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Head and neck immunoglobulin G4 related disease: systematic review

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Abstract

Background. Immunoglobulin G4 related disease is a recently described systemic syndrome. The head and neck region is the second most common site for presentation after the pancreas.
Methods. PubMed and the Cochrane Library were searched from 1995 to July 2017 for all the studies on immunoglobulin G4 related disease diagnosed in the head and neck compartment. Patient-specific data were extracted and basic statistical analysis was performed.
Results. Ninety-one patients were identified. Treatment was specified in 76 patients. Twenty patients received surgical treatment, eight of them in association with medical therapy. Fifty-six patients received medical treatment. The disease recurred in 25 per cent of patients treated with surgical treatment alone, in 3.6 per cent of patients treated with medical treatment alone and in 12.5 per cent of patients treated with both. All medical treatment protocols contained high-dose corticosteroids.
Conclusion. Early and correct diagnosis can avoid unnecessary surgical treatment, and glucocorticoid therapy can improve the long-term prognosis.

Review Article

Dr N Gardenal takes responsibility for the integrity of the content of the paper

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Introduction

Immunoglobulin G4 (IgG4) related disease is a recently described systemic syndrome. It is a multifocal, fibrosclerotic, inflammatory disorder, first recognised in 2001 by Hamano *et al.*, who associated autoimmune pancreatitis and elevated serum IgG4 levels.[1] Immunoglobulin G4 related disease has since been described in several organs. There is a spectrum of immune-mediated diseases that share clinical, pathological and serological features, gathered together under the definition of 'IgG4-related disease'.[2,3]

The hallmark of the disease is a tumour-like swelling of the involved organ, characterised by a dense lymphoplasmacytic infiltration with a predominance of IgG4-positive plasma cells.[4] Patients present with diffuse organ swelling or focal mass formation in the pancreas, biliary tree, aorta, retroperitoneum, lung, salivary and lacrimal glands, thyroid, kidney, meninges, pituitary gland, prostate, breast, and other organs.[5] Symptoms depend on the localisation, and serum IgG4 levels are elevated (more than 135 mg/dl) in about 60 per cent of patients.[6]

The head and neck region is the second most common site for IgG4-related disease after the pancreas.[7] Head and neck manifestations encompass several disorders that were previously considered as separate entities, such as Mikulicz's disease (painless bilateral enlargement of the submandibular, parotid and lacrimal glands), Küttner's tumour (isolated chronic sclerosing sialadenitis of the submandibular gland), Riedel's thyroiditis, and many cases of orbital pseudo-tumour, idiopathic cervical fibrosis and idiopathic hypertrophic pachymeningitis.[8]

Given its relatively recent discovery, there is a paucity of high-quality publications on this topic. Most data on patients' management and treatment outcome of IgG4-related disease with head and neck manifestations are in the form of case reports and small case series, which provide a low level of evidence. This systematic review aimed to examine the clinical presentation of IgG4-related disease in the head and neck, and to report existing evidence on its management and treatment outcomes.

Materials and methods

A systematic review of published reports on IgG4-related disease in the head and neck was performed. The databases PubMed (1995 to July 2017) and Cochrane Library were searched using the search terms: 'IgG4 related disease' or 'IgG4-RD', plus 'head and neck', 'cervical nodes', 'Mikulicz disease', 'Küttner tumour', 'nose' or 'salivary glands'. Two independent reviewers screened the identified articles on the basis of their relevance to the topic. Discrepancies were resolved by consensus among the reviewers. We included all original studies, case reports, case series and reviews published in English. Relevant articles were obtained and reviewed in full, and the reference lists from these sources were also reviewed for additional publications.

