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ORIGINAL ARTICLE

Characterization of primary vasculitis in pediatrics

Caracterización de las vasculitis primarias en pediatría

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What do we know about the subject matter of this study?

Pediatric primary vasculitides are a group of diseases characterized by inflammation of the blood vessel wall, with a wide clinical spectrum. Nationally, the studies published describe vasculitis in isolation; therefore, a study that includes them in a global form seems necessary.

What does this study contribute to what is already known?

We present a quantitative, retrospective, and descriptive study that analyzes the incidence and prevalence of pediatric primary vasculitides at the local level, describing their clinical presentation, laboratory parameters, imaging, treatment, and progression.

Abstract

Primary vasculitides are a group of diseases of unknown cause characterized by inflammation of the blood vessel walls. There are few published data at the national level. **Objective:** To determine the incidence and prevalence of primary vasculitis in the Chilean pediatric population and to describe the clinical characteristics, laboratory, treatment, and evolution. **Patients and Method**: Retrospective study that included patients with a diagnosis of primary vasculitis under 16 years of age, treated in a Pediatric Rheumatology clinic of a tertiary hospital in Santiago, Chile, between January 2015 and December 2019. Data was obtained from clinical records and a computer registry. The diagnoses were: IgA vasculitis (Henoch-Schönlein Purpura), Hemorrhagic Edema of Infancy , Kawasaki Disease (KD), Polyarteritis nodosa (PAN), Granulomatosis with polyangiitis (GPA), and Microscopic Polyangiitis (MPA). No cases of eosinophilic granulomatous with polyangiitis or Takayasu's arteritis were found in this sample. The variables analyzed were demographic characteristics, clinical manifestations, laboratory, images, biopsies, treatments, and evolution. **Results**: A total of 134 patients were analyzed. The overall incidence of primary vasculitis was 11 cases, and the prevalence was 21 cases per 100,000 patients under 16 years of age/year. IgA vasculitis accounted for 62.7%, KD for 31.3%, HEI for 2.2%, PAN for 1.5%, GPA for 1.5%, and MPA for 0.8%. Their clinical presentation varied according to the type of vasculitis. **Conclusion**: It is important to make known to the medical community the epidemiological data and clinical characteristics of these pathologies at the hospital and national level since they are not necessarily similar to other populations.

Keywords:
Vasculitis;
Purpura;
Henoch-Schönlein;
Kawasaki Disease;
Polyangiitis

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Introduction

Primary vasculitides are a group of diseases of unknown cause characterized by inflammation of the blood vessel wall that can potentially affect any organ.

The overall estimated incidence of pediatric primary vasculitides is 12 to 53 cases per 100,000 children under 17 years of age per year. The most frequent are Kawasaki disease and IgA vasculitis (formerly called Henoch-Schönlein purpura), and both present as an acute condition, unlike other vasculitides, which have an insidious onset[1,2,7].

The first classification criteria were proposed by the American College of Rheumatology in 1990. Subsequently, in 2005, the Paediatric Rheumatology European Society (PRES), endorsed by the EULAR, proposed the first classification criteria for vasculitis in children, and then they were validated in the 2008 Ankara consensus. Finally, in 2012, modifications were made to the nomenclature[3-6].

The objective of this study is to determine the incidence and prevalence of primary vasculitides in the Chilean pediatric population and to describe the clinical presentation, laboratory parameters, treatment, and progression.

Patients and Method

Quantitative and retrospective study in patients with a diagnosis of primary vasculitis under 16 years of age, seen at the pediatric rheumatology polyclinic of the *Hospital San Juan de Dios*, Santiago, Chile, between January 2015 and December 2019. Data were collected from clinical records and a computerized registry. For the inclusion of patients with a diagnosis of Kawasaki disease, data were also obtained from the referring hospital (*Hospital Felix Bulnes*), since they belong to the same Health Service.

The diagnoses were made by the pediatric rheumatology polyclinic specialist as follows: IgA vasculitis, hemorrhagic edema of infancy (HEI), Kawasaki disease (KD), polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA). No cases of eosinophilic granulomatosis with polyangiitis and Takayasu arteritis were found in this sample.

The variables analyzed were demographic characteristics, clinical manifestations, laboratory parameters, imaging, biopsies, treatments, and progression.

