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CLINICAL SERIES

Pediatric ANCA-associated vasculitis, a case series

Vasculitis asociadas a ANCA en pediatría, serie de casos clínicos

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

ANCA-associated vasculitis is a group of infrequent pathologies in children characterized by necrotizing inflammation of small vessels. In Latin America, there are few reports of this type of vasculitis in the pediatric age.

What does this study contribute to what is already known?

We report the first Chilean series of 5 pediatric patients with ANCA-associated vasculitis. In this series, renal involvement in microscopic polyangiitis and orbital involvement in granulomatosis with polyangiitis stand out. All patients had a favorable response to immunosuppressive treatment.

Abstract

ANCA-associated vasculitis (AAV) is an infrequent disease in childhood. International literature about pediatric vasculitis is scarce, and it mainly refers to other systemic vasculitides with a higher incidence in childhood, such as IgA vasculitis and Kawasaki disease. **Objective**: To describe the clinical and laboratory characteristics of a series of pediatric cases with AAV. **Patients and Method:** Retrospective, descriptive study of patients with diagnosis of AAV treated at a tertiary health center from Santiago, Chile, between 2000 and 2020. Electronic medical records were reviewed collecting epidemiological, laboratory, images, and biopsies data. **Results:** There were five cases of pediatric patients with AAV, with varying degrees of severity, and the age range at the onset was 5.5 to 13.5 years. We observed frequent renal involvement in microscopic polyangiitis (MPA) and eye involvement due to orbital pseudotumor in patients with granulomatosis with polyangiitis (GPA), an infrequent manifestation in the international pediatric literature. Patients were treated according to recommendations extrapolated from clinical trials in adult populations, showing excellent clinical response to induction therapy with systemic corticosteroids and cyclophosphamide or rituximab. During maintenance therapy, most of the patients were stable on rituximab, azathioprine, or methotrexate. No patient developed organ damage and all cases achieved discontinuation of the corticosteroid therapy.

Keywords:
Vasculitis;
Granulomatosis with Polyangiitis;
Microscopic Polyangiitis;
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Conclusion: This report describes the clinical characteristics of AAV in a series of pediatric patients. In this series, renal involvement was common in MPA and eye involvement due to orbital pseudotumor in GPA. The clinical response with treatment according to recommendations extrapolated from the adult population was favorable.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis are rare and heterogeneous diseases characterized by necrotizing inflammation of small blood vessels. They include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)[1]. ANCAs may be specifically directed against myeloperoxidase (MPO) or proteinase 3 (PR3) antigens, which are associated with different clinical phenotypes. In adults, GPA is the most frequent subtype, predominantly affecting men between the fourth and fifth decade of life, and is most frequently associated with anti-PR3 ANCA[2]. It is followed in frequency by MPA and EGPA, both generally associated with anti-MPO ANCA[3].

Epidemiological data on ANCA-associated vasculitis (AAV) in the pediatric population is scarce. However, it is estimated that the incidence of these diseases in children is 10-20 cases per million inhabitants per year[3], they predominantly affect the female sex[4], and the average age at diagnosis is 12-14 years[5]. The clinical manifestations of AAV are diverse and can affect several organs with varying degrees of severity. Its etiopathogenesis is unknown and appears to result from a complex interaction between genetic and environmental factors and dysregulation of innate and adaptive immunity[5].

In Latin America, there is little information on pediatric vasculitis[6], and most of the available publications refer to classic systemic vasculitis in childhood, such as IgA vasculitis (Henoch-Schönlein purpura) and Kawasaki disease[6,7]. Existing publications on AAV are mainly case reports[8] or series of predominantly adult patients[9,10]. In Chile, there are no series of pediatric patients with AAV. Therefore, it is crucial to have more clinical information to better characterize and treat pediatric AAV in Latin American patients..

This case series aims to describe the clinical and laboratory characteristics of pediatric patients diagnosed with AAV at the onset of the disease, seen in a tertiary health center. Relevant findings of the imaging and histopathological study and the treatment used to control the disease are highlighted.

