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REVIEW ARTICLE

Acute Vasculitis, Kawasaki Disease and Covid 19

Vasculitis agudas, enfermedad de Kawasaki y COVID-19

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ABSTRACT

Introduction: Acute vasculitides in childhood comprise a group of diseases characterized by inflammation of blood vessels. They have been observed in patients with SARS-CoV-2 infection and the cutaneous lesions presented are related to Kawasaki disease.
Objective: to review vasculitis, Kawasaki disease and skin lesions reported in Covid 19 infection.
Methods: A search on vasculitis was performed in Pub Med, WHO-2020, Scielo, Swisslinx, Dialnet, Redalyc journals. We selected all those documents that included the word vasculitis, Kawasaki disease and Covid 19, published in the last 5 years.
Development: Multiple studies and research are still being carried out to clarify the etiology and pathophysiological mechanisms of vasculitis. Diagnosis and therapeutic conduct require multidisciplinary intervention. They are infrequent diseases in pediatric age, being Kawasaki disease one of the best known. It is of vital importance to know about it, in order to achieve an early diagnosis and timely treatment to reduce the risk of complications in the patient. In the current context of the Covid-19 pandemic, variations in the behavior of Kawasaki disease have been reported, which constitutes a challenge for researchers and for all health personnel who provide medical care to these children.
Conclusions. This review addresses the fundamental elements on Kawasaki and its modifications in SARS-CoV-2 infected patients, which in the current pandemic are essential in the teaching and care activity.

Keywords: Vasculitis; Inflammation; Mucocutaneous Lymph Node Syndrome; Covid 19.

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RESUMEN

Introducción: las vasculitis agudas en la infancia comprenden un grupo de enfermedades caracterizadas por la inflamación de los vasos sanguíneos. Estas se han observado en pacientes con infección por SARS-CoV-2 al relacionar las lesiones cutáneas presentadas con la enfermedad de Kawasaki.
Objetivo: realizar una revisión sobre las vasculitis, la enfermedad de Kawasaki y las lesiones cutáneas reportadas en la infección por COVID-19.
Métodos: se realizó una búsqueda sobre vasculitis, en PubMed, WHO-2020, Revistas Scielo, Swisslinx, Dialnet, Redalyc. Se seleccionaron todos aquellos documentos que incluyeran la palabra vasculitis, enfermedad de Kawasaki y COVID-19, publicados en los últimos cinco años.
Desarrollo: aún se realizan múltiples estudios e investigaciones para esclarecer la etiología y mecanismos fisiopatológicos de las vasculitis. El diagnóstico y la conducta terapéutica requieren de una intervención multidisciplinaria. Son enfermedades poco frecuentes en la edad pediátrica; la enfermedad de Kawasaki es una de las más conocidas. Resulta de vital importancia el conocimiento acerca de la misma, a la hora de lograr un diagnóstico precoz y un tratamiento oportuno que disminuyan el riesgo de complicaciones en el paciente. En el contexto actual de la pandemia por COVID-19 se han reportado variaciones en el comportamiento de la enfermedad de Kawasaki lo cual constituye un reto para investigadores y para todo el personal de salud que brinda asistencia médica a estos niños.
Conclusiones: se abordaron los elementos fundamentales sobre Kawasaki y sus modificaciones en los infectados de SARS-CoV-2, que en el panorama de la actual pandemia resultan imprescindibles en la actividad docente y asistencial.

Palabras clave: Vasculitis; Inflamación; Síndrome Mucocutáneo Linfonodular; Covid 19.

INTRODUCTION

Vasculitis in children is a difficult but fascinating field of pediatric rheumatology, shared by other pediatric specialists.[1] The study of vasculitis in children dates back to 1866 when Kussmaul and Maier made the first macroscopic postmortem description.[2] The diagnosis is challenging and rarely performed.

