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Case Report

MRI findings of hypomyelination in adenylosuccinate lyase deficiency

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ARTICLE INFO

Article history:

Received 16 August 2018

Revised 1 November 2018

Accepted 3 November 2018

Available online 22 November 2018

Keywords:

Adenylosuccinate lyase deficiency

Hypomyelination

ABSTRACT

Adenylosuccinate lyase deficiency is a rare genetic disorder with few reported cases in the United States. Magnetic resonance imaging findings in the brain include hypomyelination and low generalized parenchymal volume. Presented here is a case in a 3-month-old male who presented with hypotonia and seizures and was subsequently diagnosed with adenylosuccinate lyase deficiency. Given the rarity of this diagnosis, findings demonstrated in this case may prompt ordering physicians to broaden their approach to genetic testing in the setting of hypomyelination. Comparison is also made to more common hypomyelinating leukodystrophies.

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Introduction

Adenylosuccinate lyase deficiency is a rare autosomal recessive disorder of purine metabolism. The disease was described in 1984 in 3 patients with severe psychomotor delay, autistic features, encephalopathy, hypotonia, and elevation of succinylpurines in the urine, cerebrospinal fluid (CSF), and plasma [1]. The accumulation of succinylpurines, succinyladenosine and succinylaminoimidazole carboxamide riboside in biologic fluids is evidence of this disturbance of purine

de novo synthesis and purine nucleotide recycling pathways [2,3].

This enzymatic deficiency can present with a wide array of neurologic symptoms ranging from a fatal neonatal form to a milder clinical presentation with onset during infancy. There have been 3 distinct types of adenylosuccinate lyase deficiency described on a continuum of physical and clinical features. The fatal neonatal type is characterized by encephalopathy, hypotonicity, intractable seizures, and ultimately death within the first week of life [4]. Type I is milder than the fatal neonatal type and is the most common

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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<https://doi.org/10.1016/j.radcr.2018.11.001>

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form. It is characterized by microcephaly, severe psychomotor retardation, and seizures. Type II has an onset within the first few years of life and is more slowly progressive with epilepsy, visual impairment, and mild psychomotor retardation as characteristic features. Furthermore, patients with adenylosuccinate lyase deficiency can present with variable dysmorphisms characterized by microcephaly (most common), brachycephaly, flat occiput, prominent metopic suture, divergent strabismus, small nose, smooth philtrum, thin upper lip, and low set ears [2–6].

Progression of the disorder can be assessed with magnetic resonance imaging (MRI) of the brain. Atrophy of the cerebral cortex, corpus callosum, cerebellar vermis, lack of myelination, delayed myelination, and anomalies of the white matter have been reported [1–3,6,7]. Here, we present a case of an infant with adenylosuccinate lyase deficiency.

Case report

A male child was born at term by an uncomplicated pregnancy. The patient was hypotonic, irritable, and demonstrated poor feeding by breast and bottle in the first week of life. He had a history of in utero hiccups, which persisted as a neonate. At the age of 3 months, he was admitted to the hospital with Respiratory Syncytial Virus (RSV) and seizure-like activity, which prompted an MRI. Videos obtained by family showed that the child had been having seizures since birth.

MRI showed myelination confined to the brainstem, central cerebellum, and posterior limbs of the internal capsule (Fig. 1). There was T2 hyperintensity of the white matter (Fig. 2) and superior vermian volume loss (Fig. 3). The corpus callosum was unmyelinated. MRI spectroscopy revealed a low N-acetylaspartate (NAA) peak with no lactate peak (Fig. 4).

The patient's hospitalization was complicated by seizures requiring prolonged video electroencephalogram (EEG) monitoring and anticonvulsant therapy. CSF analysis yielded an acellular CSF with normal protein and glucose. He was subsequently discharged with a nasogastric tube on phenobarbital therapy at a dose of 10 mg twice a day and levetiracetam at a dose of 75 mg per day. He continued to exhibit excessive hiccupping, episodes of extensor spasms, and multifocal seizures. A follow-up study of the patient's CSF was found to demonstrate abnormally high concentrations of succinyladenosine and succinylaminoimidazole carboxamide riboside. The elevation of these 2 compounds confirmed the diagnosis of adenylosuccinate lyase deficiency.

