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Conflict of interest

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Ethical statement

This article did not involve patients but studies. Informed consent was obtained from all individual participants of the included studies in this systematic review.

IgG4 related sclerosing disease of the temporal bone: A systematic review

Abstract

Objective: IgG4-related disease (IgG4-RD) involving the temporal bone is an uncommon and underrecognized pathology often mistaken for malignancy. This systematic review is the first that aims to thoroughly analyse IgG4-RD of the temporal bone.

Databases Reviewed: Ovid Medline, Embase, Cochrane library and Google Scholar

Methods: We used the search keywords: ‘’lgG4-RD’’, ‘’skull’’, ‘’skull base’’, ‘’cranial’’, ‘’temporal bone’’, ‘’inner ear’’. We additionally manually searched the bibliographies of relevant articles. The JBI Critical Appraisal Checklist for Case Reports and Case Series were used to assess the risk of bias; due to the scarcity of the reports data were available through limited case series and reports; thus, data synthesis was not possible.

Results: We identified 17 studies with 22 cases with temporal bone involvement. The commonest presenting symptoms were hearing loss, otalgia and headache. The mastoid and petrous bone were the most affected anatomical areas. Both computed tomography (CT) and magnetic resonance (MRI) were used. Biopsies showed the characteristic lymphoplasmacytic infiltrate in all cases with histopathology being the diagnostic modality that set the diagnosis. Most patients were treated with corticosteroids +/- surgery or a combination of corticosteroids and immunosuppressants with 95.5% symptomatic response and disease control.

Conclusion: IgG4-RD of the temporal bone radiologically manifests as space-occupying, lytic lesions; clinically it presents with vague otological symptoms. Diagnosis involves a thorough workup, with histopathology being crucial in setting a definite diagnosis. IgG4-RD tends to

respond well to systemic corticosteroids, while surgery is mostly required for diagnostic purposes.

Key Words

Corticosteroids; IgG; Hearing loss; Temporal bone

Introduction

IgG4-related disease (IgG4-RD) is an emerging fibroinflammatory condition that can involve any anatomic site and often presents as a tumefactive lesion.[1–3] Hamano et al[4] first described the disease spectrum in 2001, associated with autoimmune pancreatitis, increased serum IgG4 levels and the characteristic histological findings of dense lymphoplasmacytic infiltrates, storiform fibrosis and obliterative phlebitis. Cases of organ failure and even death have been reported as a result of the disease.[2,5] Common head and neck manifestations of IgG4-RD include Riedel thyroiditis, Mikulicz disease and Kuttner tumour.[1,3,6–8] IgG4-RD involving the skull base is uncommon and often mistaken for malignancy, infection, or other immune-related diseases like ANCA vasculitis, eosinophilic granuloma or neurosarcoidosis.[5]

Original diagnostic guidelines were developed by Deshpande et al[7] in 2011 at the first international meeting for IgG4-RD. Histologically, the diagnostic findings include lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, a ratio of IgG4+/IgG plasma cells >40% and/or >10 IgG4+ plasma cells per high powered field.

Some skull base locations of IgG4-RD documented in the literature include the meninges, sphenoid bone, sphenoid and maxillary sinus, orbit, clivus, internal auditory canal, brain parenchyma, infratemporal fossa, pterygopalatine fossa, suprasellar region and temporal bone.[9–13] The most recent guidelines from the American College of Rheumatologists and European League Against Rheumatism Guidelines[5] have shifted towards a point-based system where IgG4-RD diagnosis is based on a spectrum of classic features and absence of other plausible diagnoses. Skull base manifestations, including temporal bone disease were, however underrepresented by these guidelines.[13] Various studies have found that the exact histological findings vary greatly depending on the tissue affected and clinical presentations.[13,14]

Currently, temporal bone IgG4 disease is an underrecognized entity leading to a large delay to diagnosis. This systematic review is the first that aims to examine the presentation of IgG4-RD in the temporal bone, outline the histological findings and contrast them with current guidelines, review the symptomatology, management, and prognosis of the disease.