The inclusion criteria were: original clinical studies, case series, case reports and reviews reporting data on patients with histologically confirmed IgG4-related disease in

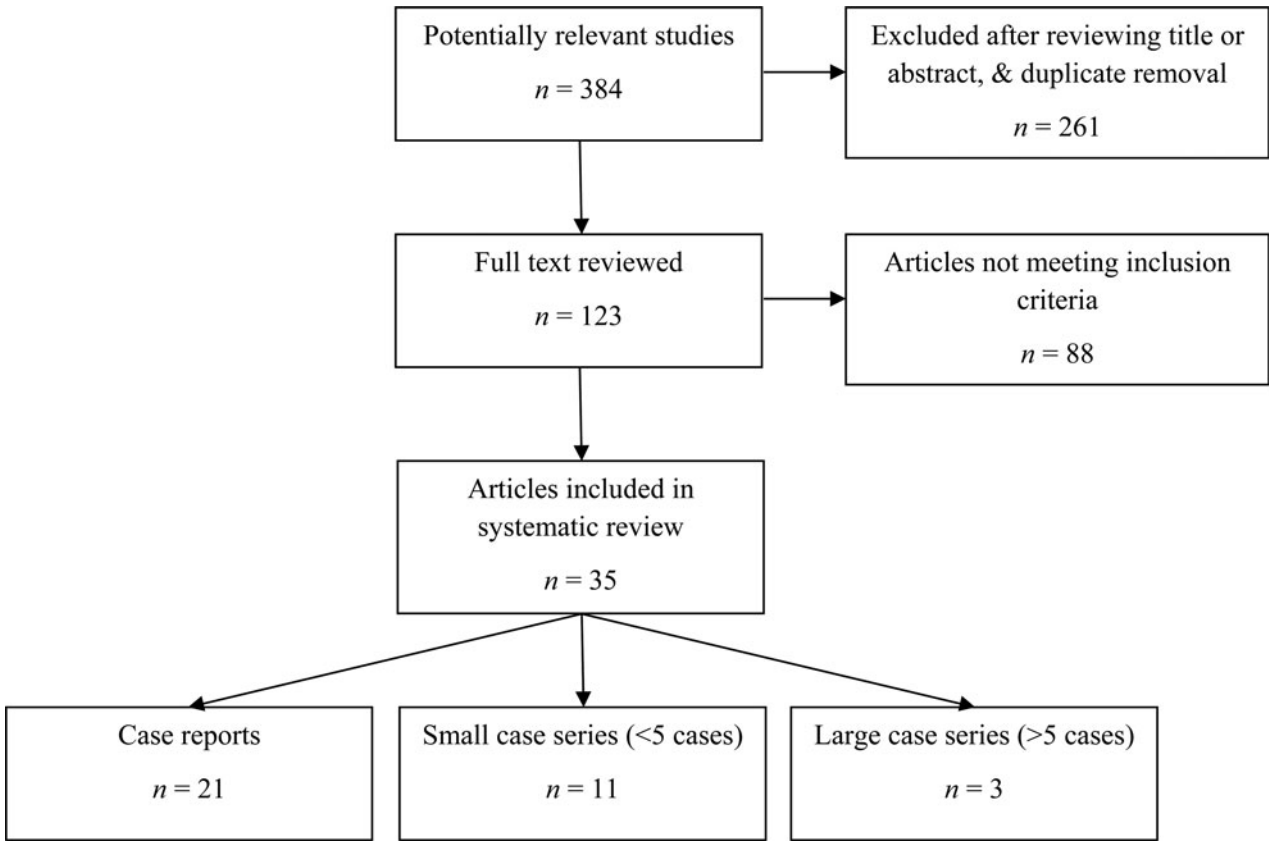

Fig. 1. Flow chart of eligible and excluded studies, and type of included studies.

the head and neck. We selected manuscripts in which the histological diagnosis of IgG4-related disease was specified and tissue biopsy came from a head and neck subsite. The histological diagnosis of IgG4-related disease had to be based on the identification of more than 10 IgG4-positive plasma cells per high-powered field, an IgG4-positive/IgG plasma cell ratio of 40 per cent or greater, and characteristic findings of fibrosis, sclerosis and phlebitis.[4–9] We excluded papers with no specific clinical data for each patient, in particular age, sex, disease localisation, symptoms, IgG4 serum level, treatment type and clinical outcome.

Patient-specific data were extracted, and basic statistical analysis, including descriptive statistics, was performed using Excel spreadsheet software (version 14.0, Microsoft®).

Results

We initially identified 384 potentially relevant studies; 261 articles were excluded in light of duplication and after reviewing the title or the abstract. Thus, 123 articles were reviewed in full text form. Of these 123 papers, 88 were excluded because they did not meet all the inclusion criteria for this review. Finally, 35 articles were included in this systematic review. A flow chart of the eligible and excluded studies, and the type of included studies, is shown in Figure 1.

