Case Report

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Case Report and Current Literature Review of Adult Cerebrotendinous Xanthomatosis: Evaluation of Treatment Response Based on Gait Analysis Adult Cerebrotendinous Xanthomatosis

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Abstract

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive neurometabolic disease caused by a mutation in the *CYP27A1* gene and deficiency of the mitochondrial 27-sterol hydroxylase enzyme. Deficiency of this enzyme leads to the accumulation of cholestanol and cholesterol in various systems (brain, lens, tendons), resulting in chronic diarrhea, juvenile cataracts, tendon xanthoma, and progressive neurodegeneration. Neurological manifestations include ataxia, dystonia, parkinsonism, seizures, dementia, and peripheral neuropathy. We report a 55-year-old woman who presented with chronic and progressive difficulty walking with a history of juvenile cataracts and a family history of parkinsonism. She was found to have cognitive decline, pyramidal-cerebellar signs, and xanthomas at her distal extremities. The diagnosis of CTX was confirmed by a homozygous pathological variant of the *CYP27A1* gene, and treatment with chenodeoxycholic acid was initiated. Because CTX is treatable and preventable, accurate diagnosis and initiation of treatment at the earliest stages are crucial.

Keywords: Rare disease, xanthoma, treatment, chenodeoxycholic acid, gait analysis

Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive neurometabolic disease. Cerebrotendinous xanthomatosis develops due to a deficiency of the mitochondrial 27-sterol hydroxylase (CYP27) enzyme, which is necessary for bile acid synthesis, and mutations in the *CYP27A1* gene. First described by Van Bogaert in 1937, deficiency of the CYP27 enzyme leading to the accumulation of cholestanol and cholesterol in various systems (brain, lens, tendons), resulting in chronic diarrhea, juvenile cataracts, tendon xanthomas, and various progressive neurological symptoms (1). Neurological manifestations include ataxia, dystonia, parkinsonism, seizures, dementia, and peripheral neuropathy (2). According to our knowledge, approximately 500 cases of CTX have been reported up to date (3). The small number of reported cases suggests that the disease may not have been recognized well and may not have been adequately diagnosed. The heterogeneity of clinical findings and the absence of classical symptoms (juvenile cataracts and tendon xanthomas) in every case or their occurrence after the onset of neurological symptoms can make diagnosis challenging. However, early diagnosis and prompt initiation of appropriate treatment are crucial to prevent potential severe neurological consequences.

Herein, we aimed to describe the clinical, electrophysiological, and genetic characteristics of a 55-year-old female patient diagnosed with CTX and to report her treatment response via gait analysis.

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Case Presentation

A 55-year-old female patient presented with progressive walking difficulties, instability, and forgetfulness that persisted for over 10 years. Her walking condition worsened over the last five months, and the frequency of falls increased. She was a primary school student with a history of normal neurodevelopmental milestones. There was no history of neonatal jaundice or chronic diarrhea during childhood. It was later found out that she underwent bilateral cataract surgery for juvenile cataracts at the age of 8. In her family history, there were symptoms of Parkinsonism in her sister (Figure 1).

During the neurological examination, she presented with cerebellar-type dysarthria, bilateral dysmetria, dysdiadochokinesia, and ataxic gait. The plantar reflexes were bilaterally extensor, and the deep tendon reflexes were hyperactive. The Mini-Mental State Examination revealed moderate cognitive impairment (a score of 13). On physical examination, smooth, firm, ovoid-shaped, non-tender swellings (xanthomas) were observed on the left triceps tendon, bilateral tuberosity of the tibia, and Achilles tendons (Figure 2).

All laboratory tests were within normal limits, including complete blood counts, biochemical tests, and triglyceride and cholesterol levels. Magnetic resonance imaging (MRI) scans showed signs of cerebellar atrophy and hyperintense lesions on T2-weighted imaging in the left internal capsule's posterior limb, the mesencephalon's anterior aspect, dentate nuclei, and deep cerebellar white matter. T1-weighted imaging revealed hypointense lesions in these areas. Additionally, FLAIR imaging revealed hypointense areas in the dentate nuclei and deep cerebellar white matter (Figure 3).