This study was approved by the Ethics Committee of the *Hospital San Juan de Dios*. Exempt Resolution N° 024667.

Results

A total of 134 patients with primary vasculitis were found in 5 years, 67 were female and 67 were male, with a male/female ratio of 1:1. The mean age at diagnosis was 5.8 years (0.3 to 15), with a median of 6 years.

The estimated incidence of total pediatric vasculitis was 11 new cases per 100,000 children per year and the estimated prevalence was 21 cases per 100,000 patients per year under 16 years of age.

The analysis according to the type of vasculitis was IgA vasculitis 84 cases (62.7%), KD 42 cases (31.3%), HEI 3 cases (2.2%), PAN 2 cases (1.5%), GPA 2 cases (1.5%), and MPA 1 case (0.8%) (figure 1).

The incidence according to the type of vasculitis was IgA vasculitis 6.8; KD 3.4; HEI 0.24; PAN 0.16; GPA 0.16; and MPA 0.08, cases per 100,000 children per year.

IgA vasculitis

It accounted for 84 patients (62.7%), of which 46 were female (54.8%) and 38 male (45.2%), with a female/male ratio of 1.2:1. The mean age at diagnosis was 6.9 years, with a median of 6 years (2 to 15 years). The mean delay in diagnosis was 4.8 days (1 to 21 days).

As possible triggers, a history of infection before the onset was found in 37 patients (44% of the total), describing respiratory infection in 32 cases (86.5%; 1 adenophlegmon, 8 pharyngotonsillitis, 19 respiratory viral infections, and 2 acute bronchitis), intestinal infection in 4 patients (10.8%), and skin infection in 1 patient (2.7%). A history of vaccination was not found as a possible triggering factor in this casuistry.

Of the skin manifestations at the onset, purpura was present in 100% of the patients, observing petechiae, erythematous macules, and urticarial lesions. Pruritus was reported in only 4.8 %. The localization observed was 100% in the lower extremities (84 patients) which were associated with lesions in the upper extremities (7 children), trunk (5 children), face (4 children), and genital region (1 child) (figure 2).

Joint involvement (arthritis or arthralgias) was present in 76 cases (90.5%), mainly in the lower extremities.

Gastrointestinal involvement was observed in 56 patients (66.7%), characterized by abdominal pain in 28 cases (50%), vomiting in 13 cases (46%), lower gastrointestinal bleeding in 7 cases (25%), diarrhea in 5 cases (18%), upper gastrointestinal bleeding in 1 case (3.6%), intussusception in 1 case (3.6%), and acute appendicitis in 1 case (3.6%).

Renal involvement was observed in 20 patients (23.8%), manifesting as proteinuria and hematuria in 9 cases (45%), isolated proteinuria in 9 cases (45%), and isolated hematuria in 2 patients (10%). Nephrotic

syndrome was present in 1 case (1.2%) and impure nephrotic syndrome in 2 cases (2.4%). Renal biopsy was required in 3 patients all with class III glomerulonephritis. Regarding the onset of renal involvement, this was present at the beginning of the disease in 13 patients (65%), at 1 month in 4 patients (20%), at 2 months in 2 patients (10%), and at 5 months in 1 patient (5%).

Neurological involvement (headache) occurred in 4 patients (4.8%) and urological (orchitis) in 3 patients (3.6%).

Regarding laboratory parameters, erythrocyte sedimentation rate (ESR) was elevated in 7 patients (8%), ranging from 27 to 102 mm/hr, increased serum IgA levels in 25 of 36 patients (69%), with a range of 162 to 561 mg/l, and elevated anti-streptolysin O antibody levels in 13 of 35 patients (37%).