Diagnosis is a challenge and is rarely made easily since its symptoms can be very similar to those of other more frequent pediatric diseases. In many cases the origin is unknown and is most likely due to a combination of genetic, infectious and environmental factors that have not yet been characterized.[3]

The limited number of specific studies in children means that many aspects of their management are extrapolated from published experience in adults.[4]

Pediatrics is not exempt from this problem and sometimes there are difficulties in the identification and diagnosis of acute vasculitis in pediatric patients.

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Kawasaki disease is the most frequent vasculitis in the pediatric age group and is prevalent in Asian countries, especially in Japan, where the incidence has increased to 330/100 000 children under five years of age. In the USA the incidence is around 25/100,000 children under five years of age and in Europe between 5,4 and 15/100,000 children under five years of age. Eighty-five percent of cases occur in children under five years of age, with peak incidence between 18 and 24 months of age. It is less frequent in children under three months or older than five years, in both groups the risk of developing coronary artery aneurysms is higher.[4]

Currently, the world is in the midst of a pandemic originating from SARS-CoV-2, spread in more than 188 countries and infecting more than 15 million individuals after it was discovered in the city of Wuhan, China in late 2019. The scenario showed, mainly, a specific behavior with greater affectation in individuals at risk of death, with comorbidities and of advanced age. Then, infections began to occur in young and pediatric patients in whom the virus caused only mild symptoms and rapid recovery. Thus, over the past months, new findings have been recorded in patients with COVID-19, such as asymptomatic carriers and repercussions in different organs. One of these atypical manifestations started with case reports related to Kawasaki disease.[5]

The aim of this work is to systematize the current knowledge related to acute vasculitis in childhood, Kawasaki disease and COVID-19. In addition, it will provide bibliographic material to support teaching in the training of students, residents, masters and specialists.

METHODS

A review of scientific articles published in peer-reviewed journals and books by specialists in the field was carried out.

A search on vasculitis was carried out in PubMed, WHO-2020, Scielo, Swisslinx, Dialnet, Redalyc journals. All documents that included the word vasculitis, published in the last five years, were selected.

DEVELOPMENT

Definition
The term vasculitis refers to a group of clinically heterogeneous diseases, but with a common histological substrate: the presence of an inflammatory infiltrate in the thickness of the blood vessel wall (arteries, arterioles, capillaries, venules and veins).[1,5,6]

Classification
Nosologic classification is difficult because along with well-defined clinicopathologic entities there are numerous cases that do not adequately fit into any of the admitted categories.[1,2] Not only the size of the vessels is important, but also the combination of clinical, demographic, histologic and serologic data is required.[7]

They are currently classified on the basis of clinical and histological data, using the 1990 American College of Rheumatology criteria and the criteria issued at the 1992 Chapel Hill Consensus Conference Criteria (revised in 2012) (Table 1).[1,2,3]

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Table 1 Classification of childhood vasculitides Nomenclature of vasculitides from the Chapel Hill Consensus Conference of 2012.[8]

Large vessel vasculitis Takayasu's arteritis Giant cell arteritis
Medium vessel vasculitis Polyarteritis nodosa Kawasaki disease
Small vessel vasculitis. **Vasculitis associated with antibodies to neutrophil cytoplasm (ANCA).** • Microscopic polyvasculitis • Granulomatosis with polyvasculitis • Eosinophilic granulomatosis with polyvasculitis Immune complex of small vessel vasculitis • Glomerular basement membrane disease (anti-GBM) • IgA vasculitis (Henoch-Schönlein purpura) • Hypocomplementemic urticarial vasculitis
Variable vessel vasculitis Behçet's disease Cogan's syndrome
Single organ vasculitis Cutaneous leukocytoclastic vasculitis Cutaneous arteritis Primary central nervous system vasculitis Isolated aortitis Other
Vasculitis associated with systemic disease Lupus vasculitis Rheumatoid vasculitis Sarcoid vasculitis Other
Vasculitis associated with probable etiology Hepatitis C virus-associated cryoglobulinemic vasculitis Hepatitis B virus-associated vasculitis Aortitis associated with syphilis Drug-associated immune complex vasculitis Drug-associated ANCA-associated vasculitis Cancer-associated vasculitis Other

Epidemiology

Generally speaking, vasculitides are infrequent diseases.[6] Some are relatively common in childhood, e.g., childhood immunodeficiency disease (IgA).