Electromyography (EMG) revealed sensory-predominant axonal polyneuropathy in the lower extremities. Genetic testing was performed with a presumptive diagnosis of CTX. Complete gene sequencing of CYP27A1 (Koc University Hospital, Genetic Diseases Evaluation Center) revealed a homozygous mutation (pathogenic variant) [CYP27A1 c.646G>C (p. Ala216Pro)] compatible with CTX (OMIM 2131700). The same genetic mutation was detected in her sister by Sanger DNA sequencing analysis. The treatment was initiated with a gradual increase in the dosage of chenodeoxycholic acid (CDCA) to 750 mg/day, alongside simvastatin (20 mg/day). Walking and balance analyses were performed before treatment initiation and at the 4th and 12th weeks of treatment. Due to the patient's inability to comprehend commands and cooperate with the analysis before treatment, the assessments could not be conducted. At weeks 4 and 12 of treatment, sensory-based gait analysis and balance functions were evaluated using APDM motion sensors (Noraxon-myoMOTION Research Pro System) and Zebris gait analysis. Zebris gait analysis showed a 135.3% reduction in the center of pressure (COP) oscillation area (from 1468 to 690 mm^2) between the two assessments, with an increased weight bearing on the rear foot (14-29%), indicating that the patient exhibited a more stable and balanced posture while standing (Figure 4).

In the sensory-based gait analysis using motion sensors, comparing two assessments, spatial-temporal walking parameters (such as speed, cadence, step duration, swing, and stance phases) remained similar, but the step width was found to have increased by 19.4% (12±4 to 14±4). At the clinical follow-up in the 4th week of treatment, significant improvements in walking balance and intellectual capacity were observed. Additionally, a reduction in xanthoma size and decreased rigidity compared with the initial examination were noted. However, by the 12th week follow-up, xanthomas appeared more consolidated than

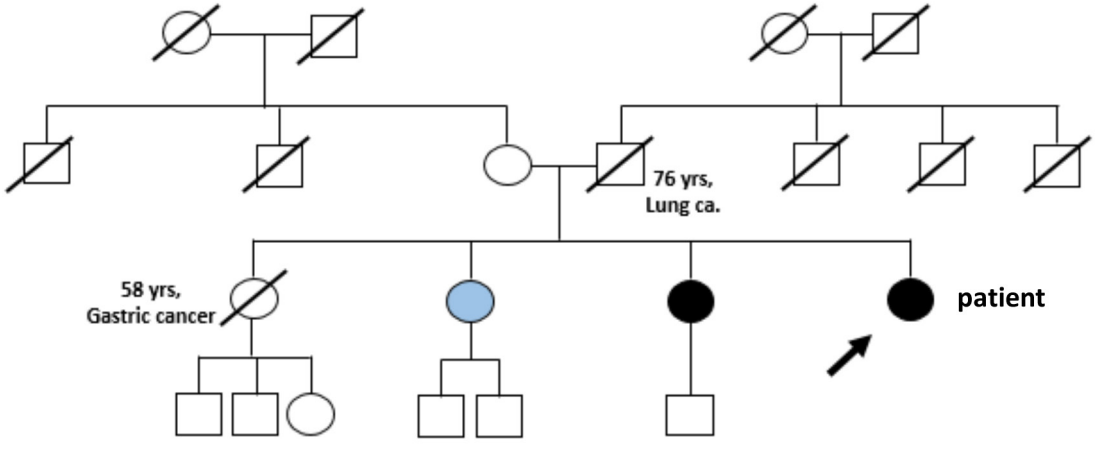

Figure 1. Pedigree, patient and her sister with homozygous pathological variant in *CYP27A1* gene

in the previous evaluation, and no changes were observed in walking and balance. Upon detailed questioning, it was found that the patient had discontinued CDCA treatment due to nausea and indigestion. Emphasizing the importance of adhering to the recommended doses and regimens, the medication dosages were readjusted, and the clinical follow-ups were continued.

Discussion

Cerebrotendinous xanthomatosis, also known as cerebral cholesterinosis, is a rare autosomal recessive disease caused by a mutation in the *CYP27A1* gene, resulting in a deficiency of the mitochondrial 27-sterol hydroxylase enzyme (1). This leads to decreased synthesis of cholic acid and chenodeoxycholic acid and accumulation of cholestanol via upregulation of 7α-hydroxy-4-cholesten-3-one (4). The abnormal accumulation of cholesterol and cholestanol compounds in various tissues leads to multisystemic involvement and heterogeneous clinical symptoms, primarily affecting the neurological, ocular, and musculoskeletal systems (2). The characteristic features of the disease are cataracts (80.3%), cognitive