Materials and Methods

Basic settings

This review was conducted in accordance with the PRISMA guidelines for systematic reviews.[15] All studies were included if they met the following criteria: (1) confirmed cases of IgG4 disease made by histopathology and immunostaining, (2) disease involving the temporal bone as demonstrated by imaging. Studies or cases from studies with insufficient data or radiological evidence showing temporal bone involvement were excluded. This review was not registered.

Search strategy

A detailed literature search was performed with the help of a medical librarian from four different databases namely: Ovid Medline, Embase, Cochrane library and Google scholar using a combination of keywords and controlled vocabulary including the terms ''lgG4-RD'', ''skull'', ''skull base'', ''cranial'', ''temporal bone'', ''inner ear''. Additionally, we manually searched the bibliographies of relevant articles for any new articles. All search strategies and manual citation searching were completed on the first of October 2021.

Study selection

Due to the scarcity of temporal bone involvement of IgG4RD, all the published studies are either case reports or limited case series. Our search strategy from the four databases identified 30 studies after removing duplicates, all of which were screened for relevance. Additionally, from our manual citation searching, we identified 27 more studies. Five studies were excluded as they were conference abstracts and there was a lack of information about primary data. Eight reports could not be retrieved. A total of 44 full-text articles were read and assessed for eligibility. Of those, 27 were excluded for the following reasons: one was a limited review without reporting any new cases, three did not fulfil the criteria for diagnosing IgG4 disease and 23 of them did not involve the temporal bone. This review ultimately included a total of 17 studies. (Figure 1)

Data collection process

Variables collected from each study included:

- date of publication and first author
- geographical origin of the study
- number of included patients with age at presentation and gender
- anatomic location of disease
- time from the first presentation to diagnosis
- main symptoms
- diagnostic and radiological findings
- treatments
- follow up time and relapses. Relapses were defined as a disease exacerbation following a definite period of improvement after treatment.

Risk of bias and heterogeneity assessment

Each included study was critically appraised using the JBI Critical Appraisal Checklist for Case Reports[16] and Case Series[17] by two independent reviewers to reduce the risk of bias and evaluate the methodological quality and synthesis of each article. The Case Report tool assesses eight domains using eight tick box questions (Tool Answers: Yes, No, Unclear or Not/Applicable). The Case Series tool assesses ten domains using ten tick box questions (Supplement). Articles that had more than two No/Unclear domains were excluded. The heterogeneity of the data was also assessed as part of the above tools; given the number of the available case reports and limited case series, as well as the variety in disease manifestation, there was significant heterogeneity in the included studies

We used descriptive statistics to summarize the data, including frequencies and percentages for categorical variables.

Results

We identified 22 cases of IgG4-RD with temporal bone involvement from 17 different studies. (Table 1)[18–35] Results are presented exactly as reported in original publications without solicitation of additional information from their authors. Table 2 summarizes the location of diseases involvement and symptoms for each case.

Clinical characteristics and patient symptomatology

A total of 22 patients (eight male and 14 females) with IgG4 temporal bone disease were identified. The mean age at presentation was 52.5 years (Range: 19-73 years). The mean delay in diagnosis from the time of initial symptom was 34.1 months (Range: 0-120 months). Follow up time was reported in 15 out of 22 cases with a mean of 14.5 months. (Range: 2-33 months)

The most common presenting symptoms were hearing loss (77.3%; 17/22), otalgia (45.5%; 10/22), headache (36.4%; 8/22), diplopia (36.4%; 8/22), tinnitus (31.8%; 7/22), middle ear effusion and otitis media (27.3%; 6/22), vertigo (31.3%; 5/16) and facial nerve palsy (31.3%; 5/16). Table 3 summarizes the other presenting symptoms.

