WITHDRAWN:
IgG4-related Disease Presenting With Ataxia

George Hondag Tse

g.tse@sheffield.ac.uk

Department of Neuroradiology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK https://orcid.org/0000-0002-5656-9509

Marios Hadjivassiliou

The University of Sheffield Medical School

Vikrant Devgire

The University of Sheffield

Esther Hobson

The University of Sheffield

Daniel JA Connolly

Sheffield Teaching Hospitals NHS Foundation Trust

Nigel Hoggard

The University of Sheffield

Case report

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EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background:

Immunoglobulin G4 related disease is a relatively rare multi-system disorder which can present with diverse manifestations including mass-lesions and, or, organ dysfunction. Although the orbits, salivary glands and sinuses are comparatively common sites of involvement there are few reports of isolated intracranial presentation.

Case presentation:

Although large vessel IgG4-RD vasculitis is an uncommon entity we report a case of a 84-year old male presenting with cerebellar ataxia. CT at presentation demonstrated bilateral low-density change in the middle cerebellar peduncles, which corelated to areas of elevated T2 signal demonstrating restricted diffusion on MRI. CT angiogram demonstrated marked thickening of the common carotid arteries and branches extending to the skull base. In addition, the vertebral arteries also demonstrated significant wall thickening and occlusive narrowing. Serum immunoglobulin IgG and IgA were elevated and in particular IgG immunoglobulin was extremely high.

Conclusions:

Bilateral symmetrical restricted diffusion in the middle cerebellar peduncles is a striking radiological feature and reported to occur with multiple aetiologies, we believe this is the first report to associate this with IgG4-RD and ataxia.

Background

Immunoglobulin G4 related disease (IgG4-RD) is a multi-system fibroinflammatory disease that can result in tumour like mass-lesions and, or, multiple organ dysfunction and was not identified as a medical entity until recently in the 21st century. The pathological features include lymphoplasmacytic infiltration, obliterative phlebitis and fibrosis [1]. Fibrosis is a histological hallmark reported to be present in all cases, with a particular ‘storiform fibrosis’ pattern, characterised by radially arranged collagen fibres that weave through the tissue typifying IgG4-RD.

The underlying pathophysiology of IgG4-RD is still to be fully elucidated. There is evidence that the process may be driven by CD4+ T-cells leading to activation of an innate inflammatory response. There is subsequent generation of activated B-cells and plasmablast induction, as such, it is not necessarily the IgG4 molecule itself that drives the process. The immunological trigger is unclear. As with many autoimmune disorders it is hypothesised that genetically susceptible individuals, generally older men experience an environmental insult, such as a specific pathogen / micro-organism, which triggers tissue damage and a break in immunological tolerance and the subsequent self-antigen-driven fibrotic response.

Several conditions, previously known by historical eponymous names, are now identified in the IgG4-RD spectrum including Mikulicz disease, Küttner tumour, eosinophilic angiocentric fibrosis, multifocal fibrosclerosis, sclerosing pancreatitis, inflammatory pseudotumour, fibrosing/sclerosing mediastinitis, Ormond disease (retroperitoneal fibrosis), periaortitis/periarteritis and idiopathic tubulointerstitial nephritis [2]. Although the orbits, salivary glands and sinuses are comparatively common sites for manifestation of this uncommon disorder [1], there are few reports of true intracranial involvement. Hypertrophic pachymeningitis has been recognised as part of the IgG4-related disease spectrum [3], and can present with intracranial hypertension [4], as well as leptomeningitis, hypophysitis, pseudotumor and cranial neuropathy.

We report a case of a patient presenting with cerebellar ataxia and striking large vessel IgG4-RD vasculitis on radiological imaging.

Case Presentation

An 84-year old right-handed gentleman presented with slurred speech and reduced mobility. Antecedent history included two stone weight loss and general decline associated with iron deficiency anaemia. The patient was a lifelong smoker on rivaroxaban for atrial fibrillation but lived independently with his wife.

On examination he had broken pursuit and bilateral gaze evoked horizontal nystagmus. He had cerebellar dysarthria, bilateral dysmetria and dysdiadochokinesis. There was normal tone and power, areflexia and equivocal plantar reflexes. He had significant gait ataxia and was unable to mobilise as a result. There was no evidence of sensory deficit to suggest sensory ataxia.

