Onset of Adreno-Leukodystrophy After Medulloblastoma Therapy: Causal Connection or Coincidence?

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Received: 20 December 2010 / Revised: 12 April 2011 / Accepted: 3 May 2011 / Published online: 6 September 2011
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Abstract X-linked adreno-leukodystrophy (ALD) is a peroxisomal disorder affecting the white matter of the central nervous system and the adrenal cortex. It is caused by mutations in the *ABCD1* gene encoding for a peroxisomal membrane protein. The absent genotype–phenotype correlation implies a contribution by environmental factors to explain the phenotypical heterogeneity. We report on a 4-year-old boy with a biochemically confirmed diagnosis of ALD after birth. At the age of 32 months, the additional diagnosis of a medulloblastoma was made. After treatment of the medulloblastoma, he developed active areas of

demyelination representing the characteristic neuroimaging features of ALD. The clinical history of our patient supports the hypothesis that external factors, like neurosurgical intervention as part of medulloblastoma treatment, may accelerate or initiate cerebral ALD-related demyelination. A postsurgical inflammatory reaction may facilitate the inclusion of abnormal fatty acids in myelin. The opening of the blood–brain barrier following neurosurgery may enhance the recognition of previously sequestered antigens considered to play a role in ALD onset. Consequently, neurosurgical disruption of the BBB can precipitate the immune-mediated inflammatory process, which progressively destroys myelin in ALD patients. Tumor-related chemotherapy and/or radiotherapy may also play a contributing role. We suggest that X-ALD patients who undergo neurosurgical intervention need close follow-up imaging to identify active demyelination early.

Communicated by: Gregory M. Pastores.

Competing interests: None declared.

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Abbreviations

ALD	Adreno-leukodystrophy
AMN	Adreno-myeloneuropathy
BBB	Blood-brain barrier
CALD	Childhood cerebral ALD
CNS	Central nervous system
MRI	Magnetic resonance imaging
PLP1	Proteolipid protein 1
VLCFA	Very long chain fatty acids

Introduction

X-linked adreno-leukodystrophy (ALD) is a peroxisomal disorder affecting the white matter of the CNS and the adrenal cortex (Moser et al. 2007). Two main phenotypes

affect the CNS: CALD and AMN. CALD typically manifests with behavioral or learning deficits between 4 and 8 years. Progressive impairment of cognition, behavior, vision, hearing, and motor function follows and often leads to total disability and death within a few years. AMN most commonly presents between the age of 20 and 40 with progressive paraparesis and sphincter disturbances. The symptoms are progressive over decades. About 35% of AMN patients additionally develop cerebral symptoms (cerebral AMN) sharing the same poor prognosis as children with CALD. Additional five phenotypes including the “Addison-only” presentation and “asymptomatic patients” are recognized (Moser et al. 2007).

ALD is caused by mutations in the *ABCD1* gene encoding for a peroxisomal membrane protein (Mosser et al. 1993). Significant phenotypical heterogeneity is reported in siblings with identical genotype showing absent genotype–phenotype correlations (Moser et al. 1992). This suggests that modifier genes or environmental factors might be responsible for the phenotypical heterogeneity of ALD. While modifier genes could not be identified, the pathogenetic implication of environmental factors such as head trauma has been shown (Raymond et al. 2010).

We report on a four-year-old boy with biochemically confirmed ALD and a posterior fossa medulloblastoma. Neuroimaging studies showed an “activation” of demyelination after treatment for medulloblastoma.

Case Report

In an asymptomatic male child, the diagnosis of ALD was made shortly after birth because of a positive family history. MRI of the brain at the age of two years was normal. The VLCFA profile was abnormal at this stage (C26:0 1.18 $\mu\text{g/ml}$, normal 0.23 ± 0.09 ; C24/C22 1.839, normal 0.84 ± 0.10 ; C26/C22 0.086, normal 0.01 ± 0.004). Prophylactic treatment with Lorenzo’s oil was started. At 32 months of age, he presented to an outside hospital with vomiting. Subsequent brain MRI demonstrated a posterior fossa tumor, which was completely resected. Histopathological examination revealed medulloblastoma with classical features without evidence of metastatic spread. His postoperative course was uneventful and he exhibited no signs of cerebral ALD. He was treated with five cycles of cisplatin, cytoxan, etoposide, and vincristine (“Head Start” II, Dhall et al. 2008) and then received conformal radiation therapy (2,340 Gy to the posterior fossa with 3,660 Gy boost to the tumor bed). MRI after completion was unremarkable without evidence of residual or recurrent tumor. In addition, no signs of ALD-related cerebral demyelination were identified.

Fig. 1 Axial (a, c) and coronal (e) T2-weighted and contrast enhanced T1-weighted (b, d, f) MR images at 4.3 years show bilateral, symmetrical T2 hyperintensity with matching contrast enhancement of the corticospinal tracts at the level of the midbrain and pons (white arrows), the lateral lemnisci (black arrows) and red nuclei. Incidental note is made of a contrast enhancing focal lesion in the right temporal medial lobe (d, short white arrow) representing a metastatic lesion of the posterior fossa medulloblastoma

Unfortunately, 14 months later multiple metastatic lesions were seen within the supratentorial and infratentorial brain as well as in the spinal canal. Again, no lesions suggestive of cerebral ALD were noted. Chemotherapy was started with topotecan and cyclophosphamide. After two cycles, stable disease was noted. Chemotherapy was adjusted to temozolamide and etoposide. He then developed worsening ataxia and loss of speech. Follow-up imaging at the age of 4.3 years revealed a decrease in the size of the contrast enhancing metastatic lesions within the brain and spinal canal (Fig. 1). However, in contrast to the previous MRI studies, bilateral, symmetrical linear foci of enhancement and abnormal T2 high signal had appeared following the course of the corticospinal tracts extending from the posterior limb of the internal capsule to the pontomesencephalic junction (Fig. 1). Additional increased T2 signal with matching contrast enhancement was seen in the splenium of the corpus callosum, lateral lemnisci, and red nuclei (Fig. 1). Signal characteristics and distribution of these lesions were characteristic for cerebral ALD. At this stage, the child presented with truncal ataxia and speech and language difficulties.

