

## Original Article

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## Magnetic resonance imaging evaluation of head and neck involvement in IgG4-related disease

Umur Anil Pehlivan<sup>1✉</sup>, Kamil Karaali<sup>2</sup>, Hatice Deniz Ilhan<sup>3</sup>, Mehmet Soy<sup>4</sup>, Didem Arslan<sup>5</sup>, Omer Kaya<sup>6</sup>, Rabia Miray Kisla–Ekinci<sup>7</sup>, Burcak Cakir–Pekoz<sup>8</sup>, Ummuhan Cay<sup>9</sup>, Arbil Acikalin<sup>10</sup>, Ahmet Muhtesem Agildere<sup>11</sup><sup>1</sup>Department of Radiology, Başkent University Adana Dr. Turgut Noyan Application and Research Center, Adana, Turkey<sup>2</sup>Department of Radiology, Akdeniz University Faculty of Medicine, Antalya, Turkey<sup>3</sup>Department of Ophthalmology, Akdeniz University Faculty of Medicine, Antalya, Turkey<sup>4</sup>Department of Internal Medicine and Rheumatology, Bahçelievler Medical Park; Altınbaş University Faculty of Medicine, İstanbul, Turkey<sup>5</sup>Department of Internal Medicine and Rheumatology, Çukurova University Faculty of Medicine, Adana, Turkey<sup>6</sup>Department of Radiology, Çukurova University Faculty of Medicine, Adana, Turkey<sup>7</sup>Department of Pediatric Rheumatology, Adana City Training and Research Hospital, Adana, Turkey<sup>8</sup>Department of Radiology, Adana City Training and Research Hospital, Adana, Turkey<sup>9</sup>Department of Pediatric Infectious Disease, Çukurova University Faculty of Medicine, Adana, Turkey<sup>10</sup>Department of Pathology, Çukurova University Faculty of Medicine, Adana, Turkey<sup>11</sup>Department of Radiology, Başkent University Faculty of Medicine, Ankara, Turkey

## ABSTRACT

**Objective:** To evaluate the radiological features of IgG4-related disease (IgG4-RD) in the head and neck region.

**Methods:** In this radiology-based study, radiological features, clinical, laboratory, pathological findings, and prognosis of nine patients with head and neck involvement diagnosed with IgG4-RD were investigated retrospectively.

**Results:** The median age of the patients was 38 years (range: 25–79 years), and there were six males and three females. The most common symptoms and clinical findings of the patients were eyelid and lacrimal gland swelling, painless exophthalmos, and ophthalmoplegia. The most common site of involvement on MRI was the orbit. Orbital involvement was followed by branches of the trigeminal nerve, sinonasal cavity, cervical lymph nodes, and dural involvement. The most common and remarkable imaging features were T2 hypointensity and diffuse homogeneous contrast enhancement.

**Conclusions:** Head and neck involvement of the IgG4-RD, has specific imaging features that can help with diagnosis. Thus, early diagnosis and better outcomes can be achieved with increasing awareness of these features of this relatively new pathology.

**Keywords:** IgG4; Head and neck imaging; Magnetic resonance imaging; Orbit; Perineural spreading

## 1. Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated and fibroinflammatory pathology with multisystemic involvement identified in the last two decades[1,2]. The initial description of IgG4-RD was the detection of elevated IgG4 levels in serum and biopsy

## Significance

IgG4-RD is a relatively new pathology that can present with mass-like lesion that can also cause involvement in the head and neck. IgG4-RD has specific imaging features such as showing T2 shortening and diffuse contrast enhancement. It should be kept in mind that also one of the pathologies that can cause perineural spreading is IgG4-RD.