Computed tomography (CT) of the head at presentation demonstrated bilateral low-density change in the middle cerebellar peduncles (Figure 1A), which corelated to areas of elevated T2 signal demonstrating restricted diffusion on Magnetic resonance Imaging (MRI). These foci did not demonstrate enhancement following gadolinium administration. Small foci of restricted diffusion where also demonstrated in the pons. The initial impression was of an inflammatory disorder, or a possible para-neoplastic disorder, and standard stroke treatment was instigated given the foci of pontine restricted diffusion. Serology revealed an elevated Erythrocyte Sedimentation Rate (ESR) in keeping with an inflammatory process.

Lumbar puncture was performed and cerebrospinal fluid (CSF) examination showed a slightly elevated total protein but no oligoclonal bands (Table 1).

Following hospital admission general neurological deterioration was observed with progressive dysarthria, dysmetria and progressive cerebellar ataxia. A CT angiogram was performed and this demonstrated marked thickening of the common carotid arteries and branches extending to the skull base (Figure 2). In addition, the vertebral arteries also demonstrated significant wall thickening and occlusive narrowing on the right side in the V3 segment. The intracranial portion (V4) was significant narrowed and possibly occluded, however patency of the anterior inferior cerebellar arteries was confirmed on MR angiography (Figure 2), an important feature as the anterior inferior cerebellar arteries

supply the middle cerebellar peduncles. As such the bilateral middle cerebellar changes was not felt to be purely ‘ischaemic’ in origin but represented an inflammatory process. At this point the patient received 1g of intravenous methylprednisolone and after 5 days this was converted to 60mg oral prednisolone to treat a large vessel vasculitis.

F18-Flurodeoxyglucose Positron Emission Tomography (PET-CT) demonstrated no evidence of FDG avid malignancy, however there was significant increased vascular uptake in the subclavian and proximal femoral arteries bilaterally suggestive of large vessel vasculitis. The patient had already been commenced on oral corticosteroids several days prior to PET-CT which may have reduced the degree of aortic or carotid artery uptake.

Serum immunoglobulin IgG and IgA were elevated and in particular IgG immunoglobulin was extremely high. It was of note that previous investigations by the general practitioner in the preceding weeks to admission had also demonstrated markedly elevated serum immunoglobulin as part of investigation of chronic weight loss. Immunoglobulin sub-class analysis confirmed elevated IgG4. The patient had further cerebellar symptoms and MRI at day 39 from admission demonstrated new foci of restricted diffusion in the cerebellar parenchyma, presumed to be ischaemic (Figure 3), the middle cerebellar changes persisted with regression of restricted diffusion and peripheral T2 shine-through, suggesting established post-inflammatory change. As screening for infection diseases was satisfactory mycophenolate mofetil 500mg twice daily was commenced. At day 60 surveillance imaging demonstrated a similar appearance to the middle cerebellar peduncles and established cerebellar infarcts (Figure 3).

Although pathological diagnosis for IgG4-RD is the gold-standard the current corona virus (COVID-19) pandemic restrictions, meant that the diagnosis was made without any tissue examination. We felt that the overall picture was compatible with IgG4-RD and the presence of high IgG4 in the serum was in keeping with the proposed diagnosis. Over the course of two months in-patient rehabilitation was slow but progressive with return to aided walking and improvement in gait and balance.

Discussion

Bilateral symmetrical restricted diffusion in the middle cerebellar peduncles is a striking radiological feature and although not pathognomonic has been reported to occur with multiple aetiologies including cerebrovascular disease (infarction and hypertensive encephalopathy), metabolic disorders (adrenoleukodystrophy, Wilson disease, alcoholic liver cirrhosis, hypoglycaemic coma, Cyclosporin-A encephalopathy), inflammation (multiple sclerosis, acute disseminated encephalomyelitis, Behçet’s disease, Erdheim-Chester disease 2, HIV encephalopathy), neoplasia (primary CNS lymphoma, brainstem glioma, leptomeningeal carcinomatosis) and neuro-degenerative disorders (multiple systemic atrophy, spinocerebellar atrophy).[5] As such this feature alone can raise significant diagnostic dilemma and may precipitate multiple further investigations. In our experience ataxia with bilateral cerebellar middle peduncle changes has been seen with multi-system atrophy-cerebellar phenotype (MSA-C) and fragile X tremor ataxia syndrome as well as some immune ataxias. Discussion in clinical-radiological meetings is

of great benefit to obtain opinion from other neurologists and radiologists, which may well advance patient care in a timely manner and avoid unnecessary tests and delays.