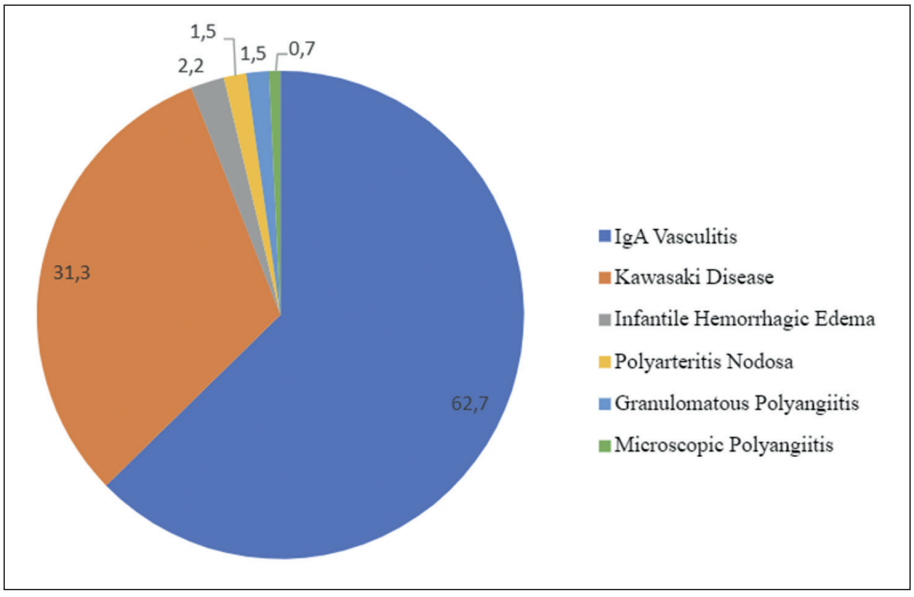


Figure 1. Primary vasculitis.

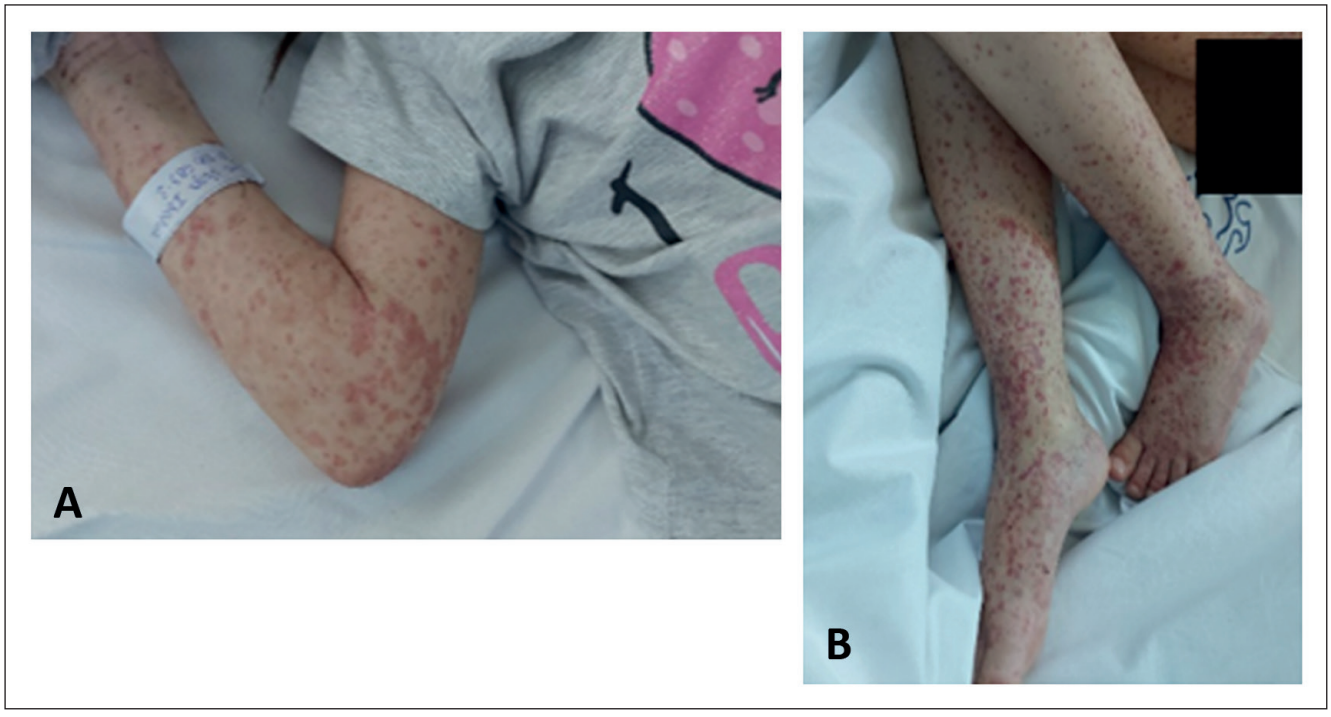


Figure 2. IgA vasculitis. **A:** purpura on upper extremities. **B:** purpura on lower extremities.

