# IGG4-RELATED DISEASE: A SYSTEMATIC REVIEW OF A RARE PEDIATRIC CONDITION

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*Immunoglobulin G4 related disease (IgG4-RD) is an immune-mediated fibroinflammatory disorder, marked by tumor-like mass-forming lesions. IgG4-RD is a recently recognized condition and has a few conducted research on the pediatric population. This study aims to provide some insights into the epidemiology, histological findings, diagnosis, and treatment of this condition in children. A systematic literature search was performed on Embase, PubMed, and Web-of-science for case reports and case series of IgG4-RD in children published between 1/2015 and 12/2023. 58 case reports and case series including 62 cases of IgG4-RD in children were identified. The mean age was 12 ± 4.4 years old, of which 54.8% were male. The orbit and central nervous system were two organs predominantly affected. Multi-organ involvement was reported in 14 cases (22.6%). Of 53 patients with serum IgG4 concentration reported, 60.4% of them had elevated serum IgG4 level. 21 patients (33.8%) had fulfilled the definitive diagnosis of the 2020 revised comprehensive diagnostic criteria. Prednisone was the first choice of treatment in 81.8% of the cases. 77.6% of the patients were treated with steroid-sparing DMARDs.*

**Keywords: IgG4 related disease, pediatric, systematic review.**

## I. INTRODUCTION

Immunoglobulin G4 related disease (IgG4-RD) is an immune-mediated fibroinflammatory disorder, marked by tumor-like mass-forming lesions.[1,2] This condition presents three major features: (i) elevated levels of IgG4 in the bloodstream; (ii) infiltration of IgG4+ plasma cells into affected tissue regions; and (iii) good response to corticosteroid therapy.[3,4]

Acute, severe, or highly inflammatory clinical presentations are atypical in IgG4-RD. Patients may experience subtle symptoms or signs of the disease for extended periods before seeking medical attention, or they may have symptoms that go unrecognized by healthcare providers for significant durations.[3] IgG4-RD can affect numerous organs, with manifestations observed in nearly all organ systems.[5]

Despite increased serum IgG4 level and tissue IgG4+plasma cells, which are characteristic of IgG4-RD, aberrant T cell activity is considered the primary immune dysfuction in IgG4-RD.[2] The progression of IgG4-RD follows 2 phases: the “inflammatory phase” that eventually leads to a “fibrotic” state.[6]

IgG4-RD is a rare and recently recognized condition of which the diagnosis is often delayed, the disease is still misdiagnosed as neoplastic, inflammatory, and infectious conditions.[7] When untreated, the disease can lead to irreversible organ damage because of the fibrosis. Therefore, early recognition and therapy is critical.[8,9]

Additionally, there is a scarcity of systematic reviews on pediatric IgG4-RD in the literature. Therefore, we conducted a systematic review of case reports published between 2015 and

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2023 to analyse the characteristics of pediatric IgG4-RD comprehensively; moreover, in Vietnam, only one pediatric case has been reported to date. For this reason, we have decided to conduct this study in order to provide pediatricians with an overview of the disease and insights into the epidemiology, histological findings, diagnosis, and treatment of this condition in children

## II. OVERVIEWS

### 1. Materials and methods

The research was performed and reported in accordance with the PRISMA statement for systematic reviews.

***Data source***

Case reports and case series of IgG4-RD were retrieved from Embase, PubMed, and Web-of-science with a publish date between 1/1/2015 and 21/12/2023. Only articles reported in English were included. See the Appendix for full search strategies for each database.

***Study selection and data extraction***

After extracting duplicates, all titles and abstracts went under screening using the following *inclusion criteria*:

(1) Case report or case series of IgG4-RD.

(2) Patient age < 18 years of age.

(3) Articles in English.

*Exclusion criteria included*

(1) Study with data not reliably extracted, duplicate or overlapping data

(2) Abstract-only papers as preceding papers, conference, editorial, and author response theses and books, and

(3) Articles without available full text.

Methodologic quality was graded using Critical Appraisal Tools (JBI) checklist for case reports and case series, and full-text assessment, final selection followed by data extraction was done by two authors independently.

