Ocular manifestations of IgG4-related disease in children. More common than anticipated? Review of the literature and case report

Roubini G Smerla[1], Dimitra Rontogianni[2], George E Fragoulis[1,3]

1. Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Greece
   Mikras Asias 75 str, Athens, Greece, 11527
2. Department of Pathology, "Evangelismos" General Hospital, Athens, Greece
   Ipsilantou 45-47 str, Athens, Greece, 10676
3. Institute of Infection, Immunity and Inflammation, University of Glasgow
   120 University place, GBRC building, Glasgow, United Kingdom, G12 8TA

Corresponding author: George E Fragoulis, e-mail address: geofragoul@yahoo.gr and George.Fragkoulis@glasgow.ac.uk , Telephone number: (44) 0141-330-2282

Funding: This study was not supported by any specific funding

Aknowledgements: We would like to thank Professor Haralampos M Moutsopoulos, MD, for critically reviewing our manuscript and for his continuous mentorship, guidance, inspiration, and support.

We would also like to thank Dr. Ioannis Nikas for his valuable contribution in interpreting the radiological images of our case.

ABSTRACT

IgG4-related disease (IgG4-RD) is an entity with various clinical manifestations. Histopathologically, it is characterised by lymphoplasmacytic infiltrates enriched in IgG4 (+) plasmacytes and usually fibrosis of the affected tissue. Most of the patients have also increased IgG4 serum levels and they respond to glucocorticosteroids. In children, due to its rare occurrence, IgG4-RD is ill defined. From the published studies, so far, it appears that ocular manifestations are very common in the paediatric population with IgG4-RD. Herein, we describe a new case of a child with IgG4-RD with ocular involvement manifested with orbit and eyelid swelling, successfully treated with steroids. In addition, we review the clinical, laboratory, histopathologic and radiologic characteristics of the published paediatric cases with IgG4-RD and ocular involvement, critically comparing them with the characteristics of the adult population. It seems that ocular manifestations are more frequently observed in children than in adults. Also, the pattern of involvement is different, with extraocular muscles and soft tissues being more commonly affected than the lacrimal glands.

Keywords: IgG4-related disease, ocular involvement, children, orbit swelling

INTRODUCTION

Since its first description in 2001, IgG4-related disease (IgG4-RD) has been increasingly recognised as an entity with many diverse clinical presentations [1] and a great mimicker of various conditions [2]. It is characterized by tumefactive tissue lesions, usually but not always, accompanied by increased IgG4 serum levels. Almost every organ could be affected, with the histopathologic hallmark of the disease being the lymphoplasmacytic infiltrates in which IgG4-positive plasma cells predominate. Fibrosis, usually of storiform pattern is also observed most of the times. Other histopathological characteristics such as obliterative phlebitis and eosinophils are also occasionally present [3].

IgG4-related ocular involvement/disease (IgG4-ROD) is a rather frequent manifestation encountered in about 17-23% of patients with IgG4-RD, however, not many studies have been published [4-6]. Every part of the orbit and ocular adnexa could be affected, including: lacrimal glands, orbital soft tissues, extraocular muscles, eyelids, optical and trigeminal nerves, bones and sclera [4,5] .

Due to its rare occurrence, IgG4-RD in the paediatric population is ill defined so far and is unknown whether it shares the same clinical, serological and histopathological features with those observed in adults. According to a recent systemic literature review, it seems that ocular manifestations are very common (44%) amongst children with IgG4-RD [7].

Herein, we describe a young boy with IgG4-RD and ocular involvement and we review all published paediatric IgG4-RD cases with ocular manifestations, describing their characteristics and highlighting their differences from the adult population.

CASE REPORT

A four-year-old boy was referred to the paediatric rheumatology clinic with a two-month history of orbital and upper right eyelid swelling without pain. His past medical history was unremarkable, while his maternal grandfather suffered from myositis and thyroiditis Hashimoto.

On physical examination, ptosis and swelling of the upper right eyelid were evident. His visual acuity, movement of the eyes, as well as fundoscopic examination were normal.

Differential diagnosis included infectious diseases, vasculitis, sarcoidosis, malignancies, idiopathic orbital inflammation (IOI), orbital benign lymphoid hyperplasia (OBLH) and IgG4-RD with ocular manifestations.

