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Case

Neurobehavioral characterization of adult-onset Alexander disease

A family study

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Alexander disease is a clinically heterogeneous condition associated with glial fibrillary acidic protein (*GFAP*) gene mutations initially described in infants, but juvenile and adult forms exist. Adult-onset Alexander disease (AOAD) has an insidious onset of symptoms localized largely to brainstem, but may also include cognitive dysfunction.

Though only a minority of patients with AOAD are reported with neurobehavioral dysfunction,[1] formal neuropsychological testing in adults has not been reported. Here we present the neurobehavioral findings of 3 siblings with genetically proven AOAD.

The affected family was ascertained through the University of British Columbia Hospital Clinic for Alzheimer Disease and Related Disorders. Research ethics protocols for the study were approved and informed consent was obtained.

Clinical and genealogic histories and neurologic examinations were performed for all 3 siblings. In addition, 2 of the siblings each underwent 2 standard neuropsychological examinations, along with the State Trait Anxiety Inventory, Beck Depression Inventory, and the Behavioral Rating Scale to quantify behavioral impairment.

Neuroimaging was performed with GE Medical Systems (Chicago, IL) Signa HDxt 1.5T scanner.

Blood samples were collected from affected siblings and unaffected mother. Genomic DNA was extracted using standard protocols. Sibling 1 had whole exome sequencing performed, and selected candidate mutations were validated through Sanger sequencing as previously described.[2]

The siblings' father developed dementia, bulbar signs, and spastic quadriplegia, and died at age 67. Their paternal aunt and grandfather developed progressive parkinsonism in midlife.

All affected siblings had MRI signs highly suggestive of AOAD (figure e-1 at Neurology.org/cp). Whole exome sequencing found sibling 1 to be heterozygous for a missense substitution in *GFAP* p.N386S (c.1157A>G; NM_002055.4). Sanger sequencing of DNA samples from siblings 2 and 3 and their unaffected mother confirmed that this mutation segregates with disease.

Table 1 summarizes neurologic findings. Sibling 1's initial presentation was described previously.[3] Later difficulties with memory, multitasking, judgment, apathy, empathy, compulsive

Practical Implications

Consider adult-onset Alexander disease in the differential diagnosis of possible behavioral-variant frontotemporal dementia.

Supplemental Data

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Table 1 Neurologic findings

	Sibling 1	Sibling 2	Sibling 3
Age at assessment, y	58	53	51
Age at first symptoms, y	47	43	49
Age at diagnosis, y	51	53	51
First symptoms	Balance, oculomotor abnormalities	Irritability, withdrawal, increased appetite	Mild balance, depression, insomnia
Nystagmus	++	+	–
Bulbar signs	+	+	–
Weakness	+	–	–
Ataxia/imbalance	++	+	+
Hyperreflexia/Babinski	+	+	–
Incontinence	+	+	–
Dysautonomia	++	–	–
MoCA	22/30	19/30	25/30

Abbreviations: ++ = Strongly present; + = present; – = absent; MoCA = Montreal Cognitive Assessment.

behaviors. and insight emerged. While there was no social or occupational impairment at initial assessment, follow-up revealed clear functional deterioration, meeting criteria of dementia due to AOAD.

Sibling 2 was evaluated at age 53. Earlier he was diagnosed with depression, with symptoms of irritability and social withdrawal leading to loss of employment. Lacking insight, he progressively became apathetic and impulsive, gaining 40 pounds from uncontrolled appetite. With cognitive and functional impairment, he met criteria for dementia due to AOAD.

Sibling 3 developed imbalance at age 49. She reported insomnia and depression at initial assessment. She met criteria for mild cognitive impairment, with inefficiencies in attention, planning, concentration, and verbal memory retrieval, without reported functional impairment. Observed behavior included inflexibility and reduced insight and affective range. She declined neuropsychological evaluation.

Siblings 1 and 2 underwent 2 neuropsychological examinations 13 months apart. Table 2 summarizes results. Sibling 1's scores fell within the average range and Sibling 2's in the borderline range of general ability and overall intellectual function, adjusted for age and education.

Behaviorally, both showed impairments in insight, affective range, expressive deficit, and impulsivity. On testing, sibling 1 developed rule violations. Sibling 2 demonstrated problems with effort, perseverance, and latency of response. Neither endorsed symptoms of depression or anxiety.

Both siblings showed deficits in attention and executive function domains, with declining abilities between assessments. In verbal memory/learning, both siblings showed poor initial learning, free recall, and retrieval, with sibling 2 performing worse. For both, visual memory was less markedly impaired and visuospatial/visuomotor and language skills were relatively preserved.