Discussion

Abnormal myelination in a newborn can be seen with several genetic disorders. Though rare, adenylosuccinate lyase deficiency is a differential consideration in an infant with hypomyelination. Fewer than 100 cases of adenylosuccinate lyase deficiency have been reported with greater prevalence in Belgium and the Netherlands [8]. The low parenchymal

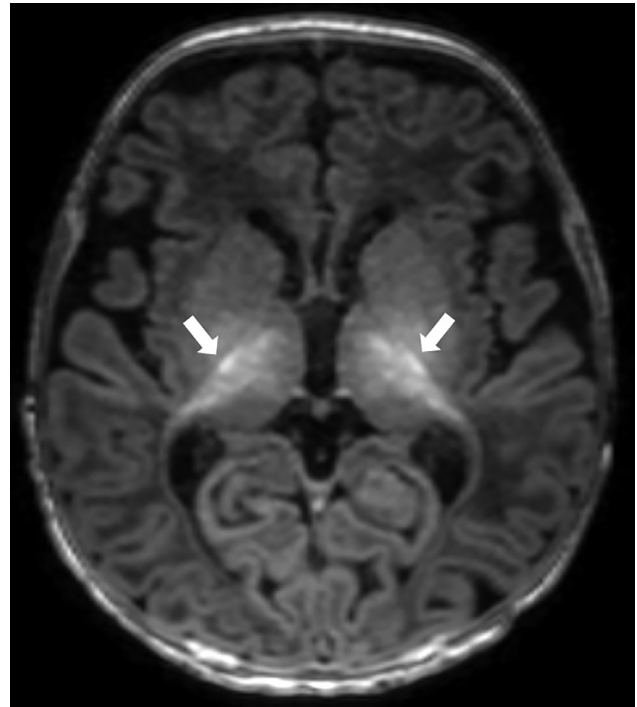


Fig. 1 – Axial T1-weighted images of the brain acquired at 3.0 T demonstrate myelination limited to the posterior limbs of the bilateral posterior internal capsules (white arrows).

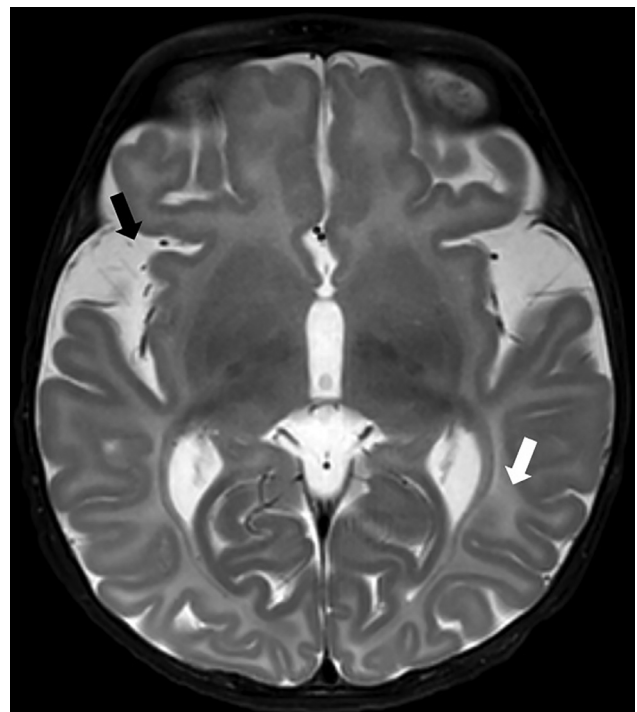


Fig. 2 – Axial T2-weighted images of the brain acquired at 3.0 T show increased T2 signal in the periventricular white matter (white arrow). There is overall low parenchymal volume with prominence of the extra-axial spaces (black arrow).

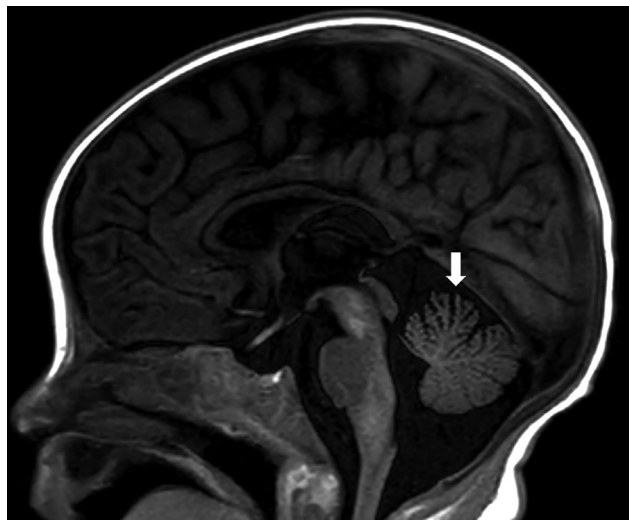


Fig. 3 – Sagittal T1-weighted images reveal low parenchymal volume of the superior folia with prominence of the extra-axial spaces (white arrow). The corpus callosum is unmyelinated.