✉To whom correspondence may be addressed. E-mail: uapehlivan@gmail.com

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specimens in patients with autoimmune pancreatitis in 2001[3]. In 2003, it was described that this condition is not only unique to the pancreas and can affect more than 40 different organs including some organs in the head and neck[2,4–7]. The exact etiology of IgG4-RD is still not clear. However, the relationship between IgG4-RD and some environmental factors, and genetic predisposition has been suggested[7,8]. The definitive prevalence and incidence of IgG4-RD are unknown since it is a new entity and there is no widespread awareness of the disease[6,8]. Systemic involvement of IgG4-RD is more common in males, while the involvement of the head and neck is more common in females. Although not always, it is often accompanied by an increase in serum IgG4 levels[5,6,8]. The most important clinical feature of IgG4-RD is that it responds very well to corticosteroid therapy[6,8,9]. The head and neck involvement is the second most commonly involved region after the pancreas in IgG4-RD. Diagnosing and treating head and neck involvement can be confusing[2,5–7]. Various symptoms and clinical findings according to involvement sites in the head and neck region can be observed in IgG4-RD[10–15].

Depending on the degree of fibrosis of the disease, head and neck involvement in IgG4-RD may present with different radiological findings. Generally, iso-hypointense swollen lesions are usually seen on T1- and T2-weighted images, while homogeneous contrast enhancement is observed on post-contrast images[5,7,16,17]. Lesions may show diffusion restriction on diffusion-weighted images (DWI) due to intense cellularity[7]. In addition, CT and 18F-FDG PET/CT are of great importance for the evaluation of multi-organ involvement[5]. With 18F-FDG PET/CT, information about functional activity related to the disease, evaluation of response to treatment, and information about optimal biopsy sites is obtained[18]. On head and neck CT, remodeling, and erosion of the surrounding bone structures at the site of involvement can be observed[5,16,17]. On 18F-FDG PET/CT, diffuse or multifocal FDG uptake is observed in the area of involvement[18]. Orbital and salivary gland involvement is usually bilateral, but can also be seen unilaterally. Cases presenting with perineural spread, involving the cranial nerve in the head and neck region have been described. In cases of unilateral lesions and perineural spread, malignant processes are involved in the differential diagnosis, and diagnosis may be difficult[5,11,19].

T-cell lymphocyte infiltration, irregular fibrosis, and obliterative vasculitis are seen in the histopathology of IgG4-RD[5,8]. While the cardinal pathological sign of IgG4-RD is diffuse infiltration of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis have also been added to diagnostic criteria[9].

Herein we aimed to evaluate the radiological features of nine patients with head and neck involvement diagnosed with IgG4-RD, retrospectively.

## 2. Subjects and methods

### 2.1. Study design and ethical approval

This is a retrospective cohort study that has a multicenter plan and was performed in accordance with the ethical standards of the Institutional Clinical Research Ethical Committee and with the 2013 Helsinki Declaration. This study has obtained approval from the Local Research Ethical Committee (decision No: 47 date: 13.05.2022). Informed consent for the publication of data was obtained from all participants included in this study.

### 2.2. Patient selection

Nine patients with IgG4-RD involvement in the head and neck region diagnosed in five centers participating in this study were included. The cases were diagnosed between May 2018–March 2022. The criteria for inclusion in this study were 1) To provide IgG4-RD diagnostic criteria described by the Japanese IgG4 team organized by the Ministry of Health, Labor and Welfare of Japan[9], 2) To be evaluated by MRI at the time of diagnosis, and 3) To follow up on the response to treatment. Patients with suspicious findings in terms of malignancy were excluded from the study. The 2020 revised comprehensive diagnostic criteria for IgG4-related disease include three items. If all three items are fulfilled, the diagnosis is definite, if the 1st and 3rd items are fulfilled the diagnosis is probable, if the 1st and 2nd criteria are fulfilled the diagnosis is possible. These items are described below:

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.)
2. Serological diagnosis (Serum IgG4 levels greater than 135 mg/dL)
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[9].

### 2.3. Clinical and radiological findings and follow-up

In this study, patients' data including demographic characteristics, clinical symptoms, findings, serum IgG4 level, radiological involvement zone in the head and neck region, whether there is the involvement of another region, treatment type, treatment response, and prognosis were retrospectively evaluated.