*Data variations*

- Age (year).
- Gender (male/female).
- Clinical manifestation (organ).
- Multiple organ involvement: ≥ 2 affected organs.
- Serum IgG4: mg/dL (normal range: < 135 mg/dL).
- Diagnosis criteria: The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD.[10]

+ [Item 1] Clinical and radiological features:

• One or more organs show diffuse or localized swelling or a mass or nodule characteristic of IgG4-RD.

• In single-organ involvement, lymph node swelling is omitted.

+ [Item 2] Serological diagnosis:

• Serum IgG4 levels greater than 135 mg/dl.

+ [Item 3] Pathological diagnosis: positivity for two of the following three criteria:

• Dense lymphocyte and plasma cell infiltration with fibrosis.

• Ratio of IgG4-positive plasma cells/IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high powered field

• Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis

→ Diagnosis: Definite: 1) + 2) + 3); Probable: 1) + 3); Possible: 1) + 2).

- Patients' response[11]

+ No response: no improvement or worsening of the disease.

+ Partial response: improvement of the disease, but not complete remission was required.

+ Good response was defined as complete remission or stable without treatment.

+ Relapse: No/Yes.

## 2. Results

Out of 527 articles identified from the mentioned databases, 64 were eligible for full-text assessment, resulting in 58 studies included in this review. 2 articles reported multiple cases (3 and 2 respectively), leading to a total of 62 IGG4-RD pediatric patients.