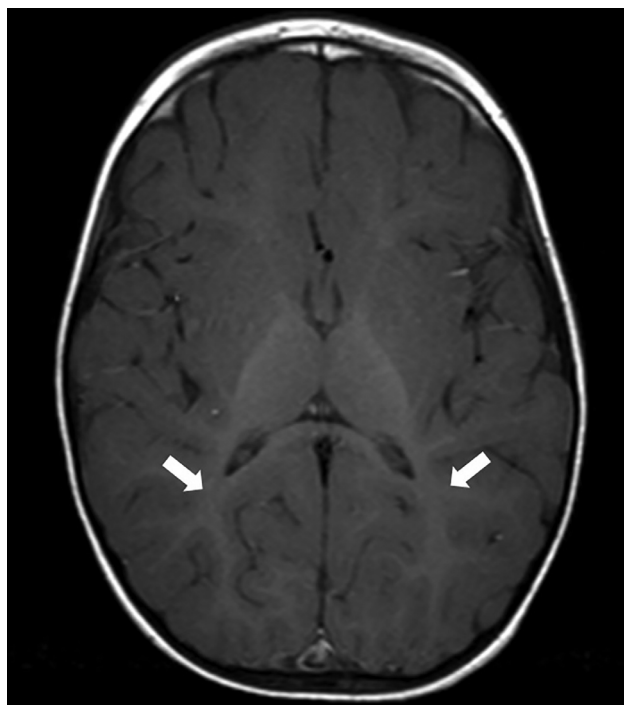


Fig. 5 – Comparison Case. Axial T1-weighted image from a 5-year-old patient with Pelizaeus-Merzbacher disease. Severely delayed myelination is present with limited myelination of the posterior white matter (white arrows). The anterior white matter is not myelinated.

volume and prominent cortical sulci may make this disorder distinct from hypomyelination disorders without widened cortical sulci (Figs. 5 and 6).

Hypomyelinating disorders are heterogeneous with multiple known mutations that affect different metabolic processes related to myelin formation. Pelizaeus-Merzbacher disease

