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Neuropsychological Functioning in Alexander Disease: A Case Series

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Abstract

Limited information is known about neuropsychological outcomes in Alexander disease, a rare leukodystrophy. Two pediatric cases are summarized. Case 1 (evaluations at 6, 7, 9, and 12 years of age) represents Type I Alexander disease with associated seizures. Case 2 (evaluations at 12, 13, and 16 years of age) represents Type II Alexander disease without additional complications. Case 1 experienced declines in intellectual functioning, visual motor skills, receptive vocabulary, verbal memory, and academic achievement. Case 2 experienced variable neurocognitive change and academic functioning, with average word reading and spelling. Verbal memory also remained intact. Taken together, individuals with Alexander disease may experience cognitive decline to variable degrees. Type I Alexander disease, associated with earlier onset and additional neurological complications, may presage greater cognitive decline than Type II. Due to variability in functioning over time, it is critical to follow individuals across development to make recommendations for educational and treatment planning.

Keywords

Alexander disease, leukodystrophy, neuropsychology, cognition

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Introduction

Alexander disease is a rare leukodystrophy that causes progressive destruction of myelin. Changes are usually most notable in the frontal lobes and leads to increased nervous system dysfunction over time.[1,2] Alexander disease has an autosomal dominant inheritance pattern; however, most cases result from a de novo mutation in the glial fibrillary acidic protein (GFAP) gene.[2-5] Alexander disease is associated with medical and developmental challenges, including macrocephaly, seizures, spasticity, speech issues, ataxia, hydrocephalus, intellectual disability, and developmental delay.[1]

Alexander disease is often described as two distinct types.[6] Type I is characterized by symptoms mostly emerging before age 4, including seizures, macrocephaly, encephalopathy, paroxysmal deterioration, failure to thrive, developmental delay, and classic MRI features.[6] Prior to the availability of molecular testing, van der Knaap and colleagues[7] described the classic MRI features required to make a clinical diagnosis of Alexander disease without the need for brain biopsy to demonstrate Rosenthal fibers, which included the presence of at least 4 of 5 MRI findings (extensive cerebral white matter changes with frontal predominance, a periventricular rim with high signal on T1-weighted images and low signal on T2-weighted images, abnormalities of basal ganglia and thalami, brain stem abnormalities, and contrast enhancement of particular gray and white matter structures). Type II is characterized by symptoms emerging across the lifespan, including autonomic dysfunction, bulbar symptoms, ocular movement abnormalities, palatal myoclonus, lack of neurocognitive deficits, and atypical MRI features.[6] Atypical MRI features that are characteristic of Type II Alexander disease include spinal cord atrophy, cerebellar atrophy, and brain stem atrophy.[6,8] Additionally, the abnormalities typically occur in the posterior fossa region in Type II Alexander disease, as opposed to the frontal lobe that is typically seen in Type I Alexander disease.[6]

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There is a paucity of literature about cognitive functioning in children with Alexander disease.[9,10] Due to the variability in white matter changes, cognitive patterns have been relatively unpredictable in previously published case studies.[9] Furthermore, it is unclear what the typical cognitive profile and trajectory is for each of the two types of Alexander disease.[9] Type I Alexander disease has been associated with greater involvement of neurocognitive domains primarily localized in the frontal lobes including attention and executive functions (eg, problem solving, organization, planning, set shifting).[6,9] Localization of changes in Type II Alexander disease in the posterior fossa region and cerebellum, are more heavily involved in motor coordination.[6] There is some evidence that cognition may be relatively spared in individuals with Type II, who also experience reduced rates of additional neurological complications.[6,11] Cognitive change associated with Type II Alexander disease may present similarly to other diseases with white matter changes.[9]

To better understand neurocognitive functioning in this diagnosis, longitudinal neuropsychological assessments from two cases, one with Type I and one with Type II Alexander disease, are presented.

Patients and Methods

The pertinent medical history and neuropsychological evaluation data are presented for two cases of Alexander disease. Both cases were evaluated in an outpatient setting at the Mayo Clinic, an academic medical center in the Midwest. This case series was determined to be exempt from Institutional Review Board review. One patient allowed use of data for research through a state-wide research authorization system, and the other gave verbal consent. We used the CARE checklist when writing our report.[12]

Case Report 1 (Age 6 at Baseline, Age 12 at 6-Year Follow-up)

Case 1 is a male, born full-term via spontaneous vaginal delivery, weighing 5 pounds, 13 ounces. Labor was complicated by a nuchal cord and fetal decelerations. He was adopted at birth and limited information is known about family history. During early infancy, Case 1 had reflux and tended to choke on foods. He had speech and motor delays. At 20 months, he was only using 3 words and not yet walking. His examination was notable for macrocephaly, diffuse hypotonia with hyperreflexia and clonus in the lower extremities.

