

ANEURISMAS ARTERIAIS SISTÉMICOS NA DOENÇA DE KAWASAKI

SYSTEMIC ARTERY ANEURYSMS IN KAWASAKI DISEASE – A COMPREHENSIVE REVIEW

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RESUMO

Introdução: A Doença de Kawasaki (DK) é uma vasculite de pequenos e médios vasos, autolimitada e de causa indeterminada. Frequentemente acomete crianças até aos 5 anos de idade. Para além do atingimento coronário, alterações aneurismáticas podem ocorrer concomitantemente noutros territórios. Contudo, aneurismas sistémicos são descritos em menos de 2% dos casos, sendo por isso escasso o conhecimento que temos acerca da sua distribuição anatómica, evolução e *outcome*. Realizámos uma revisão sistemática da literatura acerca dos aneurismas arteriais sistémicos associados à DK (AAS-DK).

Métodos: revisão sistemática da literatura, através da base de dados MEDLINE

Resultados: foram selecionados 9 artigos, correspondendo a um total de 38 doentes e 134 AAS-KD. Os segmentos arteriais mais acometidos foram a artéria umeral (29,8%), a artéria íliaca interna (18,6%) e comum (16,4%) e a artéria subclávia (11,2%). O envolvimento de eixos arteriais de forma simétrica e a história de envolvimento coronário concomitante foi constatado em quase todos os doentes. Apenas 5 dos AAS-DK (3,7%) careceram de intervenção (cirúrgica convencional ou endovascular), 3 dos quais nos casos de apresentação tardia. O tratamento médico isolado associou-se regressão dos aneurismas em quase metade dos casos, sendo mais efetivo quando instituído precocemente. Os doentes mais novos e com formas mais agressivas da doença tiveram maiores taxas de morbimortalidade, sendo o prognóstico ditado pelas sequelas cardíacas.

Conclusões: Tendo em conta a sua raridade, apenas a realização de estudos multicêntricos e revisões da literatura poderão fornecer mais dados que permitam inferir acerca do tratamento e *outcome* dos AAS-DK. A apresentação tardia de um AAS-DK pode trazer alguns desafios quer em termos diagnósticos, quer em termos terapêuticos tendo em conta uma mais provável necessidade de intervenção, uma vez ultrapassado o timing para o tratamento médico.

Palavras-chave

Doença de Kawasaki, vasculite de pequenos e médios vasos, aneurismas arteriais sistémicos, aneurismas periféricos

ABSTRACT

Introduction: Kawasaki Disease (KD) is a self-limited, unknown-cause febrile vasculitis that predominantly addresses medium-sized arteries and most patients are under 5-years-old. In addition to life-threatening coronary artery involvement, aneurysms may develop in almost any medium-sized vessel, however systemic artery aneurysms (SAA) are described in only 2% of cases. The objective of this study was to identify cases of KD associated SAA and to analyze their frequency, anatomical distribution, treatment and outcomes.

Methods: systematic literature review, performed using MEDLINE database.

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Results: Literature review retrieved a total of 9 reports corresponding to 38 patients and a total of 134 KD-SAA. The most affected arteries were the brachial artery (29.8%), the internal iliac artery (18.6%), the common iliac artery (16.4%) and the subclavian artery (11.2%) with bilateral involvement being a common feature. History of concomitant coronary involvement was present in almost every patients. Only 5 SAA (3.7%) required intervention. Medical therapy was associated with SAA regression in approximately half of the patients, with better results when initiated promptly after diagnosis. Worst outcomes were found in younger patients, showing higher rates of morbimortality. The underlying coronary sequelae dictated the prognosis.

Conclusions: Considering their rarity, only multicenter collaboration and literature research can provide more insight about KD-SAA treatment and outcomes, defining the potential role of KD as a primary cause of late vascular lesion. Late presentation KD-SAA may present some diagnostic and therapeutic challenges in view of a more likely need for intervention once the benefit of medical treatment has been outweighed.

Keywords

Kawasaki disease, small and medium-sized arteries vasculitis, systemic artery aneurysms, peripheral aneurysms

INTRODUCTION

Kawasaki Disease (KD) is an self-limited, unknown-cause febrile vasculitis that predominantly addresses medium-sized arteries.⁽¹⁾ It has an ethnic bias towards Asian children, with Japan having the highest incidence (138/100 000). In USA and UK, the incidence is 17.1/100 000 and 8.1/100 000, respectively. Most patients are under 5-years-old and males are affected 1.5 times more often than girls.⁽²⁾ It is an exclusion diagnosis, based on clinical "pathognomonic" manifestations (table 1).⁽¹⁾

life-threatening coronary artery ectasias and aneurysms can develop in almost one third of patients.^(3,4) Although KD prognosis is mainly dictated by the coronary involvement, systemic artery aneurysms (SAA) can also occur in approximately 2%.⁽⁵⁾ SAA can be associated with rupture, embolization or occlusion and may have a delayed presentation, years after KD acute phase.⁽⁶⁾ Relatively little literature has been published on the frequency, distribution, treatment and outcomes of KD-SAA. The objective of this study was to identify cases of KD-SAA and to analyze their frequency, anatomical distribution, treatment and outcomes.