The most common locations of IgG4 disease within the temporal bone were the mastoid (45.5%), the petrous part of the temporal bone (40.9%) and the middle and inner ear; 16 out of 22 cases reported involvement of the middle and inner ear. The middle ear (tympanic cavity) was the most frequently affected in nine cases (40.9%) while the inner ear was involved in seven cases (31.8%). Other common locations aside the temporal bone involvement included the middle cranial fossa (27.3%), the posterior fossa (18.2%) and the cavernous sinus (18.2%). Detailed anatomic location is summarized in Table 3.

Diagnosis

Biopsies were performed in all patients. The common biopsy methods used were mastoidectomy (16/22), endoscopic transsphenoidal sinus approach (5/22) and nasopharyngeal biopsy (1/22) in one case, where the extent of the disease allowed it.

Dense lymphoplasmacytic infiltrate were found in histopathological specimens of all patients, some degree of fibrosis was reported in all patients but only 10/22 reported the storiform fibrous pattern and 3/22 reported obliterative phlebitis.

A total of 45.5% (10/22) reported raised serum IgG4 levels while 63.6% (14/22) reported ratio IgG4+: total IgG+> 40%. Four patients did not have data on the ratio of IgG4: IgG plasma cells. In the remaining four cases, the ratio did not exceed 40%, their ratios were as follows: 35%, 30%, 20% and 10%; 81.8% (18/22) reported IgG4+ plasma cells >10/high power field.

In all cases, MRI along with CT scans were performed with images demonstrating disease involvement of the temporal bone. In most cases, imaging identified the involvement of the petromastoid portion, the middle ear, the inner ear and other neighbouring regions. (Table 3)

Treatment and patient outcomes

Most patients had a combination of surgery and corticosteroids or corticosteroids and another one immunosuppressant +/- surgery. Detailed treatment regimens for each patient are shown in Tables 4a and 4b with 90.9% of patients having corticosteroids as part of their initial treatment and 77.3% of patients were treated with a regimen that included surgery. The most common type of surgery performed was mastoidectomy (canal-wall-up or even modified radical mastoidectomy as described in the reports), which essentially facilitated biopsy and histological diagnosis. It is worth mentioning that the precise type of surgery was dictated by the extent of the disease, the anatomy (for example due to small mastoid cavity, modified radical mastoidectomy was performed with a view to eradicate the inflammatory disease but eventually to obtain biopsies and set diagnosis[20]) but also the unknown of the precise diagnosis at the time of the surgery. The other types of surgery performed were dependent on location of disease involvement and are described in Table 5. Overall, 95.5% of patients demonstrated positive symptomatic response with their initial treatment regimen.

Relapses

Seven patients relapsed after the initial symptomatic response. Five of the relapses occurred when steroids were tapered off. Three of them were then treated with high dose steroids, one with rituximab, one with cyclophosphamide, one with a combination of rituximab and corticosteroids and the last one with steroids and radiotherapy of a total dose of 20 Gy in 10 fractions. All of the patients with relapses responded well and were in remission again.

Corticosteroid cessation

Two patients (Case No: 3 and 10) experienced side effects with corticosteroids (One suffered from steroid-induced myopathy and the other one experienced a 10kg weight gain). They were switched to mycophenolate mofetil and azathioprine respectively and were both in remission with no disease relapse.

Discussion

Summary of evidence

IgG4-RD encompasses a multisystemic disease that may present with lesions involving the head and neck.[35] It was first described in 2001 involving the pancreas.[4] Since then, there has been an increasing number of skull base cases reported. However, IgG4-RD of the temporal bone remains rare. The first confirmed case was reported in 2010 by Masterson at al[19]. Although several reviews have been conducted recently, there is no evidence-based systematic attempt specifically focussing on temporal bone IgG4-RD. This review highlights the rarity of the disease with only 22 confirmed cases documented; possibly under-diagnosed.[19–35]

Diagnosis

IgG4-RD activity in the temporal bone has ranged from space-occupying lesions causing cranial nerve palsies to locally invasive lesions exhibiting bony destruction with involvement of mastoid, bony labyrinth, inner ear, middle ear and other neighbouring locations.[19–35] Hearing loss, otalgia, tinnitus, vertigo, otitis media, mastoiditis, facial nerve palsy and headache were among the presenting symptoms/ conditions.

