Ataxia and autonomic dysfunction as presenting symptoms in late-onset Alexander disease

Meike Jost, MD; Michel Rijntjes, MD; Horst Urbach, MD; Karl Egger, MD; Philipp T. Meyer, PhD, MD; Lars Frings, PhD; Cornelius Weiller, MD; Stephan Klebe, MD

Alexander disease (AD) is a rare leukodystrophy first described in 1949 with infantile, juvenile, or adult-onset Alexander disease (AOAD).¹ The pathophysiologic hallmark of AD is the presence of corkscrew-shaped intracytoplasmic eosinophilic inclusions in astrocytes (Rosenthal fibers) on histologic examination.² A noninvasive diagnosis is possible since the discovery of the corresponding gene (*GFAP*) encoding the glial fibrillary acidic protein in 2001.³ An autosomal dominant transmission with 100% penetrance has been described, but many patients with AD have de novo mutations not found in either parent.³⁻⁶ Disease progression, clinical phenotype, and imaging findings in AD differ enormously according to the age at onset (AAO). The phenotype in the poor prognostic infantile AD (AAO <2 years) (seizures, cognitive decline, development deficit, and megalencephaly) is associated with white matter abnormalities predominantly in the frontal lobe but also in the basal ganglia, thalamus, and brainstem. In juvenile AD (AAO 2 years to mid-teens), the phenotype may consist of coordination, swallowing, and speech difficulties with a slower progression. In the slow progressive AOAD, which is sometimes associated with a palatal myoclonus or tremor,⁴ involvement of the brainstem or spinal cord reflects both the phenotype and MRI.^{4,5,7}

Case

We present the clinical and imaging follow-up data of a 59-year-old man with a 10-year disease history before the diagnosis of AOAD was made. Our patient first presented at age 49 years with gait impairment, frequent falls, and autonomic dysfunctions (orthostatic hypotension, bladder, and sexual dysfunction). During the disease course, he developed gait ataxia, dysarthria, dysphagia, upper motor neuron signs, and reduced vibration sense but normal memory. Now aged 59 years, he is still capable of walking 500 meters with Nordic walking poles, with a score of 10/40 points on the Scale for the Assessment of Ataxia (SARA) due to mixed sensory and cerebellar ataxia (video at Neurology.org/cp). The patient also has urge incontinence and relapsing diarrhea. Regarding the family history, the patient's sister has multiple sclerosis (MS) (AAO 35 years) and his brother died of amyotrophic lateral sclerosis (ALS) at 57 years (AAO 50 years) (figure 1). The patient's parents both had gait disturbance (AAO >60 years). The first brain MRI at 51 years and the follow-up examination after 6 years at 57 years revealed stable atrophy of the medulla oblongata, cerebellum, and dentate nucleus (figure 2A). Spinal MRI at 59 years revealed a long cervical myelopathy signal with contrast enhancement (figure 2). [¹²³I]FP-CIT-SPECT at 53 years was normal. [¹⁸F]FDG-PET at 56 years showed hypometabolism of the upper parts of the cerebellum (figure 2B).

Practical Implications

Cerebral or spinal MRI signal changes of the medulla, spinal cord, or dentate nucleus are important to distinguish late-onset Alexander disease from sporadic ataxia of unknown origin or multiple system atrophy type C.

Video

Neurology.org/cp

Freiburg University Medical Center and Medical Faculty, Freiburg University, Germany.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp.**

Correspondence to: stephan.klebe@uniklinik-freiburg.de

Figure 1 Pedigree of the family

The arrow indicates the index patient carrying the heterozygous (+/M) pArg258Cys mutation in the *GFAP* gene. His sister has multiple sclerosis. The index patient's brother died of amyotrophic lateral sclerosis (ALS) at age 57 years. For both parents, gait disorders have been reported. The genotypes of the index patient's siblings and parents are unknown.

Somatosensory evoked potentials after stimulation of the lower limbs were prolonged, and electronystagmography showed saccadic eye movements and gaze-evoked nystagmus. Motor evoked potentials, nerve conduction studies, and biochemical testing of serum, CSF, and

Figure 2 MRI of the index patient

Axial T2-weighted turbo spin echo (A.a–A.c), coronal fluid-attenuated inversion recovery turbo spin echo (A.d, A.e), and axial T1-weighted contrast-enhanced and fat-saturated magnetization-prepared rapid gradient echo (A.f) images show severe upper cervical and medulla atrophy and widespread bilateral symmetric T2 signal increase with involvement of several white matter tracts such as the medial longitudinal fascicles (A.a, arrows) and spinocerebellar tracts, hili of the dentate nuclei (A.b, arrows), and superior cerebellar peduncles (A.c–A.e, arrows). Note also the faint contrast enhancement in the posterior medulla (A.f, arrow). (B) [18 F]Fluorodeoxyglucose ([18 F]FDG) PET 7 years after disease onset. The patient showed moderate hypometabolism of the superior cerebellum, whereas cerebral glucose metabolism exhibited no substantial abnormality. (A) Transaxial and sagittal cross-sections. (B) Three-dimensional stereotactic surface projections of the left lateral view depict regional FDG uptake (left) and its voxel-wise statistical deviation from age-matched normal controls (right; regional hypometabolism, negative z score map).

gastroscopy (exclusion of Whipple disease) were normal. Molecular diagnostic testing excluded the spinocerebellar genes *SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7*, *SCA8*, *SCA10*, *SCA12*, and *SCA17*. Spinal MRI raised the suspicion that the patient has an AOAD. The genetic analysis finally showed a known heterozygous mutation in exon 4 (c.772C>T; p.Arg258Cys) of the *GFAP* gene.