Laboratory investigation including whole blood test, acute phase reactants, biochemical analysis, thyroid function and urine test, were all within normal limits. Infectious diseases, sarcoidosis and neuroblastoma were ruled out. Anti-neutrophil cytoplasmic (c-ANCA, p-ANCA), antinuclear, anti-double stranded DNA, Extractable Nuclear Antigen antibodies and rheumatoid factor were all negative. C3 and C4 serum levels, immunoglobulin electrophoresis and serum immunoglobulins were all within normal limits, apart from the elevated IgG4 levels: 222mg/dl, [normal value for a 4-year old boy: (1-189) mg/dl].

Brain Magnetic Resonance Imaging (MRI), orbit MRI and Computerized Tomography (CT). revealed a diffuse extraconal lesion with intermediate signal intensity in T1w and T2w images, and homogeneous contrast enhancement, at the superior-lateral part of the right orbit. A moderate swelling of the right lateral rectus muscle was also noted. The lacrimal gland, the superior rectus muscle and the superior oblique muscle were also involved. No intracranial extension or bone erosion was observed (Figure -1). The remaining extraocular muscles, the optical nerves and the chiasm were normal and appeared unremarkable.

Biopsy was obtained from the superior-lateral part of the right orbit and the lacrimal gland. It showed fibro-adipose tissue and dacryoadenitis, respectively. The inflammatory infiltrates of the latter were composed of lymphocytes, histiocytes and eosinophils. In the fibro-adipose tissue, storiform fibrosis and dense lymphoplasmacitic infiltrates were observed. In a single focus, IgG4 staining demonstrated the presence of more than 10 IgG4-positive plasma cells/hpf with a IgG4/IgG ratio>50%. Eosinophils were also present. Granulomas or evidence of vasculitis, lymphoproliferative disease or other neoplasms were not detected.

Based on the clinical picture, the laboratory findings and the histopathological findings, the diagnosis of IgG4-related disease with ocular manifestations was undertaken. The patient was treated with prednisolone (0.5 mg/kg) for two months followed by slow tapering. Four

months later, an orbit MRI-CT was repeated. All the previously described findings had been resolved.

LITERATURE REVIEW

Adult population

In the adult population, data available from big IgG4-RD registries, investigating the frequency of ocular manifestations in IgG4-RD, support that IgG4-ROD is being encountered in about 17-23% of the patients [4-6]. In accordance with other retrospective published studies, it seems also that IgG4-ROD could be the diagnosis in patients previously thought to have idiopathic orbital inflammation (IOI) or orbital benign lymphoid hyperplasia (OBLH) in about 5-23% and 40-50%, respectively [8]. Many different criteria have been used by the investigators for the diagnosis of IgG4-ROD. These include: Consensus diagnostic criteria [IgG4 (+) plasmacytes >100/hpf and IgG4(+)/IgG(+) ratio>40%] [3], Comprehensive diagnostic criteria [IgG4 (+) plasmacytes >10/hpf and IgG4(+)/IgG(+) ratio>40%] [9] and the Japanese Study Group criteria for IgG4-related ophthalmic disease [IgG4 (+) plasmacytes >50/hpf and IgG4(+)/IgG(+) ratio>40%] [10].

Males seem to be more commonly affected compared to females [4,5]. Involvement is bilateral in more than 60% of the patients with IgG4-ROD [4-6] while extraophthalmic manifestations are found in about 70-80% of the patients [4-6]. Lacrimal gland is the most frequently affected part followed by extra-ocular muscles and soft tissues involvement. In about 10% of the patients trigeminal or optic nerves are affected. Also, in a minority of patients, bone involvement is evident usually manifested as bone remodelling rather than destruction [4-6]. Presenting symptomatology of IgG4-ROD may include: orbital mass/eyelid swelling, proptosis, pain, reduction of visual acuity, diplopia and restriction of eye movements [6]. As observed generally in IgG4-RD patients, about one-third of IgG4-ROD patients appear to have normal IgG4 serum levels [4,5]. From a histopathological point of view, they are characterized by lymphoplasmacytic infiltrates and fibrosis. Eosinophils are also occasionally present. Interestingly, in these patients, the characteristic storiform pattern is not described consistently amongst different investigators and it seems to be

more pronounced only in biopsies obtained from affected lacrimal glands [4-6,11]. In addition, obliterative phlebitis appears to be a rather uncommon finding, although this might be confounded by the small size of eye vessels [12]. Most of the patients respond to treatment with steroids, however about 2/3 of them relapse [4-6]. As for other IgG4-RD manifestations, steroid-sparing agents, may be used as induction therapy, along with steroids, or as treatment for relapse. Rituximab seems also to be a good alternative in the treatment of eye manifestations in the context of IgG4-RD [5].