The most common cause of large vessel vasculitis is giant cell arteritis (GCA) by a significant fold compared to IgG4-RD or Takayasu arteritis. Both GCA and Takayasu's disease are multisystem disorders and can affect any large vessel usually resulting in multi-organ involvement. Our patient did not have any headache. This does not exclude GCA but large vessel vasculitis-like presentations have been described in the context of IgG-RD. Furthermore, we have never observed pure cerebellar ataxia as a presenting feature of GCA. Although our patient's age was greater than 50 years clinical features that did not support giant cell arteritis included the ESR below 50mm/hour and headache was not a prominent feature (as given in the American College of Rheumatology classification criteria) [6]. Takayasu's arteritis is a disease of young people, particularly demonstrating an east Asian predominance. Large-vessel involvement with IgG4-RD may result in secondary vascular involvement due to a perivascular tumefactive lesion [7] but this was not the case on radiological imaging in this case.

As with most chronic non-specific multi-system disorders histopathological diagnosis by tissue biopsy is the gold standard. The peculiar setting of the COVID-19 pandemic where 'normal' healthcare activities are extremely curtailed meant that a biopsy was not immediately feasible. Diagnostic criteria for IgG4-RD liver and kidney disease exist but no such criteria exist for vasculitis [8]. However, in this case serum IgG4 concentration was >135 mg/dl and which although can be limited in its positive predictive value, does serve as a threshold for diagnosis [9]. In addition, IgG4 to IgG1 ratio was elevated above normal, again a feature supportive of IgG4-RD.

Glucocorticoids are the main initial treatment which are commonly maintained for 2-4 weeks then tapered slowly over 3-6 months depending on response. Some authors advocate a steroid-sparing agent such as Methotrexate, Azathioprine, Mycophenolate, 6-Mercaptopurine and cyclophosphamide. The use of Rituximab monotherapy to induce remission has demonstrated promising results and is the focus of more recent reports. Maintenance therapy for IgG4-RD after remission induction is recommended for patients with higher risk of organ dysfunction or high risk of relapse. Currently there is no consensus on the optimal regimen or duration for maintenance therapy.

Conclusion

Although large vessel IgG4-RD vasculitis is an uncommon entity we report a case presenting with cerebellar ataxia with interesting radiological features. Unexplained elevated total protein of IgG subclass should instigate Immunoglobulin G subclass assay and discussion in clinical-radiological meetings can instigate appropriate imaging strategies. We also highlight the clinical severity of this disorder and difficulties in diagnosis.

Abbreviations

IgG4-RD: Immunoglobulin G4 related disease

CT: Computed tomography

MRI: Magnetic resonance imaging

PET-CT: Positron emission tomography CT

GCA: Giant cell arteritis

Declarations

Ethics approval and consent to participate:
Not applicable

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Authors' contributions

GT, DC, MH, NH designed and conceptualised the study, analysed the data and drafted the manuscript for intellectual content. All the authors revised the manuscript, and read and approved the final version.

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Authors' information (optional):

Dr George H Tse, Department of Neuroradiology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK

References

1. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet. 2015;385:1460-71.
2. Stone JH, Khosroshahi A, Deshpande V, Chan JKC, Heathcote JG, Aalberse R, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum. 2012;64:3061–7.
3. Chan S-K, Cheuk W, Chan K-T, Chan JKC. IgG4-related sclerosing pachymeningitis: a previously unrecognized form of central nervous system involvement in IgG4-related sclerosing disease. Am J Surg Pathol. 2009;33:1249–52.
4. Williams T, Marta M, Giovannoni G. IgG4-related disease: a rare but treatable cause of refractory intracranial hypertension. Pract Neurol. 2016;16:235–9.
5. Okamoto K, Tokiguchi S, Furusawa T, Ishikawa K, Quardery AF, Shinbo S, et al. MR features of diseases involving bilateral middle cerebellar peduncles. Am J Neuroradiol. 2003;24:1946-54.
6. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33:1122-8.
7. Perugino CA, Wallace ZS, Meyersohn N, Oliveira G, Stone JR, Stone JH. Large vessel involvement by IgG4-related disease. Medicine (Baltimore). 2016;95:e3344.
8. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012;22:21–30.
9. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Ann Rheum Dis. 2015;74:14–8.