Table 1 Classical Clinical Features of Kawasaki Disease

Fever of at least 5 days duration* and presence of at least **4 of the following** principal features:

- Bilateral bulbar conjunctival injection (nonpurulent)
- Oral mucosal changes (erythema, cracked lips, strawberry tongue, pharyngeal injection)
- Polymorphous exanthema
- Extremity changes (Acute: palmar/sole erythema, edema of hands and feet. Subacute: periungual peeling of digits)
- Cervical lymphadenopathy (usually unilateral and diameter > 1.5 cm)

*Recent guidelines include acceptance of > 5 days of fever when diagnosis established by experienced clinician or in the presence of more than 4 principal criteria. Also, less than 4 principal criteria accepted when coronary artery changes are detected by echocardiography (or angiography)

Current standard treatment consists of a combination of intravenous immunoglobulin (IVIG), acetylsalicylic acid +/- corticosteroids. This aggressive medical intervention has improved prognosis, in the last decades.⁽¹⁾ When untreated,

METHODS

A literature review was performed using MEDLINE database with the following query: ((Kawasaki disease) OR (Kawasaki syndrome)) AND ((non-coronary arterial aneurysms OR systemic arterial aneurysms OR peripheral arterial aneurysms). All reports that did not provide information about therapeutic approach and outcomes were excluded. Only English language papers were included.

RESULTS

Literature review retrieved a total of 9 reports that meet the eligibility criteria (table 2).^(5,6,7,8,9,10,11,12,13) Thirty eight patients (25♂ and 13♀) were identified, corresponding to a total of 134 KD-SAA. Although most SAA were diagnosed in children under 5-years-old, three delayed presentations were found in previously undiagnosed patients.^(8,10,13) The most affected arteries were the brachial artery (29.8%), the internal iliac artery (18.6%), the common iliac artery (16.4%) and the subclavian artery (11.2%). Bilateral involvement was a common feature. History of concomitant coronary involvement was present in almost every patients.



Table 2 Summary of selected cases of KD-associated SAAs

Author (journal, year)	Type of study	Gender, age*	Involved artery (frequency)	Symptoms	Coronary involvement	Treatment	FU	Outcome
Tomita et al. (Clinical Infectious Diseases, 1992)	Case Report & Literature Review	5♂, 6♀ 3,6 months (mean)	Subclavian (2), Axillary (3), Brachial (4), Aorta (1), Renal (1)	Peripheral gangrene	100%	Medical (heparin, vasodilators, steroids)	NA	Minor amputation 82% Major amputation 9% Death 9%
Bradway et al. (J Vasc Surgery, 1997)	Case Report	♂, 43 years	Common femoral (1), Popliteal (1)	Acute limb ischemia	Yes	Surgical (bypass graft)	NA	Good
Bachiri et al. (Arch Pédiatr, 2000)	Case Report	♂, 9 months	Brachial (bilateral)	Peripheral gangrene	Yes	Medical (IVIg, heparin, fibrinolysis)	2 years	Minor amputation, Aneurysm regression
Ferrante et al. (EJVES, 2004)	Case Report	♂, 12 years	Brachial (1)	Compressive symptoms	Yes	Aneurysmectomy and autologous grafting	3 years	Death (15 years, myocardial infarction)
Heran et al. (Pediatr Cardiol, 2011)	Case Report	♂, 4 years	Common iliac (bilateral), internal iliac (bilateral), axillary artery (bilateral), brachial artery (bilateral)	Asymptomatic	Yes	Medical (IVIg, heparin, aspirin)	NA	Stability of brachial aneurysms Regression of the other SAA
Bajolle et al. (Arch of Cardiovasc Disease, 2013)	Case Report	♂, 7 weeks	Subclavian (bilateral)	Compressive symptoms E	Yes	Covered stent	5 months	Good
Malekzadeh et al. (Iran J Pediatr, 2015)	Case Report	♂, 4 months	Subclavian (bilateral), external iliac (bilateral), internal iliac (bilateral), renal (bilateral)	Asymptomatic	Yes	Medical (IVIg, heparin, aspirin)	1 year	Regression of CAA Peripheral aneurysms did not improve
Hoshino et al. (J of Pediatrics, 2015)	Case Series (from 1980 to 2013)	14♂, 6♀ 9,5 months (mean)	Brachial (30), common iliac (20), internal iliac (21), subclavian (9), Others (20)	NA	80%	Medical (IVIg, heparin, aspirin) ABF bypass (1)	Median of 18 years	Regression 50% AS Stenosis 25% Intervention 5% Death 20%
Coelho et al. (EJVES Short reports, 2019)	Case Report	14 years, ♀	Brachial (1)	Compressive symptoms	No	Aneurysm exclusion & artery transposition	2 years	Good

