	25.0 (17 - 68.0)	47.0 (21.3 - 124.1)	0.32
Albumin (g/L)	32 (28 - 36)	34 (28 - 39)	0.90

Data are expressed as mean ± standard deviation or n (%). WBC : white blood cell, ESR : erythrocyte sedimentation rate, CRP : C-reactive protein, AST : aspartate aminotransferase, ALT : alanine aminotransferase.

The majority (78%) of infants and children aged ≥6 months were initially diagnosed with KD, compared with only 33.3% of infants under 6 months (OR = 0.16, 95% CI 0, 08 to 0.33, P<0.0001).Infants under 6 months were 11 times more likely to be initially diagnosed with sepsis or septic shock (25 versus 2%, OR = 13.8, 95% CI 6.2 to 34.2, P < 0.0001) (**Table 2**). Furthermore, infants younger than 6 months were 4 times more likely to be initially diagnosed with a urinary tract infection (14.7 versus 3.8%, OR = 4.4, 95% CI 1.7 to 11 .5, P = 0.011) and more likely to be suspected of occult bacteremia initially (16.6 versus 2%, OR = 5.1, 95% CI 1.8 to 14.9, P = 0.014) as compared to older infants and children.

Table 2. Initial clinical diagnosis on admission.				
Diagnosis	**Group A (<6 months old)**	**Group B (≥6 months old)**	***P -value***	***OR (95% CI)***
Kawasaki disease	**4 (33.3%)**	**39 (78%)**	<0.0001	0.16 (0.08 - 0.33)
Scarlet fever	1 (8.33%)	3 (6%)	>0.99	-
Cutaneous staphylococcal disease	0 (0.0%)	1 (2%)	-	-
Septic shock	3 (25%)	1 (2%)	<0.0001	13.8 (6.2 - 34.2)
Erythema multiforme	1 (8.33%)	1 (2%)	0.45	-
Urinary tract infection	2 (16.6%)	2 (4%)	0.013	4.3 (1.6 – 12.1)
Unspecified fever	3 (25%)	11 (22%)	0.68	-
Occult bacteremia	2 (16.6%)	1 (2%)	0.014	5.1 (1.8 – 14.9)

Data are expressed as n (%).

Expression of clinical features of KD was more frequently observed in the older cohort (group B) including oral involvement (90 vs 75%, P = 0.0023), extremity involvement (76 vs 50%, P = 0.029) and cervical adenopathy (66 versus 33.3%, P = 0.0004) (**Table 3**).

Patients were classified as having a complete (typical) or incomplete form of KD, based on the 2017 AHA Guidelines (5). Thus, we found significantly more older infants and children (group B) with complete KD (41.6 versus 78%, OR = 0.24, 95% CI 0.12 to 0.45, P < 0.0001). The younger cohort (group A) was 4 times more likely to be diagnosed with incomplete KD than the older ones (58.3 vs. 22%, OR = 4.1, 95% CI 2.2 to 8, 1, P<0.0001).

Table 3. Comparison of the clinical manifestations (diagnostic criteria) of infantile Kawasaki disease patients and older patients.				
Clinical Presentation	**Group A (<6 months old)**	**Group B (≥6 months old)**	***P -value***	***OR (95% CI)***
Rash	10 (83.3%)	44 (88%)	0.45	-
Conjunctival injection	10 (83.3%)	43 (86%)	0.31	-
Oral changes	9 (75%)	45 (90%)	0.0023	0.24 (0.11 - 0.61)
Cervical lymphadenopathy	4 (33.3%)	33 (66%)	0.0004	0.28 (0.14 - 0.55)
Extremity changes	6 (50%)	38 (76%)	0.029	0.45 (0.23 - 0.88)
Complete KD, N (%)	5 (41.6%)	39 (78%)	<0.0001	0.24 (0.12 - 0.45)
Incomplete KD, N (%)	7 (58.3%)	11 (22%)	<0.0001	4.1 (2.2 - 8.1)
Number of diagnostic criteria (before admission)	2 ± 1.8	3.5 ± 1.4	<0.05	-
Number of diagnostic criteria (before IVIG administration)	4 ± 1.5	4.5 ± 0.4	0.018	-

Data are expressed as n (%) or mean ± standard deviation. IVIG : intravenous immunoglobulin.

Biologically, infants younger than 6 months had a higher mean white blood cell count at diagnosis (19.5 versus 14.2, P < 0.0001; **Table 1**). Other inflammatory markers, such as CRP, ESR and platelets, were not significantly different between the two age groups. The younger cohort had lower levels of AST, ALT, and albumin, but only the difference in AST was statistically significant between age groups (24 versus 42 IU/L, P = 0.00027).