Tables

Table 1. Patient’s investigations results

Serology		
Full blood count	121 g/L Normocytic anaemia.	(131-166)
ESR	**25mm/hr****	(1-10)
C-reactive protein	**84 mg/L****	(0-5)
Liver, renal, lipid profile, TFT, glucose, Ca, Mg, Zn	Within normal range	
Immunoglobulins		
Total Protein	**78.0 g/L****	(60-74)
IgG	**27.57 g/L****	(6.0-16.0)
IgA	**6.64 g/L****	(0.8-4.0)
IgM	0.63 g/L	(0.5-2.0)
IgG subclasses		
- IgG 1	6.59 g/L	(3.2-10.2)
- IgG 2	3.04 g/L	(1.2-6.6)
- IgG 3	0.76 g/L	(0.2-1.9)
- IgG 4 subclass	**1.48 g/L****	(0-1.3)
Anti-cerebellar antibody screen panel	Negative (including Purkinji cell Ab Anti-Yo, Neuoronal nuclei Ab Anti-Hu/Ri, Amphiphysin Ab, Anti-CV2/CRMP-5 Ab, Anti-PNMA2 (Ma2/Ta) Ab, Anti-Tr Ab).	
Auto antibody screen	Negative (Rheumatoid Factor Ab, sDNA IgG, ANA, ENA)	
Coeliac Screen	Negative (Endomysium IgA Ab, t-Transglutaminase IgA Ab, IgA-Gliadin Ab, IgG Gliadin Ab)	
HIV . Heo B . Hep C	Negative	
Quantiferon Tb Gold + assay	Negative	
CSF		
Glucose	**4.7 mmol/L ****	(2.3-3.9)
CSF Protein	**0.73 g/L****	(0.15-0.45)
Oligoclonal bands	Negative	
- CSF/Serum IgG/Albumin ratio	0.5	(0.2-0.7)

Pathology/Cytology	Mildly hypercellular reactive-looking lymphocytes. Neoplastic cells not identified. Mild non-specific chronic inflammatory reaction.
Radiology	
CT thorax, abdomen and pelvis	Emphysematous change in the lungs. Enlarged right ventricle and both atria.
CT head	Old infarct in the left parietal lobe. Within the posterior fossa there are 2 areas of low attenuation, one within the right middle cerebellar peduncle, the second lies at the junction between the pons and left middle cerebellar peduncle.
MR head with MR cerebral angiogram	Bilateral restricted diffusion in the cerebellar peduncles with a small focus in the left side of the pons. Areas of stenosis in the left V3 segment of the vertebral artery and occlusion in the right intracranial V4 segment. Anterior inferior cerebellar arteries patent.
MR cerebellar spectroscopy	NAA to creatinine ratio in vermis reduced to 0.77 and in right cerebellar hemisphere 0.73 but no significant atrophy.
CT angiogram	Gross wall thickening of the internal and external carotid and vertebral arteries.
PET FDG-CT	328 MBq F18-FDG administered. No evidence of FDG avid malignancy. Increased vascular uptake in the subclavian and proximal femoral arteries bilaterally and to a lesser extent the aorta. Vascular uptake raises possibility of large vessel vasculitis.
Trans-thoracic echocardiogram	Negative
Other	
HSV/ SARS COVID-19 PCR	Negative
Urine, CSF, Blood cultures	Negative

