Cerebrotendinous Xanthomatosis Revealed in Drug-Resistant Epilepsy Diagnostic Workup

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Abstract: Cerebrotendinous xanthomatosis (CTX) is a treatable disorder of bile acid production caused by mutations in the mitochondrial enzyme sterol 27-hydroxilase. This inborn error of bile acid metabolism results in lipid pathologic accumulation in multiple tissues. Progressive neuropsychiatric disturbances are a frequent manifestation of this disease. Although seizures have been frequently noted as part of CTX manifestations, there have not been reports of CTX being diagnosed in drug-resistant epilepsy diagnostic workup or of seizure response to chenodeoxycholic acid treatment. Here, the authors present a case of a drug-resistant epilepsy patient with a complex phenotype where a diagnosis of CTX was done and showed a significant reduction in seizure frequency after chenodeoxycholic acid supplementation. This report illustrates the importance of considering treatable neuro-metabolic disorders in epileptic patients showing complex phenotypes.

Key Indexing Terms: Epilepsy; Cerebrotendinous xanthomatosis; Chenodeoxycholic acid; Genetics; Inborn errors of metabolism. [Am J Med Sci 2011;XXX(XX):1–1.]

Cerebrotendinous xanthomatosis (CTX) is a treatable disorder of bile acid production caused by mutations in the mitochondrial enzyme sterol 27-hydroxilase. Its symptomatology usually starts during the first decade of life which characteristically includes the presence of chronic diarrhea and bilateral cataracts. A progressive neurological deterioration manifesting as learning difficulties, behavioral changes and ataxia is frequently observed. Although seizures have been reported as part of CTX presentation, there have not been reports of drug-resistant epilepsy caused by CTX and its treatment response to chenodeoxycholic acid (CDCA) supplementation. Here, we describe a case of an Argentinian boy who was diagnosed CTX during epilepsy diagnostic workup.

CASE REPORTS

A 16-year-old boy born from a consanguineous marriage was referred to our epilepsy center with a diagnosis of drug-resistant epilepsy. Although his magnetic resonance imaging (MRI) showed signs of unilateral hippocampal sclerosis, there was a history of particular medical conditions that make us suspect a complex etiology for their epilepsy. The first clinical manifestation was chronic diarrhea from early infancy persisting until the time of consultation. Bilateral posterior subcapsular cataracts were found at the age of 6 years and removed a year after. Learning difficulties, attention deficit and marked hyperactivity were reported at school age. He had to be institutionalized because of these behavioral problems. His first seizure was at the age of 7 years. Although it was difficult to get a clear description of the seizure semiology from patient and family, anamnesis and findings from an inpatient video-EEG suggested a diagnosis of temporal lobe epilepsy. Epilepsy remained resistant to different anticonvulsive drugs used which included classical and new medicines. The patient presented to our center with a seizure frequency of 3 to 4 a month. His physical examination showed a normal height, long upper extremities, scoliosis, lumbar hyperlordosis and brownish dental enamel. There were not tendon xanthomas. Neurological examination was remarkable for the presence of limb ataxia, action tremor, mild multidirectional nistagmus, osteotendinous reflexes diffusely hyperactive and uncoordinated gait. X-rays of both legs did not show alterations. EEG showed a disorganized background with slow waves predominantly localized in right temporal electrodes. T1-W MRI showed diffuse cortical atrophy, and T2-W MRI revealed a hyperintense right hippocampus. The urinary bile acid profile showed increased 27-norcholestanepentol and cholestanepentol levels. Sequencing the 8 exons of CYP27A1 gene revealed the presence of c.1213C>T (see Figure 1) mutation in homozygosis which resulted in the pathogenic substitution of Arginine with tryptophan at codon 405, already described in patients from different countries. Treatment with 750 mg/day CDCA was followed by progressive improvement of diarrhea and a significant reduction in seizure frequency (1 a month or less). Urinary bile acid profile was normalized after 3 weeks of treatment.

DISCUSSION

First description of CTX was made by Van Bogaert et al in 1937. The discovery of the pathogenic molecular defect in CYP27A1 leads to an increase in worldwide diagnosis of CTX, including Argentina. Although EEG abnormalities were classically described in CTX, epilepsy was not considered a major feature of the disease until recently. However, there have not been reports of CTX recognized in the diagnostic workup of a drug-resistant epileptic patient or of seizure response to CDCA treatment.

Different mechanisms have been hypothesized to explain CTX pathophysiology. Among them, circulating high levels of bile alcohols could damage blood-brain barrier (BBB), leading to abnormal and toxic brain levels of cholesterol and low-density lipoprotein cholesterol Apolipoprotein B. BBB dysfunction has been proposed as a common pathogenic injury in focal epilepsy. Moreover, bile acids mediated damage of BBB has been proposed as an epilepsy experimental model.

On the other hand, steroids might overexpress ABC2 gene which has been implicated in epilepsy treatment failure processes. Thus, it is tempting to propose that drug-resistance
epilepsy experienced by our patient could be a consequence of sterols disturbances provoked by CYP27A1 mutation and partial recovery secondary to a better sterol metabolism in response to CDCA treatment. In conclusion, this report illustrates the importance of considering neurometabolic disorders such as CTX in epileptic patients showing complex phenotypes. This is particularly relevant when a specific treatment is available which is benefit for not only the underlying condition but also the epilepsy itself.

REFERENCES


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