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# Histopathological proof of the pathogenicity of a rare GFAP mutation in a patient with flaccid paraparesis

Case Report

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### Abstract

Infantile Alexander disease is a rare progressive leukodystrophy caused by autosomal dominant mutations in the (GFAP) gene typically presenting with psychomotor retardation, progressive macrocephaly and refractory epilepsy. Neuroradiological hallmarks are extensive white matter lesions with frontal preponderance as well as signal intensity changes of basal ganglia and medulla oblongata with variable contrast enhancement. Here, we report an atypical manifestation in a 21-month-old boy presenting with flaccid paraparesis and areflexia. Cognitive, visual as well as fine motor skills and muscular strength of the upper extremities were appropriate for age. Weight and height as well as head circumference were within normal range. Clinical or electroencephalographic signs of seizures were absent. Cranial MRI demonstrated bifrontal cystic tumorous lesions with partial contrast rims, as well as space-occupying focal lesions of the caudate nuclei. Spinal MRI revealed swelling of the lumbar and cervical spinal cord. CSF and blood chemistry showed normal results. Histopathology of a subcortical lesion showed large amounts of Rosenthal fibers and protein droplets characteristic of Alexander disease. Sequencing detected a heterozygous mutation of the GFAP gene (c.205G > A; p.(Glu69Lys)) that has been reported before as probably pathogenetic in another case of lower spinal involvement.

This well documented case draws attention to atypical spinal manifestations of Alexander disease and gives histopathological proof of the pathogenetic role of a rare GFAP mutation with marked spinal involvement.

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Keywords: Alexander disease; Leukodystrophy; GFAP; Spinal manifestation

## 1. Introduction

Alexander disease is a rare progressive disorder of the cerebral white matter caused by mutations in GFAP

gene, encoding glial fibrillary acidic protein [1,2]. Two main clinical subtypes are characterized. Type I with infantile manifestation presents with psychomotor retardation, progressive macrocephaly and refractory epilepsy while cranial MRI shows predominantly frontoparietal white matter lesions, while type II is a continuous spectrum of clinical features from juvenile to adulthood and is characterized by spastic gait, cerebellar ataxia and atrophy of the medulla [3]. Typical

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magnetic resonance imaging (MRI)-findings consist of hyperintense white matter lesions in T2-weighted images predominantly in the frontal lobes, often together with peripheral contrast enhancement in T1-weighted images. Moreover, swelling or atrophy of basal ganglia, thalami, and brain stem can be seen [4]. Diagnosis is confirmed by autosomal dominant mutations of the GFAP gene [3]. The histopathological hallmark of Alexander disease is the presence of Rosenthal fibres, cytoplasmic inclusions in astrocytes that contain the intermediate filament protein GFAP [5], but have been described in astrocytic tumors as well [6].

We report a patient with atypical infantile presentation and give histopathological proof of a pathogenetic GFAP mutation that seems to be particularly associated with lower spinal involvement.

# 2. Clinical report

The boy was presented in the neuropediatric outpatient clinic at the age of 21 months for weakness of the lower limbs. He was born after uneventful pregnancy with auxological parameters within normal range. Slow motor development was noted at the end of his first year of life and weakness of the legs was retrospectively reported. He had learned to roll over at the age of 8 months and did not crawl before the age of 15 months. Since the age of 19 months he tried to walk aided but could not hold his body weight. He went to a regular nursery and started to use single words at the age of 15 months. At presentation, auxological data including head circumference were within normal range (75th percentile). Flaccid paraparesis and areflexia of the legs were present while fine motor skills and muscular strength of the upper extremities were appropriate for age. Hearing and visual skills were normal. Assessment of mental development (Bayley Scales of Infant Development II) confirmed age-appropriate performance. There were no signs of neurogenic bladder or bowel dysfunction. Laboratory results including creatine kinase showed normal results. Clinical or electroencephalographic signs of seizures were absent.

Brain MRI revealed fluid-filled cavities in both frontal lobes and the genu of the corpus callosum with an enhancing rim after intravenous administration of gadolinium. Moreover, irregular patchy T2 hyperintensity was detected, involving most of the frontal white matter and extending posteriorly to the edematous caudate heads (Fig. 1, a-e). MRI of the spine showed a small T2 hyperintense lesion in the cervical spinal cord and diffus heterogeneous T2 hyperintensity of the swollen conus medullaris (Fig. 1, f), both with mild contrast enhancement. CSF analysis showed normal results. Since malignancy had to be considered in the differential diagnosis of the extensive space-occupying frontal cMRI



Fig. 1. MRI of the brain and the spine at age 22 months. Axial TIRM dark fluid images (a, d, e), sagittal postgadolinium T1-weighted image (b) and sagittal T2-weighted image (c) of the brain. Fluid-filled cavities with partial rim enhancement are seen in both frontal lobes (a, b) and the genu of the corpus callosum (c), together with patchy T2 hyperintensity of the frontal white matter (d) and edematous swelling of the caudate heads (e, *arrows*). Sagittal T2-weighted image of the lumbar spinal cord reveals heterogeneous hyperintensity of the swollen conus medullaris (f, *asterisk*).

changes, biopsy of a cerebral subcortial lesion was performed.

