CASE REPORT

CEREBROTENDINOUS XANTHOMATOSIS: PRESENTED AS NEUROPSYCHIATRIC MANIFESTATION

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INTRODUCTION: Cerebrotendinous Xanthomatosis (CTX) is a rare autosomal recessive lipid storage disease first described in 1937 by van Bogaert et al⁽¹⁾ In 1974, Setoguchi et al. made the finding that CTX is linked to a defect in bile acid synthesis.⁽²⁾ It is caused by mutations in the CYP27A1 gene, which lead to deficiency of the mitochondrial enzyme, sterol 27-hydroxylase, resulting in the accumulation of cholestanol in the serum and many affected tissues⁽³⁾ CTX manifests as tendon xanthomas, juvenile cataracts and seizures multiple progressive neurological symptoms. Systemic manifestations including osteoporosis⁽⁴⁾ heart involvement and premature atherosclerosis are often found. Chronic infantile diarrhea due to defective bile acid synthesis, is often the earliest symptoms of CTX.⁽⁵⁾ Replacement treatment with chenodeoxycholic acid (CDCA) has been reported to improve clinical symptoms of CTX.

CASE REPORT: A 20-year-old male presented to our hospital with history of decrease in school performance since the age of 11 years. Later on he developed forgetfulness and change in behavior. Two year later he developed one episode of generalized tonic-clonic seizure. Seizures started when he was 13 years old. At the onset, his parents reported one seizure per week. His family history was unremarkable.

In the following two years, his seizures became more frequent, requiring hospitalizations. Levetracetam (1000mg daily) was started but patient developed seizures due to poor compliance. Since two years patient was not on any antiepileptic drug. Patient developed three episodes of GTCS before hospitalization. During hospital stay valproic acid started with good seizure control.

Bilateral cataracts were diagnosed when he was seven and operated for cataract at the age of eight years. Since the age of fourteen years patient developed ataxic gait and change in voice. When he was seventeen, there was a progressive increase of volume in the bilateral calcaneal and right patellar regions, and tendon xanthomas were identified. (Fig.1) In Neurological examination his MMSE was 18 and cerebellar signs were present.

Brain magnetic resonance imaging (MRI) disclosed white matter lesions and bilateral symmetrical hyperintensity in both dentate nuclei. (Fig.2) electroencephalograms (EEG) during asymptomatic periods showed no epileptic discharges. Ultrasonography of bilateral ankle shows well defined homogeneous iso-hyperechoic lesion likely benign etiology. General metabolic screening and cholesterol profile were total cholesterol 220mg/dl TGs-83mg/dl, HDL-41.6mg/dl, LDL -185mg/dl routine blood reports were normal.

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Figure 1

Figure 2

DISCUSSION: Cerebrotendinous xanthomatosis is an autosomal recessive lipid storage disorder caused by mutations in CYP27A gene, located in 2q33-qter, which codes for hepatic mitochondrial sterol 27-hydroxylase, involved in the normal biosynthesis of bile acids.⁽⁶⁾ The major symptoms are produced by accumulation of cholestanol and cholesterol, particularly in the nervous system, atherosclerotic plaques, and bone and tendon xanthomas⁽⁷⁾ Classic clinical features resemble progressive cerebellar ataxia associated with premature juvenile-onset cataracts and intractable chronic diarrhea, jaundice in infancy, and later, with tendon xanthomas (prominently in the Achilles tendon, in tibial tuberosity, in the triceps brachialis, and in the extensor tendons of the fingers), osteoporosis, and myocardial infarction Tendon xanthomas typically develop after the second decade.

Generally, systemic symptoms develop earlier than neurologic signs.⁽⁸⁾ Neuropsychiatric manifestations are rarely present as early symptoms in CTX. Psychiatric manifestations in CTX follow a bimodal/bitemporal pattern, that is, they would either appear early in the disease course in the form of a behavioral/personality disorder associated with learning difficulties or mental retardation, or they would manifest in advanced disease in the context of dementia as rich neuropsychiatric

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syndromes, such as frontal, orbitofrontal or front temporal syndromes of cortico-subcortical dementia encompassing affective/mood disorders, psychotic disorders or behavioral/ personality disturbance⁽⁹⁾ the main psychiatric symptoms are aggressive behavior, irritability and personality changes, paranoid delusion, and suicidal tendency catatonia and occasional hypersexuality⁽¹⁰⁾ Other neuropsychiatric manifestations include spastic paresis, frontal lobe dementia, extrapyramidal symptoms, mental retardation, delusions, depression, agitation, and hallucinations can also be seen.

MRI shows diffuse or focal hypersignals in the white matter affecting the dentate nuclei and cerebellar white matter in T2-weighted image sometimes with the globus pallidus involvement. Laboratory studies show elevated plasma cholestanol levels in gas chromatography or HPLC-a hallmark of the disease, with normal or decreased cholesterol levels. Cerebrotendinous xanthomatosis treatment includes chenodeoxycholic acid and HMG-CoA-reductase inhibitors. Early diagnosis of CTX is crucial, because early treatment with CDCA leads to improvement or even prevention of CTX-associated symptoms.

REFERENCES:

1. Van Bogaert H. J. Scherer, L., E. Epstein, Une forme cerebrale de la cholestérinose generalisée. Masson et Cie, Paris, 1937.
2. Setoguchi T., G. Salen, G. S. Tint, E. H. Mosbach, A biochemical abnormality in cerebrotendinous xanthomatosis: impairment of bile acid biosynthesis associated with incomplete degradation of the cholesterol side chain, J. Clin. Invest. 531 (1974) 1393–1401.
3. Gallus GN, Dotti MT, Federico A. Clinical and molecular diagnosis of cerebrotendinous xanthomatosis with a review of the mutations in the CYP27A1 gene. Neurol Sci 2006; 27: 143–9.
4. Federico A., M. T. Dotti, F. Lore, R. Nuti, Cerebrotendinous xanthomatosis: pathophysiological study on bone metabolism, J. Neurol. Sci. 115 (1993) 67e70.)
5. Cruysberg R., Cerebrotendinous xanthomatosis: juvenile cataract and chronic diarrhea before the onset of neurologic disease, Arch. Neurol. 59 (2002) 1975.
6. Rafiq M, Sharrack N, Shaw PJ, Hadjivassiliou M. A neurological rarity not to be missed: cerebrotendinous xanthomatosis. Pract Neurol 2011; 11 (5): 296–300. Gallus GN, Dotti MT, Federico A. Clinical and molecular diagnosis of cerebrotendinous xanthomatosis with a review of the mutations in the CYP27A1 gene. Neurol Sci 2006; 27 (2): 143–9.
7. Federico A, Dotti MT. Cerebrotendinous xanthomatosis: clinical manifestations, diagnostic criteria, pathogenesis, and therapy. J Child Neurol 2003; 18 (9): 633–8.
8. Castelnovo G, Jomir L, Bouly S. Cerebrotendinous xanthomatosis. J Neurol Neurosurg Psychiatry 2003; 74 (9): 1335.
9. Fraidakis MJ: Translational Psychiatry (2013) 3, e302; doi: 10.1038/tp.2013.76.
10. Berginer VM, Foster NL, Sadowsky M, Townsend 3rd JA, Siegel GJ, Salen G.
11. Psychiatric disorders in patients with cerebrotendinous xanthomatosis. Am J Psychiatry 1988; 145: 354–357.

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