Regarding treatment, corticosteroids were prescribed to 45 patients (53.6%). The indication was due to abdominal involvement in 29 cases (64.4%), both abdominal and renal in 8 cases (17.7%), cutaneous in 4 cases (8.8%), articular in 3 cases (6.6%), and cutaneous and articular in 1 case (2.2%). The corticosteroids used were prednisone in 45 cases, intravenous methylprednisolone in 3 cases, and intravenous hydrocortisone in 1 case. Immunosuppressants were used in 1 case (azathioprine) due to skin involvement with frequent relapses.

Kawasaki disease

It accounted for 31.3% (42/134 patients) of the vasculitides. The mean age at diagnosis was 3.4 years (range: 0.3-11), a mode of 1.5, and a median of 3 years. 25 patients were male and 17 were female, with a Male/Female ratio of 1.5:1.

Regarding treatment, all patients received intravenous immunoglobulin. We did not find reliable data on the number of patients who received methylprednisolone. Of 45 patients, only 4 were referred to the pediatric rheumatology polyclinic, while the rest continued follow-up in cardiology or infectious disease.

Hemorrhagic edema of infancy

Of the total vasculitides, it was present in 3 patients (2.2%) aged 0.7, 2, and 2.4 years. All presented purpura located in ears, face, thorax, abdomen, and/or extremities. The 3 cases presented edema located in the auricle and chin, in 2 cases in the hands and feet, and 1 case in the forehead and eyelids. Arthralgia was present in 2 patients and renal involvement in 1 patient, with a protein/creatinine index (PCI) of 1.41 at the onset, which normalized after 6 months of progression. Two patients had a history of upper respiratory infection. Treatment was rest only.

Polyarteritis nodosa

PAN was observed in 2 cases (1.5%), one male and one female. In both cases, the age at the onset was 6 years and the delay in diagnosis was 14 days. The common clinical manifestations were fever, general condition (weight loss, asthenia, decreased appetite), subcutaneous nodules on palms and soles, palpable purpura, arthralgias, hand edema, and polyneuropathy. One of them presented myalgias, testicular pain, hypertension, heart murmur, and abdominal pain (figure 3). A history of upper respiratory infection was found in one patient.

Both children had leukocytosis (19700-23600 ul), anemia (hemoglobin 9.1 and 11.9 g/dL), thrombocytosis (568000/uL), elevated ESR (121-77 mm/hr), elevated C-reactive protein (177-120 mg/l, NV< 5), normal renal function, elevated antistreptolysin O antibodies, and ANCA (-) antibodies.

In the ultrasound, one of the patients presented hepatomegaly. Skin biopsy was required in both children to confirm the diagnosis.

In both patients, the induction treatment was intravenous methylprednisolone (3 pulses) and one required intravenous cyclophosphamide (6 pulses). Maintenance therapy in both patients was prednisone and azathioprine.

The progression during the study period was favorable in one of the cases in which immunosuppressive treatment was suspended. The other patient progressed with severe cutaneous relapses and peripheral polyneuropathy, continuing follow-up in adult rheumatology.

Granulomatosis with polyangiitis

This vasculitis occurred in 2 patients, one male and one female, whose age at diagnosis was 13 and 14 years, and the delay in diagnosis was 21 and 150 days, respectively.

The common clinical manifestation was fatigue. Patient 1 presented at the onset with chronic otitis media, mastoiditis, arthralgias, severe headache, peripheral facial palsy, hearing loss, bilateral non-granulomatous anterior uveitis, and pachymeningitis. Patient 2 presented at the onset with low weight, fever, purulent rhinitis, abdominal pain, septic shock, polyneuropathy with bilateral VI par syndrome (strabismus) and unilateral XII par syndrome (tongue deviation), and right palpebral ptosis secondary to pseudo palpebral abscess.

