CASE REPORT

Molybdenum Cofactor Deficiency: Report of a New Case and Literature Review

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Abstract
We report a case of genetically confirmed molybdenum cofactor deficiency in an infant presenting with difficult to control neonatal seizures, and a severe cystic leukoencephalopathy on brain magnetic resonance imaging (MRI). This is a rare disease entity that can be easily missed or confused with hypoxic ischemic encephalopathy. Raising awareness regarding this condition has significant implications regarding genetic counseling, prognostication, and possibly medicolegal liability. We report a case confirmed by genetic testing that revealed a mutation previously unreported to the best of our knowledge. We discuss the clinical presentation, imaging findings, and review the literature on this under-recognized disease.

Introduction

Molybdenum cofactor deficiency is a rare autosomal recessive inborn error of metabolism that is often fatal. More than 90% of the cases present early, in the first few days of life, with seizures, hypertonia, and feeding difficulties. Death at an early age is common, and patients who survive usually progress to severe psychomotor delay (1).

Molybdenum cofactor deficiency is typically characterized by severe neonatal convulsions not responsive to therapy. Facial dysmorphic features such as narrow bifrontal diameter, long face, puffy cheeks, and elongated palpebral fissures resemble the appearance observed in patients with hypoxic ischemic brain injury (1). Molybdenum cofactor deficiency can be easily missed as a cause of neonatal convulsions and encephalopathy (2,3); hence, it is important to maintain a high index of suspicion in order to screen for and confirm the diagnoses of this lethal disorder.

In this case, we report on the clinical presentation, MRI findings, electroencephalography, results of DNA sequencing, and one year follow up of a patient with genetically confirmed Molybdenum cofactor deficiency type A.