Intraoperatively, cystic lesions with xanthochomatous fluids showed next to somewhat sclerotic brain tissue. The nervus olfactorius was altered to a tube-like hollow structure (Fig. 2 D).

Histopathology examination revealed a lesion with presence of numerous Rosenthal fibres and abundant protein droplets with diffuse and also perivascular arrangement (Fig. 2 A and B). The Rosenthal fibres presented with strong GFAP immunoreactivity (Fig. 2 C). These changes were associated with profound loss of myelin. In summary, the observed alterations were



Fig. 2. Histopathological and macroscopic view of cerebral biopsy. H&E (Hematoxylin and Eosin) staining showing abundant Rosenthal fibres and protein droplets with frequent perivascular arrangement (A, black arrows, Scale bar in A: 200 µm). H&E staining at higher magnification demonstrating the characteristic appearance of Rosenthal fibres (B, Scale bar in B: 50 µm). GFAP immunohistochemistry with strong labelling of Rosenthal fibres (C, white arrow, Scale bar in C: 100 µm, D,E; scale bar in D: 100 µm). H&E-Luxol-fast-Blue histochemistry shows almost complete loss of myelin with only few remaining myelinated fibres (F, white arrows). Macroscopically nervus olfactorius presented as a hollow tube-like structure (arrow, G, rostral direction to the right).

characteristic of Alexander's disease. A strong histological involvement of the nervus olfactorius with Rosenthal fibres and loss of myelin has been described in animal models of Alexander's disease before [7].

Sequencing detected a heterozygous mutation of the GFAP gene (c.205G > A; p.(Glu69Lys)) that has been reported previously as probably pathogenetic in another case of lower spinal involvement. Parents declined genetic testing.

## 3. Discussion

Atypical presentations of pediatric neurodegenerative disease may cause relevant diagnostic difficulties. The patient reported here lacked typical clinical findings of infantile Alexander disease such as progressive macrocephaly, seizures and cognitive deterioration. Subacute flaccid paraparesis with affection of the lower spinal cord and the space-occupying character of intracerebral, contrast enhancing lesions led to the differential diagnosis of malignancy. Others have recently reported a case in which chemotherapy was introduced assuming a chiasmatic astrocytoma after MRI investigation and even biopsy with Rosenthal fibres [8]. Spinal manifestations of Alexander disease have been rarely reported although information on spinal MRI is missing in many cases [9]. Interestingly, the specific GFAP mutation found in our patient has been described in two particular instances. Davison et al. [10] reported a 6-year-old girl with multifocal space-occupying brainstem lesions that presented with dizziness and vomiting while head circumference and early neurodevelopment were normal. This patient was thought to have CNS malignancy until further MRI characteristics and MRI spectroscopy suggested Alexander disease, and the mentioned GFAP mutation Glu69Lys was detected. Parents were not analyzed [10]. Previously, Busch et al. reported about a 7 year old girl with gait abnormalities and bladder dysfunction in which a prominent swelling of the conus medullaris lead to the presumptive diagnosis of an inflammatory disorder until genetic analysis revealed the p.(Glu69Lys) mutation [11]. In line to our case, the parents were not available for genetic analysis to confirm de novo origin of the mutation. The p.(Glu69Lys) mutation affects a highly conserved amino acid, and computed prediction programs project pathogenicity (MutationTaster, Poly-Phen2). Strictly speaking this well documented case gives histopathological proof of the suspected pathogenetic GFAP mutation p.(Glu69Lys).

Genotype-phenotype correlation in Alexander disease is unclear. Some mutations are consistently associated with severe forms of Alexander disease (e.g. p.Arg239His mutation) while others are associated with a broad spectrum of atypical clinical symptoms [9]. Taken together, at least two of the three cases with p.(Glu69Lys) mutations reported so far are associated with spinal cord involvement without other typical characteristics of Alexander disease, and a third case with prominent changes in the medulla without information on the rest of the spinal cord. Based on these observations, we suggest a distinct involvement of the spinal cord associated with this GFAP gene mutation (c.205G > A; p.(Glu69Lys)).

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