The laboratory parameters of both patients showed anemia, increased ESR (120-87 mm/hr), and CRP (77 mg/l, NV< 5); in one of the cases, there was leukocytosis and thrombocytosis, and in one there was alteration in renal function (microscopic hematuria and proteinuria in non-nephrotic range with PCI 1.17). Both patients had positive pANCA antibodies by IIF and negative MPO and PR3.

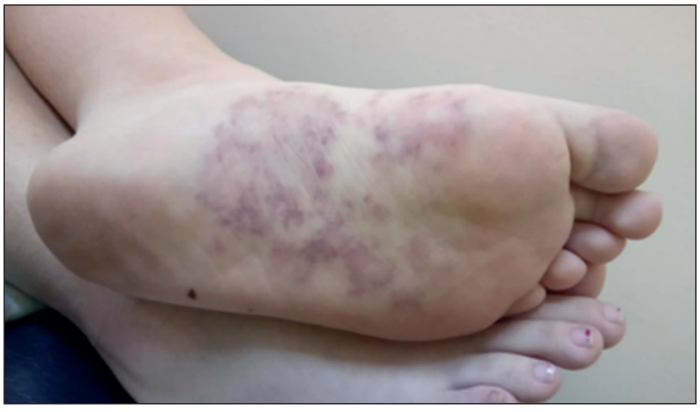


Figure 3. Polyarteritis nodosa.

On imaging, patient 1 showed pleural effusion, hepatomegaly, and intraperitoneal free fluid; brain MRI showed stenosis, infarction, and thrombosis of cavernous sinuses, pansinusitis, and subperiosteal abscess of right orbit. Sinus biopsy showed chronic inflammation and fibrosis compatible with rhinosinusitis and chronic active otitis (figure 4).

In patient 2, peritoneal free fluid was observed and brain MRA showed pachymeningitis. The tympanic cavity biopsy confirmed chronic inflammation and fibrosis compatible with chronic otitis and the meningeal biopsy ruled out infectious and neoplastic causes.

Induction therapy consisted of methylprednisolone (3 pulses) and intravenous cyclophosphamide (6 boluses) in both cases and Rituximab in one case. Maintenance therapy was prednisone associated with azathioprine or methotrexate. Both patients presented good progression and are currently in remission without treatment with follow-up in adult rheumatology.

Microscopic polyangiitis

MPA occurred in one female case. The age at diagnosis was 10 years. The delay in diagnosis was 30 days because the initial clinical manifestations were suggestive of IgA vasculitis such as palpable purpura (bullae), abdominal pain, hematemesis, vomiting, lower extremity edema, arthralgias, and hypertension requiring prednisone therapy (figure 5). Skin biopsy showed small vessel vasculitis without immunofluorescence. Renal biopsy showed proliferative glomerulonephritis type IIIa with direct immunofluorescence for IgG and IgA (-), compatible with micro polyangiitis, therefore ruling out IgA vasculitis.

Laboratory analysis, P and C ANCA antibodies were negative. She received treatment with methylprednisolone pulses and intravenous cyclophosphamide for 3 months and maintenance therapy with azathioprine. Corticosteroids were discontinued after 4 months.

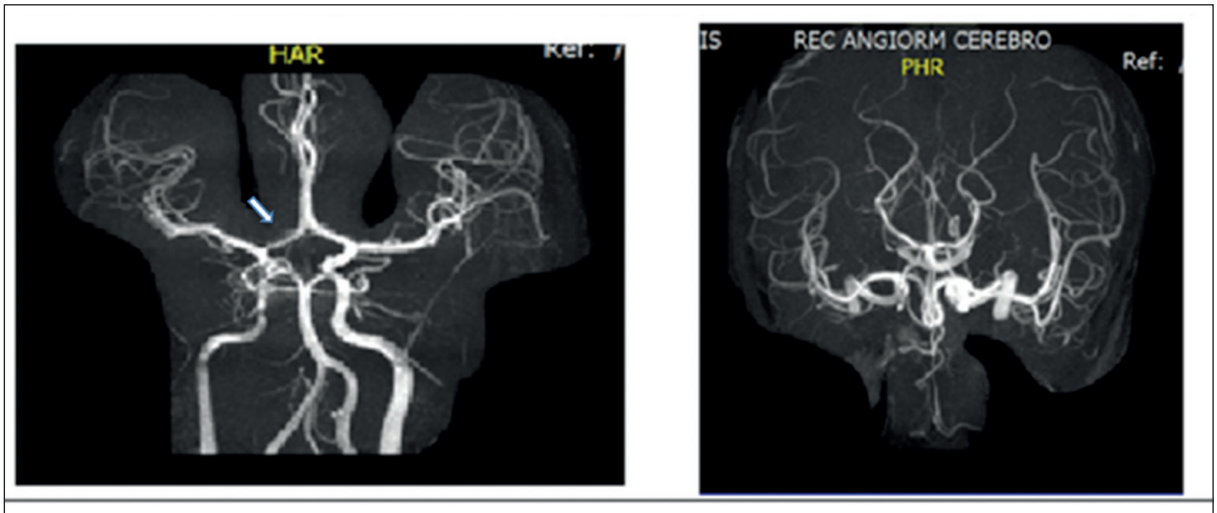
There was no mortality in the total group of patients during the study period.