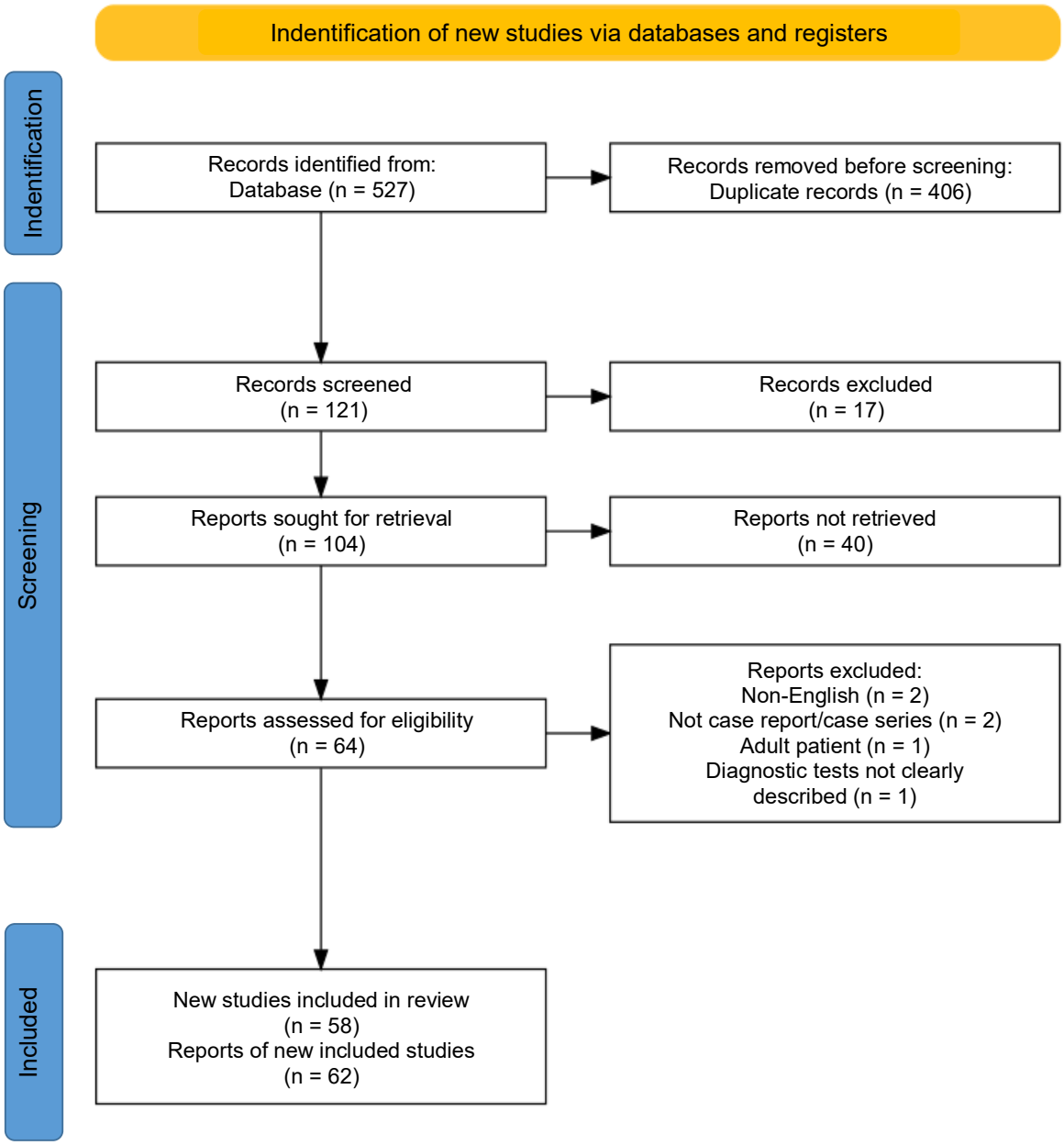


**Figure1. Search strategy and selection of the articles**

***Patient***

62 patients under 18 years of age were identified between 1/1/2015 and 23/12/2023, of which 54.8% were male (n = 34) and 43.6% were female (n = 28) (1 unspecified case). The average age was 12 ± 4.4 years, ranging from 1 to 17 years old.

**Table 1. Outcome reported in case reports and case series of IgG4-RD in children**

| No | Reference | Age | Sex | Organ manifestation | Serum IgG4 (mg/dl) | Therapy | Comments |
|---|---|---|---|---|---|---|---|
| 1 | Goag 2015[12] | 16 | M | Lymph node and lung | EI (1650) | Pred 1 mg/kg, Aza, surgery | Good clinical result |
| 2 | Gabrovska 2021[13] | 17 | F | Tracheal | EI (825) | Pred | Maintenance dose of 8mg daily, developed iatrogenic Cushing after 2 years |
| 3 | Özdel 2020[14] | 14 | F | Biceps muscle | EI (606) | Pred 2 mg/kg/d, MMF 1200 mg/m$^2$/d, RTX | Good clinical result |
| 4 | Galloway 2016[15] | 8 | F | Pancreas | EI (320) | Pred 0.7 mg/kg/d | Good clinical result |
| 5 | Bolia 2016[16] | 14 | M | Pancreas, bile duct system | EI (370) | Ursodeoxycholic acid, steroid, AZA | Refused initial treatment of corticoid -> colitis after 6 months. Frequent relapses -> AZA |
| 6 | Bolia 2016[16] | 11 | F | Pancreas, bile duct system | EI (616) | Steroid, AZA, tacrolimus, infliximab, MTX | Initial response with steroids but not sustained -> changed into AZA -> Bowel symptoms: tacrolimus, infliximab and MTX |
| 7 | Bolia 2016[16] | 7 | M | Pancreas, bile duct system | N (109) | Steroids, ursodeoxycholic acid, AZA | Good clinical results. |
| 8 | Choi 2021[17] | 17 | M | Pancreas | NM | Pred 37.5 mg/d, infliximab, surgery | Good clinical result |
| 9 | Qing 2022[18] | 14 | F | The lacrimal glands, the brain parenchyma spinal cord, and the lymph nodes | EI (345) | Pred, CsA, IVIG, MP, IFN-B, | Good clinical result |

| No | Reference | Age | Sex | Organ manifestation | Serum IgG4 (mg/dl) | Therapy | Comments |
|---|---|---|---|---|---|---|---|
| 10 | Pal 2020[19] | 16 | M | Craniopharyngioma involves the pituitary and dura mater | N (101) | Surgery, levothyroxine, hydrocortisone, testosterone, and desmopressin | No residula tumor issue but vision had not regained. |
| 11 | Chen 2018[20] | 9 | M | Lymph nodes | EI (142) | Pred 0.6 mg/kg/d | Good clinical result. |
| 12 | Qi 2022[21] | 8 | F | Orbits | EI (461) | Pred, RTX 375 mg/m$^2$ x 4w | Good clinical result |
| 13 | Mohammadzadeh 2023[22] | 15 | F | Coronary artery and orbits | - | Aspirin 100 mg/d, Rosuvastatin 5 mg/d, Bisoprolol 0.625 mg/d, Cellcept 1500 mg/d, adalimumab 40mg every 2w | Good clinical result |
| 14 | Emirog˘ lu 2023[23] | 7 | G | Pancreas, bile duct system, lung | EI (6950) | Pred, AZA | Partial remission and has no pseudomembranes. |
| 15 | Akkelle 2020[24] | 7 | G | Pancreas, bile duct system, lacrimal gland | N (177) | MethylPred 1.5 mg/kg/ day, oral mesalazine 60 mg/kg/day | Good clinical result |
| 16 | Saad 2023[25] | 13 | F | Pericardium and lung | EI (168) | Pred 0.6 mg/d, AZA 2.5 mg/kg, MMF, RTX 500mg/w x 4w | Passed away |
| 17 | Wu 2017[26] | 17 | F | Parasailer tumor | EI (511) | Methyl pred 500 mg/d x 3d, RTX 500mg every 2 weeks x 2 doses, CsA 500mg every month x 3 doses | Good clinical result |