The imaging procedures were not homogeneous due to being obtained from five different centers. All patients were re-evaluated with brain and/or neck and/or orbital MRIs by two senior and one junior neuroradiologists (with 5, 29, and 34 years of radiology experience). Images of all patients were performed by 1.5-3T MRI services (1.5T Signa, GE Medical Systems, Milwaukee, USA; 3T Philips Achieva Scanner, Phillips Medical Systems, Best, Netherland; 1.5T Siemens Aera, Siemens Healthcare, Erlangen, Germany; 1.5T Siemens Avanto, Siemens Healthcare, Erlangen, Germany). Brain MRI procedures included fast spin-echo T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images, spin-echo pre-contrast, and post-contrast T1-weighted images, DWIs (with b-values of 0-1 000 s/mm<sup>2</sup>), and apparent diffusion coefficient (ADC) maps. Orbital and neck MRI procedures included fast spin-echo T2-weighted images (with and/or without fat saturation), and spin-echo pre-contrast and post-contrast T1-weighted images (with and/or without fat saturation). In addition, the patients were evaluated with imaging modalities such as thoracic, abdominal CT, and/or 18F-FDG PET/CT in terms of additional involvement region in the institutes where they were diagnosed.

### 3. Results

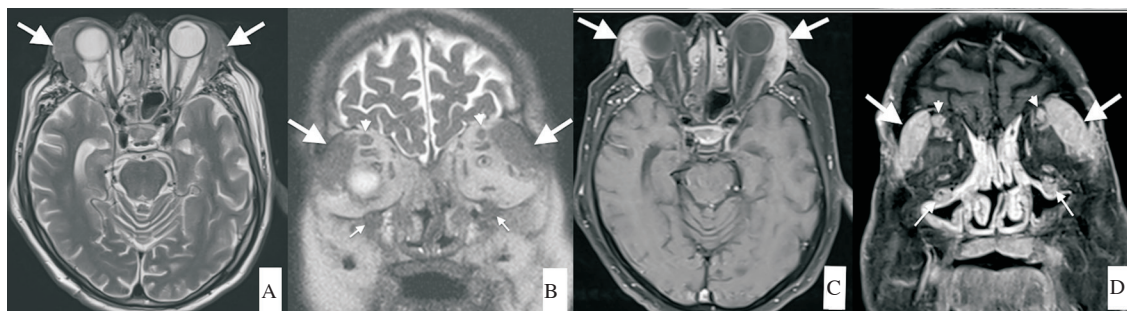
Nine patients with diagnosed IgG4-RD [six females, three males; median age: 38 years (range: 2.5-79 years)], were admitted with various symptoms and findings. The median serum IgG4 value of the patients at the time of diagnosis was found to be 1.69 g/L (min-max: 0.11-23.9 g/L). General clinical and laboratory features of patients were outlined in Table 1.

The most common site of involvement on MRI was the orbit ( $n=9$ ), which included the lacrimal glands ( $n=7$ ), extraocular muscles ( $n=4$ ), and orbital apex ( $n=2$ ) (Figure 1-3). Bilateral involvement was observed in five of the seven patients with lacrimal gland involvement, and in three of the four patients with extraocular muscle involvement. Both of the two patients with orbital apex involvement were unilateral. The second most common site of involvement was the cranial nerve branches ( $n=3$ ) (Figure 1, Figure 4, Figure 5). In all