Discussion

Information about the incidence and prevalence of primary vasculitides in children is limited and we found no national data available on vasculitis globally. In our study, IgA vasculitis was the most prevalent, followed by KD, similar to a Chinese study of 1896 pediatric patients over 14 years that reported a prevalence of 58% for IgA vasculitis, 40% for KD, and 2% for other vasculitis[15].

IgA vasculitis

This occurred more frequently in females (54.8%), similar to a Colombian study with 61% but different from a Turkish study with 48.1%. The mean age of presentation in our cohort was 6.9 years, similar to the Mexican study which was 6 years and somewhat youn-



Stenosis of the right internal carotid artery in the petrous and cavernous segments, associated with a pseudoaneurysm in the cavernous segment measuring 3 mm in length. Partial thrombosis of the right cavernous sinus.

Figure 4. Granulomatosis with polyangiitis.

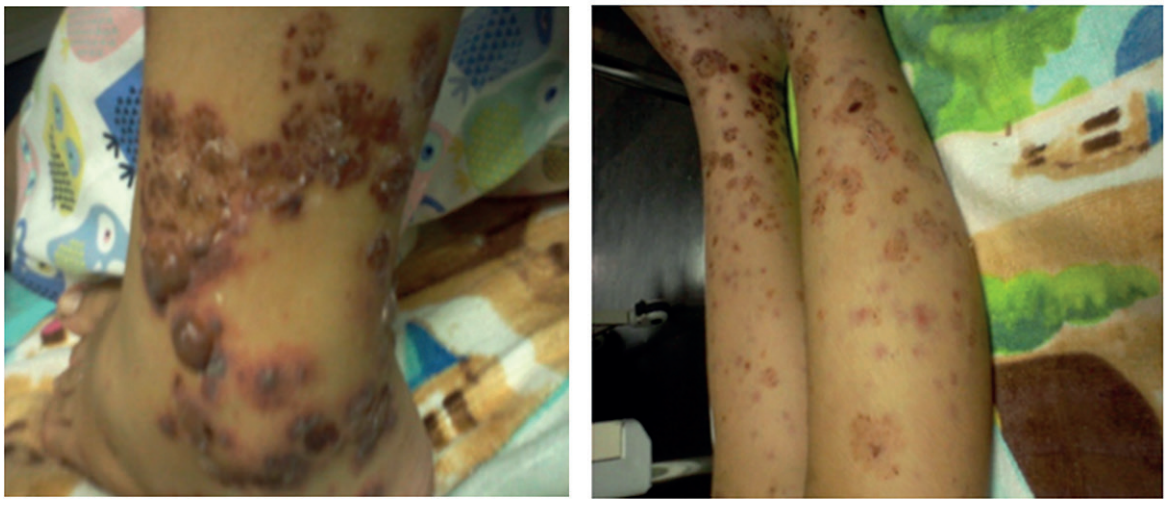


Figure 5. Microscopic polyangiitis.

ger than the Turkish study with 8.1 years[8-10]. Our mean delay in diagnosis was 4.8 days. We did not find other publications with this data. The history of a triggering factor (respiratory infection) was found in 44% of cases, similar to Colombian and Turkish studies, with 31% and 50%, respectively[8,9]. Joint involvement was 90.5%, similar to the Colombian study with 80% and higher than the Turkish study with 55.6%[8,9]. Gastrointestinal involvement was 66.7%, similar to the Chinese study with 74.2% and higher than the Colombian and Turkish studies with 33% and 37%[8,9,11]. Renal involvement in our study was 23.8%, similar to the Turkish and Italian studies with 31.5% and 28%, respectively, and a greater renal involvement was reported in the Chinese study with 54.2%[9,11].