Epidemiology

Generally speaking, vasculitides are infrequent diseases.[6] Some are relatively common in childhood, e.g. Kawasaki disease, while others are rare and their exact frequency is unknown.[9]

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The small number of registries of patients with these diseases makes it difficult to know the true incidence, variable figures between 0.5-6.39 cases/million children/year are described.[10]

Etiopathogenesis

The exact cause of these diseases is unknown. Most probably they are due to a combination of different genetic, infectious and environmental factors. Some genes that may condition their appearance have been studied; however, these diseases are not hereditary. In most cases, the patient is the only one affected in a family and it is very unlikely that siblings have the same disease. Infections sometimes act as triggers for the immune response that provokes vasculitis.[8,9]

They are included in the group of immunocomplex diseases. Most are due to immunopathogenic mechanisms that occur in reaction to antigenic stimuli; however, the evidence supporting this hypothesis is almost entirely indirect. Three fundamental pathophysiologic mechanisms have been proposed: immunologic damage, direct infection of the vessels, and a third group in which the cause is unknown. The most widely accepted mechanism is the deposition of immune complexes on vessel walls. Upon binding to the endothelial cell surface, the constant fraction (Fc) of immunoglobulin fixes complement and thus initiates the complement cascade, with production of C5a and C3a, which are potent neutrophilic chemotactics. They phagocytize immune complexes, release lysosomal and proteolytic enzymes and lead to tissue damage. The reaction peaks in 12 hours and the neutrophils are subsequently replaced by monocytes in 24-48 hours.[2]

The blood vessel is the main target of the disease. The reduction of the space that the infiltrate itself creates at the level of the vascular wall, or the structural alterations that it undergoes (aneurysms, rupture of the elastic layer, hyperplasia of the intimal layer), or thrombotic or reparative phenomena that will cause the lumen of the vessel to be compromised, produce ischemia or tissue stasis, which causes organic dysfunction. Its inflammation and necrosis lead to occlusion that produces tissue ischemia.[1,2] Its wall becomes more "porous", which allows the liquid inside it to pass into the adjacent tissues and causes swelling of these tissues. These effects are responsible for rashes and skin changes. [9] The increase of the vascular bed facilitates blood extravasation from which palpable purpura or pulmonary alveolar hemorrhage will result. The consequences of this process depend on the size of the affected vessel and the extension that can be universal or be restricted to a certain organ or system.[1,3,9]

This process is also accompanied by an intense release of inflammatory molecules, which causes general symptoms such as fever, malaise, as well as abnormal results in clinical tests that detect inflammation: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[9]

Clinical picture

The manifestations derive from ischemia due to vascular occlusion and increased permeability or rupture of the inflamed vessels.[7]

Symptoms vary according to the type of vessel (large, medium, small), the extension (generalized or more delimited), its location (brain, heart, skin or muscles), as well as the degree of involvement of the blood supply.[1,9,10] Any organ or system can be affected in different combinations and, therefore, the clinical manifestations can be very diverse. Even patients with the same disease may have few symptoms in common.[7]

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Patients share common clinical features such as: [1,2,5,11]
Constitutional manifestations: weight loss, fever of unknown origin, asthenia and adynamia.
Musculoskeletal manifestations: myalgia, myositis, arthralgia and arthritis.
Skin lesions: urticaria, palpable purpura, papules, nodules, livedo reticularis, necrotic bullae and ulcers.
Respiratory manifestations: alveolitis, pulmonary hemorrhage, serositis, infiltrates, nodules, asthma and sinusitis.
Renal manifestations: hypertension and necrotizing glomerulonephritis.
Gastrointestinal manifestations: diarrhea, nausea, vomiting, abdominal pain and gastrointestinal bleeding.
Neurological manifestations: headache, visual disturbances, cerebral vascular disease, seizures, alterations of consciousness, mononeuritis multiplex and sensory peripheral neuropathy.