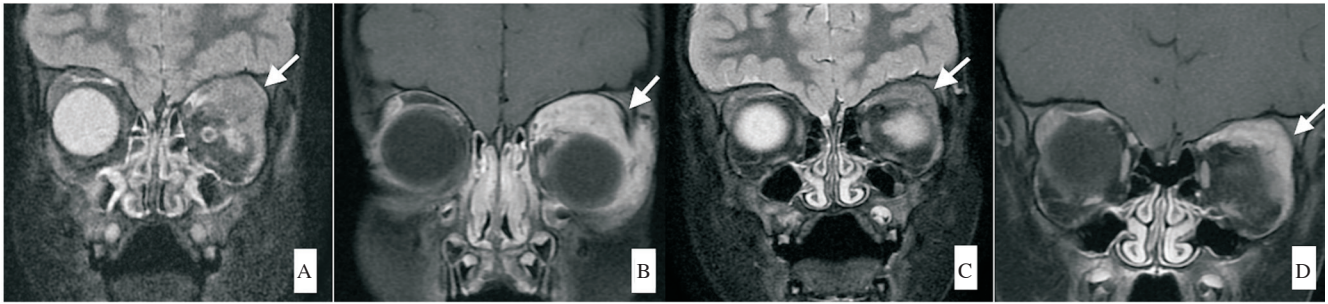
of these three patients, the branches of the fifth cranial nerve showed involvement. In two patients (Patients 1 and 6), the perineural spread was unilateral; in the other remaining patient (Patient 7), it was bilateral. In patient 1, involvement of the infratemporal fossa-masticator space, cavernous sinus, pachymeninx, orbital apex, and perineural spreading through the mandibular nerve, were observed (Figure 4). In patient 6, maxillary and infraorbital nerve involvement, and pterygopalatine fossa involvement due to perineural spread were observed (Figure 5). In addition, sinonasal cavities involvement was also detected in one patient. The lesions at the sites of involvement had swollen showed iso- or hypointensity compared to the brain parenchyma on T1- and T2-weighted images and diffuse contrast enhancement on post-contrast T1-weighted images. In all three patients with perineural spread, enlargement of the neural foramen in the nerve tracts and tubular contrast enhancement were observed (Figure 4). In the evaluation in terms of additional involvement zone other than the head and neck region, pancreatic involvement was detected in one patient.

Microscopic evaluation was obtained by biopsy in all patients except for patient 4. Lymphocytic infiltration was observed in all biopsy specimens. Obliterative phlebitis and tissue fibrosis were observed in eight patients. The definitive histopathological diagnosis of IgG4-RD was achieved in all eight patients who had biopsy specimens available.

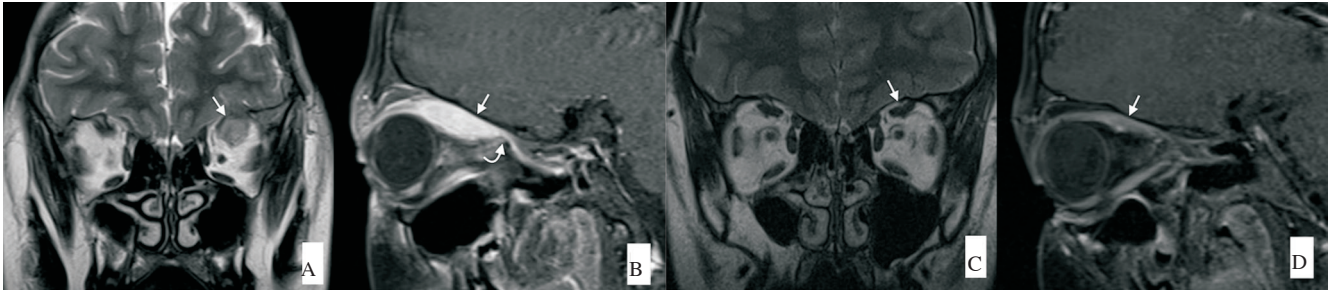
All patients were treated with systemic corticosteroids. In addition to this treatment, three patients were added with methotrexate and one patient with azathioprine. After treatment, all patients responded to treatment. However, patient 1's 10th-month of follow-up MRI was obtained because of the beginning of perioral numbness again, and a recurrence with the involvement of the mandibular nerve's inferior alveolar branch was observed. Rituximab therapy was started as the second-line treatment. The patient is still in the follow-up period and due to the fact that Rituximab therapy has just started, an assessment of response has not been carried out. Patient 3, on the other hand, received three doses of Rituximab due to inadequate response to azathioprine and corticosteroid therapy. This patient has been stable for 3.5 years under treatment with azathioprine and methylprednisolone.