A significant number of studies were from Asia ($n = 17$; 48.6 per cent), nine of which were from Japan (25.7 per cent) (Table 1). Ninety-one patients were identified: 41 females (45 per cent) with a mean age of 56 years, and 50 males (55 per cent) with a mean age of 62.8 years. Table 2 shows all the subsites involved in the clinical manifestations of IgG4-related disease in this patient series.

Table 1. Country of origin of included articles

Country of origin	Articles (*n* (%))*
Australia	2 (5.7)
Europe	5 (14.3)
Asia	17 (48.6)
USA	11 (31.4)

*Total $n = 35$

Immunoglobulin G4 serum level was specified in 67 patients, and, of these patients, 53 (79 per cent) had elevated serum IgG4 concentrations (more than 135 mg/dl) (Figure 2). A histological diagnosis was obtained on a surgical head and neck specimen in 20 patients (22 per cent) and on a tissue biopsy in 71 patients (78 per cent).

Treatment was specified in 76 patients (Table 3). Twenty patients received surgical treatment (nine had unilateral sialoadenectomy, two had bilateral sialoadenectomy, three underwent neck dissection, two received radical mastoidectomy, three underwent endoscopic debulking of the nasal fossa and one underwent oropharyngeal laser carbon dioxide mass resection), eight of them in association with medical treatment. Fifty-six patients received medical treatment alone. In this case series, the disease recurred in 25 per cent of patients treated with surgical treatment alone, in 12.5 per cent of patients treated with surgical and medical treatment, and in 3.6 per cent of patients treated with medical treatment alone. All medical treatment protocols contained high-dose corticosteroids; in 12 patients, immunosuppressive medication was utilised with steroid therapy.

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Table 2. Clinical manifestations of IgG4-related disease in this patient series

Sites of clinical manifestations	Number (%)*
Glands	68 (60)
– Parotid	23
– Submandibular	45
– Lacrimal	18
– Sublingual	12
– Labial	8
Nose	15 (13)
– Ethmoid	5
– Maxillary	5
– Sphenoid	2
– Nasal fossa	2
– Nasal septum	3
Lymph nodes	17 (15)
Other	13 (12)
– Mastoid	2
– Oral-oropharyngeal cavity	6
– Larynx	3
– Cervical fascia	2

*Total *n* = 113. IgG4 = immunoglobulin G4

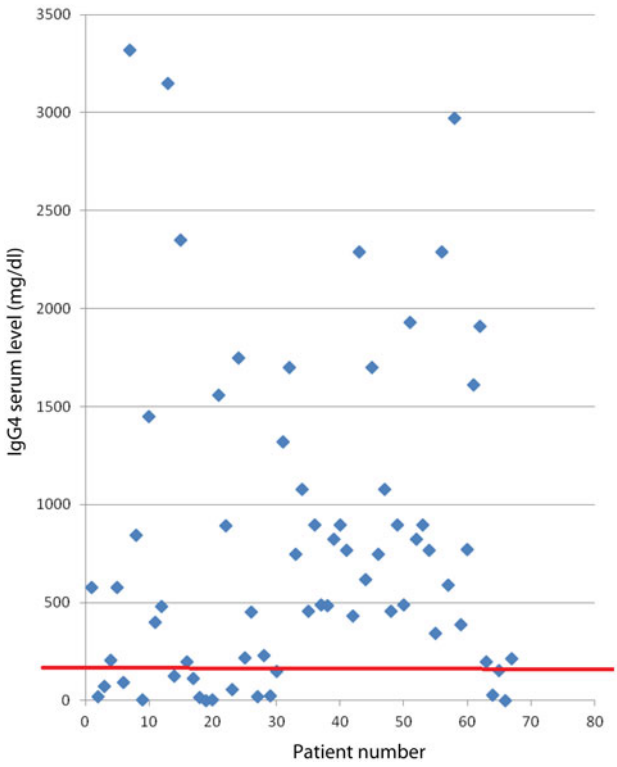

Fig. 2. Immunoglobulin G4 (IgG4) serum level (values above red line are more than 135 mg/dl).