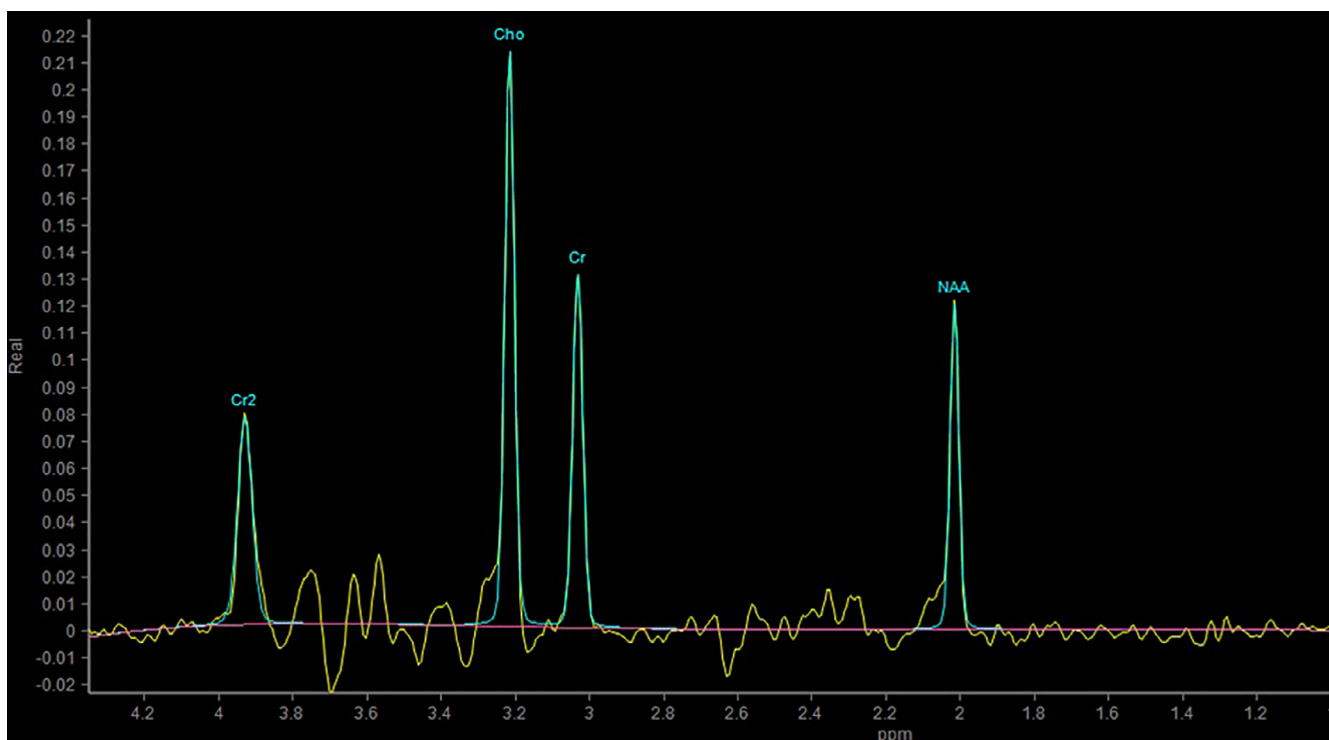


Fig. 4 – Magnetic resonance spectroscopy performed at TE = 144 ms with a voxel placed in the right posterior parietal white matter demonstrates a dominant choline peak and a diminished N-acetyl aspartate peak.

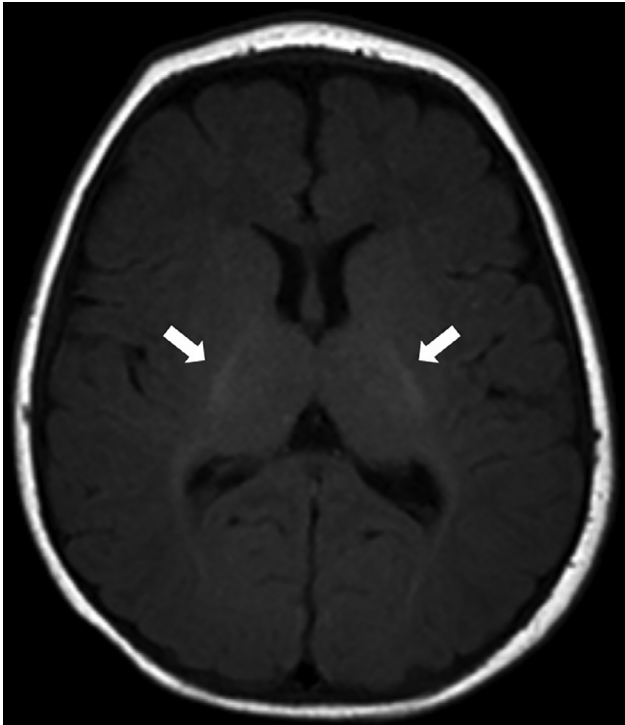


Fig. 6 – Comparison Case. Axial T1-weighted image from a 4-month-old female with ring chromosome 18, also a separate hypomyelination disorder. Myelination is confined to the posterior limbs of the bilateral internal capsules (white arrows). The cortical sulci are not widened.

(Fig. 5), often considered to be the prototypical hypomyelinating disorder, is a genetic neurologic disorder arising from mutations in the proteolipid protein 1 gene [9]. Clinically, the syndrome can present as a spectrum with variable leg weakness, ataxia, hypotonia, and cognitive impairment. MRI findings typically include pronounced frontal lobe predominant hypomyelination [9,10]. Parenchymal atrophy is seen later in the disease. Patients may also demonstrate signal abnormalities in the basal ganglia and thalami suggestive of iron storage disease, a potential differentiating factor from other pediatric leukodystrophies [9,10].

Chromosome 18 mutations commonly result in hypomyelination. Ring chromosome 18 (Fig. 6) is a combined deletion involving the long and short arms of chromosome 18. This disorder represents a heterogeneous combination of traits arising from deletions of the short arm (18p) and long arm of the chromosome respectively [11,12]. The genetic abnormality results in a variable phenotype, which may include developmental delay, seizures, behavioral issues, microcephaly, and obesity among numerous other symptoms [11,12]. MRI of the brain usually demonstrates hypomyelination in the superior frontal, parietal, and occipital lobes. Myelination is more likely to be normal in the lower frontal and temporal lobes [11]. Ring chromosome 18 patients may also demonstrate ventriculomegaly and occasionally focal lesions such as porencephalic cysts [11]. In common with adenylosuccinate lyase deficiency, cerebellar hypoplasia may mani-

fest with hypomyelinating leukodystrophies caused by mutations on chromosome 18 [13].

