

Neuroimaging in Juvenile Alexander Disease: Tumour-like Brainstem Lesions

Dear Editor,

Alexander disease (AD) is a progressive degenerative leukodystrophy, which typically presents in infancy. Neonatal, juvenile and adult-onset forms of AD are relatively rare, with a more variable clinical course compared to the infantile subtype. This disorder is a consequent of de novo heterozygous missense mutations in the *glial fibrillary acidic protein (GFAP)* gene. Characteristic imaging findings in AD have been described in the literature and are primarily supratentorial in distribution, with a frontal predominance. We describe 2 cases of genetically confirmed juvenile-onset AD, presenting as focal tumour-like lesions within the brainstem. Magnetic resonance imaging (MRI) characteristics of these lesions are discussed, along with clues to differentiate this entity from other focal brainstem lesions within the paediatric population (such as focal glioma and demyelinating lesion). These cases highlight an atypical presentation of juvenile AD and the need for consideration of metabolic diseases when focal tumour-like brainstem lesions are encountered, thus allowing an accurate diagnosis and avoiding invasive investigation by means of tissue biopsy.

Case 1

A 7-year-old boy was referred to our neuro-oncology unit for a presumed tumour within the dorsal medulla oblongata. The child had a longstanding history of motor developmental delay, congenital hip dysplasia and progressive weakness of the lower limbs. At the time of referral, no definitive cause for his symptoms had been found. One year prior to presentation, he developed intractable vomiting resulting in emaciation. MRI of the brain demonstrated a well circumscribed symmetrical lesion in the dorsal medulla (Figs. 1A-E), concerning for a brainstem glioma. The case was presented at the neuro-oncology meeting for consideration of biopsy or initiation of proton beam therapy. However, the unusually symmetric appearance of the lesion prompted the consideration of atypical AD. Mutation analysis of the *GFAP* gene revealed a pathogenic *GFAP* gene mutation (heterozygous C>T nucleotide substitution in exon 4 at amino acid position 258), confirming the diagnosis of AD.

Case 2

A 14-year-old girl was referred to the local paediatric services for failure-to-thrive and learning difficulties. This

was associated with persistent vomiting and severe weight loss. No motor symptoms were present at the time of presentation. Neurological examination was unremarkable apart from slight brisk reflexes in the lower limbs. MRI of the brain showed a well defined, bilobulated, enhancing lesion within the dorsal medulla on a background of leukodystrophy with some cystic elements and mild frontal predominance. The lesion within the dorsal medulla was not present in a MRI study done 5 years prior to current presentation for investigation of developmental delay (Figs. 1F-I). The overall imaging appearances were suggestive of juvenile AD. Sequencing of *GFAP* revealed a mutation in exon 1: c.262C>T: p.Arg88Cys, confirming the diagnosis of juvenile AD. Three years later, the patient presented to the emergency department for dense right hemiplegia and hemineglect after prolonged seizure. Repeat MRI of the brain showed progression of leukodystrophy as well as a new area of signal abnormality within the left cerebral hemisphere, involving predominantly the cortical grey matter. The lesion in the dorsal medulla showed interval regression. There was heterogenous signal abnormality within the atrophic medulla. Extensive neuro-metabolic and neuro-inflammatory investigations were performed but yielded no significant abnormality. The case was discussed at the neurology meeting and it was felt that the patient's new onset right hemiplegia was likely due to evolution of her genetically confirmed AD.

Discussion

AD is a progressive degenerative leukodystrophy associated with the presence of Rosenthal fibres on histology and dominant mutations in the *GFAP* gene on chromosome 17q21.^{1,2} Rosenthal fibres are eosinophilic inclusion bodies found in astrocytes that contain *GFAP*, ubiquitin as well as small stress proteins $\alpha\beta$ -crystalline and heat shock protein.^{3,4} Neonatal, infantile, juvenile and adult forms of AD have been described.⁵ In 2011, Prust et al proposed a revision of the subtypes of AD into 2 major groups—Type I and Type II. Type I AD is characterised by early onset and typical MRI features. Type II, on the other hand, is characterised by later onset, bulbar symptoms and atypical MRI features,⁶ as illustrated in both cases.