Patients and Method

Retrospective and descriptive study of patients evaluated in the UC CHRISTUS Health Network in Santiago, Chile. Electronic records of patients under 18 years of age with a diagnosis of AAV seen by the Pediatric Rheumatology unit between 2000 and 2020 were reviewed. The diagnosis of AAV was made according to compatible clinical findings and the presence of positive ANCA antibodies, either by indirect immunofluorescence assay (IFA) or ELISA, supported by histopathological study if performed. In addition, data were obtained on demographic characteristics, clinical manifestations, laboratory tests, images, biopsies, treatments, and clinical evolution during follow-up.

Results

Five patients diagnosed with ANCA-associated vasculitis were included; four women and one man. The age range at disease onset was 5.5 to 13.5 years. Two cases corresponded to MPA, one to systemic GPA, and two to localized GPA. There were no cases of EGPA. In four of five patients, histopathological studies were performed and supported the diagnosis of AAV. Table 1 summarizes the main characteristics of the patients.

One of the patients with GPA had previous diagnoses of asthma and recurrent sinusitis; the remaining children were previously healthy. The most frequent manifestation at the onset were constitutional symptoms (malaise, fatigue, and loss of appetite). Three patients presented renal involvement at the onset (two with MPA and one with systemic GPA). Renal biopsy was performed in all of them and showed pauci-immune crescentic glomerulonephritis (figures 1 and 2). The three patients with GPA had ocular involvement at the onset of the disease, with ptosis and orbit MRI consistent with inflammatory pseudotumor (figure 3A). Other causes of orbital mass, including IgG4-related disease, were ruled out. One case of MPA had upper and lower respiratory involvement, with bilateral pulmonary nodules. The patient with systemic GPA had extensive lower respiratory involvement, with diffuse ground-glass opacities in lung images and multiple nodules on CT scan (figure 3B and C).

Regarding serology, the presence of ANCA antibodies in serum was confirmed in all patients by IFA (n = 3) or ELISA (n = 4). Both patients with MPA had p-ANCA/ANCA-MPO (+), two patients with GPA had p-ANCA/ANCA-MPO (+), and one patient with localized GPA was ANCA (-) by IFA and ANCA-MPO and PR3 (+) by ELISA. Patients with systemic vasculitis had elevated inflammatory parameters at the onset; in contrast, patients with localized GPA had normal inflammatory parameters.

Regarding initial and induction treatment, all patients received systemic corticosteroids, two patients with renal involvement received intravenous cyclophosphamide (one MPA case and one systemic GPA), and three patients received rituximab (one MPA, and 2 GPA), the latter in doses of 750 mg/m^2 twice, 14 days apart. The patient with systemic GPA had a severe clinical course, with extensive renal and pulmonary involvement, and received plasmapheresis. During the maintenance phase, four of the five patients received rituximab, which effectively maintained remission. One patient with MPA received methotrexate, and the second received azathioprine. The systemic GPA patient was maintained on azathioprine. One patient with localized GPA was maintained on mycophenolate mofetil and the other one on methotrexate.

In the follow-up of patients with localized GPA, patient 5 had a favorable clinical evolution. However, patient 4 evolved with persistent hypogammaglobulinemia after treatment with rituximab, associated with recurrent infections and requiring monthly replacement immunoglobulin until the present day. The patient had normal immunoglobulin levels before starting rituximab and a primary immunodeficiencies genetic panel did not show variants that could explain her clinical manifestations and hypogammaglobulinemia.

Both patients with localized GPA were able to discontinue systemic corticotherapy, with resolution of symptoms secondary to orbital pseudotumor. The case of systemic GPA with renal and pulmonary involvement (Patient 3) also had a satisfactory clinical evolution, with discontinuation of corticosteroids and azathioprine without incident. Both patients with MPA remain in follow-up with intercurrent reactiva-