At 2 years of age, brain MRI revealed symmetric confluent T2 hyperintensities in the periventricular and subcortical white matter in both cerebral hemispheres, most prominently in the frontal region, including both subinsular cortices, with relative sparing of the occipital lobes. There were also less intense hyperintensities in the basal ganglia bilaterally. These MRI images are presented in detail in Matarese & Renaud (2008).[13] In view of the frontally predominant white matter changes with involvement of the basal ganglia, targeted molecular testing revealed a mutation in Exon 1 of the GFAP gene (R79C) confirming a diagnosis of Alexander disease. Given his age of onset, MRI findings, and symptoms; he was classified as having Type I Alexander disease. An MRI scan of the brain performed at age 13, as part of an Alexander Disease natural history study, separate from neuropsychological follow-up, revealed progressive bilateral confluent white matter abnormalities involving the supratentorial white matter and extending into the midbrain and pons, associated with ventriculomegaly and thinning of the corpus callosum. Stable signal abnormality was also present in the basal ganglia.

Shortly after diagnosis, Case 1 had a tonic-clonic seizure associated with a febrile illness. He had two additional seizures associated with febrile illnesses and began taking levetiracetam which he has taking at the time of his neuropsychological evaluations. No additional seizure activity was observed. Additionally, Case 1 had scoliosis and experienced increasing ambulation issues over time resulting in shuffling gate and frequent falls. He eventually required braces for walking and used a wheelchair for distances by age 12. As of his last assessment (at age 12), Case 1 participated in speech therapy twice a week, occupational therapy three times a month, and physical therapy once a week.

Table 1 presents data from the four neuropsychological evaluations conducted across 6 years (age at evaluations: 6, 7, 9, and 12 years old). At baseline (age 6), he was identified to have fine motor weaknesses, as well as information processing deficits in the context of islands of strength. Follow-up conducted a year and a half later (age 7) indicated ongoing motor difficulties, as well as relative weaknesses in nonverbal/visuospatial processing and mathematics, and variability in memory. Additional assessment, conducted 3 years post-baseline assessment (age 9), revealed limited cognitive growth. At that time, his overall presentation was consistent with moderate intellectual disability. Academics were well below average in most areas, with only word reading remaining broadly within normal limits. Inattention was also observed on standardized testing. At follow-up 6 years post-baseline assessment (age 12), neurocognitive and academic skills continued to plateau or decline. Receptive language and word reading, which were initially preserved, were ultimately impaired. Expressive vocabulary continued to be an area of relative strength.

Comparing across the six years (from age 6 to 12), Case 1 experienced decline in intellectual functioning (FSIQ = 68 to 43), visual motor skills (SS = 63 to 45), receptive vocabulary (SS = 98 to 63), verbal memory (Z = −2.00 to −4.00), and visual memory (SS = 85 to 63). Academic achievement was variable, but generally declined over time and was impaired at 6 year follow-up. Expressive vocabulary remained an area of relative strength, consistently falling in the low average range (SS = 89 to 80).

Case Report 2 (Age 12 at Baseline, Age 13 at 6-Month Follow-up, Age 16 at 3 ½ Year Follow-up)

Case 2 is a female born full-term via vaginal delivery after an uncomplicated pregnancy, weighing around 8 pounds at birth.

Table 1. Standard Scores[a] for Neuropsychological Tests Administered to Case 1 (Type I) at Baseline and Subsequent Evaluations.

