Fulminating Autoimmune Demyelination with Optic Neuropathy in a Case of Pediatric Cerebral Adrenoleukodystrophy: Case Report and Review of the Literature

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Abstract

X-linked adrenoleukodystrophy (ALD) is a leukodystrophy characterized not only by progressive loss of myelin in the central nervous system due to dysmyelination, but also by acute, subacute, or chronic inflammatory demyelination. This results in the phenotypic variability of cerebral ALD (cerALD), which is independent of the genotype. In this article, we reported a fulminant presentation with fluctuating encephalopathy and visual loss in a patient with childhood onset cerALD. Brain MRI showed symmetric confluent occipito-temporal demyelination with severe disruption of the blood–brain barrier and prechiasmal optic neuropathy. The patient's cerebral spinal fluid (CSF) demonstrated an elevated IgG index, myelin basic proteins, and oligoclonal bands. Within 48 hours of receiving immunomodulating therapy, the patient's symptoms of psychomotor slowing, visual impairment, and areflexia partially resolved. High plasma C26:0 levels and high ratios of C24/22 and C26/22 were diagnostic of ALD. It has been shown that environmental factors play an important role in the inflammatory demyelination responsible for the severe phenotypes of cerALD.

Keywords
- optic nerve atrophy
- X-linked adrenoleukodystrophy
- cerebral ALD
- oligoclonal bands

Introduction

X-linked adrenoleukodystrophy (ALD) is an uncommon genetic progressive neurodegenerative condition caused by systemic impairment of peroxisomal β-oxidation of very long-chain fatty acids (VLCFAs). ALD is caused by mutations in the *ABCD1* gene, which encodes adrenoleukodystrophy protein (ALDP), a peroxisomal transmembrane protein composed of 745 amino acids and a member of the ATP binding cassette transport protein family. ALDP helps form the channel through which VLCFAs move into the peroxisome as VLCFA-CoA. The prevalence of ALD is approximately the same in all ethnic groups. Incidence is estimated 1 in 20,000 males, and 1 in 17,000 births (combined male and female).[1] There are multiple phenotypes of ALD depending on age at presentation and gender of the carrier. In male children, ALD can present with isolated Addison's disease with or without slow progressive cognitive deterioration or cerebral ALD (cerALD). Some children develop a more rapid cerebral dysfunction with cognitive decline, frequently associated with compensated Addison's disease. In adolescence and adulthood, cognitive decline may occur with occasional insidious psychiatric disturbances mimicking psychosis or schizophrenia. Adrenomyeloneuropathy (AMN) may start in

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adolescence or later in adulthood and is characterized by a slowly progressive distal axonopathy involving the spinal cord and peripheral nerves leading to a progressive spastic paraparesis. Adolescent and adult males frequently have testicular insufficiency. Heterozygous females with ALD rarely suffer from Addison's disease but may present with an isolated myeloneuropathy.[2] CerALD is a unique leukodystrophy characterized by progressive loss of myelin in the central nervous system (CNS) due to dysmyelination and occasionally inflammatory demyelination. This results in the phenotypic variability of cerALD. Most cases of severe cerALD manifest in childhood or adolescence as a devastating degenerative disorder leading to major neurological deterioration and death within a few years. In total, 40% of boys diagnosed with ALD develop cerALD in their first two decades of life, and other 20% develop cerALD in adulthood.[1] Surprisingly, genotype does not predict the likelihood of severe cerALD phenotype. Significant intrafamilial phenotype variability has been observed as different clinical phenotypes can occur even among monozygotic twins.[3] The prognosis of cerALD is poor unless allogeneic hematopoietic stem cell transplantation (HSCT) is performed early.[4] In this manuscript, we report a case of childhood cerALD with fulminant presentation and optic neuropathy.