Table 1. Presenting clinical features and biopsy results of AAV cases

PATIENT	1	2	3	4	5
Age (Years)	5	14	5	7	13
Gender	Female	Female	Female	Female	Male
Type of AAV	MPA	MPA	GPA	Localized GPA	Localized GPA
ANCA IFA*	pANCA 1/80	pANCA >1/80	pANCA 1/40	-	ANCA IFI (-)
ANCA por ELISA**	Anti-MPO 99.4U/mL	-	Anti-MPO 4.58	Anti-MPO 10.14	Anti-PR3 10.9 Anti MPO 9.2
Constitutional symptoms	Yes	Yes	Yes	Yes	Yes
Renal	Yes	Yes	Yes	No	No
Ear, nose and throat	No	Yes	No	No	No
Pulmonary	No	Yes	Yes	No	No
Eyes	No	No	Yes	Yes	Yes
Nervous system	No	No	Yes	No	No
Biopsy	Renal: Pauci immune crescentic necrotizing glomerulonephritis.	Renal: Pauci immune crescentic necrotizing glomerulonephritis	Renal: Pauci immune crescentic glomerulonephritis.	Orbital mass: Necrotizing granulomatous angyitis	No biopsy
Induction treatment	Cyclophosphamide	Rituximab	Cyclophosphamide Plasmapheresis	Rituximab	Rituximab
Maintenance treatment	Rituximab Azathioprine	Rituximab Methotrexate	Azathioprine	Rituximab Mycophenolate	Rituximab Methotrexate

MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; MPO: Myeloperoxidase; ANCA: Antineutrophil cytoplasmatic antibody; PR3: proteinase 3. *Normal values ANCA-IFA: Negative at 1/20 dilution. **Normal values ANCA - ELISA: Anti-MPO: ≤ 9U/mL. Anti-PR3: ≤ 3.5U/mL.

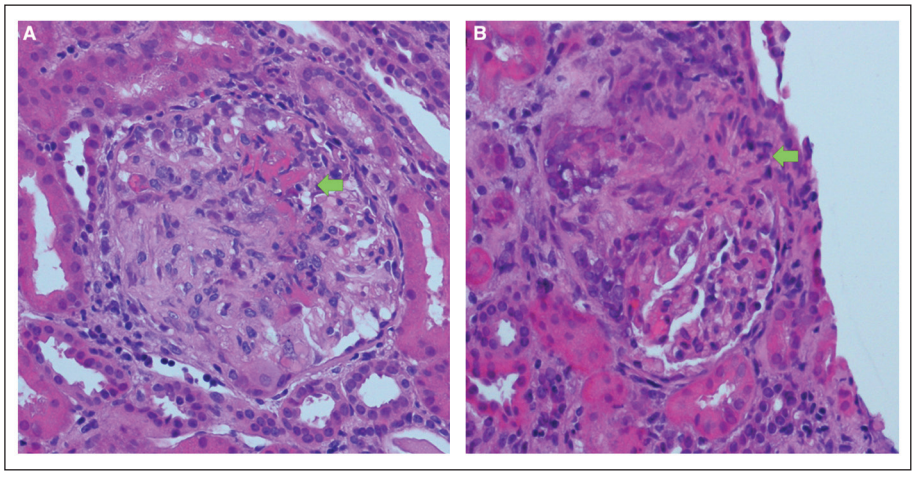

Figure 1. Renal biopsy, light microscopy findings (case 2). **A)** Segmental glomerular necrosis (arrow); **B)** Fibrocellular crescent (arrow). **A, B:** hematoxylin and eosin stain, 400x.