Discussion

X-linked ALD is a well-described peroxisomal disorder where a single enzyme defect may result in different clinical phenotypes. There is a significant heterogeneity

in the cerebral ALD neuroimaging phenotype. Loes et al. (2003) defined five different neuroimaging patterns of cerebral ALD based on the primary involvement and distribution of findings as identified on MRI. Our patient most closely fits pattern three of Loes' classification, because of corticospinal tract involvement without abnormalities of the frontal, occipital, or cerebellar white matter. While this neuroimaging pattern is the most frequent distribution of lesions seen in adult patients, it is rarely observed in children. Additionally, the red nuclei also demonstrated signal abnormalities. This finding is rare; having only been reported previously in a single adult patient (Ochi et al. 1998).

External environmental or epigenetic factors may play a pathogenetic role in ALD modulating the clinical phenotype and/or causing the onset of ALD in genetically at-risk patients. Raymond et al. (2010) recently reported the impact of moderate to severe head trauma on ALD progression. In their series, Raymond et al. (2010) reported three asymptomatic patients and two AMN patients who, after head trauma, developed a CALD phenotype. The posttraumatic neurological progression of both AMN patients was brief and severe. This is unusual for AMN patients with cerebral involvement. Based on additional similar cases from the literature (Turpin et al. 1985; Wilkinson et al. 1987; Weller et al. 1992; Carmant et al. 1998; Fatemi et al. 2003), Raymond et al. concluded that head trauma is an environmental factor that can have a modulating–causative role in some patients genetically at risk for ALD.

Our patient, who was genetically at risk for ALD, showed an onset of active demyelination after intense multimodality treatment for medulloblastoma. For reasons outlined below, we consider neurosurgical intervention to be an environmental factor that may initiate ALD-related cerebral demyelination.

The presumed pathogenesis of cerebral myelin injury in ALD includes two stages. In the first phase, the inclusion of an excess of VLCFA in the myelin destabilizes the myelin leading to a dysmyelination, followed by a second phase of an immune-mediated inflammatory process with progressive demyelination (Hudspeth and Raymond 2007).

The first phase is based on the accumulation of excessive saturated, straight VLCFA in myelin lipids and in PLP1 (Raymond et al. 2010). An excess of hexacosanoic acid (C26:0) generates reactive oxygen species altering the physiological properties of myelin and consequently destabilizing the cell membranes. This leads to a spontaneous breakdown of the affected myelin sheaths. Therefore, any factor facilitating the inclusion of VLCFA into myelin will increase myelin instability. Normally, VLCFA are relatively insoluble at normal body temperature. However, their solubility and hence their mobility increase in the case of

fever. Both accidental and surgical brain trauma may induce a systemic reaction of the organism, which is triggered by interleukin-6 and characterized by fever, leukocytosis, increased catabolism, and an activation of the coagulation system (Heesen et al. 1996). Therefore, not only post-traumatic fever (as reported by Raymond et al. in head trauma) but also febrile reaction after brain surgery may lead to an increased concentration of abnormal fatty acids in myelin.

The second phase is characterized by an inflammatory-immune demyelinating reaction. The cell membrane components containing VLCFA seem to serve as antigens driving the immune reaction after presentation by CD1 cells (Ito et al. 2001; Hudspeth and Raymond 2007). Factors facilitating the recognition of antigens may intensify the inflammatory reaction. Like head trauma, neurosurgery interrupts and increases the permeability of the BBB. This may enhance the recognition of previously sequestered antigens. Consequently, neurosurgical disruption of the BBB can precipitate the immune-mediated inflammatory process leading to demyelination in CALD patients.

The time interval between head trauma and onset of ALD symptoms varied between three and twelve months in the series published by Raymond et al. (2010). In our patient, the time between neurosurgery and development of ALD findings on MRI was 14 months. This temporal similarity supports the pathogenetic effect of neurosurgery as an environmental factor in the initiation of ALD-related demyelination in predisposed patients.

We are aware that additional factors could play a role in the acceleration/initiation of ALD in this patient. The medulloblastoma itself, by definition, results in a breakdown of the BBB, and could have precipitated this presentation. The patient's chemotherapy and/or radiotherapy could be postulated as an additional contributory factor. Based on its myelosuppressive effect, however, chemotherapy might have a protective rather than a negative effect on the inflammatory-immune component in ALD patients. Unfortunately, so far all studies exploring immunosuppressive or immunomodulating therapies with cyclophosphamide or interferon- β have not been successful (Berger et al. 2010).

In conclusion, this case suggests that, like accidental head trauma, neurosurgical brain injury with disruption of the BBB may act as an environmental factor to initiate or enhance ALD-related white matter demyelination. This finding supports the hypothesis that the phenotypical heterogeneity of ALD patients is at least partially explained by environmental external factors. In addition, our case shows that patients at risk for ALD or patients with a mild clinical course of ALD require close monitoring of their brain involvement after accidental or interventional brain injury.

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