Nevertheless, the disease poses a major diagnostic challenge. This is demonstrated by the protracted course to definite diagnosis of IgG4-RD in these patients. In the majority of cases, the diagnosis was only made after exhausting all other clinical suspicions as involvement of the temporal bone is an uncommon and underrecognized anatomical location of the disease within the head and neck. The significant delays in diagnosis reported in the literature (mean time to diagnosis 34 months) highlights the diagnostic challenge, mostly due to the vague and/ or non-specific presenting symptoms but also due to the non-specific, amorphous radiological presentation. With regards to temporal bone manifestation, the most common differential diagnoses of the IgG-RD include neurosarcoidosis, giant cell arteritis, Langerhans Cell Histiocytosis, osteosarcoma, eosinophilic granuloma and cholesteatoma amongst others; all diseases that can manifest within the temporal bone demonstrating non-specific, inflammatory appearances on imaging.[27,30,35] While exhausting imaging and blood tests, combined with the clinical picture, could narrow down the list of possible diagnoses, biopsy with histological confirmation are essential in setting the diagnosis.

Indeed, biopsy with immunostaining is considered the golden standard for diagnosis of IgG4-RD.[1,14,36] The three key histopathological features of IgG4-RD are dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. Immunohistochemistry findings include IgG4 positive plasma cells>10/HPF and a ratio of IgG4+/IgG>40%.[37] Serum IgG4 levels may be elevated; however, these are normal in 30-50% of patients with IgG4-RD. As such, they are neither sensitive nor specific for diagnosis.[22,36,37] Furthermore, rising serum IgG4 can be found in other conditions like cancer, eosinophilic granulomatosis with polyangiitis. IgG4 serum levels have been used in some cases to monitor the therapeutic response in patients with elevated serum IgG4.[38,39] Thus, histological confirmation remains of high importance for setting the diagnosis.

All cases in this review demonstrated the classic lymphoplasmacytic infiltrate. The storiform fibrosis and obliterative phlebitis pattern were, however, uncommon. The clinical significance of storiform fibrosis (45.5%) and obliterative phlebitis (13.6%) for diagnosing IgG4 of temporal bone and other skull/ skull base manifestations are still unclear given that the disease has a greater histological variability depending on the organ system involved.[27,29] For example, IgG-RD of the lymph nodes, lacrimal gland and lung have an absence of storiform fibrosis and obliterative phlebitis.[37] Another explanation for the lack of classic IgG4 features on histology could be due to the late stage of the disease at the time biopsy was taken, which can present as non-specific fibrosis rather than storiform type fibrosis.[27]

Additional radiologic investigations (CT or MRI) are necessary to assess the extent of temporal bone involvement and the erosion as well as involvement of crucial anatomic structures. MRI usually shows increased contrast enhancement of the lesion in IgG4-RD owing to substantial lymphoplasmacytic infiltration.[6] As demonstrated in a recent systematic review by Spinazzi et al[40] both CT scan and MRI are essential for better visualization and characterization of pseudotumors in the temporal bone; this applies to the IgG4-RD. Additional imaging, beyond pre- and post-contrast high-resolution CT and MRI of the area has not been emphasized in the literature; thus it is not recommended unless additional symptoms could indicate additional systemic manifestations and subsequently would warrant whole-body MRI/ CT.

Treatment and follow-up arrangements

The first-line treatment for IgG4-RD remains corticosteroids. Proposed regimens include prednisone 40 mg/day with adjustments based on disease response or prednisolone 0.6 mg/kg/day for 2–4 weeks followed by a 3–6-month taper to 5 mg/day and maintenance dose of 2.5–5 mg for up to 3 years.[41–43] A reduction in lesion size and symptomatic improvement can be expected in weeks.[42] Corticosteroids and/or surgery were the main treatment options along with other immunomodulators amongst all the patients.

