



Rice, C. M., Spencer, T., Bunea, G., Scolding, N. J., Sloan, P., & Nath, U. (2016). Intracranial spread of IgG4-related disease via skull base foramina. *Practical Neurology*, 16(3), 240-242. DOI: 10.1136/practneurol-2015-001315

Peer reviewed version

Link to published version (if available):  
[10.1136/practneurol-2015-001315](https://doi.org/10.1136/practneurol-2015-001315)

[Link to publication record in Explore Bristol Research](#)  
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via BMJ at <http://pn.bmj.com/content/16/3/240.abstract>. Please refer to any applicable terms of use of the publisher.

## University of Bristol - Explore Bristol Research

### General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:  
<http://www.bristol.ac.uk/pure/about/ebr-terms.html>

# Intra-cranial spread of IgG4-related disease *via* skull base foramina

Rice CM,<sup>1,2</sup> Spencer T,<sup>1</sup> Bunea G,<sup>3</sup> Scolding NJ,<sup>1,2</sup> Sloan P,<sup>4</sup> Nath U<sup>5</sup>

<sup>1</sup>Department of Neurology  
North Bristol NHS Trust  
Bristol, UK

<sup>4</sup>Department of Pathology  
Royal Victoria Infirmary,  
Newcastle upon Tyne, UK

<sup>2</sup>School of Clinical Neurosciences  
University of Bristol, UK

<sup>5</sup>Department of Neurology  
Sunderland Royal Hospital,  
Sunderland, Tyne and Wear, UK

<sup>3</sup>Department of Radiology  
Sunderland Royal Hospital,  
Sunderland, Tyne and Wear, UK

Corresponding author: Dr Claire Rice  
Department of Neurology  
Southmead Hospital  
Bristol, BS10 5NB, UK  
[c.m.rice@bristol.ac.uk](mailto:c.m.rice@bristol.ac.uk)  
Tel 00 44 117 414 6695  
Fax 00 44 117 414 9475

Keywords: IgG4-related disease  
dacryosialadenopathy  
pachymeningitis  
leptomeningitis  
neuroimmunology

Word count: 963

## **SUMMARY**

IgG4-related disease (IgG4-RD) is a newly-recognised, multi-organ, inflammatory disease and its full clinical spectrum remains undefined. We present a biopsy-proven case of IgG4-RD presenting with a parapharyngeal mass with intra-cranial extension and possible involvement of the brain parenchyma. We highlight the importance of considering the diagnosis in those presenting with tumefactive lesions, leptomeningitis or pachymeningitis and emphasise the value of securing a tissue diagnosis so that appropriate long-term treatment can be instigated and complications avoided.

## **INTRODUCTION**

The complete clinical spectrum of IgG4-related disease remains to be determined following its relatively recent recognition as a distinct entity. It typically causes painless swelling and can affect either one organ in isolation or multiple organs[1 2]. Fever, malaise, sweats and weight loss occur less commonly. Here, we present the case of a gentleman with both intra- and extra-cranial manifestations of IgG4-related disease with spread of the disease *via* the skull base foramina.

## **Case Report**

A 46-year-old right-handed construction worker presented with a 12-month history of fatigue, weight loss (25kg), headache, right-sided facial numbness and diplopia on gaze to the right. On examination, there was right-sided trigeminal sensory impairment (Va/b/c), partial right sixth nerve palsy and right-sided tongue wasting.

Peripheral blood markers of inflammation were elevated. Screening for immunodeficiency and mycobacterial infection was negative. Chest x-ray and chest, abdomen and pelvis CT were normal.

MRI (Figure 1A-D) demonstrated an enhancing soft tissue mass involving the right posterior nasopharynx with intracranial spread through the right carotid canal, jugular foramen and foramen ovale. There was basal pachy- and leptomeningitis in the middle cranial fossa with high signal in the overlying temporal lobe. There was no significant lymphadenopathy. MRV confirmed patency of the major dural venous sinuses. Biopsy of the parapharyngeal space on two occasions was non-diagnostic.