Factors other than metabolic abnormalities have been implicated in the myelin damage found in cerALD. Head trauma has been postulated as a risk factor for the cerALD.[5] Preliminary data have shown that low serum 25-OH Vitamin D levels may predispose patients to cerALD.[6] The intermittent nature of some patients' clinical course may lead to an incorrect diagnosis of multiple sclerosis (MS), despite previous reports of relapsing and remitting symptoms in cerALD.[7] CerALD in some patients is associated with CSF oligoclonal bands.[8–10] In adult patients, demyelinating features can be similar to those seen in MS.[11,12] CerALD and MS are inflammatory leukoencephalopathies, but only MS is considered autoimmune.

Case Description

A 10-year-old Hispanic male child was admitted for acute-onset headache, loss of balance, and sparse speech with only parroting and acute visual loss. There was no vomiting, diarrhea, or constipation. He was adopted from Mexican parents at birth and family history details were not available. His early developmental milestones were within normal limits. He had no significant illness or surgery and no recent trauma or infection. His only medical history was attention deficit hyperactivity disorder for which he was treated with lisdexamfetamine from the ages of 5 to 8 years old, at which time he developed clusters of tonic jerks of both shoulders. This resolved gradually after the lisdexamfetamine was discontinued, and he was started on methylphenidate, but his school performance continued to regress. In the months leading up to his admission, he started having sleep difficulties, headaches, and episodes of confusion (showing up to the wrong class). He also complained of occasional double vision.

He was at the 20th percentile for body mass index. He was normotensive (94/61 mmHg) with heart rate of 72 beats per minute. He was afebrile but appeared dehydrated. His neurologic exam on admission was significant for acute cognitive decline and disorientation. He was withdrawn with a flat affect and paucity of speech. He was unable to follow simple commands. He could not recognize his adoptive parents and failed the mini-mental status exam. A horizontal nystagmus was accompanied by apparent visual decline. There was left exotropia. Episodes of staring alternated with episodes of drowsiness. He could not ambulate. During the next few days, his mental status remained altered, with rapid fluctuations between a hypoactive state with cognitive impairment and confusion, and a more active state with some awareness and ambulation. During periods of lucidity, visual impairment was such that he had difficulties recognizing letters.

Laboratory studies showed normal sodium (139 mmol/L), potassium (4.4 mmol/L), and glucose (100 mg/dL) levels. Of note, 25-hydroxy vitamin D level was low (8 ng/mL; normal >20). Brain magnetic resonance imaging (MRI) demonstrated bilateral periventricular areas of symmetric confluent demyelination with serpiginous peripheral gadolinium-enhancing rim surrounded by areas of dysmyelination sparing the subcortical U-fibers in the parieto-occipital regions (►**Fig. 1**). There was also evidence of intracranial prechiasmal optic neuropathy more prominent on the left (►**Fig. 2**) with extension to the chiasma and optic radiations (not shown). Loes's score was 8/34.[13] Gadolinium intensity score (GIS) was 3.[14] A lumbar puncture tap obtained the next day showed a normal opening pressure (14 cm H_2O, normal: <25). CSF showed albuminocytologic dissociation with elevated protein (84 mg/dL; normal: 15–45) and no cells. CSF was sent for additional studies, which came back 1 week later showing elevated albumin index (14.9) suggesting damage to the blood CSF barrier. An intrathecal synthesis of immunoglobulins (IgG) was demonstrated by the presence of three oligoclonal bands (normal: 0–1), elevated IgG synthesis rate (21.7 mg/day; normal: <8) and elevated IgG index (0.93; normal: 0.28–0.66). The elevated myelin basic proteins (5.6 - ng/mL; normal: 0–5.5) was consistent with an acute breakdown of CNS myelin. As brain MRI was highly suggestive of ALD, plasma VLCFAs concentration were sent to Kennedy Krieger Institute, Baltimore. High plasma C26: 0 levels (1.02 µg/mL; normal: 0.23 ± 0.09) and high ratios of C24/22 (1.492; normal: 0.84 ± 0.1) and C26/22 (0.062; normal: 0.01 ± 0.004) suggested a defect in peroxisomal VLCFA oxidation consistent with diagnosis of X-ALD. In addition, ACTH level was elevated (5,778 pg/mL; normal: 6–55) while AM cortisol was low (6.3 mcg/dL; normal: 10–20) consistent with chronic primary adrenal insufficiency. Shortly after the spinal tap, he developed worse headaches with vomiting and decreased oral intake. There was further cognitive decline with obtundation. Repeat laboratory values were consistent with acute dehydration with elevated blood urea nitrogen (23 mg/dL; normal: 7–18) and normal electrolytes. Addison crisis was suggested by further drop of cortisol level to 5 mcg/dL.