Surgical debulking was required in many cases to improve disease response to steroids and in some cases to relieve compressive symptoms of the disease; as above, surgery was essential to obtain specimens for pathology. It is crucial to note that the precise diagnosis was unknown at the time of the surgery; the surgeons were approaching the inflammatory disease with a view to eradicate it and improve the patients' symptoms, assuming that a non-specific inflammatory pathology was the cause; the obtained biopsies set the diagnosis. From that point onwards, the treatment was medical, as stated above. Previous literature search on the natural history of the disease revealed that untreated IgG4-RD ultimately progresses to extensive organ fibrosis. This ultimately reduces the treatment responsiveness and patients diagnosed at this stage generally require surgical intervention along with medical treatments.[28,44] Various immunosuppressants such as rituximab, azathioprine, mycophenolate mofetil have been used as other treatment options in severe disease, relapses or patients who cannot tolerate steroids.[28,44] We were unable to comment on the use of radiotherapy in one relapsing case, as this seems to be an isolated case.

Long-term follow-up is normally required due to the possibility of the disease recurring. As many as 30% of patients have relapses of the disease and of these, 43% progress to other organ systems.[44] All relapsed patients usually respond well to the re-induction of steroid therapy as seen in our review.[42] Finally, it is worth mentioning that a recent trial[45] on rituximab, with the ability to rapidly deplete B- cells leading to a reduction in IgG, showed a 47% remission rate at 6 months. It has increasingly been used in recent years with corticosteroids in an attempt to reduce the relapse rate.[3,45,46] The effectiveness of such regime solely on temporal bone involvement is unknown; however, given the systemic nature of the disease, it is likely to have promising outcomes.

Limitations

There are some limitations to this thorough systematic review which arose from the quality of data available. IgG4-RD involving the temporal bone is a rare entity with a relatively small number of cases reported in the literature. The level of evidence of the studies included in this review are levels 4 and 5, which are at the base of the level of the evidence pyramid.[18] There were also some heterogeneities in the reporting of information about the course of treatment and patient outcome at last follow-up in some cases. We used the JBI Case Report[16] and Series[17] risk of bias tool to exclude low-quality studies and minimise the risk of bias. Nevertheless, this compilation of cases of the disease in the temporal bone is the first large review in the literature, which provides a platform to understand the disease.

Conclusion

Temporal bone IgG4-RD is a rare disease that should be included in the differential diagnosis of any atypical masses found on lateral skull base imaging. Biopsy with histological and immunohistochemical analysis is the golden standard for diagnosis. Corticosteroids and/or surgical resection are the most utilised management options, with surgery primarily being utilised for biopsy purposes. Recent trials have also shown promising results with rituximab, which can be used alongside corticosteroids to try to reduce the relapse rate. Additional cases need to be reported to better understand the nature and prognosis of the disease.

Conflict of interest

This research was not funded by any organisation. There is no conflict of interest to declare.

Ethical statement

This article did not involve patients but studies.

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Legends for Figures

Figure 1: Prisma Flow Diagram of included and excluded studies.

Table 1: Characteristics of studies meeting criteria for review.

Author	Year	Study type	Number of cases with temporal bone involvement	Total Case number	Age	Gender	Demographic	Oxford Centre for Evidence-Based Medicine (CEBM)[18]
Masterson et al.[19]	2010	Case report	1	1	58	F	UK	5
Schiffenbauer et al.[20]	2012	Case report	1	2	50	F	US	5
Moss et al.[21]	2012	Case report	1	3	36	F	US	5
Bittencourt et al.[22]	2013	Case report	1	4	28	M	Brazil	5
Nishijima et al.[23]	2013	Case report	1	5	66	F	Japan	5
Wang et al.[24]	2014	Case report	1	6	38	M	China	5
Cain et al.[25]	2014	Case report	1	7	66	M	US	5

