Cerebrotendinous xanthomatosis and infertility: a case report

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Abstract

Cerebrotendinous xanthomatosis is a lipid storage disorder that causes neurological, ophthalmic, vascular, and musculoskeletal disorders due to the deposition of cholesterol in the tissues. Hence, we report clinical and imaging of a 31-year-old mentally retarded man with cerebellar ataxia, bilateral swelling of the posterior aspect of Achill, and infertility.

1. Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare inherited disorder of lipid storage characterized by abnormal deposition of cholestanol and cholesterol in multiple tissues, particularly in the brain and tendons[1]. Mutations in *CYP27A1* lead to a deficiency in sterol 27-hydroxylase [2]. The deficiency of this enzyme prevents cholesterol being converted into bile acid chenodeoxycholic acid. The block in the synthesis of this bile acid creates the accumulation of bile acid pathway intermediates and cholestanol in the blood and tissues of the affected individuals. The balance between synthesis and catabolism of cholesterol should be tightly regulated to ensure normal cellular processes [3]. Up to now, more than 400 cases have been reported worldwide [4]. The clinical manifestations usually start at infancy and develop during the first and second decades of life [4]. Patients with CTX demonstrate diverse manifestations with multi-organ involvement and an extensive range of neurological and non-neurological symptoms. The neurological features of CTX reported in the literature include pyramidal and cerebellar signs, sensory-motor peripheral neuropathy, intellectual disability, and dementia. Common non-neurological disorder include early-onset bilateral cataract in childhood, formation of tendon xanthomas (most often in the Achilles' tendons), and diarrhea[5,6]. In addition, patients with CTX suffer from severe premature atherosclerosis, pulmonary involvement, and osteoporosis with repeated bone fractures [7]. A diagnosis of CTX is made based on clinical findings, biochemical testing, neuroimaging, and molecular genetic analysis [8,9]. This is the first report of a CTX patient with infertility due to azoospermia.

2. Case presentation

A 31-year-old mentally retarded man was referred to our neurologic clinic with a progressive gait disorder, impaired balance, and repeated falling episodes. The patient was the third child of kinship marriage. He was delivered following a normal term pregnancy with normal birth weight and height. No history of atheromatous disease or intractable infantile-onset diarrhea was distinguished. At the age of five, he developed a blurred vision, which was diagnosed as a bilateral cataract. The patient was a school dropout due to intellectual and neuropsychiatric disability. He had developmental delays in the mental functioning and speech with a normal physical growth. At the age of 20, he developed bilateral tendinous swelling of the posterior part of the ankles that became worse over time. He complained of severe gait disturbance and ataxia since 3-4 years ago. He had frequent falling episodes resulting in multiple bone fractures. Gait disorder progressed gradually and he became non-ambulatory and wheelchair-bound. Physical examination demonstrated bilateral and symmetrical painless hypertrophy of the Achilles tendons (Fig.1). Neurological examination showed muscle weakness predominant in the distal muscles of upper and lower limbs (MRC score of 3 in the foot

dorsiflexion and MRC score 2 in the finger adduction and abduction), hypertonia, brisk deep tendon reflexes, bilateral positive Babinski reflexes, and ankle clonus. The finger to nose was normal but the heel to shin was abnormal bilaterally. The laboratory results were normal for the thyroid, liver, and kidney function, serum electrolytes, and triglyceride and cholesterol level. A brain magnetic resonance imaging (MRI) discovered cerebral and cerebellar atrophy, high-intensity areas in the dentate nuclei, and symmetric hyperintensities in the cerebellar deep white matter and paraventricular white matter on T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) images with corresponding hypointensities on T1-weighted (T1W) images (Fig. 2). Ultrasonography demonstrated focal areas of hypoechogenicity on the bilateral Achilles tendons measuring 3, 7, 9, 12, and 16 mm on the right and 8, 15, 11, and 14 mm on the left side. Whole exome sequencing identified a homozygous splicing mutation, NM_000784: exon3: c.465C>A; p. Tyr155* in *CYP27A1*gene compatible with a diagnosis of CTX. The patient was married but he was infertile. Sex hormones tests were normal. Testicular ultrasound showed that the size of the testes was in the lower limit of normal range with a normal epididymis and vein plexus. Semen analysis showed azoospermia. Analysis of the most common Y chromosome microdeletions using multiplex polymerase chain reaction and gel electrophoresis showed no microdeletions in AZFa, AZFb, and AZFc sub-regions of the long arm of chromosome Y.

3. Discussion

Cerebrotendinous xanthomatosis is a rare autosomal recessive genetic disorder in which cholesterol cannot be converted into bile acids due to mutations in the CY27A1 gene that encodes the mitochondrial enzyme sterol 27-hydroxylase [3]. Half of the mutations in CYP27A1 have been detected in exons 6–8, 16% in exon 2, and 14% in exon 4 [10,11]. The mean age at onset of clinical manifestations has been reported 19 years, but most patients are diagnosed late (about 35 years) [12]. In our case, the patient had developmental delays in mental functioning and speech with neuropsychiatric disorders in childhood. In terms of clinical symptoms, patients with CTX often manifest non-neurological and neurological symptoms such as chronic diarrhea, cataracts, tendon xanthomas, ataxia, corticospinal tract involvement, and mental disorder. The initial presentation of non-neurological symptoms in our patient was a cataract that was revealed at the age of 5 years. In this patient, a CYP27A1 mutation was identified in exon 3. The characteristic brain MRI findings are T2/FLAIR hyperintensities in the bilateral dentate nuclei, adjacent cerebellar white matter, basal ganglia, spinal cord, and periventricular white matter as well as cerebellar atrophy. Our patient had T2/FLAIR hyperintensities in the bilateral dentate nuclei, white matter alternations, and cerebellar atrophy [13–15]. One of the symptoms in our case was infertility, which was not reported in previous studies. The cause of infertility in this patient was non-obstructive azoospermia due to a lack of spermatogenesis in the testicles. The sex hormones, prolactin, and testosterone levels were normal. Co-occurrence of azoospermia in CTX patients may be due to the accumulation of cholesterol in the scrotum sac affecting spermatogenesis and the function of the male reproductive system. Cholesterol has been revealed to cause a reduction in sperm kinetics and has negative effects on Leydig and Sertoli cells secretory capacity in rabbits. Previous studies found that changed lipid metabolism in seminal plasma plays a role in male infertility [16–18]. Accumulation of cholesterol in tissues is one of the obvious symptoms of CTX, but the resultant functional abnormalities are unknown. The relationship between infertility and cholesterol should be further investigated since it has not been addressed so far.

Conclusion

CTX was diagnosed based on clinical manifestations, biochemical analysis, neuroimaging, and molecular genetic investigation. One of the detected disorders in our patient was infertility. To date, no study has investigated the relationship between infertility and azoospermia with CTX. The association between CTX and infertility is unclear. Further research is warranted to investigate the association between azoospermia and CTX.

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Figure 1. Swelling on the posterior aspect of left Achill tendon

Figure 2. Axial image of brain MRI showing bilateral FLAIR hypersignal of the dentate nuclei and periventricular