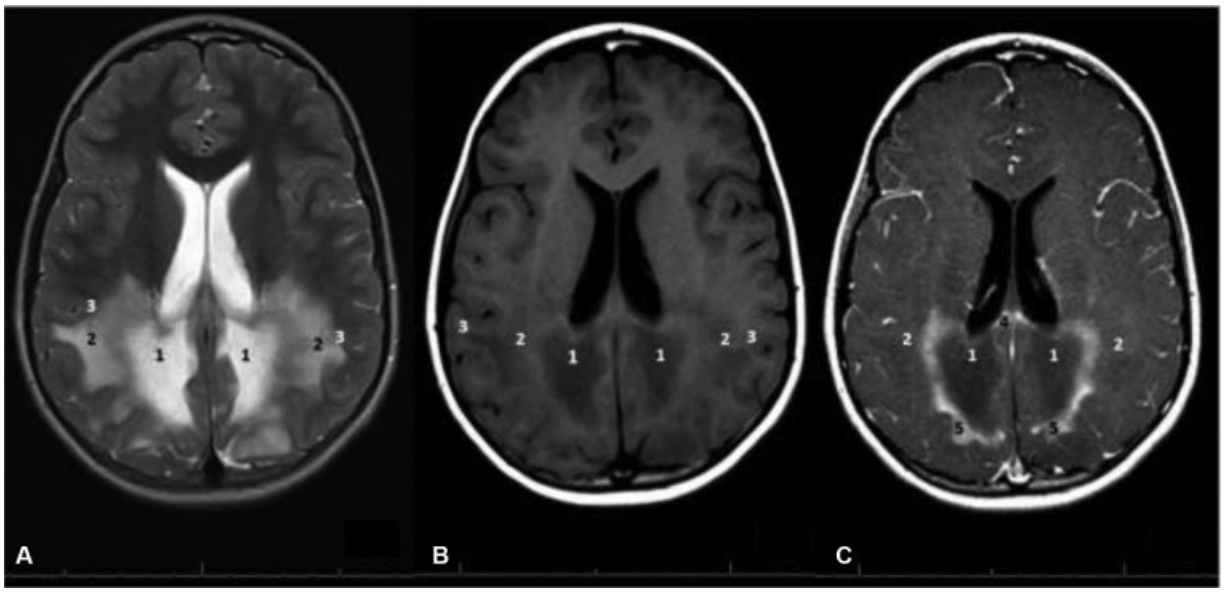

Fig. 1 Initial MRI prior to treatment. Initial axial T2- (**A**) and T1-weighted MRI without contrast (**B**) shows extensive bi-occipital periventricular symmetric confluent demyelination (1) and dysmyelination (2) sparing the U-fibers (3). T1-weighted MRI with gadolinium (**C**) shows contrast enhancement in the splenium (4) and halos of ring enhancement (5) separating areas of demyelination (1) from areas of dysmyelination (2). MRI, magnetic resonance imaging.