Case Report

A 33 week gestation premature female was the second

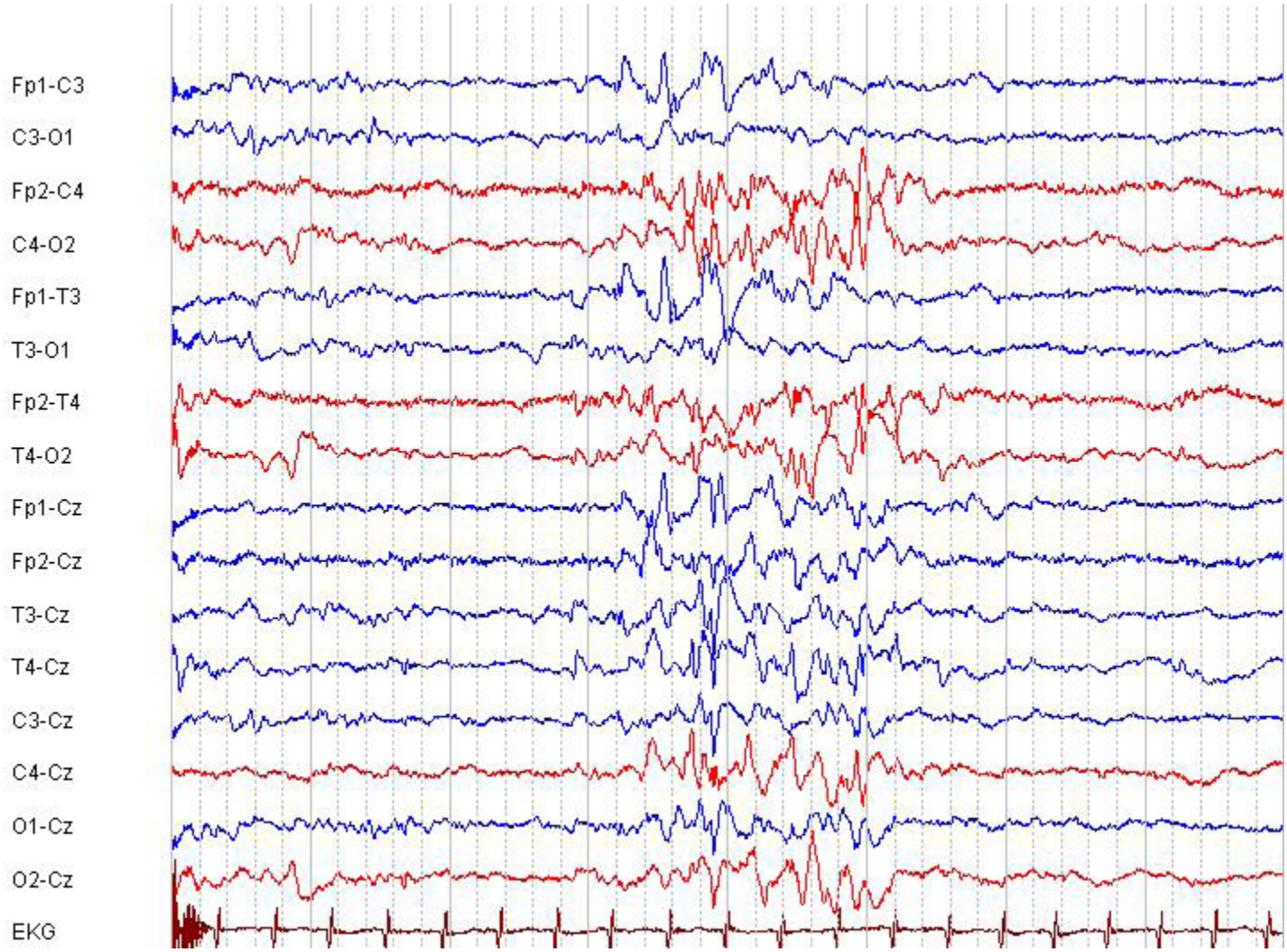

Figure 1: EEG showing a burst-suppression pattern

child of a second degree consanguineous marriage, born to a healthy mother at an outside institution. Birth weight was 1730 grams (less than 3rd percentile), head circumference 29.3 cms (3rd percentile). Her Apgar score was 8 and 9 at one and five minutes, respectively. She had mild respiratory distress requiring nasal continuous positive airway pressure for less than 24 hours. At 24 hours after birth, she was observed to have episodes of tonic seizures that persisted through 48 hours after birth, necessitating anticonvulsant therapy with Phenobarbital; eventually controlled with a midazolam infusion. An electroencephalogram (EEG) revealed a burst suppression pattern (Figure 1) indicating severe encephalopathy and raising suspicion of a metabolic cause such as non-ketotic hyperglycinemia. Investigations done at the referring institute included a cerebral ultrasound, blood ammonia, lactate, very long chain fatty acids, CMV IgM, toxoplasmosis IgM, rubella IgM, urine tandem mass spectroscopy, urine organic acids, cerebrospinal fluid (CSF) routine studies and CSF glycine. All were reported negative or within normal limits for age. The patient was referred to our institution for an MRI of the brain and neurological consultation.

At two months of age, the infant was seen in our pediatric neurology outpatient clinic. Her clinical exam revealed