Figures

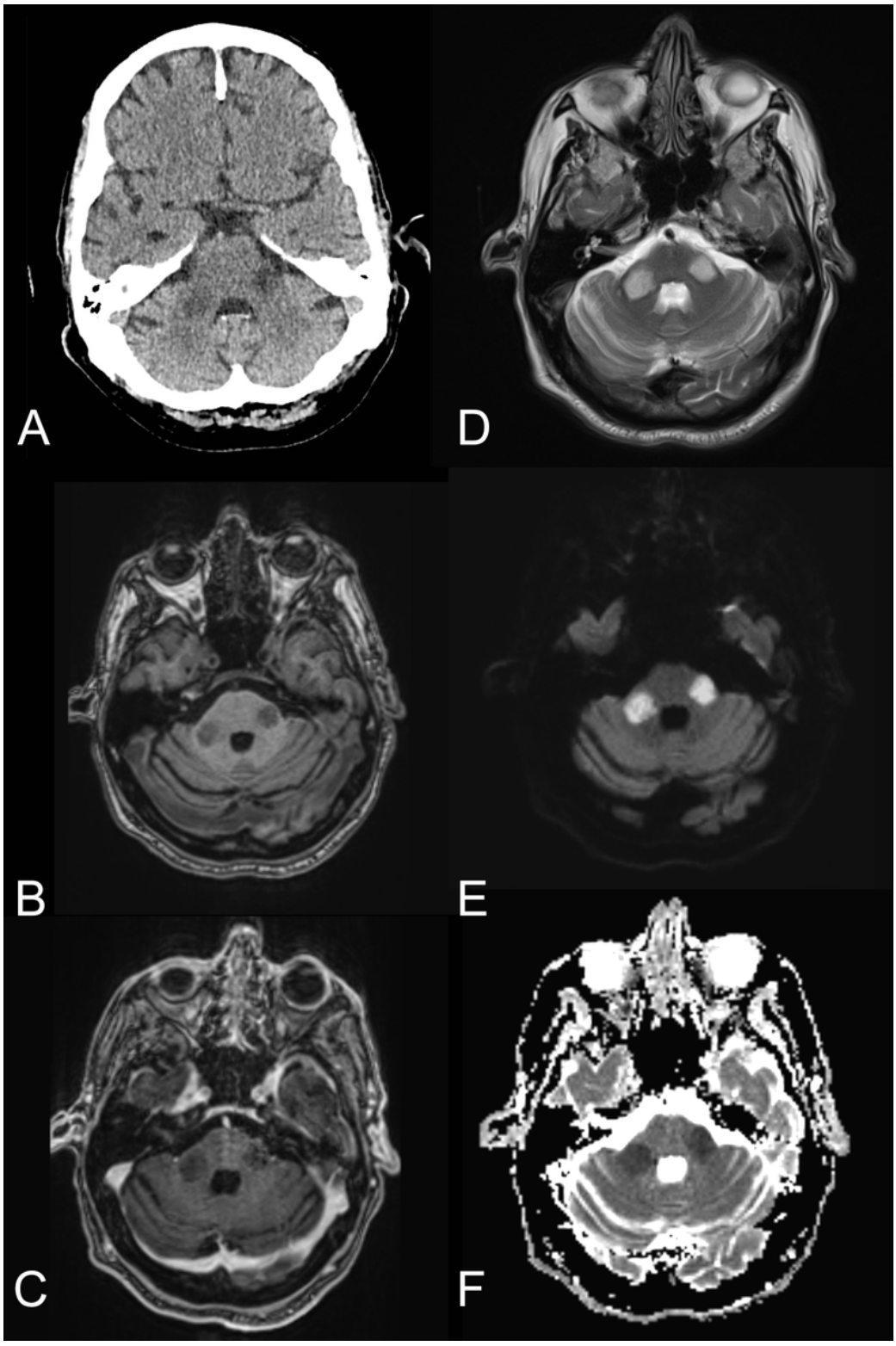

Figure 1

Magnetic resonance imaging (MRI) performed three days after admission. A. Unenhanced CT demonstrating bilateral low-density change in the middle cerebellar peduncles. B. and C. The lesions did not demonstrate contrast enhancement on intravenous gadolinium administration. D. T2-weighted MRI confirmed elevated T2 signal change at these sites with local mass effect. E. and F. Restricted diffusion was confirmed on the diffusion weighted sequence and ADC map.