Within 48 hours of receiving IVIg (1 gm/kg/day for 2 days) and high doses of corticosteroids (methylprednisolone IV 10 mg/kg/day), the patient's symptoms almost completely resolved. He was able to walk, recognize adoptive parents, maintain a conversation, speak in long sentences, tell jokes, and perform complex math problems. His activity of daily living and cooperativity along with cognitive functions were significantly improved. His expanded disability status scale (EDSS) was 3.[14] His X-linked adrenoleukodystrophy-disability rating scale (ALD-DRS) was II.[15] Allogenic HSCT was recommended, but the family refused after being informed of the associated risks and benefits. He was discharged on oral hydrocortisone (30 mg/m^2/day divided three times daily) and Vitamin D2 (ergocalciferol) 50,000 IU weekly. He remained stable while receiving weekly high doses of intravenous corticosteroids and IVIg every other week. After 1 month, oral hydrocortisone was decreased (15 mg/m^2/day divided three times daily). MRI of the brain 4 months after initiating treatment showed improvement (►**Fig. 3**) with GIS dropping from 3 to 1, while Loes's score (8/34) remained unchanged. Repeat ACTH level was normal (6 pg/mL), while AM cortisol was normal (20 mcg/dL). The eye exam suggested optic nerve atrophy worse on the left. His vision remained poor and left exotropia was noted. His neurologic exam showed no focal deficit, hyperreflexia, and Babinski's signs. There was a persistent loss of recent memory interfering with learning and reasoning, perhaps due to discontinuation of stimulant medication, but he was still able to tell jokes and ambulate.

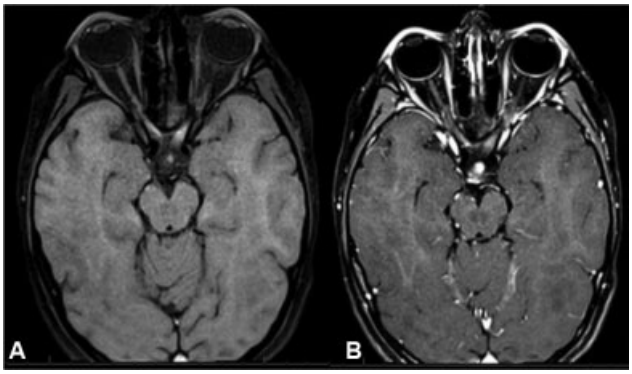

Fig. 2 T1-weighted fat suppression axial magnetic resonance imaging showing bilateral prechiasmal optic neuropathy worse on the left (**A**), with no gadolinium enhancement (**B**).

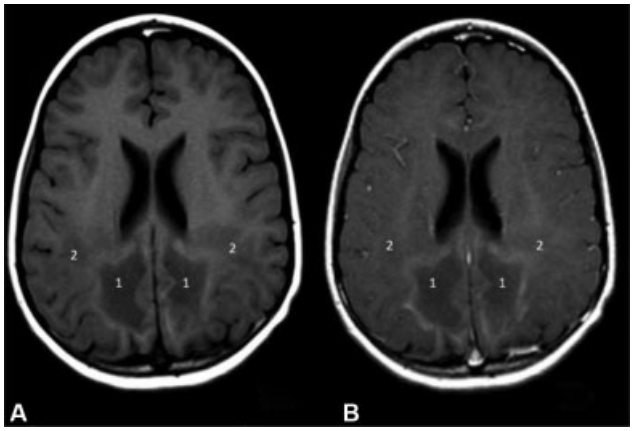

Fig. 3 Axial T1-weighted magnetic resonance imaging without (**A**) and with gadolinium (**B**) after 4 months of immunomodulation therapy shows no change in the size the demyelination area and minimal residual ring enhancement (5) separating the area of demyelination (1) from the area of dysmyelination (2).