Pelizaeus-Merzbacher-like disease is similar to Pelizaeus-Merzbacher disease with hypomyelination of the brainstem [13]. Additional rare hypomyelination diseases with known mutations include oculodentodigital dysplasia, hypomyelination with congenital cataracts, and trichothiodystrophy with photosensitivity [13].

Since metabolic disorders have heterogeneous clinical presentations, MRI may generate important clues to the etiology. In adenylosuccinate lyase deficiency, MRI can show delayed myelination, enlargement of the lateral ventricles, abnormal white matter signal, and volume loss throughout the cerebrum or cerebellum, which is apparent in the first few months of life. Ultimately, metabolic diseases such as adenylosuccinate deficiency require genetic and biochemical testing for definitive diagnosis, but the radiologist may be the first individual to prompt this testing.

Conclusion

Adenylosuccinate lyase deficiency is a hypomyelination disorder that may demonstrate additional parenchymal findings that can distinguish the disease from more common hypomyelinating leukodystrophies. The extreme rarity of adenylosuccinate lyase deficiency in the United States can hinder diagnosis, and the radiologist may suggest genetic testing in the infant presenting with hypomyelination, generalized low parenchymal volume, and superior vermian volume loss.

REFERENCES

- [1] Macchiaiolo M, Barresi S, Cecconi F, Zanni G, Niceta M, Bellacchio E, et al. A mild form of adenylosuccinate lyase deficiency in absence of typical brain MRI features diagnosed by whole exome sequencing. *Ital J Pediatr* 2017;43:65.
- [2] Mierzevska H, Schmidt-Sidor B, Jurkiewicz E, Bogdańska A, Kuśmierska K, Stepień T, et al. Severe encephalopathy with brain atrophy and hypomyelination due to adenylosuccinate lyase deficiency—MRI, clinical, biochemical and neuropathological findings of Polish patients. *Folia Neuropathol* 2009;47:314–20.
- [3] Jurecka A, Jurkiewicz E, Szymanska A. Magnetic resonance imaging of the brain in adenylosuccinate lyase deficiency: a report of seven cases and a review of the literature. *Eur J Pediatr* 2012;171:131–8.
- [4] Mouchegh K, Zikánová M, Hoffmann GF, Kretschmar B, Kühn T, Mildnerberger E, et al. Lethal fetal and early neonatal presentation of adenylosuccinate lyase deficiency: observation of 6 patients in 4 families. *J Pediatr* 2007;150:57–62. e2.
- [5] Jinnah HA, Sabina RL, Van Den Berghe G. Metabolic disorders of purine metabolism affecting the nervous system. *Handb Clin Neurol* 2013;113:1827–36.
- [6] Zulfiqar M, Lin DD, Van der Graaf M, Barker PB, Fahrner JA, Marie S, et al. Novel proton MR spectroscopy findings in adenylosuccinate lyase deficiency. *J Magn Reson Imag* 2013;37:974–80.

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- [7] Jurecka A, Zikanova M, Kmoch S, Szymańska A. Adenylosuccinate lyase deficiency. *J Inherit Metab Dis* 2015;38:231–42.
- [8] US National Library of Medicine Genetics Home Reference. Adenylosuccinate lyase deficiency. Available at <https://ghr.nlm.nih.gov/condition/adenylosuccinate-lyase-deficiency> August 15, 2018.
- [9] Hobson G, Garben JY. Pelizaeus-Merzbacher disease, Pelizaeus-Merzbacher-like disorder 1, and related hypomyelinating disorders. *Semin Neurol* 2012;32:62–7.
- [10] Silverstein A, Hirsh D, Trobe J, Gebarski S. MR imaging of the brain in five members of a family with Pelizaeus-Merzbacher disease. *AJNR Am J Neuroradiol* 1990;11:495–9.
- [11] Benini R, Saint-Martin C, Shevell MI, Marie G, et al. Abnormal myelination in Ring chromosome 18 syndrome. *J Child Neurol* 2012;27:1042–7.
- [12] Heydari S, Hassanzadeh F, Hassanzadeh Nazarabadi M. Ring chromosome 18: a case report. *Int J Mol Cell Med* 2014;3:287–9.
- [13] Barkovich AJ, Deon S. Hypomyelinating disorders: an MRI approach. *Neurobiol Dis* 2016;87:50–8.