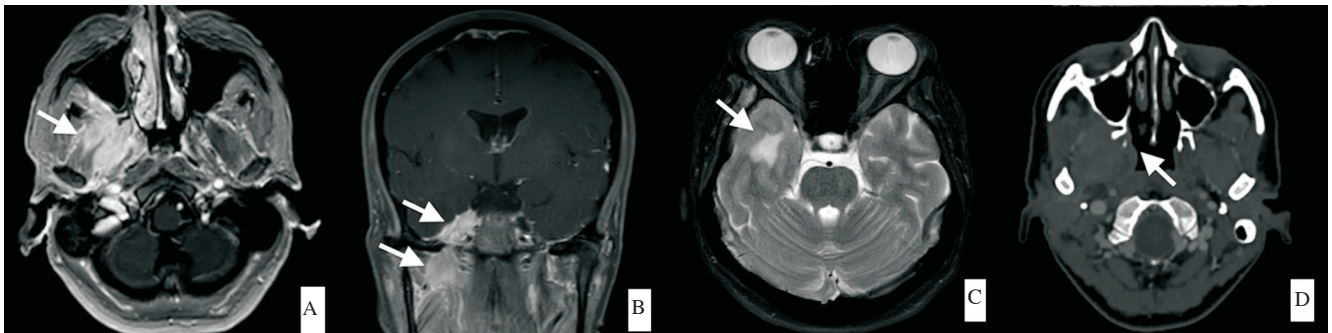
**Figure 1.** Axial (A) and coronal (B) plane orbital T2 weighted magnetic resonance images of 79-year-old male patient at the time of diagnosis showed hypointense lesions in the bilateral lacrimal gland (thick arrows), levator palpebrae superioris muscles (arrowhead), and infraorbital nerves involvement (thin arrows). Diffuse contrast enhancement in these structures (thick arrows indicate lacrimal gland involvement, arrowheads indicate levator palpebrae superioris muscles, and thin arrows indicate infraorbital nerve involvement) was observed on the axial (C) and coronal (D) plane post-contrast T1 weighted fat-suppressed magnetic resonance images.



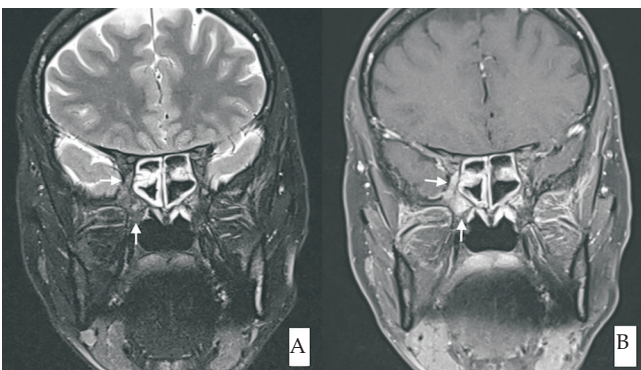
**Figure 2.** Coronal plane orbital T2 weighted fat-suppressed magnetic resonance image (A) of a 6-year-old female patient at the time of diagnosis showed expansile iso-hypointense lesion (arrows) involving the left lacrimal gland, left superior and lateral rectus muscles. Post-contrast T1 weighted fat-suppressed magnetic resonance image (B) revealed diffuse contrast enhancement in this lesion (arrow). After the systemic corticosteroid therapy for two weeks, coronal plane T2 weighted fat-suppressed magnetic resonance image (C) and post-contrast T1 weighted fat-suppressed magnetic resonance image (D) revealed remarkable regression in this lesion (arrow).



**Figure 3.** Coronal plane orbital T2 weighted magnetic resonance image (A) of a 17-year-old male patient at the time of diagnosis showed an expansile lesion in the left superior rectus muscle (arrow). Sagittal plane post-contrast T1 weighted fat-suppressed image (B) showed contrast enhancement in the left superior rectus muscle (arrow) and involvement of the orbital apex (curved arrow). After the systemic corticosteroid therapy, coronal plane T2 weighted image (C) and sagittal plane post-contrast T1 weighted fat-suppressed image (D) revealed remarkable regression in this lesion (arrow).