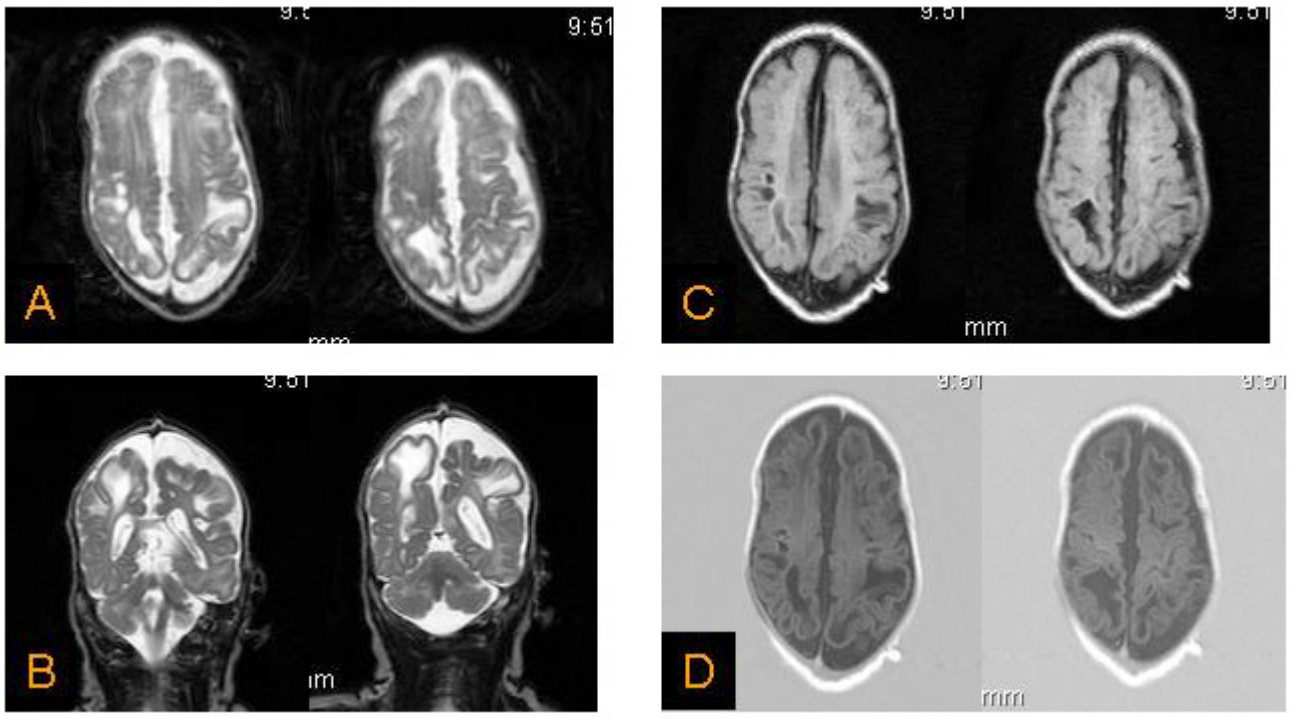

Figure 2: Brain MRI shows widespread posterior predominant subcortical cystic white matter changes and white matterhyperintensities. (A) T2 axial images (B) T2 coronal images (C) FLAIR images (D) T1 inversion recovery images

microcephaly with overriding sutures, facial dysmorphism in the form of a narrow bifrontal diameter and deep set eyes, micrognathia, large right auricle, and hypertonia with hyperreflexia and bilateral ankle clonus. The patient suffered from a severe feeding difficulty. The remainder of her physical exam was unremarkable. Her seizures were fairly controlled on a maintenance dose of phenobarbital (5mg/kg/day divided twice daily).

MRI of the brain revealed extensive subcortical and periventricular white matter loss and cystic changes with generalized volume loss (Figure 2). The MRI findings and clinical features raised the possibility of Molybdenum cofactor deficiency/ Sulfite oxidase deficiency, and the patient was subsequently tested. Urine sulfite test was positive, with no evidence of urinary uric acid, and a diagnosis of Molybdenum cofactor deficiency type 1A was thus established by molecular genetics, which revealed a 21 base pair deletion in exon 4 of MOCS1 gene. Both parents were tested and found to be heterozygote for the same deletion.

Follow up at one year of age reveals severe psychomotor delay with no language development, no head control, and inability to roll over. Her feeding difficulties progressed, with recurrent aspiration pneumonia. She eventually required gastrostomy tube placement for feeding. She has not developed lens dislocation thus far. A follow up EEG showed resolution of the burst suppression pattern and the appearance of a slow continuous background with multifocal spikes and sharp waves.

Discussion

Sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase are three enzymes dependent on a molybdenum-pterin complex named molybdenum cofactor (4). Mutations of any one of four genes (*MOCS1, MOCS2, MOCS3, GEPH*) encoding for the enzymes required for formation of active Molybdenum cofactor lead to loss of all Molybdenum cofactor dependent enzymes, with subsequent elevation of sulfite and xanthine levels (5). The neurological injury caused by Molybdenum cofactor deficiency is the result of an absence of sulfite oxidase activity leading to an accumulation of the neurotoxic metabolite (sulfite) or the deficit of the product (sulfate) (1). Sulfate is required for synthesis of sulfatide, an important component of sulfated cerebrosides required for stability of myelin. A deficit in sulfate may in theory result

in unstable myelin and subsequent neurologic dysfunction. The normal results of sulfatide analysis in a case of isolated sulfite oxidase deficiency argue against this mechanism of injury (6).Sulfite can cause a reduction in intracellular ATP resulting in an "energy crisis." This is supported by brain MRI data similar to that seen in hypoxic ischemic encephalopathy, and by data from a rat model of sulfite neurotoxicity reported by Zhang, et al (7). The clinical phenotype of both Molybdenum cofactor deficiency and sulfite oxidase deficiency is very similar (1) and supports a common pathway of sulfite mediated neuronal toxicity.

