

# Atypical Alexander disease with dystonia, retinopathy, and a brain mass mimicking astrocytoma

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Alexander disease (AD) is an autosomal dominant progressive astroglialopathy caused by pathogenic variants in glial fibrillary acidic protein (GFAP).<sup>1</sup> Clinical presentation of AD includes infantile AD, characterized by psychomotor retardation, seizures, pyramidal signs, and megalencephaly; juvenile AD, characterized by bulbar/pseudobulbar signs, hyperreflexia, lower limb spasticity, ataxia, loss of intellectual function, and macrocephaly; and adult-onset AD, characterized by progressive bulbar symptoms, ataxia, palatal myoclonus, bladder dysfunction, and spastic paraparesis.<sup>1</sup>

## Clinical report

The patient is a 35-year-old woman with progressive left hemidystonia, retinitis pigmentosa (RP), and history of brain tumor. At age 8 years, she developed vision loss, limp, afferent pupillary defect, and optic disc edema. A pilocytic astrocytoma, World Health Organization grade I, was diagnosed and resected. At age 14 years, she developed gait abnormality and progressive left hemidystonia that responded well to botulinum toxin injections. She then developed bilateral optic disc fibrosis, bitemporal hemianopia, and bilateral posterior sub-capsular cataracts and was diagnosed with RP at 22 years (figure, A–D). She also reported chronic constipation, functional megacolon, uterine leiomyomas, and dysphagia.

Family history includes nonconsanguineous unaffected parents. Physical examination showed relative macrocephaly, absent ocular horizontal and vertical pursuit, dysarthria, circumduction gait and left-sided arm dystonia, muscle atrophy, hyperreflexia, and ankle clonus. Brain MRI demonstrated a frontal resection cavity, cystic encephalomalacia, and fluctuating enhancement of the hypothalamus. At age 29 years, a new left middle cerebellar peduncle lesion was identified (figure, E and F).

The patient was enrolled in the NIH Undiagnosed Diseases Network (UDN). Whole-exome sequencing (WES) for her and her mother was completed. Her father was deceased at the time of evaluation.