The administration rates of the second IVIG and intravenous methylprednisolone were higher in group A, but not significantly (rate of the second IVIG infusion, 25% versus 16%, p = 0.466; rate of the first administration of intravenous methylprednisolone, 16.6% vs 6%, p = 0.55; and rate of the second administration of intravenous methylprednisolone, 8.33% vs 2%, p = 0.088); In addition, the rate of administration of antibiotics before the use of IVIG treatment was higher in group A (75%) than in group B (50%), with no significant difference (p=0.22) (**Table 4**).

Table 4. Comparison of treatments of infantile Kawasaki disease patients and older patients.			
Treatment	**Group A (<6 months old)**	**Group B (≥6 months old)**	*P -value*
Initial antibiotics administration	9 (75%)	25 (50%)	0.22
Second IVIG administration	3 (25%)	8 (16%)	0.466
First IMPD administration *	2 (16.6%)	3 (6%)	0.55
Second IMPD administration *	1 (8.33%)	1 (2%)	0.088

Data are expressed as n (%). IVIG : intravenous immunoglobulin, * IMPD : intravenous methylprednisolone

Table 5. Coronary artery abnormalities in KD subjects.				
Coronary artery	**Group A (<6 months old)**	**Group B (≥6 months old)**	*P*	*OR (95% CI)*
Illness Day < = 10 days				
First echo Z-score	2.42 (1.11 - 5.11)	0.81 (0.01 - 1.78)	0.006	-
Z-score max	4.71 (1.1 - 5.8)	1.23 (0.17 - 2.15)	0.002	-
Normal	3/9 (33.3%)	28/35 (80%)	0.0016	0.17 (0.048 - 0.52)
Dilated (Z-score ≥ 2.5 to ≤ 4)	1/9 (11.1%)	3/35 (8.57%)	>0.1	0.92 (0.071 - 5.22)
Aneurysmal (Z-score > 4 to ≤ 10)	5/9 (55%)	3/35 (8.57%)	0.0001	11.28 (3.66 - 37.2)
Giant Aneurysm (Z-score > 10)	0/9 (0.0%)	1/35 (2.85%)	>0.1	-
llness Day > 10 days:				
First echo Z-score	10.33 (5.70 - 14.22)	1.6 (0.32 - 4.22)	0.0064	-
Z-score max	8.12 (5.28 - 15.11)	1.88 (0.55 - 4.4)	0.0045	-
Normal	0/3 (0.0%)	9/15 (60%)	0.03	-
Dilated (Z-score ≥ 2.5 to ≤ 4)	0/3 (0.0%)	2/15 (13.3%)	>0.9999	-
Aneurysmal (Z-score > 4 to ≤ 10)	1/3 (33.3%)	3/15 (20%)	0.22	2.01 (0.45 - 22.33)
Giant Aneurysm (Z-score > 10)	2/3 (66.6%)	1/15 (6.6%)	0.046	10.50 (1.65 - 83.11)

Dataexpressed as N (%) or median ; Fisher's exact test, two sided. Classification based on Z-max score

For children hospitalized within the first 10 days of illness, infants < 6 months had a 6-fold increased risk of aneurysm compared to subjects ≥ 6 months (55% vs 8.57%, OR = 11.28, 95% CI 3.66–37.2, P = 0.0001) (**Table 5**).

Group A infants hospitalized after day 10 of illness had an increased risk of having a giant coronary aneurysm compared to older children (66.6 vs. 6.6%, OR = 10.50, 95% CI 1.65 to 83.11, P = 0.046). Infants younger than 6 months had a higher baseline Z-score and max Z-score than older patients, whether they were hospitalized during the first 10 days of illness or after the 10th day of illness. When diagnosed within the first 10 days of illness, younger patients had higher baseline Z-score and Z-max than older patients (2.42 vs. 0.81, P = 0.006; 4.71 vs. 1.23, P = 0.002), respectively. An even higher Z-score and max Z-score from baseline were observed in younger infants after the 10th day of illness (10.33 versus 1.6, P = 0.0064; 8.12 versus 1, 88, P = 0.0045).

Whether treated within the first 10 days of illness or after day 10, infants less than 6 months of age were at greater risk of developing coronary artery aneurysms than treated patients with KD ≥ 6 months of age at the same time of disease progression [≤ 10 days (55 vs. 8.57%, P = 0.0001) ; > 10 days (66.6 vs. 6.6%, P = 0.046)].

Discussion

This is the first study in our region (West Algerian) and perhaps in our entire country to compare the clinical presentation, diagnosis, and therapy, as well as the progression of coronary artery disease, between infants under 6 months and those 6 months and older.