Liu et al.[26]	2015	Case report	1	8	71	M	China	5
Li et al.[27]	2016	Case report	1	9	52	M	US (Chinese)	5
Wick et al.[28]	2016	Case report	1	10	61	F	US	5
Vuncannon et al.[29]	2017	Case report	1	11	35	F	US	5
Chowsilpa et al.[30]	2019	Case report	1	12	19	F	Thailand	5
Cheng et al.[31]	2019	Case report	1	13	54	F	China	5
Detiger et al.[32]	2020	Case series	1	14	73	M	Netherlands	4

Deshpande et al.[33]	2016	Case series	3	15	43	F	US	4
				16	52	F	US	
				17	50	F	US	
Melenotte et al.[34]	2019	Case series	1	18	58	F	France	4
Marinelli et al.[35]	2020	Case series	4	19	55	M	US/ Italy	4
				20	66	F	US/ Italy	
				21	59	F	US/ Italy	
				22	65	M	US/ Italy	
								Aggregate: 3b

Table 2: Details of location of disease and symptoms of every cases.

Case number	Year	Authors	Locations involved	Presenting symptoms
1	2010	Masterson et al.[19]	Mastoid, lateral semi-circular canal, stapes, facial nerve canal, head of malleus, temporal bone.	Sensorineural hearing loss and tinnitus, vertigo.
2	2012	Schiffenbauer et al.[20]	Left mastoid bone, external auditory canal, temporal squamosa.	CN VII palsy, otitis media, otalgia.
3	2012	Moss et al.[21]	Left petrous bone, cavernous sinus, orbital apex, middle cranial fossa, anterior cranial fossa, cerebellopontine angle.	Diplopia, headache, vision loss, CN VI palsy.
4	2013	Bittencourt et al.[22]	Right temporal bone, mastoid, posterior fossa, sigmoid sinus, transverse sinus.	Headache, otalgia, hearing loss, tinnitus.
5	2013	Nishijima et al.[23]	Middle ear, meninges, temporal bone, orbit	Ear fullness, headache, diplopia, ptosis, hearing loss, facial numbness

6	2014	Wang et al.[24]	Mass in right mastoid, enhanced in the right meninges and transverse and sigmoid sinuses, with temporal bone involvement.	Right catarrhal otitis media, right temporal headache, blurred vision.
7	2014	Cain et al.[25]	Central skull base with bilateral involvement of the nasopharynx, parapharyngeal tissue, petrous apex.	Headache, vertigo, hearing loss.
8	2015	Liu et al.[26]	Mass in the right nasopharynx, blocking the eustachian tube, mastoiditis; also infiltrated bone of the skull base and encased the internal carotid	Hearing loss, tinnitus, upper neck pain.
9	2016	Li et al.[27]	Bilateral temporal bone (labyrinth), posterior fossa.	Bilateral hearing loss, vestibular dysfunction, otalgia.
10	2016	Wick et al.[28]	Petrous apex, posterior petrous bone, middle ear, encasing internal carotid artery, cavernous sinus, posterior and middle cranial fossa, geniculate ganglion and internal auditory canal.	Otalgia, hearing loss, facial weakness, diplopia CN VI palsy, CN VII palsy.
11	2017	Vuncannon et al.[29]	Middle ear, petrous portion of the temporal bone, middle cranial fossa, carotid canal	Hearing loss, otalgia, tinnitus, dizziness

12	2019	Chowsilpa et al.[30]	Temporal bone, cavernous sinus, middle cranial fossa, petrous apex, sphenoid sinus, maxillary sinus	Left otalgia, lateral rectus palsy, headache, left hearing loss
13	2019	Cheng et al.[31]	Temporal bone, middle ear, tympanic cavity.	Otalgia, tinnitus and hearing loss in the left ear.
14	2020	Detiger et al.[32]	Left petrous bone with involvement of the prevertebral and carotid space.	Hearing loss and left otalgia and left jaw pain, otitis media.
15	2016	Deshpande et al.[33]	Temporal bone erosion, mastoid, middle ear, pterygopalatine fossa, foramen rotundum, nasopharynx, superior and inferior orbital fissure.	Pulsatile tinnitus, hearing loss, mastoiditis.
16			Mastoid, meninges, erosion of temporal bone.	Headache, hearing loss, otalgia, CN VII weakness, mastoiditis.
17			Mastoid, retrofacial space, temporal bone erosion	CN VII paresis. Serous otitis media, hearing loss, barotitis, mastoiditis