| No | Reference | Age | Sex | Organ manifestation | Serum IgG4 (mg/dl) | Therapy | Comments |
|---|---|---|---|---|---|---|---|
| 18 | Timeus 2021[27] | 6 | ? | Parotid gland | N (49.3) | Ceftriaxone, surgery, Pred | Good clinical result |
| 19 | Miglani 2010[28] | 13 | M | Pancreas | EI (603) | Pred 20 mg/d | Good clinical result |
| 20 | Demir 2021[29] | 16 | F | Pancreas, parotid gland | EI (534) | MethylPred (20 mg/kg) x 5d, cyclophosphamide 500 mg/m$^2$/dose) monthly pulse x 6mo, RTX 375 mg/m$^2$/w x 4w | Good clinical result |
| 21 | Ferreira da Silva 2016[30] | 16 | M | Sialadenitis | EI (1050) | Pred 40 mg/d x 2w | Good clinical result |
| 22 | Kato 2023[31] | 12 | F | Duodenal | EI (214) | Surgery | Good clinical result |
| 23 | Tong 2021[32] | 1 | M | Orbits | EI (205) | Pred 1 mg/kg/d x 3w, Aza, trimethoprim, MMF | Maintenance of on low dose prednisone and mycophenolate with good clinical result |
| 24 | Ewing and Hammer 2016[33] | 13 | F | Lymph nodes | EI (178) | Not mentioned | |
| 25 | Creze 2020[34] | 16 | M | Thigh muscle | EI (246) | Surgery | Good clinical result |
| 26 | Arya 2021[35] | 11 | F | CNS (pituitary) | NM | Pred, MMF, hydrocortisone | Good clinical result with maintenance dose of MMF |
| 27 | Ulas 2023[36] | 4 | F | Orbits | N(L U) | 8.8 mg pred/d x 7d IV -> 10 mg pred/d x 3mo oral | Good clinical result |
| 28 | Shakeri 2019[37] | 16 | F | Subcutaneous tissue | EI (231) | Not mentioned | |
| 29 | Rosen 2015[38] | 17 | M | Bile duct system | EI (242) | Pred 30 mg daily (0.5 mg/kg/d) | Good clinical result |

| No | Reference | Age | Sex | Organ manifestation | Serum IgG4 (mg/dl) | Therapy | Comments |
|---|---|---|---|---|---|---|---|
| 30 | Nastri 2018[39] | 7 | M | Orbits | NM | pred (1.0 mg/kg/day), cyclosporine (5.0 mg/kg/day), MMF (2 g/day) | |
| 31 | Hsu 2021[40] | 3 | M | Bile duct system | EI (220) | Pred 1 mg/kg/day, Aza 0.5 mg/kg/d Mesalamine 50 mg/kg/d, Ursodeoxycholic 10 mg/kg/d | Good clinical result |
| 32 | Bienfait 2018[41] | 9 | F | Oesophagus | NM | Surgery | Good clinical result |
| 33 | Savino 2017[42] | 10 | M | Orbit | N(L U) | MethylPred, Pred, MTX | Good clinical result |
| 34 | Kimura 2021[43] | 12 | M | CNS (pituitary hypertrophy) | EI (147) | Desmopressin | Good clinical result |
| 35 | Raab 2018[44] | 3 | M | Lacrimal gland, Orbits | NM | No treatment | Lost to follow up |
| 36 | Nambirajan 2019[45] | 16 | M | CNS | N (128) | Surgery | Good clinical result |
| 37 | Smerla 2018[46] | 4 | M | Lacrimal gland Orbits | EI (222) | Pred 0.5 mg/kg/d | Good clinical result |
| 38 | Tille 2020[47] | 16 | F | Orbits, intestine | EI (360) | Pred, MTX | Lost to follow up in 3 months |
| 39 | Jordan 2018[48] | | F | Larynx | NM | Steroid therapy (dosage unknown), RTX | Good clinical result |
| 40 | Menon 2020[49] | 14 | M | Liver and bile duct system | N (L U) | Steroid therapy, Aza 25 mg/d | Good clinical result |
| 41 | AbdullGaffar 2021[50] | 16 | M | Lung | EI (1096) | Steroid therapy, dosage unknown | Good clinical result |