Three months later, the patient experienced worsening headache and developed bilateral haemorrhagic papilloedema. Treatment with intravenous methylprednisolone (1g) for 3 days followed by 60mg prednisolone orally led to symptomatic and radiological improvement but development of steroid-induced diabetes. Weaning of prednisolone to 15mg over the course of 9 months was associated with development of right-sided facial swelling consistent with dacryosialoadenopathy. There was re-emergence of diplopia with reduced left-sided visual acuity signs were consistent with left-sided optic neuropathy. Sensation was reduced in a Vb/c distribution on the right and right-sided tongue wasting was apparent. Weber's localized to the right. There was clinical evidence to support the development of peripheral neuropathy but no other limb signs.

MR imaging was repeated (Figure 1D) and, although there was resolution of the abnormality previously noted in the right temporal lobe and stable disease along the tentorium and in the cavernous sinus, progressive changes were noted in the pterygomaxillary fissure, the muscles of the masticator compartment and throughout temporalis on the right.

A diffuse plasma cell-rich, chronic inflammatory cell infiltrate was noted on biopsy of anterior temporalis and posterior maxilla. There was prominent stromal fibrosis/hyalinization, fat necrosis with focal granulation tissue and numerous IgG and IgG4-positive plasma cells (Figure 1E-G).

High dose corticosteroid treatment was re-instigated with resolution of signs within a fortnight. FDG-PET performed after re-introduction of corticosteroid therapy did not show any enhanced uptake. Azathioprine was commenced and the dose of

prednisolone has been successfully weaned to 10mg daily over 1 year without recurrence of clinical signs.

## **DISCUSSION**

IgG4-related disease has only recently been appreciated as a distinct clinical entity although the pathological changes are now known to occur in several long-recognised conditions such as Mikulicz syndrome[3], autoimmune pancreatitis[4] and Riedel's thyroiditis[5]. Whilst the full spectrum of the clinical phenotype remains undetermined, characteristic histopathological findings have been described in almost every organ[1 6 7]. In the CNS, lepto- and pachymeningitis as well as hypophysitis, pseudotumours and cranial neuropathy are recognized manifestations but involvement of brain parenchyma is rare[8 9]. A single case report has previously documented intra-cranial extension of disease *via* the foramen ovale along the trigeminal nerve[10].

The finding of an elevated serum IgG4 concentration is supportive of IgG4-RD but is not a constant finding[2] and whether IgG4, a relatively weak activator of effector cells, is pathogenic is uncertain[11].

In the head and neck, hypointense T2 lesions on MR are typical and enhancement with gadolinium may occur[12]. <sup>11</sup>C-methionine (MET) positron emission tomography (PET) may be superior to <sup>18</sup>F-fluorodeoxy-glucose (FDG) PET for the detection of CNS disease.[13] Nonetheless, with the possible exception of autoimmune pancreatitis[14], the radiological features are not pathognomonic and cannot reliably differentiate IgG4-RD from other inflammatory, multi-organ diseases such as Wegener's granulomatosis and Sjogren's syndrome.

The diagnosis of IgG4-RD therefore relies on histology - consensus diagnostic criteria are based on morphological appearances including presence of a dense lymphoplasmacytoid infiltrate, fibrosis (usually storiform) and obliterative phlebitis[15]. An eosinophilic infiltrate may occur but is not a prerequisite for the diagnosis.

IgG4-RD typically responds to treatment with glucocorticoids but steroid-sparing agents such as azathioprine, methotrexate or mycophenolate mofetil may be required to reduce the risk of relapse with steroid withdrawal[6]. Successful treatment of CNS IgG4-RD with rituximab has also been reported[8].

We present a case of IgG4-RD with contiguity of intra- and extra-cranial disease *via* skull base foramina. Although there was radiological evidence of cerebral parenchymal involvement, this may be due to vasogenic oedema or direct brain involvement; biopsy of extra-cranial disease was preferentially undertaken in view of favourable risk profile. Nonetheless, this case adds to the reported clinical spectrum of IgG4-RD, definition of which will be important for prompt recognition of this relatively new clinical entity and subsequent initiation of appropriate treatment and avoidance of complications.

## **KEY MESSAGES**

IgG4-related disease should be considered in the differential diagnosis of CNS pseudotumour, cranial neuropathy, hypophysitis and lepto- or pachymeningitis

IgG4-related disease may present with a combination of intra- and extracranial manifestations

Early recognition of IgG-related disease and establishment of appropriate long-term treatment may avoid unnecessary investigations and morbidity

## **ACKNOWLEDGEMENTS**

The authors thank the patient for permission to publish the report and the ENT team (Mr S Carrie) in obtaining tissue samples.