DISCUSSION

We present a neurobehavioral assessment of 3 siblings with genetically confirmed AOAD. Their cognitive profile includes progressive decline in attention, executive function, and

Table 2 Neuropsychological findings

Domain measured	Test name	Sibling 1 baseline (%ile)	Sibling 1 reassessment (%ile)	Sibling 2 baseline (%ile)	Sibling 2 reassessment (%ile)
Attention, concentration, mental control	Digit span	16	16	9	5
	Mental calculations (arithmetic)	91	84	16	16
	Visual scanning (trails A)	10	4	75–90	25–50
Verbal memory	Word list initial recall	CVLT-II <1	Buschke CR <1	CVLT-II <1	Buschke CR <1
	Word list overall recall (trials 1–5)	7	<1	<1	<1
	Story recall immediate (LM-WMS-IV)	2	2	<1	<1
	Story recall delay	<1	<1	<1	<1
Visual memory	Complex figure immediate recall (Rey-O)	18	4	<1	2
	Complex figure delay recall	21	21	<1	2
Language	Confrontational naming (BNT)	42	73	10–25	10–25
	Verbal fluency (FAS)	24	4	20	<1
Visuospatial/ visuomotor skills	Perception and attention to detail	25–63	16–50	39	25
	Visuomotor speed (digit symbol)	63–75	50–63	16–25	1–9
	Complex figure copy (Rey-O)	Average	Average	Average	<1
Executive functions	Verbal abstract reasoning (similarities)	25–50	9	2	5–9
	Judgment/problem solving (comprehension)	95	63	25	2
	Visual reasoning (matrix reasoning)	25–50	63	16	5–9
	Mental flexibility (trails B)	24	24	10–25	<1
	Strategy formation and cognitive shifting (WCST)	6–10	Refused	<1	<1
	Perseverative errors	6–10	Refused	<1	Did not finish

Abbreviations: BNT = Boston Naming Test; Buschke CR = Buschke Cued Recall; CVLT-II = California Verbal Learning Test II; FAS = Verbal Fluency Test; LM-WMS-IV = Logical Memory–Wechsler Memory Scale IV; Rey-O = Rey-Osterrieth Complex Figure Test; WCST = Wisconsin Card Sorting Test.
Results are reported as standard scores derived relative to age and education-equivalent population samples.

memory. Behavioral changes include reduced insight and affective range, expressive deficits, and impulsivity. Their neurobehavioral profile reflects frontotemporal dysfunction, meeting criteria[4] for possible behavioral-variant frontotemporal dementia (bvFTD).

The predominant neurobehavioral findings in our patients are consistent with other neurocognitive reports in noninfantile Alexander disease.[5,6] *GFAP* p.N386S was previously described presenting only with transient diplopia,[7] suggesting that other factors possibly modify phenotypic expression, and neurobehavioral symptoms in AOAD may be underrecognized unless they are scrutinized in detail.

Structural imaging in this family did not indicate frontotemporal changes: neurobehavioral alterations are likely driven by functional network impairment.

We detail the neurobehavioral profiles of 3 siblings with AOAD, characterized as including both frontotemporal behavioral and cognitive impairments, in the context of brainstem symptoms. AOAD should be on the differential when assessing patients with possible bvFTD. Neurobehavioral symptoms in AOAD may be underrecognized. Further study is needed to better characterize phenotype of neurocognitive impairment in AOAD and investigation of network abnormalities with functional imaging is warranted to investigate the mechanism of frontotemporal dysfunction.

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AUTHOR CONTRIBUTIONS

M.L. Lichtenstein: study concept and design, acquisition of data, analysis and interpretation of data, drafting, revising, and final approval of manuscript. E. Dwosh: acquisition of data, analysis and interpretation of data, revising and final approval of manuscript. A.R. Chowdhury: acquisition of data, revising and final approval of manuscript. M.J. Farrer: acquisition of data, analysis and interpretation of data, revising and final approval of manuscript. M.B. McKenzie: acquisition of data, analysis and interpretation of data, revising and final approval of manuscript. I. Guella: acquisition of data, analysis and interpretation of data, revising and final approval of manuscript. D.M. Evans: acquisition of data, analysis and interpretation of data, revising and final approval of manuscript. H.B. Nygaard: analysis and interpretation of data, revising and final approval of manuscript. J.R. Shewchuk: analysis and interpretation of data, revising and final approval of manuscript. S. Hayden: acquisition of data, analysis and interpretation of data, revising and final approval of manuscript. J.J.S. Barton: acquisition of data, analysis and interpretation of data, revising and final approval of manuscript. H.H. Feldman: study concept and design, acquisition of data, analysis and interpretation of data, revising and final approval of manuscript.

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