| No | Reference | Age | Sex | Organ manifestation | Serum IgG4 (mg/dl) | Therapy | Comments |
|---|---|---|---|---|---|---|---|
| 42 | Maughan 2020[51] | 15 | F | larynx | N (L U) | Pred, Aza, RTX | Partial remission, no relapse in 8 year |
| 43 | Szczawinska-Poplonyk 2016[52] | 7 | M | Lung | N (42) | Surgery | Good clinical result |
| 44 | He 2019[53] | 14 | M | Stomach | EI (423) | Methylpred 40 mg/d | Good clinical result |
| 45 | Vakrakou 2020[54] | 17 | F | CNS (pituitary gland + spinal cord) | EI (146) | IV MethylPred 1 g/d, Aza 2 mg/kg/d | Good clinical result |
| 46 | Meli 2022[55] | 14 | M | Lymph nodes | EI (185) | No treatment | Good clinical result |
| 47 | Meli 2022[55] | 16 | M | Lymph nodes | EI (198) | No treatment | Good clinical result |
| 48 | Bullock 2017[56] | 14 | F | CNS (pituitary gland) | N (L U) | Surgery, Pred 40 mg/d, RTX1000mg IV | Good clinical result, loss to follow up at 20 months |
| 49 | Jalaj 2018[57] | 9 | F | Lacrimal gland | NM | Pred (dosage unknown) Adalimumab 40mg | Good clinical result with the maintenance of biweekly subcutaneous injections of 40mg adalimumab |
| 50 | Dylewska 2020[58] | 13 | M | pterygopalatine fossa, orbital | EI (350) | Pred 0.6 mg/kg | adequate control of the symptoms |
| 51 | Adouly 2016[59] | 12 | M | Salivary gland | EI (180) | Pred 1 mg/kg/d | Good clinical result |
| 52 | Zeybek 2021[60] | 17 | M | lumbar spine/ bone | EI (336) | Steroid therapy (dosage unknown) | Good clinical result |
| 53 | Basu 2016[55] | 12 | M | Lung | EI (1210) | Steroid therapy (dosage unknown) Surgery | Good clinical result |

| No | Reference | Age | Sex | Organ manifestation | Serum IgG4 (mg/dl) | Therapy | Comments |
|---|---|---|---|---|---|---|---|
| 54 | Johnson 2018[61] | 11 | M | Kidney | N (L U) | Surgery | Good clinical result |
| 55 | Morris 2017[62] | 15 | F | Retroperinium | N (83) | Steroid therapy (dosage unknown) RTX | Good clinical result |
| 56 | Mulay 2015[63] | 7 | M | Lacrimal gland Orbits | El (1093) | Pred (dosage unknown) | Good clinical result |
| 57 | De Jesus 2021[64] | 8 | M | Orbits Salivary gland Lymph nodes CNS | NM | Pred (dosage unknown) | Good clinical result |
| 58 | CabralesEscobar 2021[65] | 17 | M | Lymph nodes Retroperineum Appendix | El (523) | Pred 30 mg/d | Good clinical result |
| 59 | Esmaeilzadeh 2022[66] | 16 | F | CNS | N (27) | Pred, MTX | Good clinical result |
| 60 | Esmaeilzadeh 2022[66] | 15 | M | CNS | N (111) | Pred 30 mg/d, MTX 20 mg/w, RTX | Good clinical result |
| 61 | Nayak 2020[67] | 16 | M | Liver and bile duct system | El (227) | Steroid therapy, Aza 50 mg/d | Good clinical result |
| 62 | Gillispie 2015[68] | 7 | F | Orbits, Kidney, nerve (3rd nerve palsy) | N(L U) | Steroid therapy, RTX | Good clinical result |