Discussion

In all forms of ALD with cerebral dystrophy, there is an accumulation of saturated VLCFAs that are then incorporated into complex lipids such as gangliosides or phosphatidylcholine in the myelin sheets leading to instability, oxidative stress, and dysmyelination.[16–18] In childhood ALD, this results in a slow progressive deterioration of motor function with behavioral and cognitive decline due to dysmyelination. Abnormal MRI signaling in the centrum semi ovale, pyramidal tracts, and internal capsule have been reported in asymptomatic patients with childhood ALD[19,20]; however, at this stage, the dysmyelinating lesions do not yet show an enhancement on T1 sequences indicating an intact blood–brain barrier (BBB) and the absence of inflammation. Approximately 10% of boys or adolescents with dysmyelinating ALD will not progress to the demyelination stage. The Loes scale using T1-weighted sagittal images and T2-weighted axial images evaluates the severity of brain MRI findings in ALD based on the location and extent of white matter involvement and on the presence of either focal or global atrophy.[13] The Loes's score can range from 0 (normal) to 34 (maximal). A score of 10 or more, in general, is considered predictive of poor neurologic outcome. In our patient, Loes's score was 8. Besides, brain MRI identified bilateral acute intracranial prechiasmal optic neuropathy extending to chiasm and optic tract. The left optic nerve was more severely involved (►**Fig. 2**). The prevalence of optic neuropathy in ALD is unknown as Loes scale never takes account of chiasmic and prechiasmatic dysmyelination.[13] Visual signs were thought to occur late in the clinical course of cerALD,[21] but more recent reports have shown that visual disturbances are common initial symptoms with the most frequent ophthalmological abnormality being strabismus.[22,23] It has been previously stated that the demyelination of central visual pathway without optic nerve involvement is the cause of early visual impairment in cerALD.[24] In our patient, optic nerve involvement occurred early before the onset of cognitive decline. Follow-up funduscopic examination showed optic nerve atrophy worse on the left. Optic atrophy has been previously reported in childhood and adult cerALD, where it is accompanied by loss of retinal ganglion cells.[25,26] One histopathologic study of a patient with cerALD showed characteristic bileaflet inclusion laden (loaded with VLCAs) macrophages in the optic nerve.[27] To our knowledge, the present report is the first to show early onset optic neuropathy in childhood cerALD.

In childhood, cerALD with inflammatory demyelination typically presents with a rapid neurologic decline without periods of recovery. Patients lose the ability to understand language and to ambulate within weeks or months.[28] Although the risk of developing inflammatory cerALD peaks in childhood and decreases with age, it remains substantial even in older children. The lifetime risk of developing the inflammatory form of cerALD in males is an estimated 60%.[29] Approximately 20 to 25% of adult males with AMN develop an acute neurologic decline consistent with cerALD.[30] Adults with psychiatric disturbances mimicking schizophrenia or psychosis may also be at risk of developing the inflammatory form of cerALD.[31,32]

MRI with contrast in inflammatory cerALD reveals leakage of the BBB and infiltration of mononuclear cells, predominantly macrophages. The process of inflammatory demyelination starts most often in the midline of the corpus callosum and spreads outward into the periventricular white matter.[33] In boys with inflammatory cerALD, decreased signal on the T1 sequence with ring enhancement at the periphery is frequently extensive and confluent. The initial involvement is in the splenium and parieto-occipital region and internal capsule in approximately 80% of the case. The genu and frontal white matter are the sites of initial involvement in 20% of cases.[13] On T2 and FLAIR sequence, increased signal extending outside of the ring enhancing lesion corresponds to the underlying dysmyelination (►**Fig. 1**). In rare heterozygous adult females with cerALD, neuroimaging may resemble that of patients with MS, with multifocal lesions disseminated in the periventricular, juxtacortical (involving U-fibers), and infratentorial compartments and gadolinium-enhancement of the acute lesions.[9] The molecular mechanisms responsible for the conversion of dysmyelination into inflammatory demyelination in cerALD are poorly understood.[33] Circulating VLCFA levels fail to correlate with either the development of disease or the timing of disease onset.[34,35] Therapeutic manipulation of VLCFA levels using "Lorenzo oil" is ineffective in preventing cerALD in asymptomatic patients or stopping cerALD progression.[2,36]