	Baseline (Age 6)	1.5 Year Follow Up (Age 7)	3 Year Follow Up (Age 9)	6 Year Follow Up (Age 12)
Intellectual Functioning (WISC-IV)				
Full Scale IQ	68	62	48	43
Verbal Comprehension Index	77	81	63	55
Perceptional Reasoning Index	82	69	53	55
Working Memory Index	77	65	56	50
Processing Speed	53	56	56	50
Academic Achievement (WJ-III)				
Reading Skills				
Letter Word Identification	82	92	84	70
Passage Comprehension	–	70	61	50
Math Skills				
Calculation	77	67	14	20
Applied Problems	–	58	50	41
Writing Skills				
Spelling	68	84	71	62
Writing Samples	–	–	44	22
Other Neurocognitive Domains				
Visual Motor Skills				
Beery Visual Motor Integration	63	70	–	45
Beery Visual Perception	83	100	–	56
Beery Motor Coordination	65	80	–	57
Expressive and Receptive Vocabulary				
PPVT	98	84	–	63
EOWPVT	89	103	–	80
Verbal Memory				
CVLT-C Delay FR (Z)[b]	–	−2.0	−2.5	−4.0
Visual Memory				
CMS Visual Immediate	–	72	–	50
CMS Visual Delayed	–	85	–	63
Attention				
CPT-II # Omissions (T)[c]	–	–	84.20	76.99
CPT-II # Commissions (T)[c]	–	–	35.25	42.38
CPT-II Hit RT (T)[c]	–	–	90.84	86.15

Abbreviations: WISC-IV, Wechsler Intelligence Scale for Children, fourth Edition; WJ-III, Woodcock Johnson Tests of Academic Achievement, third Edition; Beery, Beery-Buktenica Developmental Test of Visual-Motor Integration, fifth or sixth Edition; PPVT, Peabody Picture Vocabulary Test, fourth Edition; EOWPVT, Expressive One Word Picture Vocabulary Test, fourth Edition; CVLT-C Delay FR, California Verbal Learning Test, Children's Edition, Delayed Free Recall; CMS, Children's Memory Scale; CPT-II, Connors Performance Test, second Edition.

[a]Standard scores have a mean = 100 and standard deviation = 15; lower scores suggest greater weakness.

[b]Z-scores have a mean = .0 and standard deviation = 1.0; lower scores suggest greater challenges.

[c]T-scores have a mean = 50 and standard deviation = 10; higher scores suggest greater impairment.

She met her motor and speech milestones within normal limits. Despite typically developing fine motor skills, a decline in the quality of her handwriting was noted at 10 years of age. Additional symptoms that emerged over the next two years and prompted further evaluation included pervasive tiredness, intermittent leg shaking, poor balance, and difficulty breathing and swallowing.

At 12 years of age, brain MRI revealed frontally predominant, extensive cerebral white matter changes, with lesser involvement of the occipital regions and cerebellum, bright signal in the right posterior medulla, and enhancement of these abnormalities in the medulla. Importantly, there was posterior fossa involvement and atrophy in the anterior corpus callosum (Figure 1). Imaging findings were believed to be most suggestive of Alexander disease, and targeted genetic testing revealed an R416 W mutation in GFAP consistent with Alexander disease. Given her age of onset, MRI findings, and symptoms; Case 2 was classified as having Type II Alexander disease. Family history was negative for leukodystrophy; however, a first cousin had been diagnosed with multiple sclerosis.

Additional imaging completed at 14 years of age (2 years post-diagnosis) revealed changes including mildly increased hyperintensity in the posterior fossa and minimal patchy cerebellar enhancement. Additionally, the enhancement of the medulla was no longer present. This was observed in the context of stable frontally predominant white matter signal change. A spine MRI completed at age 14 due to progressive

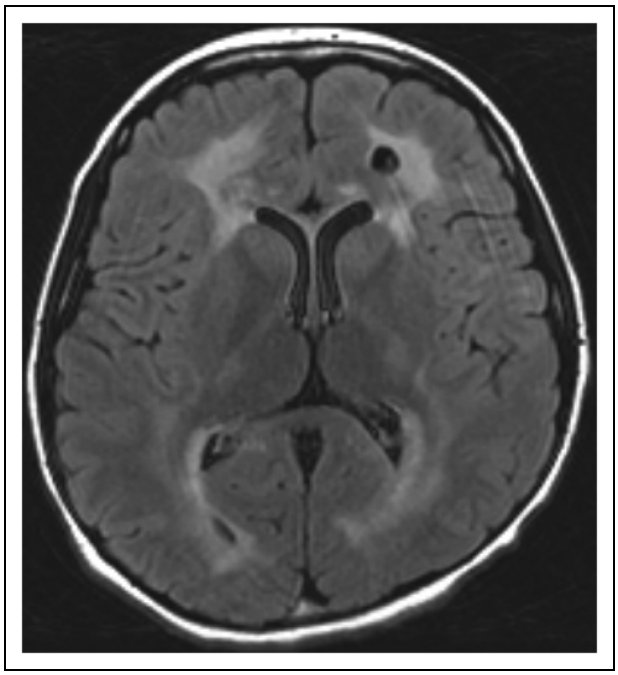

Figure 1. Axial T2 FLAIR MRI image for case 2 at age 10 demonstrating diffuse abnormal white matter signal which predominates in the frontal lobes, accompanied by scattered cystic changes. The anterior corpus callosum is thin.