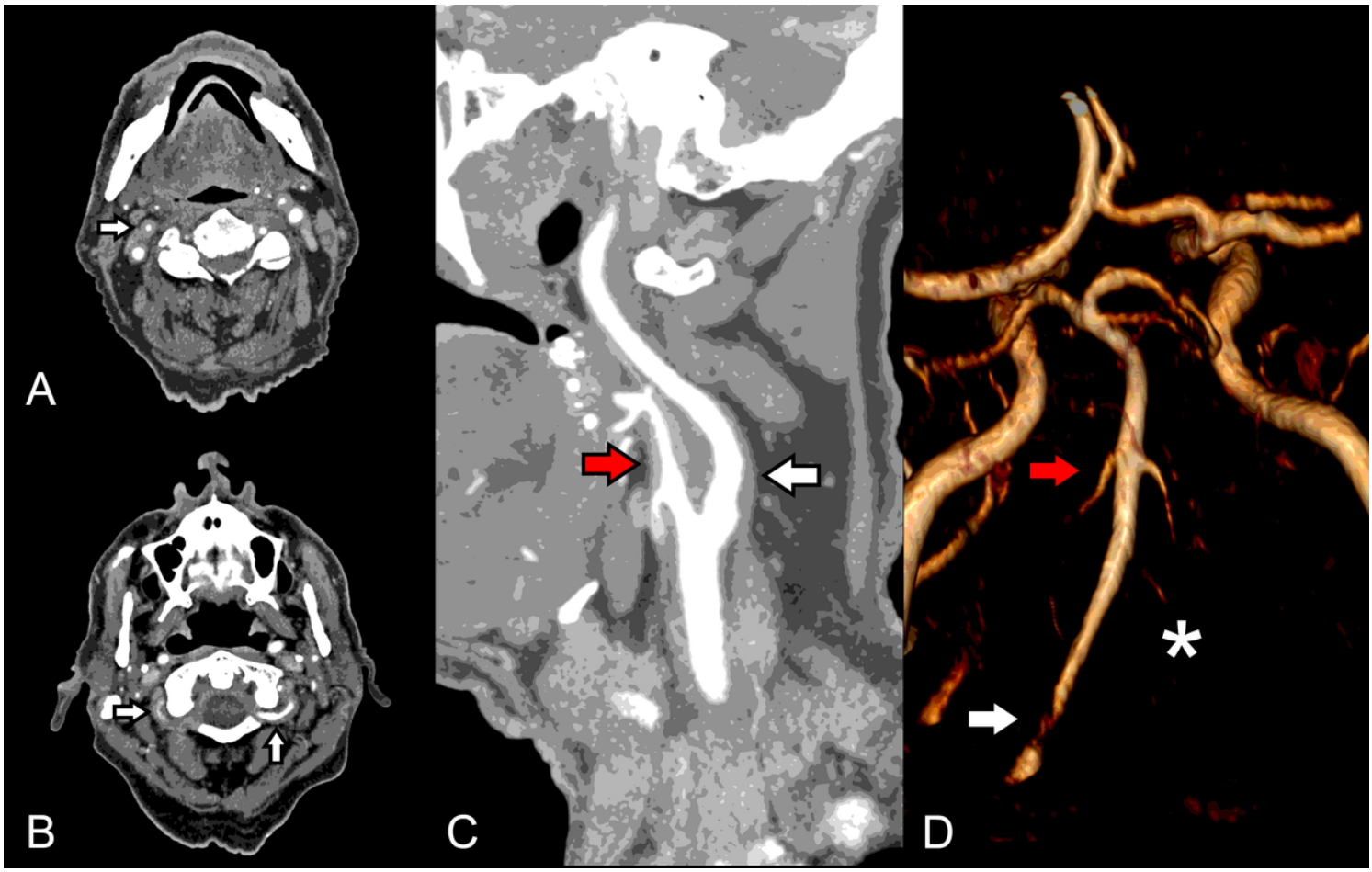

Figure 2

CT angiogram A. Gross thickening of the internal and external carotid arteries. Particularly the wall of the right internal maxillary artery is similar to the diameter of the lumen (white arrow). B. Similarly, the walls of both vertebral arteries (white arrows) where significantly thickening with stenosis of the right extracranial V3 segment on the right side. C. Sagittal reconstruction highlights the diffuse smooth nature of the arterial wall thickening extending along the external carotid artery (red arrow) and internal carotid artery (white arrow). D. Time of flight angiography confirmed patency of the anterior inferior cerebellar arteries (red arrow), occlusion of the intra-dural right vertebral artery (*) and stenosis in the left vertebral artery.