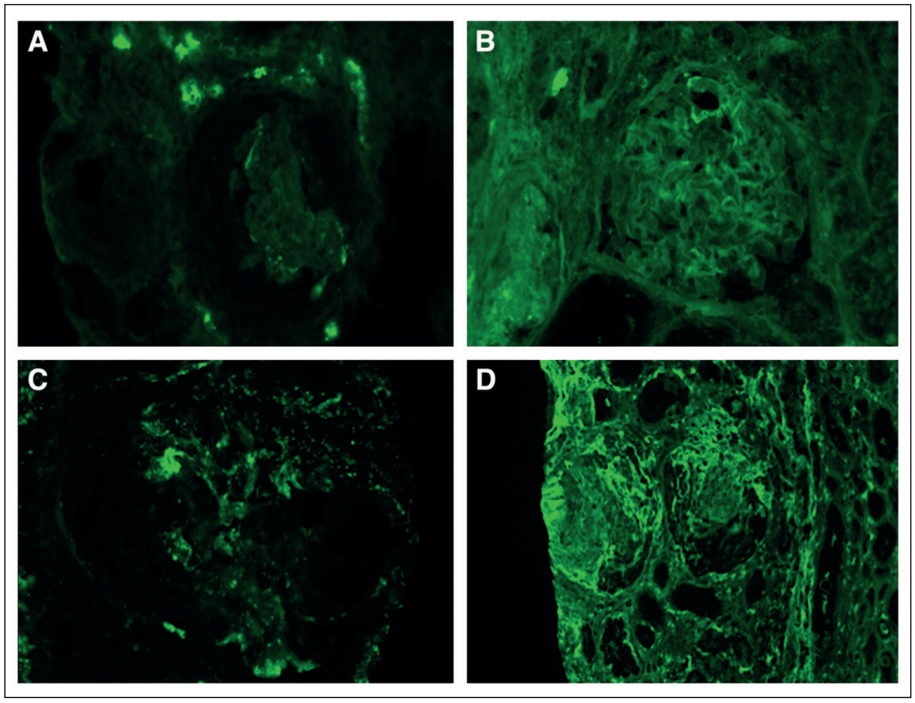

Figure 2. Renal biopsy, immunofluorescence microscopy findings (case 2). Pauci immune reaction pattern: there is no reactivity for IgA **(A)**, IgG **(B)** neither C3 **(C)**. (400x) **(D)** There is granular reactivity for fibrin in two glomeruli, consistent with necrosis (200x). **A-D:** fluorescein isothiocyanate-labeled.

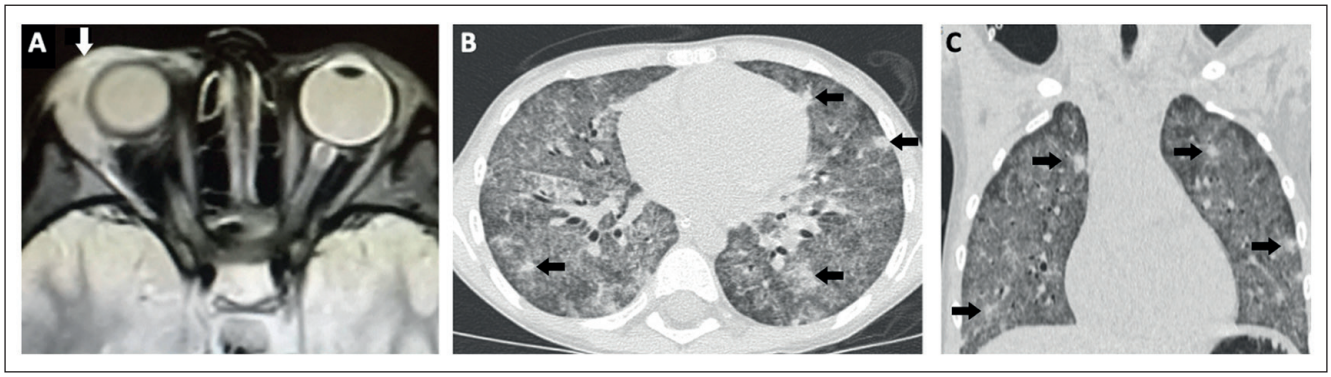

Figure 3. Case 3. **A) Orbital magnetic resonance imaging** (MRI): Extensive infiltrative bilateral orbital process, with predominant involvement of the right orbit, with compromise of the lachrymal glands and superolateral bilateral intraorbital adipose tissue of both orbits. (White arrow). **B y C)** Pulmonary computerized tomography (CT): Diffuse ground glass opacities, multiple diffuse nodules, with some predominantly excavated in the upper lobes (Black arrows)**.**

tions of the disease, both by measurement of antibodies and renal involvement, which have been managed with systemic corticosteroids, antiproteinuric drugs, and rituximab with a favorable response and without requiring renal replacement therapy or further interventions. No patients died in this series.

Discussion

This report shows the clinical and laboratory characteristics of 5 pediatric patients with AAV, a group of pathologies infrequent in this age group[3]. In this series, renal involvement was frequent in MPA, as was ocular involvement by inflammatory pseudotumor in GPA. The diagnosis of AAV is mainly clinical and is supported by laboratory tests. Although there are suggested diagnostic criteria for diagnosing GPA in the pediatric age group, there are no established criteria for MPA or EGPA in this population[11].

The determination of ANCA antibodies is helpful for the diagnosis of AAV. As observed in our series, ANCA evaluated only by IFA may not be enough for diagnosis. If there is a high clinical suspicion, it is recommended to request ANCA antibodies both by IFA and ELISA to increase sensitivity and specificity[12].