*Age = age at the identification of SAA; FU = follow-up; NA = not available, IVIG = intravenous gammaglobulin; AAA = abdominal aortic aneurysm; AS = asymptomatic; ABF = aorto-bifemoral bypass

When identified during KD acute or subacute-phase, medical therapy (IVIg, heparin, antiplatelet and/or fibrinolysis) was the mainstay of SAA treatment. Only 5 SAA (3,7%) required intervention. One during KD acute-phase due to severe compressive symptoms⁽¹¹⁾, another due to aorto-iliac aneurysm growth during follow-up (aorto-bifemoral bypass at 25 years-old).⁽⁶⁾ Intervention was also required in the three delayed presentation cases: one due to acute limb ischemia (n=1)⁽⁹⁾ and two cases with upper limb compressive symptoms (n=2).^(10,13) Medical therapy was associated with SAA regression in approximately half of the patients, with better results when initiated promptly after KD diagnosis. Worst outcomes were found in younger patients, showing higher rates of morbimortality. The underlying coronary sequelae dictated the prognosis.

DISCUSSION

KD is virtually as enigmatic today as it was when first described by Kawasaki in 1967. Five decades later, no specific inciting etiological agent was yet identified.⁽⁴⁾ Independently of the initial insult, KD-acute phase is characterized by an intense inflammatory response, leading to degeneration and weakening of the medium-sized arteries wall.^(4,5) Once systemic blood pressure has stressed the weakened vessel sufficiently, an aneurysm can form.⁽⁵⁾ Considering that blood pressures are roughly symmetric across the sagittal plane, one can expect to see a degree of symmetry in aneurysm distribution, as well as a predilection for the coronary, subclavian-axillary-brachial axis and for the iliac arteries.

As highlighted by the present results, the existence of SAA increases the likelihood of coronary involvement and SAA outcome is similar to coronary aneurysms.⁽¹⁴⁾ SAA can regress, persist with progressive growth (sometimes requiring intervention) or evolve to a stenotic lesion (found more commonly more than 20 years after KD onset).⁽¹⁵⁾ Despite its proved reduction in coronary aneurysms (from 15-30% to 3 to 5%), studies have not yet documented if there is a concomitant decrease in SAAs with early medical therapy.⁽⁵⁾

As there are no specific KD markers of worst outcome, in the absence of SAA complications adoption of a conservative strategy seems wise.^(6,16,17) Enlarging aneurysms or aneurysms causing neurologic or vascular symptoms should be treated surgically. Definitive surgical treatment involves resection of the aneurysm with arterial repair or reconstruction. In infants and small children, microsurgical techniques are required. Results of surgical interventions seem favorable, however patient age and anatomic factors must be considered. Endovascular treatment is not advisable in early ages. However, as reported by Bajolle

et al., in the setting of an extreme manifestation – exuberant arm edema and plexus brachial block, in a 7 week-newborn – endovascular aneurysm exclusion may be considered as a bridge to a more definitive intervention.⁽¹¹⁾

SAA have been described anecdotally in adult patients with a previous history of KD. However, given the survival benefit obtained with current medical therapy, late-onset SAA could have a higher incidence than previously reported. On the other hand, SAA associated with incomplete/atypical forms of KD (with mild clinical manifestations) can remain undiagnosed until compressive symptoms or limb-threatening events appear.⁽¹⁸⁾ Nevertheless, the relation with a previous KD may be difficult to establish and only the anatomopathological examination can confirm the diagnosis.

CONCLUSION

It is clear that coronary KD involvement is of paramount importance. Nevertheless, SAA should never be neglected, due to its inherent morbidity (highlighting thromboembolic complications and rupture).

Late presentation KD-SAA may present some diagnostic and therapeutic challenges in view of a more likely need for intervention, once the benefit of medical treatment has been outweighed. Considering KD rarity, only multicenter collaboration and research can provide more insight about SAA treatment and outcomes, defining the role of KD as a primary cause of late vascular lesion.

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