**Figure 4.** Axial (A) and coronal (B) plane post-contrast T1 weighted fat-suppressed images of a 38-year-old female patient, revealed signal abnormalities (arrow), which showed an extension along the right mandibular nerve from the right infratemporal fossa-masticator space to the right middle cranial fossa *via* the foramen ovale and diffuse contrast-enhanced. Axial plane T2 weighted fat-suppressed image (C) revealed vasogenic edema in the right temporal lobe (arrow). Axial plane contrast-enhanced neck computed tomography (D) revealed erosion in the right pterygoid process (arrow).



**Figure 5.** Coronal plane orbital T2 weighted fat-suppressed magnetic resonance image (A) and post-contrast T1 weighted fat-suppressed magnetic resonance image (B) of a 45-year-old female patient, revealed right pterygopalatine fossa and maxillary nerve involvement, and perineural spreading *via* foramen rotundum (arrow).

#### 4. Discussion

This radiology-based study is unique, compact, and comprehensive study due to the evaluation of the head and neck involvement of IgG4-RD, as radiological, clinical, laboratory, and pathological together. We think that it will provide essential contributions to the literature about this rare and new pathology.

Head and neck involvement of IgG4-RD may show different demographic characteristics than systemic involvement, such as occurring more frequently in females, and younger populations, and higher incidence in children[2,5,8]. Compatible with this data, it was observed a younger population and female dominance in the present study.

Head and neck involvement of IgG4-RD can be manifested as

**Table 1.** Demographic, clinical, laboratory, radiological features and follow-up results of patients with IgG4-related disease head and neck involvement

Patients	Sex	Age, years	Clinical symptoms and findings	Serum IgG4 level (g/L)	Site of involvement in the head and neck region on MRI	Biopsy region	Microscopic evaluation of the biopsy specimens	Additional involvement site other than the head and neck	Type of treatment	Response to treatment
Patient 1*	Female	38	Diplopia, perioral numbness, fifth and sixth cranial nerve palsy, right ophthalmoplegia, xerophthalmia, xerostomia	2.74	Right orbital apex, right mandibular nerve, right infratemporal fossa-masticator space, right pterygoid muscles, pachymeninx, right cavernous sinus	Infratemporal fossa	Presence of storiform fibrosis, obliterative phlebitis, and dense lymphocyte infiltration. However, the IgG4/IgG ratio was not stated	No	Systemic corticosteroid	Yes
Patient 2	Female	65	Swollen of the left lacrimal gland and eyelid, bilateral cervical lymphadenopathy, left xerophthalmia	>1.45	Left lacrimal gland, bilateral cervical lymph nodes	Left lacrimal gland	Presence of storiform fibrosis, obliterative phlebitis, and dense lymphocyte infiltration. Staining with IgG4 was available. IgG4/IgG ratio: 66%	No	Systemic corticosteroid	Yes
Patient 3	Male	46	Bilateral painless exophthalmos, chemosis, swollen of the bilateral lacrimal gland and eyelids	17.60	Bilateral lateral rectus muscles and lacrimal glands	Bilateral lateral rectus muscles and lacrimal glands	Presence of storiform fibrosis, obliterative phlebitis, and dense lymphocyte infiltration. Staining with IgG4 was available. IgG4/IgG ratio: >50	No	Systemic corticosteroid, azathioprine, and rituximab	Yes
Patient 4†	Male	17	Diplopia, left ophthalmoplegia, left painless exophthalmos	1.69	Left superior rectus muscle, left orbital apex	N/A	N/A	No	Systemic corticosteroid	Yes
Patient 5	Female	22	Swollen of the bilateral lacrimal gland, and bilateral eyelids, hyperemia of the eyelids	0.11	Bilateral lacrimal gland	Right lacrimal gland	Presence of dense lymphocyte infiltration and tissue fibrosis. Staining with IgG4 was available. However, the IgG4/IgG ratio was not stated	No	Systemic corticosteroid and methotrexate	Yes
Patient 6	Female	45	Swollen of the bilateral lacrimal gland, edema and hyperemia of the bilateral eyelids, ptosis (Right side dominance), bilateral sinonasal cavities	12.60	Bilateral lateral-superior rectus muscles and lacrimal gland (Right side dominance), right pterygopalatine fossa, right maxillary and infraorbital nerves	Right lacrimal gland	Presence of storiform fibrosis, obliterative phlebitis, and lymphocyte infiltration. Staining with IgG4 was available. However, the IgG4/IgG ratio was not stated.	Pancreas	Systemic corticosteroid and methotrexate	Yes
Patient 7	Male	79	Swollen of the bilateral lacrimal gland and eyelids, bilateral painless exophthalmos, chemosis on the right side, bilateral ophthalmoplegia	23.90	Bilateral lacrimal gland, levator palpebrae superioris muscles and infraorbital nerves, retroorbital fat tissue	Right lacrimal gland and retroorbital fat tissue	Presence of storiform fibrosis, obliterative phlebitis, and lymphocyte infiltration. The IgG4/IgG ratio is not stated	No	Systemic corticosteroid and methotrexate	Yes
Patient 8	Female	6	Swollen of the left lacrimal gland and eyelids, left painless exophthalmos, left ophthalmoplegia, low vision in left side	>1.45	Left lacrimal gland, left lateral-superior rectus muscles	Left lacrimal gland and left retroorbital muscle	Presence of storiform fibrosis, obliterative phlebitis, and lymphocyte infiltration. IgG4/IgG ratio: >50	No	Systemic corticosteroid	Yes
Patient 9	Female	2.5	Swollen of the bilateral lacrimal gland and eyelids, bilateral painless exophthalmos	0.70	Bilateral lacrimal glands	Bilateral lacrimal glands	Presence of lymphoplasmacytic infiltration. Staining with IgG4 was available. IgG4/IgG ratio: >50	No	Systemic corticosteroid	Yes

