ANEURISMS ARTERIALS SISTÉMICOS NA DOENÇA DE KAWASAKI

SYSTEMIC ARTERY ANEURYSMS IN KAWASAKI DISEASE – A COMPREHENSIVE REVIEW

Nuno Henriques Coelho¹, Paulo Barreto¹, Victor Martins¹, Clara Nogueira¹, Jacinta Campos¹, Pedro Sousa¹, Andreia Coelho¹, Rita Augusto¹, Carolina Semião¹, Evelise Pinto¹, João Ribeiro¹, Alexandra Canedo¹

1. Serviço de Angiologia e Cirurgia Vascular, Centro Hospitalar Vila Nova de Gaia/Espinho

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.

Results: were selected 9 articles, corresponding to a total of 38 patients and 134 AAS-KD. The segments arteries more affected were the ulnar artery (29.8%), the internal iliac artery (18.6%) and common (16.4%) and the subclavian artery (11.2%). The involvement of medium arteries of a symmetric form and the history of coronary artery concomitant involvement was identified in almost all the patients. Only 5 of the AAS-KD (3.7%) needed intervention (conventional or endovascular), 3 of which cases of late presentation. The medical treatment associated with regression of aneurysms in almost half the cases, being more effective when instituted early. The younger patients and those with more aggressive forms of the disease had higher rates of morbimortality, being the prognosis dictated by the cardiovascular sequelae.

Conclusions: Considering its rarity, only multicentric studies and revisions of the literature can provide more data that allows for better understanding of the treatment and outcomes of AAS-KD. The delayed presentation of an AAS-KD may bring some difficulties in terms of diagnosis and treatment, given the possible need for intervention, once the timing for medical treatment has been exceeded.

Keywords: Kawasaki Disease, vasculitis of small and medium-sized arteries, systemic artery aneurysms, peripheral aneurysms

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 sistêmicos 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-DK. Os segmentos arteriais mais acometidos foram a artéria umeral (29.8%), a artéria ilíaca 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 multicéntricos e revisões da literatura poderão fornecer mais dados que permitem inferior acerca do tratamento e outcomes 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

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 sistêmicos 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-DK. Os segmentos arteriais mais acometidos foram a artéria umeral (29.8%), a artéria ilíaca 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 multicéntricos e revisões da literatura poderão fornecer mais dados que permitem inferior acerca do tratamento e outcomes 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

1. Serviço de Angiologia e Cirurgia Vascular, Centro Hospitalar Vila Nova de Gaia/Espinho

Received on July 1, 2018
Accepted on August 27, 2019

*Autor para correspondência.
Correio eletrónico: nunoc.90@gmail.com (N. Coelho).
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. It has an ethnic bias towards Asian children, with Japan having the highest incidence (1.38/100 000). 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. It is an exclusion diagnosis, based on clinical “pathognomonic” manifestations (table 1).

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. When untreated, life-threatening coronary artery ectasias and aneurysms can develop in almost one third of patients. Although KD prognosis is mainly dictated by the coronary involvement, systemic artery aneurysms (SAA) can also occur in approximately 2%. SAA can be associated with rupture, embolization or occlusion and may have a delayed presentation, years after KD acute phase. 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.

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

A literature review retrieved a total of 9 reports that meet the elegibly criteria (table 2). 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. 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 1 Classical Clinical Features of Kawasaki Disease

<table>
<thead>
<tr>
<th>Fever of at least 5 days duration* and presence of at least 4 of the following principal features:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral bulbar conjunctival injection (nonpurulent)</td>
</tr>
<tr>
<td>Oral mucosal changes (erythema, cracked lips, strawberry tongue, pharyngeal injection)</td>
</tr>
<tr>
<td>Polymorphous exanthema</td>
</tr>
<tr>
<td>Extremity changes (Acute: palmar/sole erythema, edema of hands and feet. Subacute: periungual peeling of digits)</td>
</tr>
<tr>
<td>Cervical lymphadenopathy (usually unilateral and diameter &gt;= 1.5 cm)</td>
</tr>
</tbody>
</table>

*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.
### Table 2: Summary of selected cases of KD-associated SAA

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

*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, another due to aorta-iliac aneurysm growth during follow-up (aorta-bifemoral bypass at 25 years-old). Intervention was also required in the three delayed presentation cases: one due to acute limb ischemia (n=1) and two cases with upper limb compressive symptoms (n=2). 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. 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. Once systemic blood pressure has stressed the weakened vessel sufficiently, an aneurysm can form. 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. 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). 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.

As there are no specific KD markers of worst outcome, in the absence of SAAs complications adoption of a conservative strategy seems wise. 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.

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. 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.

**REFERENCES**