DISCUSSION

The present case illustrates that AOAD should be included in the differential diagnosis of apparently sporadic ataxia of unknown origin or multiple system atrophy type C, if cerebral or spinal MRI show signal changes of the medulla, spinal cord, or dentate nucleus. However, these imaging findings might be subtle early in the disease course. The p.Arg258Cys mutation has been described in 2 other patients,^{8,9} one of whom was also a patient with AOAD with prominent autonomic dysfunction.⁸ The existence of MS and ALS in siblings of the same generation could be coincidental. However, MS or ALS misdiagnoses should be considered in these cases in the context of a third patient with genetically confirmed AOAD. However, the siblings have not been examined in our department, and their genotypes are unknown. The present case should increase awareness for this rare, underrecognized genetic disease, as the definitive diagnosis has consequences for the clinical and genetic counseling of the family and potential future treatment options.

REFERENCES

1. Alexander WS. Progressive fibrinoid degeneration of fibrillary astrocytes associated with mental retardation in a hydrocephalic infant. *Brain* 1949;72:373–381.
2. Iwaki T, Kume-Iwaki A, Liem RK, Goldman JE. Alpha B-crystallin is expressed in non-lenticular tissues and accumulates in Alexander's disease brain. *Cell* 1989;57:71–78.
3. 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;27:117–120.
4. Li R, Johnson AB, Salomons G, et al. Glial fibrillary acidic protein mutations in infantile, juvenile, and adult forms of Alexander disease. *Ann Neurol* 2005;57:310–326.
5. van der Knaap MS, Salomons GS, Li R, et al. Unusual variants of Alexander's disease. *Ann Neurol* 2005;57:327–338.
6. Pareyson D, Fancellu R, Mariotti C, et al. Adult-onset Alexander disease: a series of eleven unrelated cases with review of the literature. *Brain* 2008;131:2321–2331.
7. Graff-Radford J, Schwartz K, GavriloVA RH, Lachance DH, Kumar N. Neuroimaging and clinical features in type II (late-onset) Alexander disease. *Neurology* 2014;82:49–56.
8. Spritzer SD, Zarkou S, Ireland SP, Carter JL, Goodman BP. Autonomic dysfunction in adult-onset alexander disease: a case report and review of the literature. *Clin Auton Res* 2013;23:333–338.
9. Yoshida T, Sasayama H, Mizuta I, et al. Glial fibrillary acidic protein mutations in adult-onset Alexander disease: clinical features observed in 12 Japanese patients. *Acta Neurol Scand* 2011;124:104–108.

Received February 24, 2017. Accepted in final form May 18, 2017.

AUTHOR CONTRIBUTIONS

M. Jost: drafting/revising the manuscript, acquisition of data. M. Rijntjes: drafting/revising the manuscript. H. Urbach: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. K. Egger: drafting/revising the manuscript, acquisition of data. P. Meyer: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. L. Frings: analysis or interpretation of data. C. Weiller: study concept or design, analysis or interpretation of data, acquisition of data. S. Klebe: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

M. Jost reports no disclosures. M. Rijntjes serves on the editorial board of *Neurologie & Rehabilitation Claustrium*. H. Urbach has received speaker honoraria from Bayer, Bracco, UCB Pharma, and Stryker and serves as Associate Editor for *Clinical Neuroradiology* and on the editorial advisory board of *Neuroradiology*. K. Egger reports no disclosures. P. Meyer performs PET and SPECT neuroimaging studies (<5% of effort) at the Department of Nuclear Medicine, University Hospital Freiburg. L. Frings reports no disclosures. C. Weiller serves on a scientific advisory board for ANR and serves on editorial boards of *Der Nervenarzt*, *Restorative Neurology and Neuroscience*, *Journal of Neurology*, *Der Onkologe*, *Neurorehabilitation & Neural Repair*, and *Neurologie & Rehabilitation*. S. Klebe has received funding for travel from AbbVie Germany and Bayer AG and receives research support from Interdisciplinary Center for Clinical Research, Würzburg University. Full disclosure form information provided by the authors is available with the **full text of this article at [Neurology.org/cp](http://www.neurology.org/cp)**.

Neurology[®] Genetics Call For Papers

Neurology: Genetics is an open access, online only journal that will provide neurologists with outstanding original contributions that elucidate the role of genetic and epigenetic variation in diseases and biological traits of the central and peripheral nervous system. We welcome all submissions. For more information on how to submit, visit <http://www.neurology.org/site/gen/gen2.xhtml>.