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Diagnosis

Diagnosis requires a high degree of suspicion and the recognition of a specific entity requires a general knowledge of all vasculitides, the peculiar characteristics of each type and the spectrum of clinical presentations.[1] Its signs and symptoms are nonspecific and can be confused with many other pathologies such as infectious, neoplastic or connective tissue diseases. In order to reach an accurate diagnosis it is important to combine clinical, radiological, histopathological and laboratory findings.[12]

The definitive diagnosis can be divided into three conceptual phases:[1,7]
Establish a generic diagnosis of vasculitis that requires histological and/or angiographic confirmation of the vascular lesion. Some, such as Schönlein-Henoch purpura and Behcet's disease, may present with such classic manifestations that it is possible to diagnose them with clinical data alone.
Estimate the severity and anatomical distribution of the disease to decide the aggressiveness of therapy.
Identify, if possible, the specific entity based on the combination of clinical manifestations, anatomic pattern of involvement and histopathologic features.

In the anatomopathological study, loss of vascular architecture secondary to infiltration of its walls by neutrophils, lymphocytes or histiocytes and the presence of fibrinoid necrosis are observed.[3,7]

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Direct immunofluorescence can be positive in specific etiologies and is useful in identifying the type of immunoglobulin (Ig) deposited in the vascular wall; for example, the presence of IgA is associated with HSP, while IgM can be observed in cryoglobulinemic vasculitis.[3,13]

Other alterations that can be detected from laboratory tests include: anemia, leukocytosis, eosinophilia, thrombocytosis, increased factor VIII, increased erythrocyte sedimentation rate and C-reactive protein, hypocomplementemia, cryoglobulinemia, circulating immune complexes, elevated liver enzymes, abnormal renal sediment, proteinuria, hematuria, presence of ANCA and rheumatoid factor.[2,7]

Other useful complementary studies are: electromyography, nerve conduction study, electrocardiogram and/or echocardiogram, ultrasound, arteriography, chest and sinus radiography and in some cases CT or MRI.[2]

Treatment

As in most diseases, treatments need to be individualized according to the type of vasculitis, the degree of systemic involvement, the extent of vascular damage, the time of evolution, as well as other individual patient factors.[6]

Glucocorticoids are the first-line drugs to control the inflammatory process. When it is localized, low doses (0.5 mg/kg body weight), less than 15 mg/day, are used. When life-threatening organs are affected, high doses are used (1 mg/kg body weight) and even very high doses with methylprednisolone.

Other immunosuppressors are used when the disease progresses rapidly with visceral involvement (intestinal, renal and cardiac, among others) and when it is refractory to glucocorticoids or it is not possible to reduce the dose of these. The most commonly used are: oral or intravenous cyclophosphamide, azathioprine and methotrexate. Remission is achieved within the first three to six months after the onset of the disease. Methotrexate has shown efficacy in patients with giant cell arteritis, Takayasu's disease, Wegener's granulomatosis; as has cyclophosphamide in microscopic polyangiitis nodosa and Wegener's granulomatosis.[2,9]

Other treatment alternatives include anti-thymocyte globulin, immunoglobulin, cyclosporine, deoxyspergualin, monoclonal antibody therapy, plasmapheresis, and peripheral blood-mobilized stem cell transplantation.[2,14]

New drugs called "biologics", which block specific cytokines in the inflammatory cascade, are currently being proposed.