*M male, F female, N normal, El elevated, NM not measured, L U level unknown, Pred prednisone, MethylPred methylprednisolone, Aza azathioprine, RTX rituximab, MTX methotrexate, CsA cyclosporin*

***Clinical manifestations:***

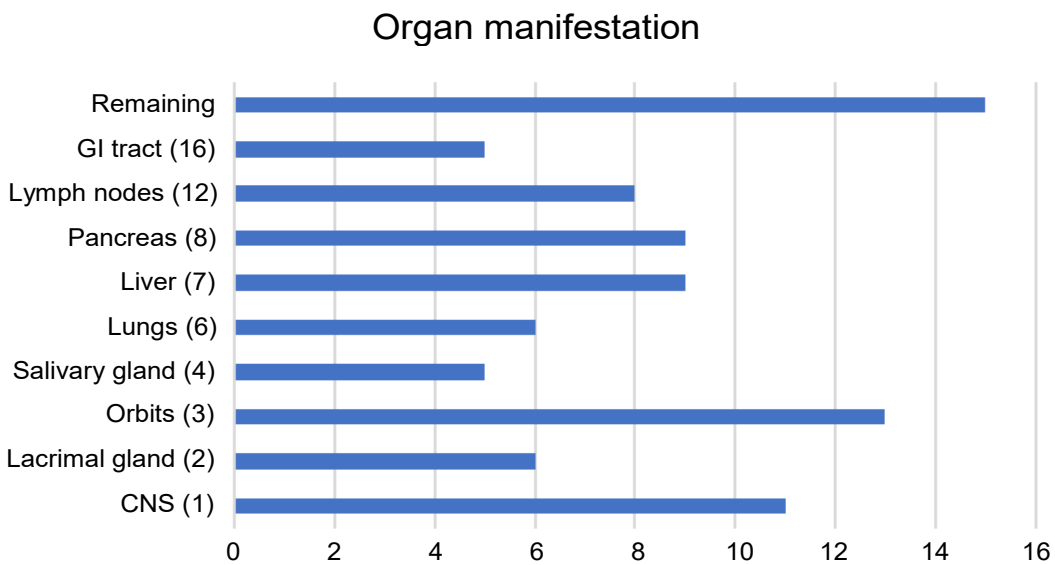


**Figure 2. Organ manifestation of IgG4-RD in paediatric population**

The most common organs involvements were orbits (n = 14) (22.6%) and central nervous system (n = 11) (17.7%). Among the patients presented with central nervous system symptoms, 6 (54.5%) were confirmed to sustain pituitary lesions. The remaining group consisted of organ manifestations with a frequency smaller than two, including 2 cases presented in muscles and 1 case in bone. Multi-organ involvement (≥ 2 organs involved) was reported in 14 cases (22.6%) central nervous system lesions associated with IgG4-RD are scarce. We present a case of IgG4-related brain parenchymal lesions that mimics multiple sclerosis in a young girl.

***Serum IgG4***

**Table 2. Serum IgG4 in paediatric patients**

| Serum IgG4 | Number of patients (n = 53) | % |
|---|---|---|
| < 135 mg/dl | 15 | 28.3 |
| 135 - 270 mg/dl | 17 | 32.1 |
| > 270 mg/dl | 21 | 39.6 |

Out of 62 cases registered, serum IgG4 levels were assessed in 53 patients. 38 cases (60.4%) exhibited elevated IgG4 concentrations (> 135 mg/dL), in which 21 (55.3%) cases surpassed 270 mg/dL (2x upper limit of normal).

The average blood test of IgG4 concentration in patients diagnosed with multiple organ involvement (1072.9 mg/dl) is three times as high as of the single organ involvement group (354.5 mg/dl).

***Diagnosis***

According to the 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD, out of the 62 cases examined, 21 patients (33.9%) fulfilled the requirements for a definitive diagnosis, 17 patients (27.4%) were

considered as possible cases, and 16 patients (25.8%) as probable cases. 8 patients (12.9%) did not meet the criteria for diagnosis. Among the 21 patients with a definitive diagnosis of IgG4-RD, 10 of them (47.6%) had IgG4 levels exceeding 270 mg/dL.