Paediatric population

IgG4-RD is increasingly being described in the paediatric population [7]. Interestingly, amongst these patients, ocular involvement was by far the most commonly reported manifestation, reaching 44%, according to a recent systemic literature review [7].

Until September 2017, to the best of our knowledge, 13 cases -10 females and 3 males- of children with ophthalmic manifestations have been described [13-22]. The most common symptomatology was unilateral protrusion/swelling (11/13, 84.6%), while eyelid involvement was also mentioned in 6/13 (46.1%) cases (Table-1). Interestingly, only 3/13 (23.1%) presented extra-ophthalmic manifestations and other two had history of ophthalmic disease (preseptal cellulitis, uveitis and retinopathy of prematurity).

Serum IgG4 levels were found to be increased in 5/13 (38.5%) of the patients, inflammation markers in 3/6 (50%), while autoimmune profile was negative in all the patients for whom data were available (Table-1)

Clinical findings and imaging studies, in these patients, suggested “orbital mass” as the most common finding. Extraocular muscle involvement and bone involvement were also described in 7/13 (53.8%) and 3/13 (23.1%) cases, respectively. A case with optic nerve sheath enhancement, amongst other findings, has also been described. Interestingly, lacrimal gland involvement has been observed in only two children so far (Table-2).

Histopathologically, the cases described were characterized by lymphoplasmacytic infiltrates. Fibrosis was referred in 6/11 (54.5%) of the available biopsies with storiform pattern being present in only one. Obliterative phlebitis was also present in two cases.

Number of IgG4-positive plasmacytes/hpf ranged from 14 to more than 150 and the IgG4/IgG ratio ranged from 30 to 60 % (Table-2).

The vast majority of the patients were initially treated with steroids (by mouth or intravenously) with or without steroid-sparing agents, such as methotrexate or mycophenolate mofetil. Eight out of 11 patients, (72.8%), for whom data were available, relapsed or didn't respond and they were retreated with other immunosuppressants such as azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab in 3 cases and anti-TNF in one case, with good response (Table-1).

DISCUSSION

Ocular manifestations in the context of IgG4-RD have been described in the adult population in big IgG4-RD registries and from pooled analyses of the published literature. However, in the paediatric population IgG4-RD is not well described and possibly underdiagnosed.

Differential diagnosis of IgG4-ROD includes lymphoproliferative disorders, granulomatosis with polyangiitis, sarcoidosis, tuberculosis, infections, thyroid eye disease, malignancies, idiopathic orbital inflammation (IOI), orbital benign lymphoid hyperplasia (OBLH), xanthogranulomas, Erdheim-Chester disease and Rosai-Dorfman disease. Importantly, lymphoma needs to be thoroughly excluded as it is a great mimicker of IgG4-ROD and could have positive staining for IgG4 plasmacytes [6].

In this article, we reviewed the paediatric cases published with IgG4-ROD and we present also one new case of a child with IgG4-ROD.

From the cases described up to August 2017, it seems that IgG4-ROD in paediatric population has some striking differences compared to that of adults. Firstly, frequency of ophthalmic manifestations is higher in children. Secondly, the pattern of ocular involvement differs. In children, involvement is usually unilateral. Orbital soft tissue and extraocular muscles are the most common affected sites, whilst lacrimal glands have been very infrequently described to be involved. Extra-ophthalmic manifestations are also rare in children with IgG4-ROD.