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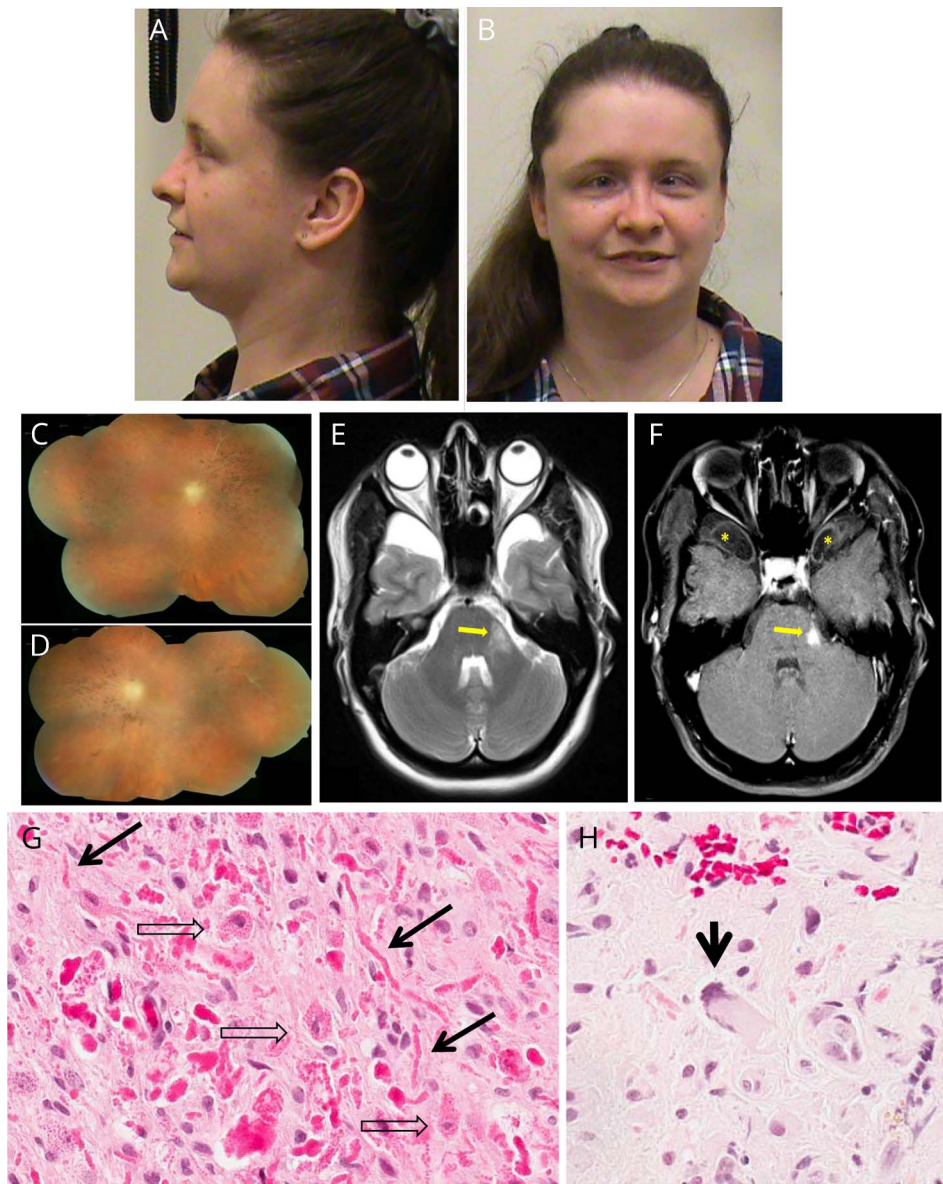
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A 35-year-old woman with juvenile-onset Alexander disease (AD) (A and B). Note relative macrocephaly (FOC 56 cm, 94th centile) and esotropia. The photomontage of the right (C) and left (D) eyes shows the atrophic gliosis from prior optic disc edema and the marked retinal atrophy and secondary pigmentary degeneration. The retinal vasculature appears to show glial sheathing and peripheral vaso-obliteration in each eye. Brain MRI with contrast at 29 years (E and F). (E) Axial T2 image demonstrates a T2 hyperintense lesion centered in the left middle cerebellar peduncle (yellow arrow). (F) Axial T1 image with contrast shows an area of central enhancement within the lesion (yellow arrow). Partially imaged is cystic encephalomalacia within the frontal lobes bilaterally (yellow asterisk) with surgical changes in the right frontal lobe not included. Slides from patient's brain lesion (G and H) demonstrating AD histologic features. The prototypical histologic feature of AD is prominent Rosenthal fiber formation (G, solid arrows). An additional feature unique to AD is the presence of Rosenthal fiber-like eosinophilic cytoplasmic inclusions in astrocyte cell bodies (G, open arrows). The cell body inclusions are generally not seen in other Rosenthal fiber-rich conditions such as low-grade primary brain tumors. Astrocytes with markedly atypical nuclei (H, solid arrow) are also a characteristic morphologic feature of AD and can mimic the neoplastic cells of astrocytoma or ganglioglioma. FOC = fronto-occipital circumference.

## Results

WES revealed a novel heterozygous variant of uncertain significance (VUS) in *GFAP* (MIM\_137780) c.989G>C (p.R330P, NM\_002055) and a heterozygous VUS c.6196G>A (p.D2066N, NM\_006269) in *RPI* (MIM\_603937), both absent in the mother. The parental origin of the *GFAP* mutated allele could not be concluded based on WES data and available DNA samples. The variant in *RPI* was reported in 127 heterozygotes among 138,396 unrelated, unaffected individuals in gnomAD database (gnomad.broadinstitute.org). Both variants are predicted as damaging in SIFT (sorting intolerant from tolerant; sift.jcvi.org/) and Polyphen-2 (genetics.bwh.harvard.edu/pph2). No other contributory variants were detected in 256 known retinal disease genes.

