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Head trauma can initiate the onset of adreno-leukodystrophy

Gerald V. Raymond [a], Roberta Seidman [b], Teshamae S. Monteith [c], Edwin Kolodny [d], Swati Sathe [d], Asif Mahmood [e], James M. Powers [f,g,*]

[a] Kennedy Krieger Institute, Baltimore, MD, USA
[b] Department of Pathology, Stony Brook University Medical Center, Stony Brook, NY, USA
[c] Department of Neurology, University of California, San Francisco, San Francisco, CA, USA
[d] Department of Neurology, New York University Langone Medical Center, New York, NY, USA
[e] Department of Neurology, University of Texas Medical Branch, Galveston, TX, USA
[f] Department of Pathology, University of Rochester Medical Center, Rochester, NY, USA
[g] Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA

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ABSTRACT

X-linked adreno-leukodystrophy and its adult variant, adrenomyeloneuropathy, are caused by mutations in *ABCD1* that encodes a peroxisomal membrane protein of unknown physiological significance. In spite of identical mutations, they can have markedly divergent neurological and neuropathologic characteristics. Adreno-leukodystrophy classically presents in normal boys with mild neuropsychiatric features, which progress to frank neurological signs, the vegetative state and death in approximately three years. Adrenomyeloneuropathy typically affects young men with spastic paraparesis and sensory ataxia that can progress over decades. The neuropathologic correlate for adreno-leukodystrophy is severe inflammatory demyelination of posterior cerebral white matter, while a chronic distal axonopathy of spinal cord and peripheral nerve occurs in adrenomyeloneuropathy. Consequently, both modifier genes and environmental factors have been implicated in their pathogeneses. We report five cases of adreno-leukodystrophy whose onsets were initiated by moderate to severe head trauma, two of whom were conversions from adrenomyeloneuropathy. Their clinical courses were rapidly incapacitating, short (i.e., weeks to a few years) and fatal due to marked cerebral inflammatory demyelination. These cases, in concert with several previous reports, indicate that head trauma is one environmental factor that can have a profoundly deleterious effect on those genetically at risk for, or with milder clinical phenotypes of, this disease. Avoidance of potential head trauma and a rapid response to episodes of moderate to severe head trauma in this patient population seem prudent.

1. Introduction

The classic clinico-pathologic paper on X-linked adreno-leukodystrophy (ALD), published in 1975, included one 12-year-old boy who developed his neurological disease one to three months following an episode of severe head trauma without cerebral contusions but that caused coma for twelve days [1]. A causal connection between the head trauma and the onset of ALD was not considered. However, since that time, a small number of case reports have suggested the possibility of this relationship, particularly in adults [2–6]. In view of our increased understanding of the inflammatory-immune pathomechanisms operative in the demyelinative lesion of ALD [7,8], such a causal relationship appears to be highly plausible.

The childhood cerebral phenotype of ALD classically presents in normal boys, six to nine years of age, with mild neurological or psychiatric signs and symptoms. Shortly thereafter, frank neurological signs appear, leading to the vegetative state and death in approximately three years. The neuropathologic correlate for this fulminant clinical course is profound inflammatory demyelination of cerebral white matter, predominantly posterior. The slightly more common adult variant of ALD, adrenomyeloneuropathy (AMN), typically displays neurological and neuropathologic features of a slowly progressive spinal and peripheral axonopathy [9]. Approximately one-half of male AMN patients do not have any cerebral white matter lesions on magnetic resonance imaging (MRI), referred to as pure AMN; while approximately 34% demonstrate abnormalities that resemble, but are more limited than, those of ALD (AMN-cerebral) [10]. One or more modifier genes have been proposed to explain the dramatic heterogeneity of ALD and AMN, even in the same family with an identical genetic defect in the *ABCD1* gene [11]. *ABCD1* normally encodes a peroxisomal membrane protein, ALDP or ABCD1 [12], whose precise physiological function is still unknown. Twenty to

* Corresponding author. University of Rochester Medical Center, Department of Pathology, Box 626, 601 Elmwood Avenue, Rochester, New York 14642, United States. Tel.: +1 585 275 3202; fax: +1 585 273 1027.
E-mail address: james_powers@urmc.rochester.edu (J.M. Powers).

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twenty-five percent of male AMN patients also may develop a superimposed fulminant cerebral inflammatory demyelination clinically and neuropathologically identical to that of childhood cerebral ALD [7,8,13]. The failure to identify a modifier gene in ALD and AMN has prompted the notion that environmental factors may be responsible for at least some of the clinical heterogeneity [14].

We now report three additional cases of ALD whose onsets are temporally linked to previous head trauma. Additionally, we report two patients with AMN who developed rapidly progressive cerebral inflammatory demyelination identical to that of childhood cerebral ALD shortly after head trauma. These cases, in concert with those previously published, demonstrate that head trauma may be one environmental factor that can have a profoundly deleterious effect on those genetically at risk for developing ALD or AMN, particularly adults. Furthermore, these data also suggest that perhaps any head trauma, even sports-related or recreational, should be minimized or avoided in these individuals.

2. Methods

This retrospective study consists of a review of the medical records and neuroimaging data of ALD and AMN patients evaluated at the Peroxisomal Disease Center in the Kennedy Krieger Institute and one patient seen at New York University (NYU) Medical Center, who was previously published as an abstract (Patient 1). We also include the salient neuropathologic findings of two patients lacking imaging studies, who initially had clinical features of AMN but converted to the ALD phenotype following head trauma to document that their fulminant neurological conversions were due to the same neuropathologic lesion as that of childhood cerebral ALD.