scoliosis revealed spinal cord atrophy, which is consistent with Type 2 Alexander disease. Follow up imagery at 15 years of age (3 years post diagnosis) demonstrated interval progression of the findings in the posterior fossa, with patchy enhancement of the pons, medulla and cerebellar hemispheres, and mild enlargement of the third and lateral ventricles. Additional interval progression, primarily in the posterior fossa, was seen on MRI imaging conducted at 16 years of age (4 years post diagnosis), consistent with the observed progressive dysphagia, balance and motor changes, and difficulty swallowing, which result from a combination of posterior fossa involvement and potential progressive aqueductal stenosis.

Case 2 did not have any associated seizure activity or macrocephaly. Medical complications included progressive gross motor dysfunction and scoliosis that ultimately resulted in loss of ambulation. She additionally had intermittent, uncontrollable shaking of her legs. Case 2 also developed dysphagia that affected her ability to consume food, and she eventually became g-tube dependent. Throughout her evaluations (age 12 to age 16), Case 2 received a variety of services including tutoring, therapy, fitness instruction, physical therapy, occupational therapy, and speech therapy at inconsistent frequencies and intensity.

Table 2 presents neurocognitive data from the three neuropsychological evaluations Case 2 underwent across 4 years (age at evaluations: 12, 13, and 16 years). Case 2 presented with comorbid depression and anxiety symptoms, for which she received medications which would not have interfered with her neuropsychological assessments. At baseline (age 12), Case 2's neurocognitive functioning remained relatively preserved; however, she demonstrated some deficits in processing speed and fine motor skills, as well as a mild math problem solving weakness. Findings at 6 months post-baseline (age 13) remained consistent with the previous evaluation and

Table 2. Standard Scores[a] for Neuropsychological Tests Administered to Case 2 (Type II) at Baseline and Subsequent Evaluations.

	Baseline (Age 12)	.5 Year Follow Up (Age 13)	3.5 Year Follow Up (Age 16)
Intellectual Functioning (WISC-IV)			
Full Scale IQ	78	–	60
Verbal Comprehension Index	79	–	75
Perceptional Reasoning Index	90	–	67
Working Memory Index	94	–	74
Processing Speed	70	–	50
Academic Achievement ‡			
Reading Skills			
Letter Word Identification	–	–	98
Reading/Passage Comprehension	90	–	72
Math Computation Skills			
Numerical Ops/ Calculation	89	–	76
Writing Skills			
Spelling	97	–	103
Other Neurocognitive Domains			
Visual Motor Skills			
Beery Visual Motor Integration	84	72	66
Beery Visual Perception	80	89	80
Beery Motor Coordination	84	91	45
Grooved Pegs (Dominant)[b]	−20	–	−114
Grooved Pegs (Non-Dominant)[b]	−79	–	−146
Verbal Memory			
CVLT-C Delay FR (Z)[b]	.0	.5	−.5

Abbreviations: WISC-IV, Wechsler Intelligence Scale for Children, fourth Edition; WJ-III, Woodcock Johnson Tests of Academic Achievement, third Edition; WIAT-III, Wechsler Individual Achievement Test, third Edition; Beery, Beery-Buktenica Developmental Test of Visual-Motor Integration, sixth Edition; Grooved Pegs, Grooved Pegboard; CVLT-C Delay FR, California Verbal Learning Test, Children's Edition, Delayed Free Recall.

‡WIAT-III was administered at Baseline; WJ-III was administered at 3.5 year Follow Up.

[a]Standard scores have a mean = 100 and standard deviation = 15.

[b]Z-scores have a mean = .0 and standard deviation = 1.0.

were not suggestive of any cognitive decline. Several areas of cognitive strength continued to be observed, including verbal memory. Additional follow-up conducted three and a half years post-baseline (age 16) revealed minimal progress in general cognitive functioning with current functioning falling in the mild intellectual disability range. She continued to demonstrate intact skills including word reading and spelling, as well as verbal memory. Greater difficulties in fine motor coordination and dexterity were observed compared to prior testing.