Currently new drugs called "biologics" are proposed, which are responsible for blocking specific cytokines in the inflammatory cascade such as anti-TNF, anti-IL 6, anti-IL 1, anti-CD20, among others.[1]

Hygienic-dietary measures: there are no specific recommendations since they depend on the clinical manifestations found, so that if the patient presents arterial hypertension, a hyposodic diet is recommended. If there is renal damage, a diet for nephropaths is recommended, since this group requires long-term treatment with glucocorticoids.[2]

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Prognosis

The prognosis is very variable because it depends, above all, on factors such as the type of vasculitis, the degree of systemic involvement and the organs affected. Early diagnosis is of vital importance to avoid the development of irreversible damage. Despite the immunosuppressive treatments available, its morbidity and mortality is high.[1,2,5]

Kawasaki disease and COVID-19 in pediatrics.

In the current COVID-19 pandemic, the association with Kawasaki disease has been noted. These pictures are characterized by unusual abdominal pain, accompanied by gastrointestinal symptoms (diarrhea and/or vomiting), with acceptable general condition. In addition, they are often accompanied by fever, vasculitis, erythroderma and conjunctival injection, hence the confusion with Kawasaki disease.

Kawasaki disease

Kawasaki disease is an acute, self-limiting, systemic vasculitis affecting medium-sized vessels. It is often associated with potentially dangerous complications. It is the most common cause of acquired heart disease in pediatric patients in developed countries. [15,16]

It was first described by Tomisaku Kawasaki in Japan in 1967 in a series of Japanese children with an "acute febrile mucocutaneous syndrome with lymphoid involvement and specific desquamation of the fingers and toes."[4,15,17]

The male to female ratio is 1.5:1.[16] A higher incidence has been observed in the winter and spring months.[15]

Its importance is due to the fact that 15-25 % of untreated children develop coronary anomalies, which may lead to myocardial infarction, sudden death or ischemic heart disease.[4]

Despite multiple investigations there is still no certainty of its etiology. Although the presence of an infectious trigger has been suggested, a definitive causal relationship has never been established.[15,16]

Currently, there are multiple studies aimed at identifying genetic markers of disease susceptibility, severity and resistance to treatment. The cause leading to coronary arteritis is not yet clear, although activation of endothelial cells, CD68 monocytes/macrophages, CD8 lymphocytes and monoclonal IgA plasma cells seem to be involved. An infectious factor would increase the production of cytokines, such as TNF-α, IL 1 and IL 6, which would induce new endothelial antigens and antibodies against them would be generated. An infiltrate of macrophages and lymphocytes is produced in the arterial wall that secrete inflammatory mediators and enzymes that contribute to vascular damage. Inflammation leads to destruction of the media and the formation of aneurysms. Extraparenchymal medium-sized arteries (celiac, mesenteric, femoral, iliac, renal, axillary and brachial) and, in particular, coronary arteries are usually affected.[4]

The course of the disease is divided into three phases:[15]

- Acute febrile period, lasting approximately 10 days.
- Subacute period, lasting between two and four weeks.
- Convalescent phase, in which most of the symptoms resolve.

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Characteristically, all clinical manifestations do not occur at the same time, so it is sometimes necessary to wait several days before making the diagnosis.[4]

It is characterized by the appearance of high fever, bilateral non purulent conjunctivitis frequently intense, labial and oral erythema, laterocervical adenopathies.[15]
Characteristic manifestations are described as follows:[4,15]
Oral alterations: lips may be dry, cracked, as well as thickened, with a raspberry-like tongue. There may be enanthema.

Exanthema: it is polymorphous, and can be maculo-papular, scarlatiniform or multiform. It frequently begins on the extensor surfaces of the limbs and then spreads to the trunk. Perineal involvement is characteristic.

Changes in the extremities: erythema of palms and soles associated, or not, with indurated edema, without pitting. At the end of the second week there is a decamation starting at the periungual level, characteristic of the disease, although it may be absent.