***Treatment***

**Table 3. Choice of therapy in treating paediatric patients with IgG4-RD**

| | Firstline | | Overall | |
|---|---|---|---|---|
| | **Patients** | **% (n = 55)** | **Patients** | **% (n = 58)** |
| Steroid | 45 | 81.8 | 47 | 81.3 |
| Traditional DMARDS | 10 | 18.2 | 30 | 51.7 |
| Bio DMARDS | 4 | 7.3 | 15 | 25.9 |
| Surgery | 9 | 16.4 | 13 | 22.4 |
| Other | 3 | 5.5 | 3 | 5.17 |

**Table 4. Response to steroid therapy as sole first-line treatment**

| | Initial response | | | Worsen condition or relapse upon tapering/ discontinuation |
|---|---|---|---|---|
| | **Good** | **Partial** | **No response** | |
| Patients (n = 34) | 22 | 7 | 9 | 12 |
| % | 68.8 | 21.9 | 9.4 | 26.4 |

Out of 55 cases that treatment was mentioned, steroid therapy remained the first-line treatment of 45 cases (81.8%), and 34 patients (61.8%) used glucocorticoids alone. In this group of 34 patients, 68.8% responded well to the therapy, yet 21.9% were only able to achieve partial remission, and 9.4% of them showed no improvement after the initial dose. 12 patients (26.4%) worsening conditions or relapses upon tapering or discontinuation of steroid therapy. In 2 cases no assessment of the response was mentioned. Corticosteroid doses (if specified) were in the range of 0.5 mg/kg/d to 2 mg/kg/d of oral prednisolone. A higher dose of glucocorticoid administered through IV was prescribed in at least 5 cases.

45 patients (77.6%) were treated with steroid-sparing DMARDS, with traditional DMARDs still prevail over biological ones (30 versus 15 cases). DMARDs were the second preferred choice as first-line drugs, either alone or combined with glucocorticoids (14 cases, 23.5%). Conventional DMARDs were attempted in 10 cases (18.1%), with the most frequently used being Azathioprine (5 cases). Rituximab was initiated in 3 patients, 2 of them had CNS involvement, and the remaining showed symptoms in the larynx.

Surgery, on the other hand, was performed as the first treatment in 9 patients (16.4%), in which 7 resulted in remission without the need to combine with other medicines. 4 other patients underwent surgery due to insufficient improvement from first-line therapy. 2 pediatric patients followed the “wait-and-see strategy” with no treatment initiated, both first and only presented with lymph node enlargement.

## 3. Discussion

The predominant gender distribution varies across different studies. A prospective study which included 737 patients by Lu. et al indicated a higher proportion of males in the overall surveyed population but an equal percentage of males and females in the subgroup of patients who were under 39 years old.[69] A systematic review focusing on the pediatric population by Karim et al reported a higher prevalence of female patients compared to males.[70] In our study, we observed a higher number of males than females. The rationale behind this is still controversial. According to Wallace et al when classifying the IgG4 patients into 4 groups, those with head and neck limited had a higher female percentage than male while other groups exhibited a male predominance.[71] This can lead to the outgrowth number of female over male in studies where head and neck organs are more frequently affected.

IgG4-RD is registered to manifest in almost every organ.[5,72] In adults, the disease mostly causes lesions in orbit.[8,73] A Japanese research in children also showed that orbit involvement was reported in 44% of cases.[70] Similarly, our own research findings align with this pattern, with the orbit being the most frequently affected organ. Central nervous system is considered as a rare manifestation of IgG4RD in adults.[74] In contrast to other research, we found the central nervous system to be the site of the second most common lesions. Specifically, hypophysitis, which is recognized as a common manifestation of central nervous system involvement occurred in 6 out of 11 cases among our registered patients, highlighting a shared aspect of our findings compared to existing literature.[75,76]