BBB dysfunction is the hallmark of acute neurodegeneration in cerALD. Astrocyte activation plays a pivotal role in the loss of endothelial cell tight junctions.[37,38] Similarly, astrocyte activation is critical to the development of MS[39] and experimental autoimmune encephalopathy.[40] Reactive astrocytes lose their surface contact with blood vessels of the BBB, enhancing the infiltration of leukocytes to the CNS.[41] Astrocytes are reactive to environmental factors and are key players in the pathogenesis of cerALD.[42] The role of environmental stress as a trigger of acute neurodegeneration in cerALD is supported by multiple observations. For example, it has been reported that catastrophic presentations of cerALD can be triggered by traumatic brain injury. The inflammatory demyelinating lesion appears to begin at the same site as the original contusion.[5,43,44] Musolino et al reported that an increase in BBB permeability precedes inflammatory demyelination, suggesting that disruption of the BBB may trigger pro-inflammatory demyelination in ALD.[45] It is thus possible that head trauma triggers the inflammatory cerebral ALD presumably due to the BBB disruption. Interestingly, the role of concussion in triggering MS has recently been suggested by the findings that a single concussion between the age of 10 and 20 increases the risk of MS by 22% and that the risk of MS is increased by more than 50% in those who had more than one concussion.[46]

Another potential environmental factor is vitamin D deficiency. Vitamin D deficiency is a recognized risk factor for MS and is associated with increased disease activity. The active form of vitamin D, $1,25(OH)_2$ D, has been shown to prevent BBB disruption in MS.[47] More recently, it has been

shown that particular variants of the vitamin D receptor gene play an important role in the pathogenesis of MS.[48] Preliminary data have shown that Vitamin D deficiency may predispose a patient to cerALD.[7] Vitamin D deficiency was documented in our case of cerALD. Other environmental factors such as fever, infection, and toxic exposure, may play a role but have not been well explored or characterized.

The inflammatory nature of the demyelinating lesion in inflammatory cerALD aligns it with MS, the most common demyelinating disease. Oligoclonal bands seen in MS result from intrathecal antigen-driven immune response. Like MS, much of the destruction of myelin in cerALD appears to be driven by humoral immunity. Inflammatory cerALD is an organ-specific autoimmune disease limited to the brain.[18] Although there is as yet no compelling experimental evidence of to what extent immune-mediated mechanisms contribute to CNS demyelination in X-ALD, the presence of B cells in perivascular inflammatory infiltrates and complement factors in degenerating myelin point to a pathogenic role of autoantibody responses in patients with the cerebral form of ALD.[49,50] Inflammation in ALD may be associated with autoantibodies. Increased CSF IgG synthesis and a CSF oligoclonal banding pattern are found in most adult patients with inflammatory cerALD,[8–10,32,51] but the prevalence of these findings in childhood cerALD appears low.[52]

In our patient, brain MRI showed bilateral parieto-occipital, confluent, and symmetrical demyelination with ring enhancement at the periphery. U-fibers were not involved. A gadolinium intensity score (GIS) evaluates the maximal intensity of the gadolinium enhancement at the leading edge of the active demyelination,[14] using the intensity of choroid plexus as an internal control. GIS is a 4-point scale between 0 and 3, with 0 corresponding to no enhancement and 3 maximum intensity, higher than the choroid plexus. Our patient had GIS of 3 on presentation. In MS, lesions are more patchy, asymmetrical, frequently discrete, and perpendicular to the lateral ventricles with some enhancing lesions. Juxtacortical U-fiber lesions can occur. In the Marburg variant of MS, ring enhancing lesions can be confluent and bilateral; however, such lesions are never symmetrical.[53] Optic neuropathy in MS is most likely unilateral, intraorbital, involving a short segment of the nerve, and there is substantial enhancement. In neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOG-AD), lesions are frequently seen along the ependymal lining of the ventricles and can be large and confluent, but typically remain asymmetrical sparing the U-fibers. In both NMOSD and MOG-AD, optic neuropathy typically is bilateral, longitudinally extensive, preferentially compromising intracranial prechiasmal optic nerve, and chiasm and optic tracts with gadolinium enhancement. In both conditions, intrathecal synthesis of IgG is not increased, and oligoclonal bands are rarely detected differentiating them from MS and our patient with fulminant cerALD. Although serum anti-MOG antibodies have been demonstrated in 50% of patients with cerALD, their possible pathogenic relevance remains speculative as MOG antibodies can also be seen in MS.[54,55] Anti-MOG antibodies were not tested in our patient.