MRI: Magnetic resonance imaging; N/A: Not available; \* There was a recurrence (inferior alveolar branch involvement) in the 10th month of follow-up; † A patient who has not had a biopsy and is probably, therefore, considered a possible diagnosis according to the diagnostic criteria.

various symptoms and findings depending on which sites are involved. There were some described symptoms and clinical findings such as lacrimal and salivary gland swelling, exophthalmos, eyelids swelling, vision problem, ophthalmoplegia, chemosis, lymphadenopathy, headache, dizziness, diabetes insipidus, xerophthalmia, xerostomia, tinnitus, hearing loss, dysphagia, cranial nerve palsy, seizures, cognitive decline[10–17]. It has been observed that symptoms and findings recur with the discontinuation of steroid therapy, and are especially more frequently present in the event of attacks[19]. In the present study, symptoms and clinical findings were observed similar to the literature.

Salivary and thyroid glands, orbit, sinonasal cavities, and lymph nodes are the most common areas of involvement in the head and neck region. Less commonly pituitary, cranial nerves (especially trigeminal nerve branches), larynx, and pachymeninx can be involved[5,10–14]. In this study, the most common site of involvement was the orbit. However, contrary to the literature, salivary gland involvement was not detected in any patients. In addition, one patient who displayed no salivary gland involvement radiologically complained of xerostomia. This situation suggested that there may be non-visible radiologically, involvement processes. In radiological follow-up in such cases, more attention is necessary to whether the disease has caused involvement in the symptom-related region. The lacrimal glands are the most commonly involved structure in the orbit[2,10,16]. Lacrimal and salivary glands are generally affected bilaterally and coexist[10,16]. While bilateral involvement was observed in five of seven patients with lacrimal gland involvement in this study, any clinical and radiological findings of the salivary gland involvement were not observed in any of these patients.