AD presenting as an isolated lesion within the brainstem is rare. To our knowledge, only 3 cases of juvenile AD

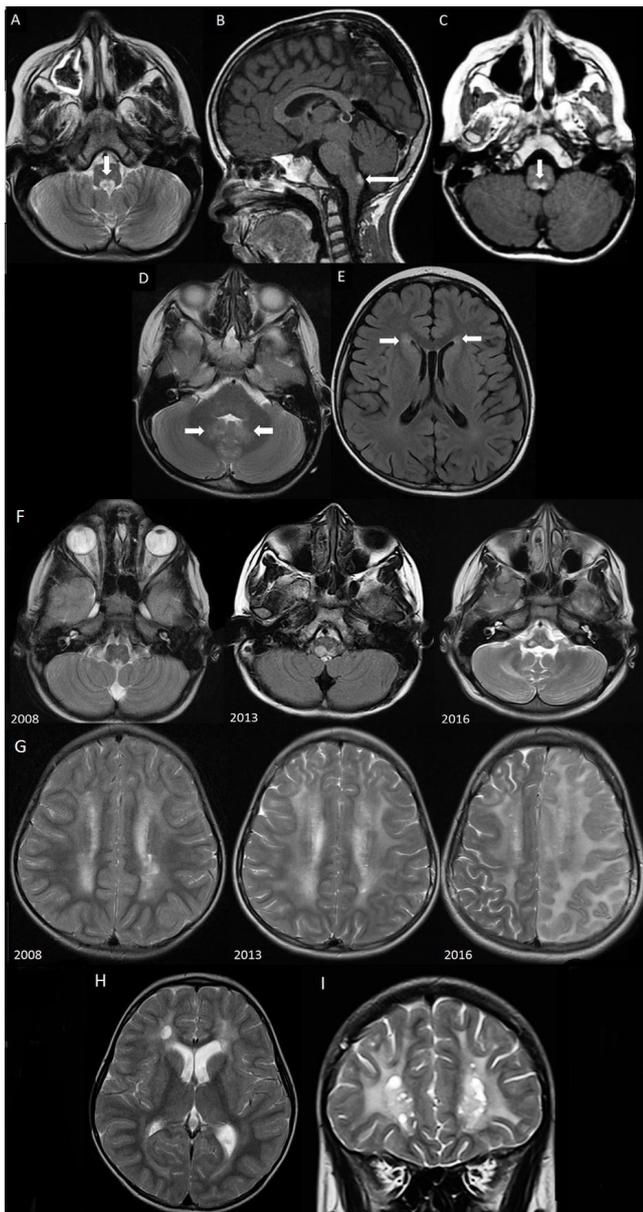


Fig. 1. Patient 1: Axial T2-weighted image (A) demonstrates a well circumscribed, hyperintense and symmetrical lesion in the dorsal medulla oblongata with minimal mass effect. Sagittal (B) and axial (C) postcontrast images show avid homogeneous enhancement of the prior described lesion within the dorsal medulla. Ill-defined non-enhancing signal abnormality is also seen in the dentate nuclei (D) and frontal periventricular white matter (E). Patient 2: Serial MRI studies were performed from 2008 to 2016, illustrating the progression of imaging findings. (F) Serial axial T2-weighted images show a well defined, bi-lobulated enhancing lesion within the dorsal medulla, first seen in 2013 and subsequently underwent regression in 2016, associated with atrophy of the medulla. (G) Serial axial T2-weighted images showed temporal progression of the leukodystrophy. In 2016, new diffuse signal abnormality is seen within the left cerebral hemisphere, involving predominantly the cortical grey matter. This was presumed to be an atypical pattern of disease progression. Axial (H) and coronal (I) T2-weighted images demonstrate cystic changes within the frontal lobes.