Lymphadenopathy: this is the major criterion that appears on fewer occasions, approximately 70 %. Cervical lymphadenopathy is usually unilateral, with involvement of a single lymph node, painful, hard and more than 1,5 cm in diameter, which remits as fever subsides. Occasionally there may be more generalized lymph nodes.

Cardiac involvement: it is always necessary to think, to look for and to watch, because it is the involvement that can give gravity to the process. Cardiac manifestations are very variable: from nonspecific alterations of the electrocardiogram (ECG) without clinical repercussions, to heart murmurs, gallop rhythm, pericarditis, endocarditis, myocarditis and coronary aneurysms. In the first days of the process, coronary arteritis may be detected. After the first month is when aneurysms and thrombosis can be detected by echocardiography or angiographic techniques. Most aneurysms regress spontaneously within a year. The mortality rate is between 1 and 2 %.

In the first 10 days, coronary aneurysms are not usually detected, but an increase in brightness surrounding the arterial lumen or ectasias may be seen by echocardiography. This early lesion may resolve or evolve. Also, decreased ventricular function, valvular regurgitation or pericardial effusion may be observed. Aneurysms are usually detected in the subacute phase (4-6 weeks of illness).[4]

Patients may present with significant irritability which may be secondary to aseptic meningitis or the result of a focal neurologic vasculitic lesion. They may also present with cough, aphonia, mucus or other symptoms suggestive of a viral respiratory tract infection. Sometimes they are accompanied by pulmonary infiltrates or otitis media. Abdominal pain (similar to that seen in children with Henoch-Schönlein purpura) may occur, with or without diarrhea.[15]

Clinical criteria include the presence of fever for five days and at least four of the following signs:[15,16]
- Bilateral conjunctival injection (non-exudative)
- Changes in the mucosa of the oropharynx (pharyngitis, fissured, erythematous or dry lips, and "strawberry" tongue).
- Alterations in the extremities, such as edema or erythema of hands and/or feet, as well as decamation usually predominantly periungual.
- Erythema polymorphous (but not vesicular)
- Cervical lymphadenopathy greater than 1,5 cm and usually single.

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It should be considered in any child presenting with prolonged unexplained fever with less than four clinical criteria, but compatible echocardiographic or laboratory findings.

Incomplete forms are very common and atypical presentations are often encountered. These create a diagnostic challenge for the treating physicians and may delay the initiation of therapy. The term incomplete Kawasaki refers to patients who, although they do not meet sufficient criteria, can be diagnosed with the disease.[4]

There is no specific test for the diagnosis, but there are laboratory studies to support it in atypical cases. Clinical experience suggests that it is unlikely to be KD if the patient has normal ESR, CRP and platelet count within a week of symptoms.

In the hemogram, normocytic normochromic anemia, leukocytosis with predominance of immature forms and thrombocytosis can be frequently found. Thrombocytosis usually occurs after the second week of symptom onset, peaks in the third week with average values of 700,000 per mm3 and normalizes at 4 to 6 weeks. Hypoalbuminemia is frequently present and is associated with a more severe and prolonged presentation. Urine examination may show leukocyturia in up to 80 % of children. During acute illness the ECG may show cardiac arrhythmias such as sinus node and atrioventricular node disturbance expressed as prolonged PR interval and nonspecific ST and T wave changes. In addition, it may present with low voltage if there is pericardial or myocardial involvement. For the diagnosis of coronary artery alterations, transthoracic echocardiography or angiography can be performed. The echocardiogram study is considered the ideal noninvasive imaging test and should be performed as soon as possible when the disease is suspected, although if it is normal in the first week, it does not rule out the diagnosis.[16]

Assessing the severity of the disease at baseline is important when choosing treatment. The criteria described below correlate with the risk of developing coronary aneurysms. High-risk patients will be considered those who present at least one of the following criteria:[18]

- Age <12 months.
- Hematocrit <35 % or with progressive decrease since diagnosis.
- Platelets <300 000/mm3.
- Na<133 mmol/l.
- AST >100 IU/l.
- CRP >200mg/l.
- Albumin <35 g/l.
- Neutrophils >80 %.
- Administration of intravenous immunoglobulin after the 10th day of fever.
- Presence of coronary involvement at diagnosis (dilatation or aneurysm, not coronary hyperrefringence).
- Shock or presence of macrophage activation syndrome.