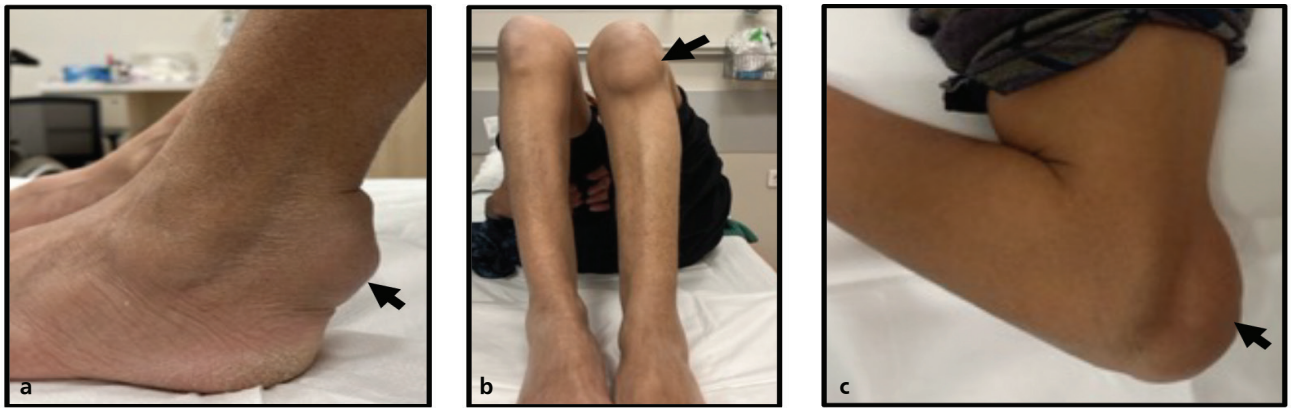

Figure 2. Xanthomas on the left achilles tendon **(a)**, bilateral tuberosity of the tibia **(b)**, and left triceps tendon **(c)**

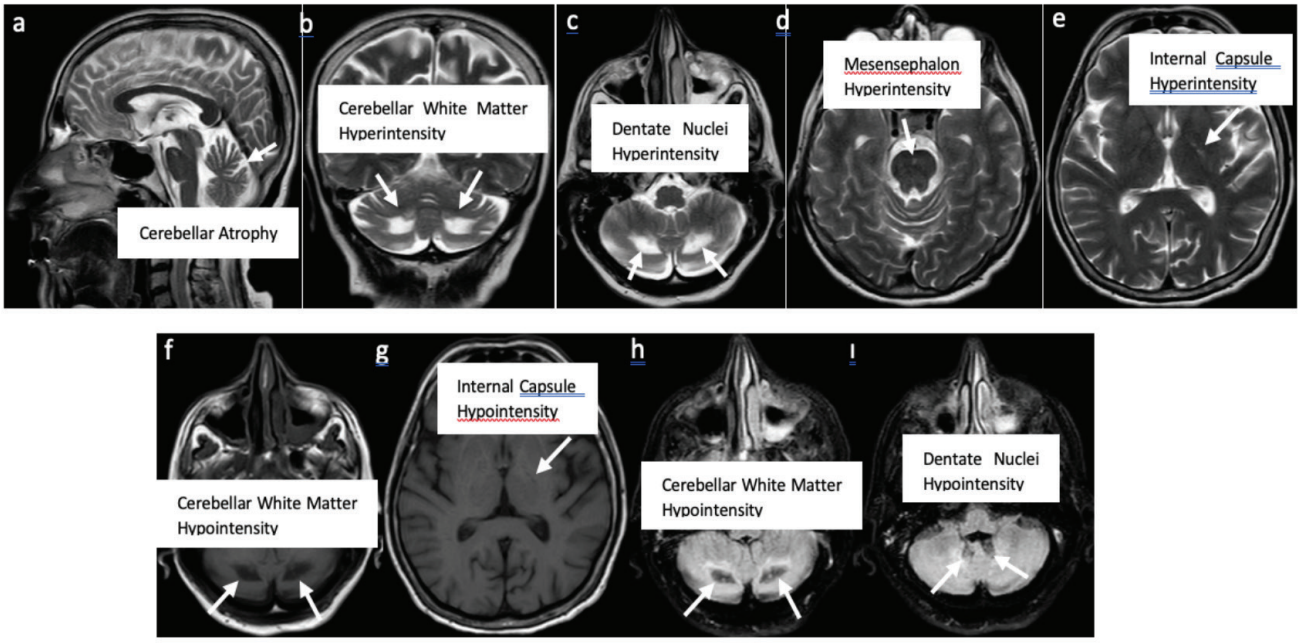

Figure 3. a) Cerebellar atrophy. **b-e)** Hyperintense lesions on T2-weighted imaging in the deep cerebellar white matter, dentate nuclei, anterior of the mesencephalon and posterior limb of the left internal capsule. **f, g)** Hypointense lesions on T1-weighted imaging in the deep cerebellar white matter and posterior limb of the left internal capsule. **h, ı)** Hypointensity areas in the deep cerebellar white matter and dentate nuclei on FLAIR imaging