presenting in this manner have been reported in the English literature. The described cases add to the existing literature that neurodegenerative disease should be considered in the differential diagnosis for focal tumour-like brainstem lesions. The other considerations for such lesions include focal tumours, typically gliomas in this age group, infections and demyelinating disorders.⁷ In 2001, van der Knaap et al proposed a MRI-based imaging criteria for establishing the diagnosis of AD.^{5,8} Over the years, the clinical and MRI phenotypic variations in AD have been increasingly recognised. In a 2005 study by van der Knaap et al,¹⁰ patients with clinical features suggestive of AD who did not meet the typical diagnostic MRI criteria were found to have *GFAP* missense mutations on genetic analysis. Atypical MRI features found in these patients include predominant or isolated involvement of posterior fossa structures (as seen in Case 1), multifocal tumour-like brainstem lesions and brainstem atrophy, diffuse signal changes involving the deep grey nuclei, garland-like feature along the ventricular wall and characteristic pattern of contrast enhancement.⁹ In both of our cases, the brainstem lesions were confined to the dorsal medulla oblongata. The brainstem lesions associated with juvenile AD tend to demonstrate avid homogenous contrast enhancement,^{9,10,11} as seen in both of our cases. In AD dominated by brainstem and spinal abnormalities, medulla involvement is invariably present.⁹

The differentiation of tumour-like brainstem lesions of AD from gliomas and demyelinating disease is crucial as the treatment varies tremendously. Gliomas are the most common brainstem neoplasm in children, accounting for approximately 90% of the cases.^{12,13} The absence of enhancement is an extremely useful imaging feature in differentiating this entity from brainstem lesions of AD, which usually shows homogenous enhancement. Unfortunately, although the absence of enhancement is the norm, there are exceptions to the rule.¹⁴ Enhancement in gliomas and demyelinating disease (if present) is usually ring-like or spotty.

Demyelinating disease is another mimic of brainstem lesions of AD. Differentiation of these 2 conditions based solely on imaging is a radiological challenge. Correlation with patient's age, clinical features and results of other investigations is mandatory. Multiple sclerosis (MS) is rare in children. MS lesions in the brainstem tend to be sited along the floor of the 4th ventricle and on the surface of the pons.¹⁵ Demonstration of typical supratentorial MS lesions (when present) may assist the reporting radiologist in reaching the correct diagnosis. Additional lesions should also be sought within the rest of the spinal cord as acute demyelinating encephalomyelitis (ADEM) rarely presents in the form of a solitary brainstem lesion without evidence of more disseminated intracranial involvement. The

clinical presentation also differs substantially and includes encephalopathy. The medulla oblongata is the most common site of involvement in neuromyelitis optica (NMO). Lesions of NMO usually show an ill defined margin, compared to those of AD. In addition, detection of blood antibody NMO-immunoglobulin (IgG) has been reported to have a 90% specificity rate and hence can be extremely useful to exclude the diagnosis of NMO.¹⁶

As high as 98% of AD cases are associated with mutations in the coding region of the *GFAP* gene.^{17,18} The availability of molecular genetic testing has opened new directions for investigation. These cases highlight an atypical presentation of juvenile AD and the need for consideration of metabolic diseases when focal tumour-like brainstem lesions are encountered. This is to ensure that the appropriate investigations such as genetic testing are conducted, bypassing the need for invasive investigation such as brainstem biopsy which carries significant morbidity.