**CONTRIBUTORS:** UN was the treating neurologist with input from the authors. CMR, TS and NJS were responsible for the first drafts of the manuscript. Radiology and pathology analyses were performed by GB and PS respectively. All authors reviewed and contributed to the manuscript.

**PATIENT CONSENT:** Obtained

**DISCLOSURES OF AUTHORS:** None of the authors have relevant financial disclosures to declare. No specific funding was received for this work. CMR receives support from the Burden Neurological Institute. On behalf of all authors, the corresponding author states that there is no conflict of interest.

## FIGURES AND LEGENDS

Figure 1 MR imaging (1A, B) demonstrated an enhancing soft tissue mass involving the right posterior nasopharynx with infiltration laterally and posteriorly into the right prevertebral strap muscles and through the pharyngobasilar fascia to involve the medial and lateral pterygoids. The right carotid and internal carotid artery was ensheathed and abnormal tissue was seen in the right carotid canal and jugular foramen. The right cavernous sinus was involved *via* perineural spread through the foramen ovale. Basal pachy- and leptomeningitis were noted along the floor of the right middle cranial fossa with high signal in the overlying temporal lobe (1C). Progressive changes were noted in the pterygomaxillary fissure, the muscles of the masticator compartment and throughout the temporalis muscle on the right at the time of re-presentation (1D).

Figure 1E-G A diffuse plasma cell-rich, chronic inflammatory cell infiltrate with prominent stromal fibrosis/hyalinization, fat necrosis and focal granulation tissue was evident on biopsy of anterior temporalis and posterior maxilla (1E). Immunocytochemistry demonstrated numerous IgG and IgG4 positive plasma cells (1F and 1G).



## REFERENCES

1. Yamamoto M, Takahashi H, Shinomura Y. Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist. *Nat Rev Rheumatol* 2014;10(3):148-59.
2. Stone JH. IgG4-related disease: nomenclature, clinical features, and treatment. *Semin Diagn Pathol* 2012;29(4):177-90.
3. Yamamoto M, Takahashi H, Ohara M, et al. A case of Mikulicz's disease (IgG4-related plasmacytic disease) complicated by autoimmune hypophysitis. *Scand J Rheumatol* 2006;35(5):410-1.
4. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38(10):982-4.
5. Dahlgren M, Khosroshahi A, Nielsen GP, et al. Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res (Hoboken)* 2010;62(9):1312-8.
6. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366(6):539-51.
7. Mahajan VS, Mattoo H, Deshpande V, et al. IgG4-related disease. *Annu Rev Pathol* 2014;9:315-47.
8. Regev K, Nussbaum T, Cagnano E, et al. Central Nervous System Manifestation of IgG4-Related Disease. *JAMA Neurol* 2014;71(6):767-70.
9. Kim EH, Kim SH, Cho JM, et al. Immunoglobulin G4-related hypertrophic pachymeningitis involving cerebral parenchyma. *Journal of neurosurgery* 2011;115(6):1242-7.
10. Katsura M, Morita A, Horiuchi H, et al. IgG4-related inflammatory pseudotumor of the trigeminal nerve: another component of IgG4-related sclerosing disease? *AJNR American journal of neuroradiology* 2011;32(8):E150-2.
11. Nirula A, Glaser SM, Kalled SL, et al. What is IgG4? A review of the biology of a unique immunoglobulin subtype. *Curr Opin Rheumatol* 2011;23(1):119-24.
12. Toyoda K, Oba H, Kutomi K, et al. MR imaging of IgG4-related disease in the head and neck and brain. *AJNR American journal of neuroradiology* 2012;33(11):2136-9.
13. Kume K, Ikeda K, Deguchi K, et al. Advantage of <sup>11</sup>C-methionine positron emission tomography for assessing IgG4-related central nervous system lesions. *J Neurol* 2014;261(3):625-7.
14. Deshpande V. The pathology of IgG4-related disease: critical issues and challenges. *Semin Diagn Pathol* 2012;29(4):191-6.
15. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25(9):1181-92.