In this study, one of the three patients with cranial nerve involvement showed cranial nerve palsy. The other two patients' cranial nerve involvement was observed only radiologically. In the symptomatic patient with cranial nerve involvement, the IgG4-RD diagnosis was very difficult due to the absence of any other head and neck or systemic involvement. There was also the destruction of adjacent bone structures, which is more often in malignant processes. Although perineural spreading is detected radiologically in about 40% of patients with perineural spread, patients can be asymptomatic. Evaluation of trigeminal and facial nerves, which are most often involved in the perineural spreading, especially in cases such as vague, recurrent headaches, sinusitis, and neck pain, is very important[20]. We observed that cranial nerve involvement is not uncommon, similar to the limited number of case studies evaluating IgG4-RD in the literature[10,16,17]. If erosion and/or invasion in the adjacent structures, unilateral involvement, and perineural spread are observed, it can be challenging to diagnose due to the fact that there are also malignant processes in the differential diagnosis[19]. We detected dural involvement in only one patient. Similar studies identified dural involvement as 11.7% (2/17) and 26.6% (4/15)[10,16].

The IgG4-RD in the head and neck region usually includes different conventional imaging characteristics according to the

degree of fibrosis. Generally, hypo- to isointense relative to the brain, mass-like lesions that are intensely contrast-enhancement, are observed[5,10–12,16,17]. In similarity with the literature data, in this study, all lesions were iso-hypointense compared to the brain on pre-contrast T2 weighted images. In post-contrast images, it was observed that all lesions showed diffuse contrast enhancement. We think that perfusion imaging procedures, which have not been tried before for IgG4-related lesions but are used in distinguishing between malignant and benign head and neck lesions, may also be useful[21,22]. In this study, DWIs were obtained in addition to the brain MRI sections; were not evaluated for the neck. Although it is stated that diffusion restriction may be shown due to intense cellularity[7,23], we did not observe any significant diffusion restriction as indicated in similar evaluation done by Seol *et al.*[11].

It may not always be possible to get a biopsy in the head and neck region, especially if lesions are deeply located and accompanied by important anatomical structures around them. However, immunohistopathology is very important for diagnosis. Depending on whether the biopsy is a fine needle or a tru-cut, excisional biopsy, the results of immunostaining may vary[9]. Therefore, it should be evaluated in accordance with the revised comprehensive diagnostic criteria for IgG4-RD, to which the criteria for storiform fibrosis and obliterative phlebitis, important components of diagnosis, were added[9].

This study has some limitations. First, the current findings, although multicenter data collection, represent the experiences of retrospective research with limited sample size. Secondly, the imaging protocols of the MRIs collected from different institutes differed from each other, which prevented a quantitative assessment. If the outcomes of this study are approved and confirmed by studies with larger sample size, they can be generalized.

In conclusion, IgG4-RD is a multisystemic and fibroinflammatory pathology that can involve many sites on the head and neck. IgG4-RD should also be included in the differential diagnosis of head and neck lesions that show T2 hypointensity and diffuse contrast enhancement. It should be kept in mind that one of the pathologies that can cause perineural dissemination is IgG4-RD. With the increasing awareness of neuroradiologists and head-neck radiologists about this issue, even in patients with ambiguous findings, early diagnoses can be obtained. Thus, effective treatments can be provided.

### Conflict of interest statement

The authors declare that they have no conflict of interest.

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The authors received no extramural funding for the study.

## Authors' contributions

U.A.P., K.K., M.S., R.M.K.E., and A.M.A. developed the conception or design of the work. U.A.P., K.K., H.D.I., M.S., D.A., O.K., R.M.K.E., B.C.P., U.C., A.A., A.M.A. contributed data collection, data analysis, and interpretation. U.A.P. wrote the manuscript. K.K., M.S., R.M.K.E., U.C., and A.M.A. supervised the manuscript. U.A.P., K.K., H.D.I., M.S., D.A., O.K., R.M.K.E., B.C.P., U.C., A.A., A.M.A. approved the final version of the manuscript to be published.

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