Histopathological findings include lymphoplasmatic infiltrates with associated fibrosis. Storiform pattern is not commonly observed, possibly reflecting the fact that lacrimal glands are not so commonly involved. Besides, as mentioned above, the frequency of storiform pattern in IgG4-ROD adult population remains as a matter open for discussion. IgG4-ROD in children, as described in adults is steroid responsive. A significant proportion of patients will relapse and need additional treatment with steroid sparing agents. Rituximab and anti-TNF have also been described to have good results in such patients.

In our case, we present a young boy with unilateral eye involvement. The presenting manifestation was eyelid and orbital swelling. MRI findings revealed diffuse soft tissue swelling and extraocular muscle involvement as well. Infectious diseases, other autoimmune diseases and thyroid dysfunction were thoroughly excluded. Macroscopically, the affected tissue was sclerotic and biopsy did not display any findings consistent with malignancy, lmphoproliferative or granulomatosous disease. Interestingly IgG4 (+) plasmacytes >10/hpf, and high IgG4/IgG ratio were identified in a single spot. Besides significant fibrosis and eosinophils were identified.

We acknowledge that our review has some certain limitations. Firstly, it is based on a retrospective analysis of published cases. Secondly, the number of paediatric reports described so far with ocular involvement is too small to draw a safe conclusion. Thankfully, we had access to the full papers of reported cases, so all available data were reviewed. Moreover, in our case, IgG4-positive plasmacytes were recognized in a single spot. It is unclear to which extent IgG4-positive plasmacytes should be present to place the diagnosis of IgG4-RD. However, the exclusion of other possible diagnoses, the clinical and laboratory features, the steroid responsiveness and the high IgG4/IgG ratio, along with fibrosis and eosinophils in the tissue, make the diagnosis most probable. Besides, the number of IgG4-positive plasmacytes needed to place the diagnosis of IgG4-ROD is still not defined, especially in the paediatric population.

IgG4-RD is an entity, very recently described. Over the two last decades, significant efforts have been made towards the description of its clinical, serological and histopathological features. There are still however many issues to be clarified. Amongst them, it is the natural history of IgG4-RD and its various manifestations in children.

Conflict of interest: the authors declare no conflict of interest

REFERENCES

1. Stone JH, Zen Y, Deshpande V (2012) IgG4-related disease. N Engl J Med 366:539-551. doi:10.1056/NEJMra1104650
2. Soliotis F, Mavragani CP, Plastiras SC, Rontogianni D, Skopouli FN, Moutsopoulos HM (2014) IgG4-related disease: a rheumatologist's perspective. Clin Exp Rheumatol 32:724-727. doi:8072 [pii]
3. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Kloppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH (2012) Consensus statement on the pathology of IgG4-related disease. Mod Pathol 25:1181-1192. doi:modpathol201272 [pii]
10.1038/modpathol.2012.72
4. Ebbo M, Patient M, Grados A, Groh M, Desblaches J, Hachulla E, Saadoun D, Audia S, Rigolet A, Terrier B, Perlat A, Guillaud C, Renou F, Bernit E, Costedoat-Chalumeau N, Harle JR, Schleinitz N (2017) Ophthalmic manifestations in IgG4-related disease: Clinical presentation and response to treatment in a French case-series. Medicine (Baltimore) 96:e6205. doi:10.1097/MD.0000000000006205
00005792-201703100-00020 [pii]
5. Wallace ZS, Deshpande V, Stone JH (2014) Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. Semin Arthritis Rheum 43:806-817. doi:S0049-0172(13)00251-5 [pii]
10.1016/j.semarthrit.2013.11.008
6. Wu A, Andrew NH, McNab AA, Selva D (2015) IgG4-Related Ophthalmic Disease: Pooling of Published Cases and Literature Review. Curr Allergy Asthma Rep 15:27. doi:10.1007/s11882-015-0530-4
7. Karim F, Loeffen J, Bramer W, Westenberg L, Verdijk R, van Hagen M, van Laar J (2016) IgG4-related disease: a systematic review of this unrecognized disease in pediatrics. Pediatr Rheumatol Online J 14:18. doi:10.1186/s12969-016-0079-3
10.1186/s12969-016-0079-3 [pii]
8. Andrew NH, Sladden N, Kearney DJ, Selva D (2015) An analysis of IgG4-related disease (IgG4-RD) among idiopathic orbital inflammations and benign lymphoid hyperplasias using two consensus-based diagnostic criteria for IgG4-RD. Br J Ophthalmol 99:376-381. doi:bjophthalmol-2014-305545 [pii]
10.1136/bjophthalmol-2014-305545
9. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H (2012) Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 22:21-30. doi:10.1007/s10165-011-0571-z
10. Goto H, Takahira M, Azumi A (2015) Diagnostic criteria for IgG4-related ophthalmic disease. Jpn J Ophthalmol 59:1-7. doi:10.1007/s10384-014-0352-2

11. Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, Tanaka T, Takata K, Morito T, Kondo E, Yoshino T (2008) Ocular adnexal IgG4-related disease has uniform clinicopathology. Pathol Int 58:465-470. doi:PIN2257 [pii]
10.1111/j.1440-1827.2008.02257.x
12. Deschamps R, Deschamps L, Depaz R, Coffin-Pichonnet S, Belange G, Jacomet PV, Vignal C, Benillouche P, Herdan ML, Putterman M, Couvelard A, Gout O, Galatoire O (2013) High prevalence of IgG4-related lymphoplasmacytic infiltrative disorder in 25 patients with orbital inflammation: a retrospective case series. Br J Ophthalmol 97:999-1004. doi:bjophthalmol-2013-303131 [pii]
10.1136/bjophthalmol-2013-303131
13. Batu ED, Arici ZS, Orhan D, Kiratli H, Ozen S (2015) Immunoglobulin G4-related orbital disease: report of two pediatric cases. Clin Exp Rheumatol 33:409-410. doi:8735 [pii]
14. Gillispie MC, Thomas RD, Hennon TR (2015) Successful treatment of IgG-4 related sclerosing disease with rituximab: a novel case report. Clin Exp Rheumatol 33:549-550. doi:8689 [pii]
15. Griepentrog GJ, Vickers RW, Karesh JW, Azari AA, Albert DM, Bukat CN (2013) A clinicopathologic case study of two patients with pediatric orbital IgG4-related disease. Orbit 32:389-391. doi:10.3109/01676830.2013.822899
16. Jariwala MP, Agarwal M, Mulay K, Sawhney S (2014) IgG4-related orbital inflammation presenting as unilateral pseudotumor. Indian J Pediatr 81:1108-1110. doi:10.1007/s12098-014-1471-y
17. Kalapesi FB, Garrott HM, Moldovan C, Williams M, Ramanan A, Herbert HM (2013) IgG4 orbital inflammation in a 5-year-old child presenting as an orbital mass. Orbit 32:137-140. doi:10.3109/01676830.2013.764449
18. Mittal R, Ganguly A, Rath S, Das B, Mishra A (2014) IgG4-related orbital inflammation presenting as bilateral proptosis in a child. Eye (Lond) 28:1264-1266. doi:eye2014154 [pii]
10.1038/eye.2014.154
19. Notz G, Intili A, Bilyk JR (2014) IgG4-related dacryoadenitis in a 13-year-old girl. Ophthal Plast Reconstr Surg 30:e161-163. doi:10.1097/IOP.0000000000000016
20. Pasic S, Ristic G, Djuricic S (2013) PReS-FINAL-2276: IgG4 related disease in a 10-year-old gir. Pediatric Rheumatology 11 (Suppl 2):266
21. Prabhu SM, Yadav V, Irodi A, Mani S, Varghese AM (2014) IgG4-related disease with sinonasal involvement: A case series. Indian J Radiol Imaging 24:117-120. doi:10.4103/0971-3026.134384 IJRI-24-117 [pii]
22. Sane M, Chelnis J, Kozielski R, Fasiuddin A (2013) Immunoglobulin G4-related sclerosing disease with orbital inflammation in a 12-year-old girl. J AAPOS 17:548-550. doi:S1091-8531(13)00275-9 [pii]
10.1016/j.jaapos.2013.05.017

Figure legends

Fig 1. A. Coronal T1 weighted image. B. Gadolinium-enhanced coronal T1 weighted image. C. Gadolinium-enhanced fat- suppressed axial T1 weighted image. Extraconal lesion at the superior-lateral part of the right orbit (arrows), with low signal intensity, presenting homogeneous contrast enhancement. A moderate swelling of the superior and lateral rectus muscles was noted