Our case highlights several important aspects. First, the early presentation with difficult to control tonic seizures in the first 24 hours of life with a burst suppression pattern on EEG may indicate Otahara syndrome (epileptic encephalopathy in early infancy with burst suppression pattern) (8); Molybdenum cofactor deficiency is yet another one of many heterogeneous etiologies of this epileptic syndrome that is probably under-recognized (2,9). Second is the brain MRI appearance of extensive subcortical and periventricular white matter loss and cystic changes with generalized atrophy. This is similar to appearance reported by other authors such as Appignani, et al, Schuirer, et al, and Ngu, et al who reported the brain MRI findings in cases of Molybdenum cofactor deficiency. They described a diffuse pattern of brain atrophy with arrested development of myelination and destructive as well as cystic white matter changes (10, 11, 12). Although neither the clinical presentation nor the MRI appearance is pathognomonic for Molybdenum cofactor deficiency, we suggest that the combination of both in the absence of documented hypoxic ischemic injury is characteristic enough to warrant screening for Molybdenum cofactor deficiency.

Third is the close mimicry of Molybdenum cofactor clinical picture to neonatal hypoxic ischemic encephalopathy. Topku, et al, have previously reported on three cases of molybdenum cofactor deficiency presenting as hypoxic ischemic encephalopathy (13). It becomes critical that such clinical presentations are not assumed to be caused by undocumented hypoxic ischemic injury, particularly that these patients are usually products of healthy pregnancies and are born with adequate Apgar scores (1). Losing the diagnoses to the assumption of hypoxic ischemic injury may have significant consequences: the opportunity to counsel parents regarding the risk of recurrence in future pregnancies is lost, the attribution to hypoxic ischemic injury may be grounds for litigation and malpractice claims, and the future progression of the disease may not be closely followed due to the assumption of a static brain injury. Low uric acid levels in the blood, and as in our case, urine, should point to the diagnoses of molybdenum cofactor deficiency (14). This along with detection of sulfite in fresh urine dipstick should help distinguish both entities and prompt further confirmation. Moreover, emerging research on animal models provides hope for future availability of effective treatments in humans. Kugler, et al, recently reported on the long term rescue of a mouse model of Molybdenum cofactor deficiency type A, the most frequent form of this autosomal recessive disorder, by adeno-associated virus mediated gene transfer (5), this provides hope for future therapeutic options in homozygous humans, hence, increased awareness and early identification of these patients may then have significant implications.

Fourth are some atypical features of our case such as the normal lactate and the absence of lens dislocation; the former being usually elevated, and the later being found in nearly all patients after neonatal period, although Parini, et al, have reported a case that developed lens dislocation as late as eight years of age (15). Atypical presentations of molybdenum cofactor deficiency have also been reported by others, such as a case of molybdenum cofactor deficiency associated with Dandy-Walker malformation presenting with severe metabolic acidosis and intracranial hemorrhage (16), also a case presenting as neonatal hyperekplexia (17), indicating a wide spectrum of clinical presentations in these patients.

Finally, our patient's genotype revealed a 21 base pair deletion in exon 4 of the MOCS1 gene (c.603del21); this is a novel mutation not previously reported to the best of our knowledge. The result of this deletion is a lack of expression of protein MOCS1A. Molybdenum cofactor deficiency type 1A affects the early steps of the Molybdenum cofactor biosynthesis, similar to patients with MOCS1B gene defects (1, 5). It is not clear whether such a large deletion will have any genotype-phenotype impact on severity, noting that our patient has survived beyond one year of age so far. Deletions of sulfite oxidase genes have been reported to have led to death at ten weeks (18), and 32 months of age (19).

On the other hand, Leimkuhler, et al, have reported on mutations in MOSC1 and MOSC2 which create a stop codon, or abolish the binding ability of molybdopterin synthase (20), the clinical significance of these in vitro characterizations warrants more study. Another important factor in the genetic aspect is providing for prenatal genetic analysis in cases of molybdenum cofactor deficiency, as first reported by Reiss, et al (21), this is particularly important in consanguineous marriages.

Conclusion

We report a novel mutation in a newborn with typical clinical and radiological features of Molybdenum cofactor deficiency, and discuss the clues that raise suspicion for the diagnoses. Although not pathognomonic, we suggest that in the absence of a clear history of hypoxic ischemic injury, all newborns presenting with a triad of early seizures, encephalopathy, and destructive white matter cystic changes should be screened for Molybdenum cofactor deficiency, particularly with family history of consanguinity. Encouraging results of rescue therapies for animal models of Molybdenum cofactor deficiency provide hope of this becoming a treatable disorder in the future.

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