REFERENCES

- Li R, Johnson AB, Salomons G, Goldman JE, Naidu S, Quinlan R, et al. Glial fibrillary acidic protein mutation in infantile, juvenile and adult forms of Alexander Disease. *Ann Neurol* 2005;57:310-26.
- Li R, Messing A, Goldman JE, Brenner M. GFAP mutations in Alexander disease. *Int J Dev Neurosci* 2002;20:259-68.
- Brenner M, Johnson AB, Boespflug-Tanguy O, Rodriguez D, Goldman JE, Messing A. Mutations in GFAP, encoding glial fibrillary acidic protein are associated with Alexander disease. *Nat Genet* 2001;27:117-20.
- Johnson A. Alexander disease: a review and the gene. *Int J Dev Neurosci* 2002;20:391-4.
- van der Knaap MS, Naidu S, Breiter SN, Blaser S, Stroink H, Springer S, et al. Alexander disease: diagnosis with MR imaging. *AJNR Am J Neuroradiol* 2001;22:541-52.
- Prust M, Wang J, Morizono H, Messing A, Brenner M, Gordon E, et al. GFAP mutations, age at onset and clinical subtypes in Alexander disease. *Neurology* 2011;77:1287-94.
- Guzman-De-Villora JA, Fernandez-Garcia P, Ferreira-Arguelles C. Differential diagnosis of T2 hyperintense brainstem lesions: part 1. Focal lesions. *Semin Ultrasound CT MR* 2010;31:246-59.
- Rodriguez D, Gauthier F, Bertini E, Bugiani M, Brenner M, N'guyen S, et al. Infantile Alexander disease: spectrum of GFAP mutations and genotype-phenotype correlation. *Am J Hum Genet* 2001;69:1134-40.
- van der Knaap MS, Salomons GS, Li R, Franzoni E, Gutiérrez-Solana LG, Smit LM, et al. Unusual variants of Alexander's disease. *Ann Neurol* 2005;57:327-38.
- van Poppel K, Broniscer A, Patay Z, Morris EB. Alexander disease: an important mimicker of focal brainstem glioma. *Pediatr Blood Cancer* 2009;53:1355-6.
- Franzoni E, van der Knaap MS, Errani A, Colonnelli MC, Bracceschi R, Malaspina E, et al. Unusual diagnosis in a child suffering from juvenile Alexander disease: clinical and imaging report. *J Child Neurol* 2006;21:1075-80.
- Kwon JW, Kim IO, Cheon JE, Kim WS, Moon SG, Kim TJ, et al. Paediatric brain-stem gliomas: MRI, FDG-PET and histological grading correlation. *Pediatr Radiol* 2006;36:959-64.
- Guillamo JS, Doz F, Delattre JY. Brain stem gliomas. *Curr Opin Neurol* 2001;14:711-5.
- Vandertop WP, Hoffman HJ, Drake JM, Humphreys RP, Rutka JT, Armstrong DC, et al. Focal midbrain tumors in children. *Neurosurgery* 1992;31:186-94.
- Yousry TA, Grossman RI, Filippi M. Assessment of posterior fossa damage in MS using MRI. *J Neurol Sci* 2000;172:S50-3.
- Park KY, Ahn JY, Cho JH, Choi YC, Lee KS. Neuromyelitis optica with brainstem lesion mistaken for brainstem glioma. Case report. *J Neurosurg* 2007;107:251-4.
- Gordon N. Alexander disease. *Eur J Paediatr Neurol* 2003;7:395-9.
- Ferreira MC, Dorboz I, Rodriguez D, Boespflug Tanguy O. Screening for GFAP rearrangement in a cohort of Alexander disease and undetermined leukoencephalopathy patients. *Eur J Med Genet* 2015;58:466-70.

Ai Peng Tan,¹MD, Chhabda Sahil,²MBBS, Robert Robinson,³MBBS, Ata Siddiqui,⁴MD, Elizabeth Wraige,⁵MD, Christopher Chandler,⁶MBBS, Kshitij Mankad,³MBBS

¹Department of Diagnostic Imaging, National University Hospital, National University Health System, Singapore

²Department of Radiology, Chelsea and Westminster Hospital, NHS Foundation Trust, United Kingdom

³Department of Neurology, Great Ormond Street Hospital, NHS Foundation Trust, United Kingdom

⁴Department of Radiology, Guy's and St Thomas', NHS Foundation Trust, United Kingdom

⁵Department of Neurology, Guy's and St Thomas', NHS Foundation Trust, United Kingdom

⁶Department of Neurosurgery, King's College Hospital, NHS Foundation Trust, United Kingdom

Address for Correspondence: Dr Tan Ai Peng, Department of Diagnostic Imaging, National University Hospital, National University Health System, 1E Kent Ridge Road, Singapore 119228.

Email: ai_peng_tan@nuhs.edu.sg