Discussion

This systematic review confirms the high tendency of IgG4-related disease to present in the head and neck region. We included 35 papers reporting the data of 91 patients with histologically confirmed IgG4-related disease in the head and neck compartment. A significant number of studies were from Japan. This is probably because of the high attention given to the disease in this country. In recent years, two IgG4-related disease study groups have been set up by the Japanese Ministry of Health, Labour and Welfare, to establish the diagnostic criteria and aetiopathogenesis of the disease. This resulted in the publication of comprehensive diagnostic criteria in 2011; these are currently considered the most rigorous diagnostic criteria (Table 4).[9]

Table 3. Treatment and local recurrences

Treatment	Patients (*n*)	Recurrences (*n* (%))
Surgical treatment alone	12	3 (25) (+ 1 lost to FU)
Surgical & medical treatment	8	1 (12.5)
– Surgical treatment with corticosteroid alone	4	0 (0)
– Surgical treatment with corticosteroid & other immunosuppressant	4	1 (25)
Medical treatment alone	56	2 (3.6)
– Medical treatment with corticosteroid alone	48	0 (0)
– Medical treatment with corticosteroid & other immunosuppressant	8	2 (25)

FU = follow up

Common salivary gland symptoms are dry mouth and salivary gland swelling. Sicca symptoms are often less severe than in Sjögren's syndrome and, when present, typically respond well to immunosuppressive therapy.[10] Lacrimal gland involvement generally causes facial and orbital swelling. Extra-ocular muscle involvement can present with exophthalmos and the restriction of ocular movements.[11] Nose and paranasal manifestations were nasal obstruction, pain, epistaxis and rhinorrhoea. Sinonasal IgG4-related disease can lead to a progressive destructive process; therefore, early diagnosis and treatment are fundamental.[12]

Cervical lymphadenopathy is a common feature of IgG4-related disease and can accompany any organ involvement. In this case series, cervical node enlargement was specified in 17 cases. Nodes are enlarged, with homogeneous enhancement, and no calcification or necrosis.[13] According to some authors, lymphadenopathy of the cervical lymph nodes should therefore also be considered an important clinical feature in the diagnosis of IgG4-related disease.[14]

Other manifestations could be summarised by their mass effect on involved anatomical structures (dysphonia and dyspnoea for the larynx, sore throat for the oropharynx, hearing loss and vestibular dysfunction for the ear). One patient exhibited an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, arising in a background of IgG4-related disease with a cervical mass.[15]

Epithelial malignancies have also been described, including sclerosing mucoepidermoid carcinoma and salivary duct carcinoma, as well as papillary thyroid carcinoma.[16,17] The relationship between IgG4-related disease and malignancy is still unclear. Malignancies occurred in 10.4 per cent of IgG4-related disease cases, approximately 3.5 times higher than the incidence of cancer in the general population.[18]

Serum IgG4 concentration has poor positive predictive value in the diagnosis of IgG4-related disease and, thus, its clinical significance must be interpreted with caution.[19]

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Table 4. Comprehensive clinical diagnostic criteria for IgG4-related disease[9]

1. Clinical examination shows characteristic diffuse or localised swelling, or masses in single or multiple organs
2. Haematological examination shows elevated serum IgG4 concentrations (>135 mg/dl)
3. Histopathological examination shows: marked lymphocyte & plasmacyte infiltration & fibrosis; & IgG4+ plasma cell infiltration (IgG4+/IgG+ cell ratio of ≥40%, & >10 IgG4+ plasma cells per high-powered field)

Diagnosis: definite = 1 + 2 + 3; probable = 1 + 3; possible = 1 + 2. IgG4 = immunoglobulin G4

Elevated serum IgG4 level can be also found in other immune-mediated diseases such as Churg–Strauss syndrome, multicentric Castleman's disease, rheumatoid arthritis, systemic sclerosis, chronic hepatitis and liver cirrhosis.[20] Serum IgG4 concentration still has valuable diagnostic utility when the pre-test probability of the disease is high. In fact, in the cases we analysed, all patients already had a histological diagnosis of disease. Nonetheless, 21 per cent of the patients had no elevated serum IgG4.