The histopathological study is useful, especially in cases of diagnostic difficulty and for the detection and grading of renal damage. The findings of granulomatosis and necrotizing angiitis of small vessels support the diagnosis of GPA or EGPA over other inflammatory diseases[13], such as IgG4-related disease. In cases of MPA, only necrotizing angiitis is observed[13]. In renal tissue, ANCA-associated glomerulonephritis usually manifests with pauci-immune, crescentic, and necrotizing glomerulonephritis, regardless of the type of AAV[14]. The most frequent findings are glomeruli with disruption of the basement membrane, necrosis, and crescents with variable degrees of organization, from cellular to fibrosing. There can also be periglomerular inflammation related to basement membrane alterations, sometimes granulomatous, and tubular damage with atrophy and fibrosis due to erythrocyte elimination. As the name of the pattern indicates, immunofluorescence is usually negative[14]. In some cases, electron microscopy may show immune complex deposits, basement membrane rupture, fibrin, or glomerular crescents[14].

Similar to the international series of pediatric AAV[3], the female sex was predominant (4 of the 5 cases). However, the mean age at onset was lower than that described in other series, usually 11 to 14 years[15,16], possibly due to the small size of this series. Renal involvement caused the most significant morbidity and the need for aggressive pharmacological therapy, as described in other pediatric series[5,17]. Likewise, cases of EGPA in pediatrics are infrequent, and in our series, no patient presented this type of AAV.

It is necessary to highlight the frequency of ocular involvement related to orbital pseudotumors in patients with GPA, where all of them presented with clinical and imaging concordance. Ocular involvement is frequent in GPA and includes diverse manifestations such as conjunctivitis, episcleritis, or retinal involvement[18]. In pediatric series, a frequency of ocular involvement of up to 52% is reported (Akikusa, et al)[19]; however, in the largest multicenter cohort published to date, of 293 pediatric patients with AAV (Cabral et al), 112 patients had some degree of ocular involvement and, of these, only 10 patients (3.41% of the total) had proptosis, pseudotumor, or retrobulbar masses[16]. This contrasts with that described in our series, where all patients with GPA had ocular involvement related to orbital pseudotumors.

Treatment was carried out according to the results of randomized clinical trials (RCTs) of AAV in the adult population[20] and recommendations extrapolated to the pediatric population[11]. In the induction phase, systemic corticosteroids associated with cyclophosphamide or rituximab were used. RCTs have shown that the use of rituximab in the induction phase is equally effective as intravenous cyclophosphamide.. Therefore, both drugs are options to consider in the initial stage of the disease[21]. Rituximab, azathioprine, or methotrexate are usually used in the maintenance phase. RCTs have shown that azathioprine and methotrexate are comparable alternatives in the maintenance stage of AAV[23]. The use of rituximab has even been associated with better maintenance of long-term remission in AAV[21]. Fortunately, all patients evolved favorably, with remission and withdrawal of systemic corticosteroid therapy.

No patient had severe residual renal compromise or need for renal replacement therapy. It is important to monitor immunoglobulin levels before and after using rituximab, given the risk of persistent hypogammaglobulinemia and secondary infections, where it is necessary to consider the use of immunoglobulin replacement therapy[24]. The importance of multidisciplinary management involving pediatric rheumatologists, nephrologists, respiratory diseases specialists, ophthalmologists, and pathologists should also be emphasized, depending on the type of organ involvement affecting the patient.

Finally, it is important to highlight the lack of RCTs of AAV in pediatrics, mainly due to the low prevalence and incidence of this disease in this age group. Recently, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) published a consensus on treatment recommendations in pediatric patients, ba-

sed on RCTs of adult patients with AAV[25]. This consensus represents a promising strategy to better standardize the treatment of AAV in children.

Conclusion

In this series of children with AAV, the frequent renal involvement in MPA and inflammatory pseudotumor-like ocular involvement in GPA stand out. Patients responded well to the indicated pharmacological treatment, extrapolated from adult AAV guidelines. It is necessary to increase the reporting of AAV in pediatric patients in Latin America to define better their demographic and clinical characteristics and response to treatment, and thus optimize the management of this group of patients.