Pathology slides from the initial brain mass were re-examined. Histologic examination showed features of AD, including profuse Rosenthal fiber formation, Rosenthal fiber-like eosinophilic cytoplasmic inclusions in astrocyte cell bodies, and scattered cells with markedly atypical nuclei (figure, G and H).

## Discussion

Radiologic findings in AD vary with age at onset, and typical characteristics have been described for the various forms of AD. Serial radiologic imaging of our patient showed sequelae of right frontal lobe resection, development of periventricular white matter changes, and fluctuating brainstem and hypothalamic lesions. Waxing and waning imaging findings, in the absence of treatment, were inconsistent with a brain tumor.

Therefore, despite her previous diagnosis of a brain tumor, these new findings were interpreted as non-neoplastic, and the working diagnosis was non-MS demyelinating lesions. Similar atypical MRI findings had been described before in patients with molecularly proven AD.<sup>2</sup> Dystonia and retinal abnormalities have never been previously reported with AD. Left hemidystonia in our patient may be secondary to AD-related encephalomalacia or a possible delayed consequence of right frontal brain resection.<sup>3</sup> The *RP1* VUS in our patient is less likely to be pathogenic, given the presence of multiple heterozygous carriers in population databases. It is unclear whether RP is a phenotypic expansion of AD or an unrelated finding (i.e., dual genetic diagnosis).<sup>4</sup>

Several histologic features of AD can mimic brain tumors. Rosenthal fiber formation in astrocytes of the brain and spinal cord, a pathologic hallmark of AD, is also seen in several low-grade primary brain tumors (e.g., pilocytic astrocytoma, ganglioglioma, and pleomorphic xanthoastrocytoma). Cytologically atypical astrocytes, a recognized feature of AD,<sup>5</sup> can also lead to misdiagnosis of pilocytic astrocytoma/ganglioglioma and unnecessary invasive interventions. The presence of Rosenthal fiber–like eosinophilic cytoplasmic inclusions in astrocyte cell bodies serves as a “red flag,” raising the index of suspicion of AD.

Over 120 pathogenic variants in *GFAP* have been reported with a possible dominant gain-of-function mechanism.<sup>6</sup> *GFAP* p.R330P substitutes arginine, located in the evolutionarily well-conserved structure of *GFAP*, with proline. Another change in the same amino acid, p.R330G, was associated previously with adult AD.<sup>7</sup> The potential functional significance of the p.R330P substitution, our patient’s phenotype, and the histologic findings all strongly support *GFAP* p.R330P being a disease-causing variant.

Although relative macrocephaly, spasticity, ocular movement abnormalities, and autonomic disturbance (functional megacolon), as seen in our patient, have been described in juvenile AD,<sup>1</sup> the diagnosis of AD was delayed because of an atypical presentation, including RP, left hemidystonia, atypical MRI findings, and histologic features confounding the diagnosis. This case emphasizes the clinical, histologic, and radiologic challenges in diagnosing AD and demonstrates the importance of considering AD in the differential diagnosis of specific Rosenthal fiber–rich brain lesions such as pilocytic astrocytoma.

### Author contributions

K. Machol: drafting the manuscript and analysis of whole-exome sequencing. J. Jankovic: neurologic management of the patient. D. Vijayakumar: drafting the manuscript. L.C. Burrage and M. Jain: analysis of whole-exome sequencing. R.A. Lewis: ophthalmologic evaluation of the patient and review and editing of the manuscript. G.N. Fuller: revision of histopathology and drafting the manuscript. M. Xu: review of RP-related genes in whole-exome sequence. M. Penas-Prado: oncologic management of the patient, drafting the manuscript,

and critical revision of the manuscript. M. K. Gule-Monroe: radiology interpretation and drafting the manuscript. J. A. Rosenfeld: coordination of patient evaluation and critical revision of the manuscript. R. Chen: review of RP-related genes in whole-exome sequence. Y. Yang and C.M. Eng: analysis of whole-exome sequencing. B.H. Lee: critical revision of the manuscript. P.M. Moretti: neurologic evaluation of the patient and drafting the manuscript. S.U. Dhar: drafting the manuscript, critical revision of the manuscript, and patient management.

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