Across evaluations, Case 2 initially demonstrated more intact skills than Case 1. However, Case 2 experienced a decline in intellectual functioning (FSIQ = 78 to 60). Declines in visual motor skills (SS = 84 to 66) and dominant hand motor skills (Z = −20 to −114) were observed. Academic functioning showed some variability with declines in reading comprehension (SS = 90 to 72) and math calculation (SS = 89 to 76), but average word reading and spelling at follow up. Verbal memory remained largely intact (Z = .0 to −.5).

Discussion

This case series presents longitudinal neuropsychological data on two cases of Alexander disease and provides deeper understanding of the neuropsychological prognosis associated with the two different types of this diagnosis. In both cases, declines in intellectual functioning to varying degrees occurred over time.

Supporting prior research, disease type appeared related to the course of cognitive change in these cases. Case 1/Type I demonstrated greater impairment at baseline and more dramatic and rapid decline than Case 2/Type II Alexander disease.[3] The later onset and initial preservation associated with Type II may be somewhat protective against more diffuse neurocognitive and academic skill change, as skills may have longer to develop and become solidified. This is possibly secondary to greater initial white matter and subcortical involvement seen on MRI imaging for Case 1 versus Case 2. As these areas are notable for being involved in many different domains, including motor function, language, memory, attention, and executive functions, changes across these regions likely result in more diffuse cognitive change. Case 1 evidenced these broad declines across verbal and visual intellectual functioning and memory, receptive language, and academic functioning. Additionally, Case 1 had other associated neurological complications, including macrocephaly and seizure activity. These complications along with medications to control seizure activity may also contribute to greater cognitive challenges at baseline and declines over time that Case 1 experienced.

Interestingly, while both cases evidenced increasing physical challenges often expected in this disease,[6] Case 2 experienced greater motor challenges, seen on testing and reported functionally, and dysarthria that impacted functional independence, despite Case 1 presenting with challenges earlier in life. This is likely secondary to greater degeneration in the brain stem and cerebellum observed in Case 2. These involved areas are responsible for balance maintenance, swallowing, coordination of voluntary movements, and with some associated with cognitive functions such as attention, arousal, and speech, but not to the same degree as other areas of the brain. As such, neurocognitive functioning and academic skill development may be less globally affected or declines may be more modest in nature, as was true for Case 2.

While most domains of cognition declined to some degree over time, both cases evidenced distinct areas of relatively spared skill, which has been seen in prior research.[9] In Case 1, expressive vocabulary remained relatively intact; however, other areas of language declined. In Case 2, word reading and spelling, measures often considered robust to injury in adult populations, were preserved, as was verbal memory. This contradicts previous findings that new learning and memory may be particularly vulnerable or potentially highlights that the degree of vulnerability may be secondary to type of disease and factors associated with disease type.[9]

Thus, while both cases continued to demonstrate areas of strength, these differed, both from each other and prior research, possibly due to locations of imaging findings. These findings indicate that progression and degree of decline may be associated with type of disease, but specific areas of functional change are likely associated with neurological changes and as a result specific to the individual's disease progression and imaging.

Conclusion

It is difficult to generalize beyond these two cases, both of which had complicating factors that can be common in individuals with Alexander disease, including neurological complications, unique imaging findings, and psychiatric comorbidities. It is critical to continue evaluating neurocognitive functioning across the lifespan to better assess the likelihood and course of neurocognitive difficulties and identify predictors of long-term functioning.

Overall, these results illustrate individuals with Alexander disease may experience broad cognitive decline, but also may evidence areas of preserved functioning despite the degenerative nature of the condition. Recommendations and programming will need to be re-evaluated and provided in increasing intensity as the disease progresses and neurobehavioral deficits become more salient, while also acknowledging and promoting areas of relative cognitive or academic strength. It is likely that individuals with Alexander disease will require supports across their lifespan. Variability in trajectories highlights the importance of following individuals closely across development, as cognitive strengths and weaknesses, as well as physical abilities and limitations will likely change over time.

Institutional Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article for one patient. Informed consent for other patient information to be published in this article was not obtained because consent was granted via institution/state-wide research authorization.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Xxxxxxx.Deborah Renaud, MD is on the editorial board of Journal of Child Neurology. There are no other conflicts of interest to declare.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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Trial Registration

Not applicable, because this article does not contain any clinical trials.

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