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

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References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1-11.
2. Watts RA, Mahr A, Mohammad AJ, et al. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transpl. 2015;14-22.
3. Jariwala M, Laxer RM. Childhood GPA, EGPA, and MPA. Clin Immunol 2020;211:108325.
4. Grajales CM, Martínez LCM, Garnica RME, et al. Childhood- Versus Adult-Onset Primary Vasculitides: Are They Part of the Same Clinical Spectrum? Pediatr Rheumatol. 2019;15(1):1-11.
5. Jariwala MP, Laxer RM. Primary vasculitis in childhood: GPA and MPA in childhood. Front Pediatr. 2018;6:1-11.
6. Iglesias-Gamarra A, Coral P, Quintana G, et al. Historia de las vasculitis primarias en Latinoamérica. Rev Colomb Reumatol. 2007;14(4):261-86.
7. Ochoa CD, Ramírez F, Quintana G, et al. Epidemiología de las vasculitis primarias en Colombia y su relación con lo informado para Latinoamérica. Rev Colomb Reumatol. 2009;16(3):248-63.
8. Grajales CM, Martínez LCM, Garnica RME. Granulomatosis con poliangitis en pediatría: A propósito de un caso con síndrome pulmón-riñón. Iatreia. 2013;26(2):207-14.
9. Rodrigues CEM, Callado MRM, Nobre CA, et al. Wegener's granulomatosis: Prevalence of the initial clinical manifestations - report of six cases and review of the literature. Rev Bras Reumatol. 2010;50(2):157-64.
10. Córdoba JP, González C, Huérfano M, et al. Síndrome pulmón-riñón: serie de casos del Hospital Universitario San Ignacio. Rev Colomb Reumatol. 2015;22(1):11-5.
11. De Graeff N, Groot N, Brogan P, et al. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides-the SHARE initiative. Rheumatology. 2019;58(4):656-71.
12. Savige J, Dimech W, Fritzler M, et al. Addendum to the International Consensus Statement on Testing and Reporting of Antineutrophil Cytoplasmic Antibodies: Quality Control Guidelines, Comments, and Recommendations for Testing in Other Autoimmune Diseases. Am J Clin Pathol. 2003;120(3):312-8.
13. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. Nat Rev Dis Primers. 2020; 6(1):71.
14. Fogo AB, Lusco MA, Najafian B, et al. AJKD Atlas of Renal Pathology: Pauci-immune Necrotizing Crescentic Glomerulonephritis. Am J Kidney Dis. 2016;68(5):e31-2.
15. Sacri AS, Chambaraud T, Ranchin B, et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: A French nationwide study. Nephrol Dial Transplant. 2015;30:i104-12.
16. Cabral DA, Canter DL, Muscal E, et al. Comparing Presenting Clinical Features in 48 Children With Microscopic Polyangiitis to 183 Children Who Have Granulomatosis With Polyangiitis (Wegener's): An ARChiVe Cohort Study. Arthritis Rheumatol. 2016;68(10):2514-26.
17. Calatroni M, Oliva E, Gianfreda D, et al. ANCA-associated vasculitis in childhood: Recent advances. Ital J Pediatr. 2017;43(1):1-9.
18. Sattui SE, Lally L. Localized Granulomatous with Polyangiitis (GPA): Varied Clinical Presentations and Update on Treatment. Curr Allergy Asthma Rep. 2020;20(10):56.
19. Akikusa JD, Schneider R, Harvey EA, et al. Clinical features and outcome of pediatric Wegener's granulomatosis. Arthritis Care Res. 2007;57(5):837-44.
20. Lee JJY, Alsaleem A, Chiang GPK, et al. Hallmark trials in ANCA-associated

vasculitis (AAV) for the pediatric rheumatologist. Pediatr Rheumatol. 2019;17(1):1-15.
21. Specks U, Merkel PA, Seo P, et al. Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis. N Engl J Med. 2013;369(5):417-27.
22. Akamine K, Punaro M. Biologics for childhood systemic vasculitis. Pediatr Nephrol. 2019;34(11):2295-309.
23. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis. N Engl J Med. 2008;359(26):2790-803.
24. Tieu J, Smith R, Basu N, et al. Rituximab for maintenance of remission in ANCA-associated vasculitis: Expert consensus guidelines. Rheumatol (United Kingdom). 2020;59(4):e24-32.
25. Morishita K, Wagner-Weiner L, James K, et al. Consensus Treatment Plans for Severe Pediatric Antineutrophil Cytoplasmic Antibody- Associated Vasculitis. Arthritis Care Res (Hoboken). 2021;0-2.