KD is an acquired heart disease most common in infants aged 6 months to 2 years. It is challenging to make a diagnosis of incomplete KD, particularly in infants younger than 6 months with fewer clinical manifestations (19,20).

The clinical manifestations of KD in this study were similar to those described in other studies. Kim et al. (21) reviewed the epidemiological and clinical characteristics of KD in between 2009-2011 and noted that conjunctival hyperaemia, redness of the lips and oral mucosa, and polymorphic skin rashes were the most common manifestations in KD patients. In this study, the most common symptom in group B was oral involvement (cheilitis, raspberry tongue, stomatitis, pharyngeal enanthema), followed by rash and conjunctival hyperaemia. However, in the KD patients < 6 months of age, skin rash and conjunctival injection were the most common symptoms, followed by mouth involvement and then extremity involvement.

Joffe et al. reported that infants aged < 6 months had fewer classic criteria for KD and a higher incidence of incomplete KD (22). Furthermore, Chuang et al. found that infants ≤ 3 months of age with KD typically had incomplete clinical manifestations (23). Similarly, in our study, group A showed fewer diagnostic criteria than group B. Group A showed a significantly higher rate of incomplete KD (58%) than group B (22%).

A recent study assessed predictors of coronary artery aneurysm. The authors suggest that anemia, low albumin, high ESR, high CRP and pyuria are the risk factors for CAA (24). Bayers et al reported that a high neutrophil count, a high ESR, low albumin, and low hemoglobin are associated with coronary artery lesions (25). In our study, group A showed high WBC and ESR, thrombocytosis, and low hemoglobin. These suggest the more severe inflammatory reaction in KD patients aged < 6 months. The low hemoglobin in group A could be due to physiological anemia, which is commonly seen in infants < 6 months of age. Significantly elevated white blood cell count in group A could be normal, as it is common in healthy infants < 6 months of age (18). Contrary to predictions, the ESR of group A was lower than that of group B, presumably because patients younger than 6 months were admitted earlier and had blood tests at an earlier stage of their fever than patients older patients. Group A showed higher levels of CRP than group B, although not significantly higher.

As demonstrated in other recent studies, infants younger than 6 months with KD are more likely to develop CAA than those older than 6 months (2, 3, 6, 9, 16-18). In our study, based on calculated max Z-scores, 55% of infants younger than 6 months with KD had an aneurysm or giant aneurysm compared to the older cohort of 11%. In comparison, other studies have shown that approximately 20% of infants younger than 6 months have developed an aneurysm or large aneurysm, whereas only 5% of infants ≥ 6 months have an aneurysm or large aneurysm (3). In the study by Rosenfeld et al., CAA present in infants less than 6 months of age reached 79%, compared to 44% in infants ≥ 6 months (6).

As for our region of Western Algeria, a high prevalence of CAA in infants under 6 months has been observed in other parts of the globe. In a study conducted in Chandigarh, India, 35% of infants under 6 months of age were reported to have CAA and 65% in a study in Taipei, Taiwan (2, 18).

Although the increased rate of CAAs in this cohort may be due to the fact that Z-scores are available, especially in the most severely affected patients, this warrants evaluating whether there is a higher rate of aneurysms in infants from western Algeria in a follow-up cohort study.

Initial diagnosis of KD was the retained diagnosis in 78% of patients ≥ 6 months, but only in 33.3% of infants under 6 months, as sepsis and urinary tract infection were the most common initial diagnoses. Since a large number of patients were initially treated with antibiotics, it is important to continue to educate the public that KD is not a diagnosis of exclusion and that in many cases, antibiotics are not needed as KD alone is the leading diagnosis.

There are several limitations to our study. First, the number of KD patients aged ≤ 6 months was significantly smaller than the number of older KD patients, which led to difficulties in statistical comparison. These data come from a single-center study and a database of children with KD and provide clinical and evolutionary data from a region of Algeria where few publications have been published on KD. Second, in many cases the blood test was done only once on admission; it was difficult to compare laboratory data before and after IVIG use.

Conclusion

Infants younger than 6 months with unexplained fever for > 5 days should be suspected of having KD, even if the main clinical features are not fully presented. Echocardiography should be used appropriately for the diagnosis of KD in suspected patients.

Our results show that, despite early treatment within the first 10 days of illness, infants younger than 6 months have a higher risk of developing a coronary aneurysm. A delay in diagnosis leads to larger coronary aneurysms in these infants. Thus, KD should be even more suspected in this vulnerable population given the likelihood of misdiagnosis and the increased risk of coronary artery aneurysm formation.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

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