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LETTER TO THE EDITORS

Late onset Alexander's disease presenting as cerebellar ataxia associated with a novel mutation in the *GFAP* gene

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Sirs,

Alexander's disease (AD) is a rare genetic disorder caused by mutations in the glial fibrillary acid protein (GFAP) gene characterized by a relentlessly progressive neurological decline in children and infants. In contrast, the clinical course of adult onset forms of AD (AOAD) is usually more protracted and the clinical presentations vary widely. Here we present a case of late onset cerebellar ataxia with marked atrophy of the lower brain stem and the medulla on magnetic resonance imaging (MRI). Molecular genetic analysis revealed a novel missense mutation (c. 1148C > T, p. T383I) in the *GFAP* gene further broadening the spectrum of clinical and MRI presentations of AOAD.

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AD is a rare leukodystrophy caused by mutations in the *GFAP* gene, typically affecting infants and children [1]. Nearly all AD mutations involve amino acid substitutions, and a dominant toxic or gain-of-function effect for mutant GFAP protein was hypothesized [2, 3]. While AD in infants and children typically presents with psychomotor retardation, seizures, ataxia and progressive spasticity leading to death within a few years [1, 2], clinical phenotypes with AOAD vary considerably and the clinical course is more protracted [4–6]. MRI criteria have been proposed for the diagnosis of AD [7]. However, more recent case series of patients with AOAD involving individuals with atypical clinical and MRI features not fully meeting the above diagnostic criteria, suggest that the spectrum of clinical phenotypes of AOAD may be broader than previously expected [4–6, 8].

A 65 year old otherwise healthy female of Caucasian origin presented with a 10 year history of slowly progressive unsteadiness of gait and slurred speech. On neurological examination, she revealed hypermetric horizontal saccades. There was moderate cerebellar dysarthria but no dysphagia or palatal myoclonus. Limb movements were hypermetric with moderate intention tremor. Reflexes of the legs were brisk, but plantar responses were flexor and there were no signs of spasticity. The gait was broad-based, ataxic. Sensory testing was normal for all modalities. There was no evidence of cognitive impairment. The family history revealed that the patient's father had a tremor and impaired taste with onset after the age of 70. Both grandmothers allegedly suffered from multiple sclerosis. All of her four children showed no signs of neurological impairment.

Previous genetic work-up including testing for spinocerebellar ataxia (SCA)-1, -2, -3, -6, -10, and -17 had revealed no abnormalities. Vitamins E and B_{12} deficiency

had been ruled out as well. Enzyme activity of arylsulfatase A and β-galactocerebrosidase in leukocytes as well as concentrations of very long chain fatty acids and their respective ratios were normal. The cerebrospinal fluid contained 1 cell/µl, and oligoclonal bands were absent.

Axial T2-weighted MR images of the infratentorial brain region (a, b, c) demonstrate the severe atrophy of the brain stem, particularly of the medulla oblongata, and upper spinal cord (b, c, open arrows). Within the atrophic brain stem linear high T2 signal abnormalities of the cortico-spinal tract can be observed (a, small arrows). In addition, bilateral abnormalities affecting the hilus of the dentate nucleus are present (a, large arrows). The sagittal fluid-attenuated inversion-recovery image (d) shows the severe atrophy of the medulla oblongata and upper cervical spinal cord (open arrows) in combination with severe cerebellar atrophy. Axial T2-weighted images of the supratentorial regions (e, f) demonstrate bilateral signal abnormities of the globus pallidus (large arrows). The MRI findings are shown in Fig. 1.

The nine exons and adjacent intronic regions of the *GFAP* gene (NM_002055 and alternative exon eight transcript NM_001131019) were PCR amplified (primer sequences available on request) and directly sequenced. A missense mutation (c. 1148C > T, p. T383I; positions according to RefSeq NM_002055) was detected in exon seven in heterozygous state. This mutation results in an amino acid exchange on position 383 from threonine to isoleucine and a loss of a predicted phosphorylation site [9]. In silico analysis revealed that this sequence alteration is "probably damaging" using the polymorphism phenotyping tool [9] or "damaging" using the "sorting intolerant from tolerant (SIFT)" tool [10]. A cohort of 181 ethnically matched healthy German blood donors was screened for the mutation by PCR followed by differential enzymatic restriction with *Bgl*II in order to further examine the functional significance of this mutation. The presence of the C > T transition at this position was not detected in any of the 362 tested control chromosomes.