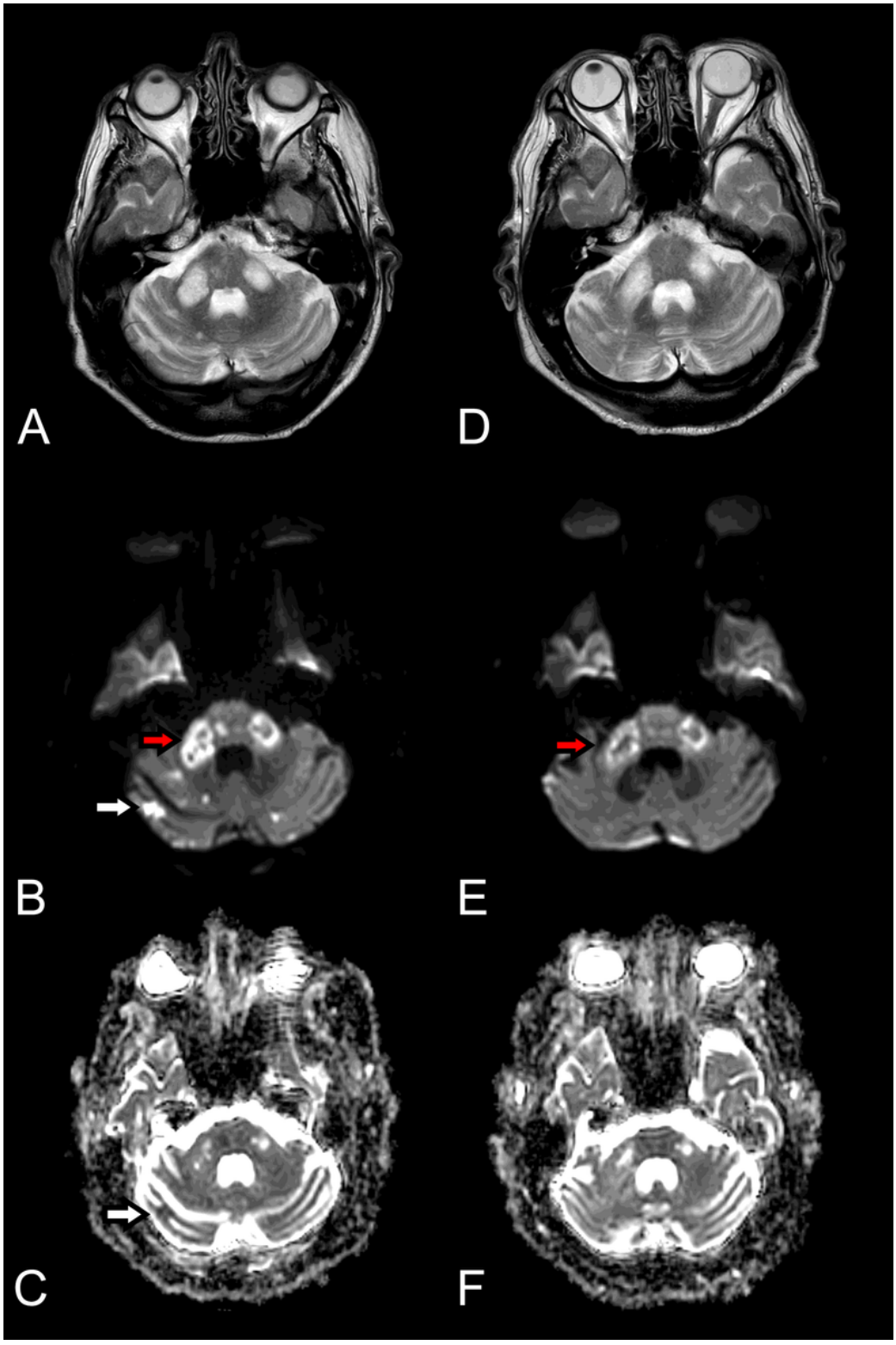

Figure 3

Magnetic resonance imaging (MRI) performed at 39 days after admission following decline. A. T2-weighted MRI demonstrated continued elevated signal change in the middle cerebellar peduncles with new foci of signal change in the folia of the cerebellum. B. and C. The middle cerebellar peduncle lesions demonstrated continued peripheral high signal on diffusion weighted sequence but no restriction on ADC map, this suggested established inflammatory change (red arrow). The new folial lesions demonstrated

restricted diffusion in keeping with no foci of infarction. MRI at 60 days after admission as surveillance demonstrated D. to F. Signal characteristics in the middle cerebellar peduncle lesions was unchanged, with some loss of the ‘mass effect’, whilst the cerebellar infarcts had become established.