18	2019	Melenotte et al.[34]	Partial temporal bone lysis, frontal skull base, fronto-temporal axial dura (meninges), orbital apex	Hallucination, aphasia, seizures, cognitive decline.
19	2020	Marinelli et al.[35]	Suprasellar/sphenoid, clivus, petrous ridge.	Headache, fatigue, weight loss, diplopia.
20			Internal auditory canal, cavernous sinus, temporal bone.	Headache, facial pain, vertigo, sensorineural hearing loss, diplopia.
21			Cavernous sinus, bilateral internal auditory canal, temporal bone.	Headache, proptosis, sensorineural hearing loss.
22			Mastoid, tympanic cavity eroding into the body labyrinth, posterior and middle fossa, temporal bone.	Vertigo, tinnitus, conductive hearing loss.

Table 3: Summary of symptoms and locations of IgG4 disease with temporal bone involvement.

Symptoms	Number (%)	Locations of IgG4 disease with temporal bone involvement	Number (%)
Hearing loss	17 (77.3%)	**Mastoid**	10 (45.5%)
Otalgia	10 (45.5%)	**Petrous part of temporal bone (excluding middle and inner ear involvement)**	9 (40.9%)
Headache	8 (36.4%)	**Middle ear**	9 (40.9%)
Diplopia	8 (36.4%)	**Middle cranial fossa**	6 (27.3%)
Tinnitus	7 (31.8%)	**Meninges (pachymeningitis)**	6 (27.3%)
Otitis media/ middle ear effusion	6 (27.3%)	**Posterior fossa**	4 (18.2%)
Vertigo	5 (22.7%)	**Cavernous sinus**	4 (18.2%)
Mastoiditis	4 (18.2%)	**Internal auditory canal**	3 (13.6%)
Cranial nerve involvement		**Nasopharynx**	3 (13.6%)
VII	5 (22.7%)	**Sigmoid sinus**	2 (9.1%)
VI	3 (13.6%)	**Transverse sinus**	2 (9.1%)
V	1 (4.5%)	**Bony labyrinth, cochlea**	2 (9.1%)
X	1 (4.5%)	**Encasing Internal carotid artery**	2 (9.1%)
Parotitis	1 (4.5%)	**Orbital apex**	2 (9.1%)
Jaw pain	1 (4.5%)	**Facial nerve canal**	1 (4.5%)

Seizure	1 (4.5%)	**Geniculate ganglion**	1 (4.5%)
Hallucination	1 (4.5%)	**Squamous part of temporal bone**	1 (4.5%)
Aphasia	1 (4.5%)	**Lateral semicircular canal**	1 (4.5%)
Proptosis	1 (4.5%)	**Anterior cranial fossa**	1 (4.5%)
		Sphenoid sinus	1 (4.5%)
		Maxillary sinus	1 (4.5%)
		Parapharyngeal tissue	1 (4.5%)
		Pterygopalantine fossa	1 (4.5%)
		Foramen rotundum	1 (4.5%)
		Retrofacial space	1 (4.5%)
		Superior and inferior orbital fissure	1 (4.5%)
		Suprasellar region	1 (4.5%)
		Cerebellopontine angle	1 (4.5%)
		Prevertebral and carotid space	1 (4.5%)
		Upper neck pain	1 (4.5%)

Table 4a: Summarizing detailed treatments, relapse and follow up time of every patient.