A fulminant presentation of childhood cerALD with acute encephalopathy or coma, as in our case, only occurs in approximately 1% of childhood cerALD cases.[56] Over first few days, our patient had brief periods of lucidity alternating with obtundation. After the spinal tap, he developed adrenal crisis with vomiting and persistent altered mental status. Na and K were normal as many males with adrenal insufficiency do not require mineralocorticoid replacement. The adrenal crisis triggered by stressors, such as MRI and spinal tap, overshadowed the autoimmune symptomatology of the previous days. The elevated GIS indicated BBB disruption. There was also evidence of autoimmunity with oligoclonal bands and increased IgG synthesis. Most likely, the adrenal crisis contributed to the exacerbation of the autoimmune flare up. He received immunomodulation therapy with IVIg and high doses of steroids. Treatment with immunomodulation therapy has been shown to have beneficial effects in a variety of autoimmune diseases. Steroids have been identified to impact several critical properties of the BBB, including tight junction integrity. In addition, glucocorticoids suppress cellular immunity. It is believed that IVIg modulates the autoimmune response and decreases inflammation. IVIg was reported to temporarily improve quality of life in childhood and adolescent cerALD.[57,58] Markers of an autoimmune process were not reported in either case. Small trials of immunomodulatory and immunosuppressive drugs in childhood and adolescent cerALD have reportedly "failed" in cerALD[16,17,59]; however, the intrathecal IgG synthesis, CSF oligoclonal bands, and vitamin D levels in these patients were not reported. To our knowledge, we are the first to show GIS improvement (►**Fig. 3**) with immunomodulation therapy in a child with cerALD and abnormal intrathecal B cell autoimmunity. CSF markers of B cell autoimmunity have been previously shown to be present in several adults with cerALD who responded to immunomodulation therapy.[9,10]

Factors predictive of worse outcome of HSCT in childhood cerALD include clinical presentation before 8 years of age, rapidly progressive disease, EDSS $\geq$2 and AL-DRS $\geq$2,[15] Loes's score $\geq$10,[60] and GIS $\geq$2.[14] The only therapy that improves Loes's score is HSCT, as it can decrease dysmyelination after normalizing plasma VLCFA. Currently, the only approved treatment to arrest cerALD is HSCT, presumably by providing bone marrow-derived monocytes with healthy *ABCD1* that migrate into the brain and differentiate into less inflammatory macrophages and microglia.[61–64] HSCT has been associated with the disappearance of contrast enhancement and normalization of perfusion in T2-weighted hyperintense cerebral tissue.[14,65] The mechanisms by which allogeneic HSCT can arrest the progression of cerebral demyelination are still unknown. Some recipients of HSCT show improvement in neurological symptoms despite plasma VLCFA concentrations remaining elevated.[66] Hence, BBB repair and decreased inflammatory demyelination seen after HSCT are not the result of normalization of VLCFA. Every patient undergoing HSCT needs a long-term immunosuppression regimen, including systemic glucocorticoids, to prevent graft-versus-host disease (GVHD). We suggest that BBB repair seen with HSCT is the result of the

immunosuppressive therapy. Our patient while receiving high doses of steroids showed BBB repair similar to the one seen with HSCT.[67] Gene therapy, using the patient's bone-marrow stem cells transfected with a lentiviral vector containing a functional cDNA copy of *ABCD1*, offer a promising alternative for the treatment of cerALD[68] but also requires immunosuppression.

Conclusion

- Optic neuropathy can be an early sign in childhood cerALD.
- In childhood cerALD, a fulminant presentation with adrenal crisis may overshadow the rapidly relapsing autoimmune symptomatology. We are the first to demonstrate GIS improvement in a child with cerALD and abnormal intrathecal B cell autoimmunity with immunomodulation therapy. As soon as the diagnosis of ALD is made, symptomatic patients should be referred to a HSCT center, as it remains the only proven treatment to improve dysmyelination after normalizing VLCFA.

Note
Informed consent was received from the patient's family for the writing of this manuscript. This case was previously presented at the annual meeting of Society for the Study of Inborn Errors of Metabolism (SSIEM) 2019.

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Conflict of Interest
None declared.

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