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REVIEW

Switching of a country wide project to a global study 'IgG4-related disease, pediatric perspective'

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ABSTRACT

IgG4-related disease (IgG4-RD) is a multisystem fibroinflammatory disorder. It has the potential to affect almost any organ, resulting in highly varied clinical presentations.

Unlike adults, who often exhibit multiple organ involvement over time, pediatric patients tend to present with localized disease, frequently affecting the orbits. Diagnosing IgG4-RD can be challenging due to its non-specific clinical manifestations and varied organ involvement. Laboratory investigations, histopathological examinations, and radiological assessments provide important information for making the diagnosis. However, the differential is important ruling out conditions such as malignancies, infections, ANCA-associated vasculitis, and sarcoidosis. Laboratory tests, histopathological findings, and radiological evaluations can help to confirm the diagnosis. As for treatment, glucocorticoids (GCs) remain the mainstay of first-line treatment either alone or in combination with immunosuppressants. Nevertheless, recurrence or relapses represent a major problem in the follow-up. The development of multicenter collaborative projects could provide important insights into the diagnosis, treatment, and long-term outcomes of pediatric patients.

Keywords: IgG4-related disease, children, multicenter study.

INTRODUCTION

IgG4-related disease (IgG4-RD) is a fibroinflammatory disease that typically affects middle-aged adults and is uncommon in children. In 2019, its incidence and prevalence were 1.39/100 000 person-years and 5.3/100 000, respectively, in an adult population-based analysis in the United States [1]. However, we lack data on the epidemiology of disease in childhood. Its rarity in childhood, together with limited awareness, contributes to under-recognition of the disease.

The clinical presentation is highly variable and may involve either a single organ or present as a multisystem disorder. The organs that are most commonly affected include the pancreas, kidneys, orbita, lacrimal and salivary glands, lungs, pleura, and peritoneum [2-4]. A diagnosis may be difficult to establish because of the nonspecific nature of the symptoms. Laboratory tests, histopathological findings, and radiological evaluation can help to reach a diagnosis. The histopathological features include lymphoplasmacytic infiltration, predominantly composed of IgG4-positive plasma cells, accompanied by fibrosis displaying a characteristic storiform pattern. A ratio of IgG4-positive plasma cells to IgG-positive cells greater than 40% and more than 10 IgG4-positive plasma cells per high-power field also supports the histopathological diagnosis of IgG4-RD [5].

It is important to exclude clinical mimickers of IgG4-RD, including malignancies, infections, ANCA-associated vasculitis, and sarcoidosis. These challenges emphasize the importance of a multidisciplinary diagnostic approach. Early diagnosis and treatment are crucial to preventing fibrosis.

Clinical features

IgG4-RD can affect almost any organ, leading to a heterogeneous clinical presentation. Although the disease can involve multiple organs, a review of the literature indicates that certain organs are more frequently affected. The first literature review of 25 pediatric IgG4-RD patients in 2016 revealed that IgG4-related orbital disease is the most common presentation (44%), following by IgG4-related pancreatitis (12%), IgG4-related cholangitis (8%), and IgG4-related pulmonary disease (8%) [6]. In a literature review of pediatric IgG4-RD patients up to January 2024, a total of 117 cases were reported, and 105 were included in the final analysis. Also, orbital involvement was the most commonly reported organ involvement, observed in 40% of patients, while constitutional symptoms were present in 52% of cases. Moreover, 68% of the patients were reported to present with localized disease [2]. Another data from French group including patients aged 9 to 25 years revealed the involvement of the organs in decreasing frequency; lymph nodes (59%), orbita (49%), salivary glands (31%), kidneys (31%), lacrimal glands (27%), pancreas (22%), liver and biliary tract (13%), lungs (13%), uveitis (13%), and mastoid (13%).

In our data of 35 pediatric IgG4-RD patients, we observed that the most common organ involvement was the eye (60%), followed by lymph nodes (34.3%), musculoskeletal system (34.3%), and neurological system (25.7%). In childhood, orbita seems to be the most commonly affected organ, which tends to be unilateral and affects the extraocular muscles and orbital soft tissues [7,8].

Diagnosis

Since there is no specific diagnostic criteria for pediatric IgG4-RD, the diagnosis is based on the adult revised comprehensive diagnostic (RCD) criteria [5,9]. These criteria consist of three components: a) clinical and radiological findings of organ involvement showing diffuse or localized swelling, mass, or nodular lesions, b) elevated serum levels of IgG4, and c) histopathological findings consistent with IgG4-RD [5]. According to these criteria, the presence of all three components is required for a definitive diagnosis. A diagnosis is considered *possible* when criteria (a) and (b) are met, and *probable* when criteria (a) and (c) are fulfilled.

Elevated levels of serum IgG4 are reported in 37.5-70% of cases in childhood [10-12]. Increased concentrations of serum IgG4 can also be observed in conditions such as infections, malignancies, bronchiectasis, and gastrointestinal system disease, resulting in a low positive predictive value for diagnostic purposes [13,14]. Additional common findings especially in adult cases include elevated IgG and IgE levels, peripheral eosinophilia, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), positivity for antinuclear antibodies (ANAs) and rheumatoid factor (RF), and reduced complement levels [15]. However, there are no diagnostic laboratory findings specific to the disease.