Treatment with intravenous immunoglobulin within the first 10 days of disease onset decreases the incidence of coronary aneurysms from 20 % to 25% to less than 5 %. It is used at high doses (2 g/kg). Aspirin is used for its anti-inflammatory (at high doses: 80-100 mg/kg/day) and antithrombotic (low doses: 3-5 mg/kg/day) effects. Although it has not been shown to reduce the incidence of coronary dilatation, it does seem to reduce the incidence of fatal myocardial infarctions.[4]

In resistant cases, corticosteroids, immunosuppressive drugs such as cyclosporine or biologic drugs such as infliximab or anakinra are usually associated.[15]

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Mortality (0,17 % in the United States) is always related to cardiac sequelae. The most frequent cause of death is myocardial infarction due to aneurysm thrombosis, which usually occurs during the first year of disease.

The long-term cardiovascular risk in patients with KD without coronary aneurysm is unknown; although it seems that it may be a risk factor for the development of early arteriosclerosis in adulthood due to endothelial dysfunction, so the recommendations on cardiovascular risk factors should be generalized to all of them: healthy diet, moderate exercise, adequate weight, blood pressure control and avoidance of tobacco use and exposure.[4]

Behavior of vasculitides in the context of the COVID-19 pandemic

In Italy, on April 24, 2020, an increase of children with symptoms of Kawasaki disease was reported by the Pediatric Society of that country, this pathology presented with somewhat different characteristics due to a resistance to treatment, specifically to intravenous immunoglobulin, in addition it produced systemic inflammatory reaction that forced children to be treated in the intensive care unit. Several tests were performed which confirmed that the patients had SARS-CoV-2 infection or had had contact with persons carrying the virus.[18]

In April 2020, Evelina London Children's Hospital, London, experienced a sudden increase in children with multisystemic hyperinflammatory syndrome. The children had a variety of symptoms, including fever, headache, abdominal pain, rash, and conjunctivitis.[19,20]

During the last week of April 2020, alerts were issued by the Rheumatology Study Group of the Italian Pediatric Society, the Royal College of Pediatrics and Child Health, the UK Pediatric Intensive Care Society and the Spanish Pediatric Association for an increase in cases of incomplete or atypical Kawasaki disease (KD) with increased resistance to intravenous gamma globulin (IVIG), tendency towards macrophage activation syndrome (MAS), hyperinflammatory shock state and need for admission to PICU. In the first weeks of May 2020, similar cases began to be reported in the United States of America (USA), especially in New York, where in a few weeks the number of cases exceeded 200.[21]

D'Antiga observed in Italy a 30-fold increase in the incidence of this Kawasaki-like disease. The children diagnosed showed an immune response to the virus, were older and had a higher incidence of cardiac involvement and findings of macrophage activation syndrome, compared to the historical cohort recorded before the epidemic.[22]

The SARS-CoV-2 epidemic was associated with elevated incidence of a severe form of Kawasaki disease and the same phenomenon is likely to occur in other countries affected by the pandemic.[23] The U.S. Center for Disease Control and Prevention (CDC) issued a modified case definition on May 14 and modified the term to MIS-C.

The U.S. Center for Disease Control and Prevention (CDC) issued a modified case definition on May 14 and changed the term to MIS-C. Finally, WHO defines this new entity as multisystem inflammatory syndrome (SIM/MIS) in children and adolescents with COVID-19. This primary case definition applies to children and adolescents zero to 19 years of age who meet the criteria of fever greater than three days, and two of the following:[20]

- Bilateral nonsuppurative conjunctivitis or signs of mucocutaneous inflammation (mouth, hands, or feet).
- Arterial hypotension or shock.