Histopathology is key in the diagnosis of IgG4-related disease, and core biopsy or surgical excision is required for a definitive diagnosis.[21] In this case series, the histology was obtained on a surgical head and neck specimen in 20 patients (22 per cent) and on a tissue biopsy in 71 patients (78 per cent). However, performing a biopsy in the head and neck is not always safe, given the non-negligible risk of damage to nervous or vascular structures, and the risk of cancer cell seeding in the case of nodal metastasis from carcinoma. Labial salivary gland biopsy has been proposed as a less invasive procedure than sialoadenectomy or incisional biopsies of the salivary glands. In a recent study, sensitivity, specificity and accuracy of labial gland biopsies were 69.2 per cent, 100.0 per cent and 71.4 per cent, respectively, whereas those of submandibular gland biopsies were all 100.0 per cent. As a result, labial gland biopsy is not recommended as a diagnostic technique.[22] To our knowledge, no literature exists regarding IgG4-related disease diagnosed by fine needle aspiration cytology or by fine needle aspiration biopsy.

Radiological imaging is mostly non-specific for IgG4-related disease, as it is unable to distinguish IgG4-related lesions from neoplastic conditions presenting with mass formation. Furthermore, these IgG4-related lesions may occasionally result in destruction of the underlying bony structures, mimicking malignancy.[23] Fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) is more sensitive than conventional imaging (ultrasound, computed tomography, magnetic resonance imaging) for detecting active localisations of IgG4-related disease. However, abnormal fluorodeoxyglucose uptake can be observed in several other inflammatory, malignant or even infectious disorders.[24] Imaging using FDG-PET/CT is useful for the staging of IgG4-related disease and mostly for assessing the response to treatment during follow up.[24]

Treatment was specified in 76 patients (Table 3). Twenty patients received surgical treatment. In all cases, surgery was carried out before the diagnosis of IgG4-related disease. Immunoglobulin G4 related disease was not recognised at an early stage in 22 per cent of patients who underwent surgical treatment for a head and neck mass before receiving a clinical diagnosis of IgG4-related disease.[25] Fifty-six patients received only medical treatment. There are limited prospective data on treatment. Immunoglobulin G4 related disease responds rapidly to steroid treatment, with a nearly 100 per cent initial response rate. Relapse is not rare (occurring in up to 47 per cent of cases), based on data from patients with autoimmune pancreatitis.[26]

Treatment protocols vary in accordance with local standards. Groups from the USA favour a four-week course of 40–80 mg prednisolone per day,[27] followed by steroid tapering until discontinuation. In contrast, the Japanese treatment guidelines for autoimmune pancreatitis recommend a two to four week course of prednisolone of 0.6 mg/kg bodyweight per day, gradually reduced by 5 mg for two weeks, and maintenance at 2.5–5.0 mg for up to three years.[28] Maintenance treatment with low-dose steroids appears to decrease the risk of relapse. Within weeks, there can be a decrease in lesion load, improvement in symptoms and a decrease in IgG4 levels. These results are excellent, but the side effects can limit use of these regimens. Such treatments should therefore be given only to patients with a definitive diagnosis of IgG4-related disease.

An alternative to corticosteroid therapy for IgG4-related disease is rituximab, the use of which was reported to lead to prompt clinical and serological improvement in refractory IgG4-related disease in all patients with active inflammation.[29] Other treatments that have been proposed include azathioprine, cyclophosphamide, methotrexate and mycophenolate mofetil, but these therapies have little supporting data.[30]

In this case series, the disease recurred in 25 per cent of patients treated with surgical treatment alone, in 12.5 per cent of patients treated with surgical and medical treatment, and in 3.6 per cent of patients treated with medical treatment alone. All medical treatment protocols contained high-dose corticosteroids. These data confirm strongly that in head and neck IgG4-related disease the first-line therapy should be medical, with a relatively large dose of glucocorticoids ('assault therapy') in the short term and a small dose as maintenance therapy in the long term. A critical aspect of the analysed studies is the short follow-up period. Follow up is not always specified, and generally ranges from one month to one year, with only three patients being followed up for several years.

Immunoglobulin G4-related disease is a clinical entity that can be underdiagnosed if not recognised or over-diagnosed if the diagnostic criteria are not respected. It is important to recognise and obtain a histopathological diagnosis of IgG4-related disease because early intervention with glucocorticoids therapy might improve the long-term prognosis.

Competing interests. None declared

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