Although elevated serum IgG4 is included in the diagnostic criteria of IgG4RD, they lack specificity for this particular condition.[10] Elevated IgG4 levels have been associated with various other conditions including malignant tumors, primary sclerosing cholangitis, cirrhosis, inflammatory bowel disease, autoimmune hepatitis, lymphoma, rheumatic diseases, and others.[77,78] However, the sensitivity and negative predictive values of elevated IgG4 blood concentration are high.[78] Carruthers et al suggest a relationship between raised IgG4 serum level with multiple-organ-involved.[78] Our research also showed that the average serum concentration in the multiple organ involvement group is higher than the single organ group. The measurement of IgG4 during the follow-up period turned out to be a valuable index to assess the response, predict relapse in patients with initial elevated IgG4 blood level.[77,78] However, there was merely a small proportion of our surveyed patients who were measured after-treatment IgG4 so we cannot include this in our study result.

According to Kogami et al, the 2020-RCD have been reported exhibit high sensitivity (100%) but moderate specificity (50%).[79] In our investigation, only 21 out of 62 patients met all three criteria. Due to resource constraints, we did not evaluate organ-specific criteria for all patients, potentially impacting the sensitivity and specificity of IgG4 diagnosis compared to prior studies.[10] Several authors have highlighted patients' favourable response to steroid therapy as a significant diagnostic criterion. This aspect could be effectively assessed by clinicians, particularly in cases where biopsy is not feasible and IgG4 levels are within the normal range.

Steroids are the recommended first-line therapy, with most patients responding well to the treatment. However, the rate of relapse upon tapering or discontinuation of the drugs remains high, and careful and slow (< 0.4 mg/day)

tapering of glucocorticoids is associated with a lower rate of worse outcomes.[70,80-82] Existing studies recommend an initial prednisone dose of 0.6 mg/kg/day or 30 - 40 mg/day administered orally for the first 2 - 4 weeks before tapering off.[80,81] In cases of unmanageable symptoms, an urgent dose consisting of a moderate-to-high dose of glucocorticoids and/or rituximab (RTX) could be initiated.[80] In this review, 7 cases were treated using IV prednisolone either alone or combined with RTX, of which 6 had multiple organ involvements or CNS involvement.

Regarding second-line agents, RTX was suggested because of its role in the mechanism of IgG4-RD pathology and the numerous existing evidence of its efficacy.[83,84] It is worth mentioning that while the efficacy of traditional DMARDs has not been thoroughly evaluated in research, they are still more frequently chosen compared to RTX in our reviews (30 compared to 15 cases). This might be attributed to their more affordable price and the effectiveness demonstrated in other case reports.

Immediate treatment is not required in every case of diagnosed IgG4-RD, as patients with asymptomatic lymphadenopathy or mild submandibular enlargements are deemed suitable to follow wait-and-see management.[80] In this review, the 2 cases presented with lymph node enlargement only were both able to remain in remission without relapse or new organ involvement at 4-year and 8-year follow-ups respectively, without any treatment.

Long-term follow-up is essential to monitor disease activity, assess treatment response, manage complications, and detect any relapses. However, there were no guideline recommending the interval time between each visit, as well as the duration of follow-up time. The longest follow-up duration reported in this study was 8 years.

**Limitations**

The current review has several limitations. Firstly, the absence of advanced statistical analyses may lead to qualitative rather than quantitative insights into the literature, thereby constraining the ability to formulate robust conclusions or quantify effect sizes. Secondly, the review heavily depends on the interpretation and synthesis of existing literature by the author(s), potentially introducing subjectivity and bias. This susceptibility arises from the potential influence of personal perspectives or preferences on the selection and interpretation of studies. Lastly, despite efforts to conduct a comprehensive literature search, the review may inadvertently omit pertinent studies due to limitations in search strategies or database coverage. Additionally, biases may be introduced by language and publication restrictions.

## III. CONCLUSION

IgG4-RD is a rare condition in the pediatric population and little systematic review has been conducted on this disease. Clinical manifestations of are diverse, reflecting the multisystem nature of this disease; therefore, a diagnosis of IgG4-RD should be considered if the patient presented with symptoms of multisystem involvement, unexplained masses or tumors, organ swelling or enlargement, fibrotic lesions, and chronic inflammatory conditions that do not respond well to typical treatments. Orbit and central nervous system are two organs mostly affected. Serum IgG4 concentration is not a reliable marker for the diagnosis. Steroids are the first choice of treatment and should be involved in the diagnosis criteria of this disease.

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