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- Findings of myocardial, pericardial, valvular dysfunction or coronary abnormalities (including echocardiographic findings or increased troponin.
- Evidence of coagulopathy (by PT, PTT, elevated D-dimer).
- Acute gastrointestinal manifestations (diarrhea, vomiting or abdominal pain).
- Elevation of inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or procalcitonin.
- Absence of other cause of inflammation such as bacterial sepsis, staphylococcal or streptococcal toxic shock syndrome.
- Evidence of COVID-19 (positive antigen test or serology), or probable contact with patients with COVID-19.

The emergence of early reports of MIS-C raised the question of whether it was a neo-disease, a variant presentation of acute COVID-19, or an exacerbated expression in frequency, given the pandemic, of known inflammatory syndromes. The overlap of symptoms with KD can generate diagnostic uncertainty. Thus, different series include it in the report of patients with MIS-C, given that they meet the diagnostic criteria of MIS-C.[21]

This particular syndrome shares some features with other pediatric inflammatory processes: atypical or incomplete Kawasaki disease, toxic shock syndrome (streptococcal and staphylococcal), bacterial sepsis and macrophage activation syndromes; however, it also has some differences that are discussed below. Unlike classic Kawasaki cases, which in 90 % of them occur in children under five years of age, SIM cases are usually schoolchildren or adolescents. It mainly affects people of African-American, Caribbean and Hispanic descent, while KD mainly affects those of Asian-East Asian descent.[20,21]

There is no established treatment for all cases, which may be attributed to the large difference in pharmacological treatment indicated in the reported cases.[17]

More data and studies from different regions are needed to provide information on this disease, as well as appropriate diagnostic techniques to provide the corresponding treatment and subsequent follow-up of affected infants.[18, 22]

Health professionals in charge of providing care to children and adolescents suffering from this disease should be aware of the characteristics of this new condition, especially in countries where the number of infections is higher and there is a possibility that there are more cases of children with multisystemic inflammatory syndrome presumably associated with COVID-19.

A condition still poorly investigated is the probable association of IgA vasculitis-type processes with SARS-CoV-2 infection. This is based on an IgA-mediated humoral immune response exacerbated in COVID-19 cases, predisposing to the deposition of IgA complexes in the vascular endothelium, and thus to the development of a vasculitis associated with this immunoglobulin.[23, 24]

COVID-19 does not represent a major risk for patients with vasculitis, as long as the disease is controlled. The same question arose 10 years ago with the previous influenza pandemic, however, patients with vasculitis were not described as being at increased risk. Currently, there is no information that patients with primary vasculitis or rheumatologic autoimmune diseases are more vulnerable.[25]

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If you develop COVID-19, it is likely that some of your medications may need to be stopped or reduced, while others could be temporarily increased, but this should be discussed personally with your physician. The presence of active, i.e., uncontrolled, vasculitis in conjunction with the development of an infection could pose a risk, in that it represents a double burden.[26,27]

There are few reports of this association, mainly in the pediatric population. Future research should pay special attention to immunologic processes in response to viral triggers.[28]

CONCLUSIONS

Vasculitis are infrequent diseases in childhood. Since ancient times they have been the subject of debate and research, but their pathophysiological mechanisms remain unclear. Patients require a multidisciplinary approach. Early diagnosis and timely treatment prevent complications and ensure that sick children progress favorably. The modifications in the behavior of Kawasaki disease in patients diagnosed with COVID-19, recently reported, have marked the beginning of a new stage of research.

Conflict of interest
The authors declare that there is no conflict of interest.

Authors' contribution
All authors participated in conceptualization, formal analysis, project management, writing - original draft, writing - revision, editing and approval of the final manuscript.

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