In our follow-up, there were no cases of end-stage renal disease, similar to the Mexican study that reports only 1 case out of 105 patients (0.95%). This suggests that this vasculitis usually has a good renal prognosis[12].

The onset of renal involvement in our study occurred in the first 5 months while in a Turkish study most presented during the first month[9]. The elevation of IgA levels (69%) in our cohort was higher than in the Turkish study (13%) and the elevation of ASO (37%) was similar (33.3%)[9,11]. Renal biopsy in our patients reported type III nephropathy, similar to Turkish and Mexican studies that reported the same nephropathy[9,12]. Corticosteroid treatment in our study was 53.6%, mainly due to abdominal involvement, and in an Italian study, it was 30%, mainly due to renal involvement. The use of immunosuppressants was infrequent[11].

Kawasaki disease

In our study, an incidence of 3.4 new cases/100,000 children under 16 years per year was observed, much lower than in another Chilean registry that included 1,404 patients, with an incidence of 8.4 cases[14]. This difference could be explained by the fact that this registry also included cases from the private healthcare system, where the incidence of KD was higher compared to the public healthcare system. The age at diagnosis in our study was 3.4 years, similar to the Spanish study with 3.3 years and higher than the Chilean registry and the Chinese study with ages 1 and 1.3 years, respectively[14-16]. In relation to sex, males had a higher prevalence in our study (Male/Female 1.5:1), similar to other studies[14,15]. All patients received intravenous immunoglobulin, unlike a Chinese study that reported its use in only 65 of 470 patients (13.8%) with incomplete KD, of which 28 cases (5.9%) required a second cycle of this drug[15]. There was no lethality in our study as in the Chinese study, unlike the Chilean registry with 0.1% lethality[14,15].

Hemorrhagic edema of infancy

In our study, it represented 2.2% of vasculitides and the mean age at the onset was 1.7 years, data similar to a Brazilian series that also reported 3 cases, all younger than 2 years, with purpura and edema as common symptoms[17]. Renal involvement in our study occurred in 1 of 3 cases (33.3%) with resolution at 6 months; it is described in a lower percentage in an Italian series with renal involvement (2.8%) and spontaneous resolution in 3 weeks in most cases, without reporting recurrences[18]. This difference could be explained since our stu-

dy has few cases. The association with an infectious trigger was found in 66% of our patients compared to 100% found in the Brazilian series[17].

Polyarteritis nodosa

In our study, we observed a lower mean age at diagnosis of 6 years than in the Indian study with 15 cases, whose age was 8.6 years, and in the Korean study with 9 cases with an age of 7.7 years. Regarding the delay in diagnosis (14 days), the Korean study reported a longer delay ranging from 30 to 249 days[19,20].

The clinical manifestations of our study are comparable with the Indian study in which 100% of the cases presented prolonged fever, severe myalgias, and skin lesions and 93% presented hypertension, and with a Korean study that reported skin lesions in 100% of the patients, fever in 87.5%, arthralgias in 77.8%, and renal involvement in 11.1%, with hypertension and increased creatinine[19,20]. In relation to the laboratory parameters, data similar to ours are found in the Indian study that reported leukocytosis (66.7%), thrombocytosis (66.6%), and 100% increase in CRP and ESR, and a Korean study that reported leukocytosis (55.6%), thrombocytosis (66.7%), and ESR elevation (100%), CRP (77.8%), and anemia (33.3%)[19,20].