More than 60 different mutations within the coding region of *GFAP* have been identified in association with AD [1] but only few studies have systematically investigated *GFAP* mutations in AOAD [4]. The differential diagnosis of adult onset cerebellar ataxia involves a wide spectrum of disorders including SCA, autosomal recessive ataxias such as Friedreich's ataxia, X-linked cerebellar ataxias such as ataxia teleangiectasia and fragile X-associated tremor/ataxia syndrome (FXTAS), abetalipoproteinemia, Refsum disease, late-onset GM2 gangliosidosis, cerebrotendinous xanthomatosis, autosomal dominant

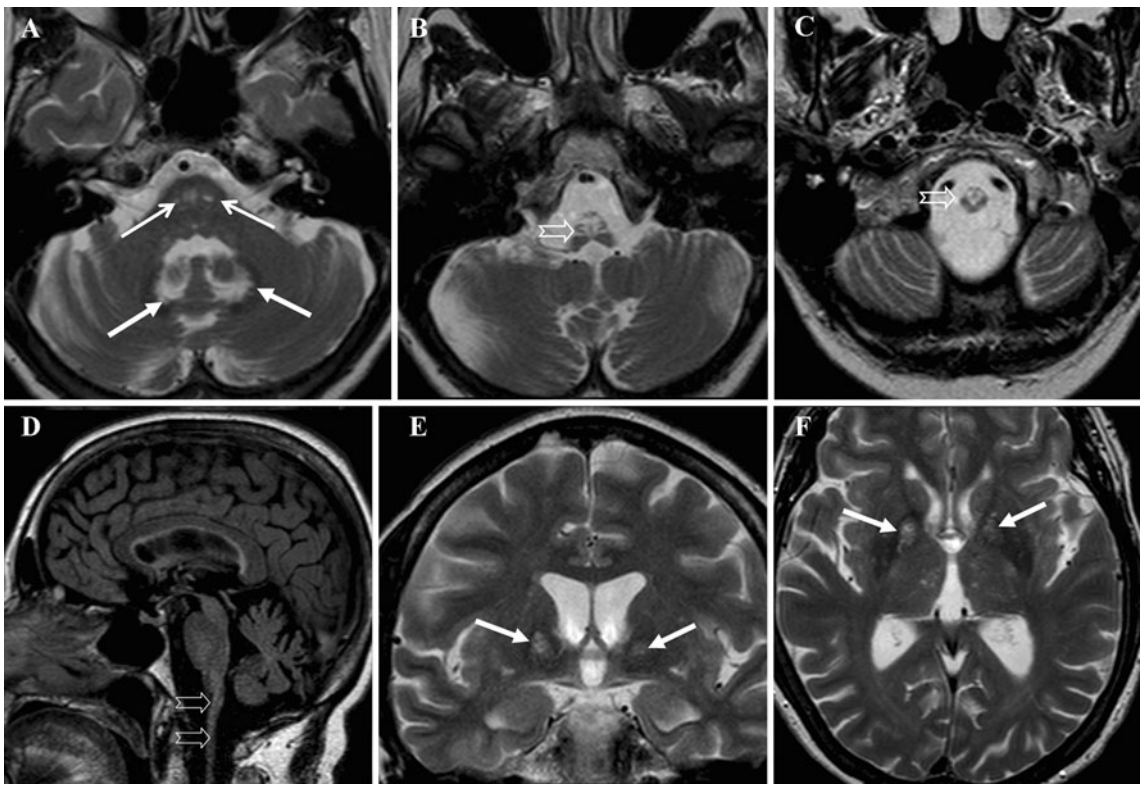

Fig. 1 MRI findings in a 65 year old woman with a novel missense mutation (c. 1148C > T, p. T383I) in the *GFAP* gene. The details are outlined in the text

mitochondrial heredoataxias as well as multisystem atrophy, vitamin B_{12} and vitamin E deficiencies, primary progressive multiple sclerosis and adult manifestations of leukodystrophies [10–12]. The present case report highlights the importance of MR imaging in the differential diagnosis of adult onset leukodystrophies. Although our patient met only three out five MRI criteria for AD [7], the severe atrophy of the medulla oblongata along with signal abnormalities in the hilus of the dentate nucleus were suggestive of AOAD [5, 6, 8]. However, the symmetrical signal abnormalities of the globus pallidus on T2-weighted images are only rarely seen in AOAD [5, 6, 8].

In accordance with previous reports of AOAD, clinical progression in our patient was relatively slow compared with that seen in childhood onset of AD [1, 4–6]. In summary, sequencing of the *GFAP* gene should be considered in cases of late onset cerebellar ataxia, in particular in the presence of MRI findings compatible with AD. The spectrum of clinical and MRI phenotypes of AOAD may still be broader than previously anticipated.

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