Subsequently, the 2019 ACR/EULAR classification criteria were published, which include exclusion criteria of clinical, serologic, radiologic, and pathologic items [16]. Its sensitivity and specificity were assessed in two independent validation cohorts, with reported sensitivities of 85.5% and 82.0%, and specificities of 99.2% and 97.8%, respectively [16]. Moreover, the 2020 RCD criteria were found to be more sensitive for identifying patients with IgG4-RD, while the 2019 ACR/EULAR criteria offered greater specificity, according to a study by Kogami et al. that compared the performance of these two criteria sets [17]. Although there is limited data on the performance of the 2019 ACR/EULAR criteria in pediatric IgG4-RD, approximately 20% of patients fulfilled the ACR/EULAR classification criteria [8]; this is due to the tendency to localised involvement of the disease in childhood. Moreover, patients with normal serum IgG4 levels tended to be younger and were more likely to present with involvement of fewer than three organs than those with elevated serum IgG4 levels [18]. This also leads to difficulty in diagnosis in childhood.

Differences between pediatric and adult forms of IgG4-RD

Pediatric IgG4-RD shares features of adult IgG4-RD but also shows many different characteristics in terms of clinical manifestations, diagnosis, and outcome. Patients with childhood-onset IgG4-RD were more likely to have constitutional symptoms, while systemic constitutional symptoms are more frequently observed in children [6,12,19]. Compared with adult IgG4-RD patients, juvenile cases with IgG4-RD were more frequently female, more likely to present with fever at diagnosis, exhibited involvement of fewer organs, and required second-line treatments more often (all $p < 0.05$) [10]. The patterns of involvement of the same organ may also vary between the two groups. For example, orbital involvement characteristically presents bilaterally with eyelid swelling and exhibits extraorbital involvement in at least 70% of adult cases. On the other hand, it typically presents with unilateral orbital swelling, with bilateral disease reported in only 15% and extraorbital disease in 20% [20]. Age-group-specific disease characteristics were assessed in one of the largest prospective studies of 737 IgG4-RD patients. In the pediatric group, male predominance was noted, and the majority of patients (70%) presented with Mikulicz's disease differently from adults. Additionally, compared to adults, a significantly smaller percentage of pediatric patients (70% vs. 92.6%, $p=0.036$) had elevated serum IgG4 [11]. As for outcome, recurrence is a serious concern with reported rates ranging from 24% to 63% in the evaluation of the six largest adult cohorts and up to 57% in pediatric patients [6,21].

Treatments

Given that children may have a longer disease duration and that the effects of fibrosis can be more severe, early treatment is essential to prevent organ damage. Current treatment approaches mainly rely on immunosuppressive drugs for both induction and maintenance of remission. Nevertheless, in some selected cases, such as IgG4-related lymphadenopathy, which is commonly asymptomatic and has been documented to persist over several decades, a watchful waiting approach may represent a management option [22,23].

Glucocorticoids (GCs) are widely used as the first-line treatment alone or in combination with immunosuppressants [24]. In a systematic review, 92 percent of the cases were reported to be treated with glucocorticoids at a dose of 0.5–2 mg/kg/day [6]. Clinical improvement typically occurs rapidly, though the rate of response may vary depending on the organs involved and the extent of fibrosis [25]. However, relapses or recurrence are common, especially during the tapering or discontinuation of glucocorticoids. Also, there is a considerable risk of toxicity with prolonged glucocorticoid exposure. Second-line treatments such as mycophenolate mofetil, azathioprine, methotrexate, rituximab, and cyclophosphamide were used as glucocorticoid-sparing agents or remission-maintenance drugs in patients as therapeutic options [26-29]. However, there are no clinical trials on their efficacy.

Relapse is a significant and common challenge in the management of IgG4-RD. In our multicenter registry in Turkey, relapse occurred in 31.4% of patients and was more frequent among those with systemic involvement [30]. A review of pediatric cases with ocular IgG4-RD also showed that 72.8% of patients relapsed or did not respond to initial treatment, necessitating treatment modification [7].

Project process: A step-by-step overview

There is a lack of knowledge on childhood IgG4-RD disease, and most of the current understanding is extrapolated from adult cohorts and case reports of pediatric cases. In this context, to contribute to the literature, we first published our single-center experience with eight pediatric IgG4-RD patients in 2022 [12]. Patients with a definite, probable, or possible diagnosis of IgG4-RD were included in this retrospective study. We showed that the disease mainly presents with orbital manifestations in the pediatric population but has wide phenotypic clinical variability. Subsequently, we established a registry through Turkey, and data of IgG4-RD patients in 13 pediatric rheumatology centers were recorded to a web-based registration system. Patient demographics and clinical and laboratory findings related to the diseases were recorded in the TRVaS (Turkish Vasculitis Study Group Longitudinal Database) system, which is a database aimed to prospectively and multicenter record patients diagnosed with vasculitis across Turkey.

A total of 35 pediatric patients were recorded, and we reported the clinical manifestations of disease in childhood and evaluated the sensitivities of the

2019 ACR/EULAR classification criteria and the 2020 RCD criteria in this group. We presented our findings at the Pediatric Rheumatology European Society (PReS) Congress in 2024, where our presentation was selected as the second-best oral communication. The study was also published in the Rheumatology journal (doi: 10.1093/rheumatology/keae497) [30]. Subsequently, we aimed to evaluate the clinical features of pediatric Ig4-RD patients across different ethnicities and countries, and to describe the clinical course, laboratory features, and outcomes in a multicenter international cohort. It also enables us to address the full spectrum of clinical manifestations of pediatric IgG4-RD in different geographic areas. The project proposal was also presented at the Vasculitis Working Party during the PReS 2024 congress in order to reach more pediatric rheumatology centers. The project is currently ongoing.

CONCLUSION

While IgG4-RD in children most often presents with orbital manifestations, its clinical spectrum remains highly variable. Despite the rarity of the disease in childhood, knowledge and awareness of the disease are essential to facilitate diagnosis and avoid delays in treatment. Developing multicentre and large-scale projects is highly valuable for improving understanding and optimising disease management in children.

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