Skin biopsy was performed on all our patients. In the Indian study, skin biopsy was performed in all patients and muscle biopsy in two children, with findings compatible with necrotizing vasculitis. In the Korean study, skin biopsy was performed in 8 of 9 patients, describing compatible findings; these results confirm the importance of biopsy in the diagnosis[6,19,20]. Regarding treatment, in our study as in others, this was adjusted to the severity of organ involvement as, for example, in the Indian study, all patients received corticosteroids and 2 of them received intravenous methylprednisolone. The immunosuppressants used in 10 patients were 7 cyclophosphamide and 3 azathioprine. In the Korean study, all patients received corticosteroids, in mild cases low doses of prednisone, and in severe cases high doses of methylprednisolone, cyclophosphamide, and in some cases Infliximab or intravenous gamma globulin. Maintenance therapy was prednisone associated with azathioprine, methotrexate, or cyclosporine[19,20].

Granulomatosis with Polyangiitis

Our study showed an incidence of 0.16 new cases/100,000 children under 16 years of age per year and a mean age at diagnosis of 13.5 years, with a delay in diagnosis of 2.8 months. An Italian multicenter study reported very similar data with an incidence of 0.1, a mean age of 11.7 years, and a diagnostic delay of 4.2 months. The clinical manifestations are very similar, reporting upper airway involvement (91%), constitutional symptoms (89%), lower airway involvement (79%), and central nervous system (14%)[21].

In our study, two patients had pANCA (+) by IIF, but ANCA (-) by ELISA. In the same Italian study, ANCA (+) by IIF in 82.7%, PR3 (+) by ELISA in 67%, and MPO (+) in 26%. From the above, we could infer that ANCA by IIF would be more sensitive than by ELISA, but both casuistries are small (21). GPA is typically associated with the presence of cANCA by IIF, directed against PR3 in ELISA. However, some patients are ANCA (-), especially those with limited forms of the disease, and it has been described that some patients may be pANCA (+), directed against MPO by ELISA[22].

Biopsies vary according to the organ affected. In our patients, biopsies were performed in the paranasal sinuses, meninges, and tympanic cavity. In another Chilean study of 3 patients, a renal biopsy was performed in one patient and an orbital biopsy in another. In our patients, methylprednisolone and cyclophosphamide pulses were indicated in both and one of them required rituximab. Maintenance therapy was with azathioprine or methotrexate. Both patients had good progress. In another Chilean study, all received intravenous corticosteroids associated with cyclophosphamide, plasmapheresis, and rituximab in two cases. Azathioprine was indicated as maintenance therapy in one case and rituximab associated with mycophenolate or methotrexate in two cases. The progression was favorable in both patients, but one of them presented persistent hypogammaglobulinemia requiring monthly gamma globulin. Treatment in both studies was similar[23].

Microscopic polyangiitis

In our cohort, there was only one case, a 10-year-old female. A Serbian study reported 7 patients (6 females and 1 male), with a mean age of 12 years (7-15 years). The delay in diagnosis in our study was 1 month, shorter than in the Serbian and Chinese studies with 6.7 and 4.5 months, respectively. This could probably be explained by the difficulty of access to the specialist[23,24].

ANCA antibodies in our case were negative. In the Serbian and Chinese series, all patients were pANCA (+). Regarding the anatomopathological study, our patient underwent skin and renal biopsy. In the Serbian and Chinese series, all patients required renal biopsy and in the Chinese series 4 of 10 cases were repeated. Regarding therapy, in the Serbian study, all patients received intravenous methylprednisolone and cyclophosphamide, followed by oral corticosteroid. Four patients presented renal failure and two progressed to end-stage renal disease. In the Chinese study, 90% received intravenous methylprednisolone pulses, 70% mycophenolate, 40% intravenous cyclophosphamide, and 10% leflunomide. There were similarities with our

study. No mortality was reported in the 3 studies described during the study period[24,25].

Of note, ANCA vasculitides include granulomatous polyangiitis, eosinophilic granulomatous polyangiitis, and microscopic polyangiitis. ANCA antibodies are useful for their diagnosis, but their usefulness in assessing disease activity is unclear. However, ANCAs are not always present[26].

In conclusion, pediatric primary vasculitides, despite being a rare pathology, can be potentially fatal, so it is important to differentiate severe forms such as PAN, GPA, and MPA from less severe forms such as IgA vasculitis. Laboratory, imaging, and biopsy are essential elements to confirm the diagnosis. Better knowledge of these conditions will favor early diagnosis and treatment, thus improving the prognosis of these children and adolescents. At the national level, there are few publications about these pathologies, hence the importance of our study.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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