3. Results

3.1. Case histories

3.1.1. Patient 1

A 21.5-year-old man sustained a closed head injury with loss of consciousness for 24 h following a motor vehicle accident (MVA) at 21 years of age. Head computerized tomographic (CT) scan at that time revealed an acute left frontal contusion with subarachnoid hemorrhage (Fig. 1A). He received cognitive therapy for loss of recent memory, but he recovered and was able to continue his college studies.

Twelve months after the episode he had difficulty understanding his teachers and family, followed by problems expressing himself accompanied by altered behavior. Twenty four months after the MVA he had a seizure that prompted another neuroimaging study, which revealed a left frontal white matter abnormality characteristic of a leukodystrophy (Fig. 1B). While the lesion displayed contralateral and posterior edge enhancement (Fig. 1C) that is almost pathognomonic of ALD in this setting, its frontal localization is atypical for ALD [1,11]. Most importantly, the oldest portion of the lesion (i.e., lacking contrast enhancement) was in the same area as the original contusion.

He became progressively confused and agitated, getting lost in his neighborhood and having episodes of inappropriate laughter. He lost sphincter control. On examination, he was restless, fidgety, echolalic and defensive. He spoke a few words and could only follow simple commands. There were no significant sensory or motor deficits. His cognitive function continued to decline, and he became bed-bound and non-verbal at age 25 years. He died four years and two months following the MVA.

Family history included a 27-year-old brother who developed clinical evidence of a myelopathy at age 19 years. His MRI at age 31 still reveals no cerebral lesions. Both brothers had a similar abnormal very long chain fatty acid (VLCFA) profile typical of ALD or AMN at Mayo Clinic Laboratories (C26:0, 4.5 μmol/l; normal, 0.0–1.3; C26/C22, 0.068; normal, 0.0–0.023). Their mother, identified as a carrier, had mild spasticity and brisk reflexes in her legs. There had been no treatment with Lorenzo's oil.

3.1.2. Patient 2

This 14-year-old boy was clinically unremarkable until a skiing accident resulted in a severe closed head injury with a brainstem contusion (Fig. 2A). MRI performed at that time revealed no abnormality of white matter (Fig. 2B). Initially, he made a good clinical recovery, but then began losing skills. A follow-up MRI at five months showed persistent midbrain changes (Fig. 2C) and extensive white matter lesions (Fig. 2D). He was unable to walk and had slow speech one month later; he died within nine months of the head trauma. VLCFA testing was positive (C26:0, 0.883 μg/ml; normal, 0.33 +/− 0.18; C26/C22:0, 0.071; normal, 0.01 +/− 0.01). An uncle had AMN. He did not receive Lorenzo's oil.

3.1.3. Patient 3

A clinically normal 21-year-old male was involved in a MVA. During the following three to four months he exhibited a steady cognitive decline. He underwent a diagnostic brain biopsy and developed an incidental post-op subdural hematoma approximately four months later, but further details are unavailable. He was in a vegetative state at thirteen months post MVA until death ten years later. VLCFA testing was positive (C26:0, 0.779 μg/ml, normal, 0.33 +/− 0.18; C26/C22:0, 0.074, normal, 0.01 +/− 0.01). DNA testing revealed a deletion of thymidine (delT) at nucleotide (NT) 1822. There was neither a positive family history, nor treatment with Lorenzo's oil.

3.1.4. Patient 4

A 50-year-old male may have had his first neurological symptoms at age 18 years following a fall, after which he experienced excessive

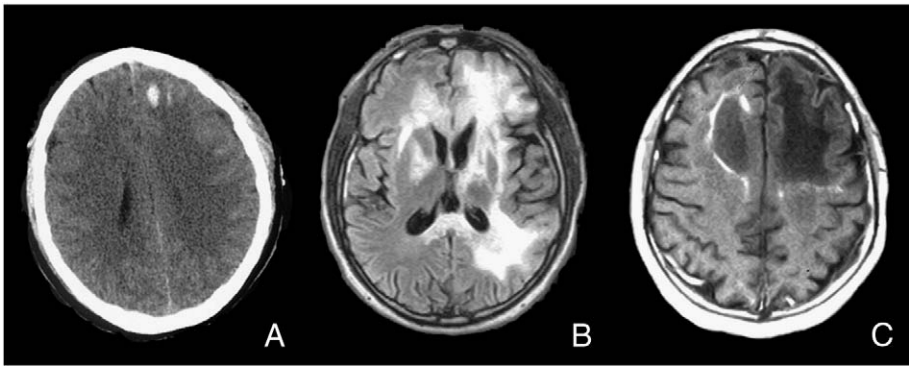

Fig. 1. A. Patient 1. CT scan at the time of injury demonstrates a small contusion in the left frontal lobe. B. Patient 1. FLAIR image of slightly lower cut of cerebrum twenty-four months after the injury exhibits a diffuse high signal abnormality of left frontal lobe with some extension across the midline. C. Patient 1. T1-MRI at twenty-four months after the injury reveals contrast enhancement at the edge, particularly on the right, a neuroradiological hallmark of the advancing edge of demyelination in ALD.