Case number	Initial treatment modality once diagnosis was confirmed	Initial treatment response	Side effects	New treatment given due to side effects from initial medications.	Relapse	Treatment of relapse	Follow up time (in months)
1	CS + MMF + S	Good	Nil	Nil	Nil	Nil	12
2	CS + S	Good	Nil	Nil	Yes	CS	12
3	CS + S	Good	Yes	MMF	Nil	Nil	18
4	S + CS + AZA	Good	Nil	Nil	Nil	Nil	12
5	CS + S	Poor	Nil	Nil	Yes	CYC	12
6	CS + S	Good	Nil	Nil	Nil	Nil	22
7	CS	Good	Nil	Nil	Nil	Nil	24
8	CS	Good	Nil	Nil	Nil	Nil	3
9	CS + S	Good	Nil	Nil	Nil	Nil	5
10	CS + S	Good	Yes	AZA	Nil	Nil	33
11	CS + S	Good	Nil	Nil	Nil	Nil	2

12	**CS + S**	**Good**	Nil	Nil	Nil	Nil	**12**
13	**S**	**Good**	Nil	Nil	Nil	Nil	**24**
14	**S + CS + HCQ**	**Good**	Nil	Nil	**Yes**	**CS + RAD**	**8**
15	**S + RAD + CS**	**Good**	Nil	Nil	**Yes**	**RTX**	**-**
16	**S + RTX**	**Good**	Nil	Nil	Nil	Nil	**-**
17	**S + CS**	**Good**	Nil	Nil	**Yes**	**CS**	**-**
18	**S + CS + RTX**	**Good**	Nil	Nil	**Yes**	**CS + RTX**	**18**
19	**CS + RTX**	**Good**	Nil	Nil	Nil	Nil	**-**
20	**CS + RTX**	**Good**	Nil	Nil	**Yes**	**CS**	**-**
21	**CS + RTX**	**Good**	Nil	Nil	Nil	Nil	**-**
22	**S + CS + RTX**	**Good**	Nil	Nil	Nil	Nil	**-**

(S=surgery, CS= corticosteroids, RTX= rituximab, CYC= cyclophosphamide, AZA= azathioprine, MMF= mycophenolate mofetil, HCQ= hydroxychloroquine, RAD= radiation therapy)

Response to treatment is based on how this has been documented in the published works.

Table 4b: Analysis of initial treatment regimen and relapses.

Initial treatment modality	
Global initial efficacy	21/22 (95.5%)
Corticosteroids alone	2/22 (9.1%)
Surgery alone	1/22 (4.5%)
Corticosteroids and surgery	9/22 (40.9%)
Corticosteroids + surgery + radiation	1/22 (4.5%)
Rituximab and surgery	1/22 (4.5%)
Corticosteroids & other immunosuppressant therapy +/- surgery	8/22 (36.4%)
• **Steroid + Rituximab**	3/22 (13.6%)
• **Steroid + Rituximab+ surgery**	2/22 (9.1%)
• **Steroid + Mycophenolate mofetil + surgery**	1/22 (4.5%)

• **Steroid + Azathioprine + surgery**	1/22 (4.5%)
• **Steroid + Hydroxychloroquine + surgery**	1/22 (4.5%)
Relapses	7/22 (31.8%)
Stop corticosteroids due to side effects	2/22 (4.5%)
Poor response to steroid switched to cyclophosphamide	1/22 (4.5%)

Table 5: Summary of surgical approach used.

Surgical Approach Used to resect/debride Temporal Bone IgG4-RD	
Characteristics	**No. of patients (n= 22)**
Number of patients who had surgery	17
Total Number of Surgical Procedures	22
Mastoidectomy (canal wall up/ modified radical)	16
Craniotomy + petrosectomy + petrous apicectomy	1
Myringotomy	2
Sphenoidotomy (functional endoscopic sinus surgery) + resection	1
Exploratory tympanotomy and functional endoscopic sinus surgery	1
Temporal bone resection	1

Figure 1

Figure 1: Prisma Flow Diagram of included and excluded studies.