FLAIR: Fluid-attenuated inversion recovery

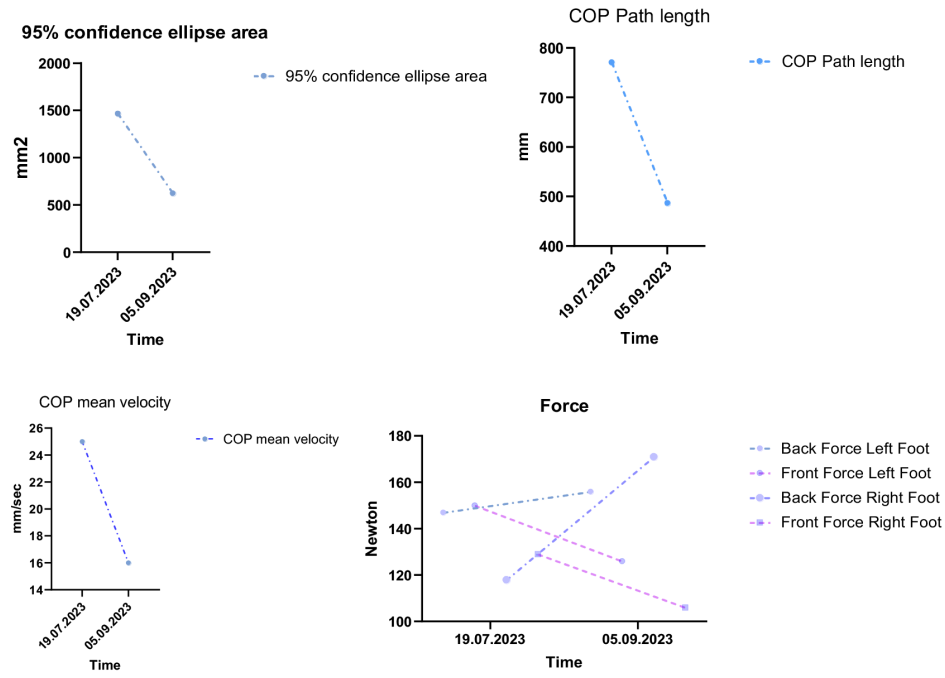

Figure 4. Zebris gait analysis data; 135.3% reduction in the COP oscillation area (135.3%, 1468 to 690 mm²) and increased weight-bearing on the rear foot (14-29%)

COP: Center of pressure

impairment (75.9%), pyramidal signs (72.9%), xanthomas (66.5%), cerebellar ataxia (63.9%), peripheral neuropathy (52.9%), chronic diarrhea (47.6%), seizures (27.4%), and parkinsonism (14.9%) (5). Additional findings include atherosclerosis, cardiovascular disease, osteoporosis, and pulmonary disease (1). In our case, there was a history of juvenile cataract, cognitive impairment, pyramidal-cerebellar signs, polyneuropathy, and xanthoma, but no history of seizures or chronic diarrhea. The patient's sister had Parkinson's disease. Typical MRI findings include cerebral and cerebellar atrophy, hyperintense lesions on T2/fluid-attenuated inversion recovery (FLAIR) sequences, and hypointense lesions on T1-weighted sequences in the periventricular white matter, posterior limb of the internal capsule, cerebral peduncles, anterior pons, cerebellar parenchyma, and dentate nuclei. These lesions appear due to demyelination and axonal damage caused by lipid accumulation. In T2/FLAIR sequences, dentate nuclei may also appear hypointense due to demyelination, hemosiderin deposition, microcalcifications, necrosis, and cystic space formation (6). Diagnosis of the disease is made through clinical, examination, biochemical, imaging, and histopathological findings and the demonstration of homozygous or compound heterozygous mutations in the *CYP27A1* gene (7). In clinical practice, the Mignarri et al. (8) predictive index, which is composed of family history, systemic features, and neurological signs of involvement, may be used to assess the likelihood of a CTX diagnosis. The diagnostic criteria for CTX were established by Stelen et al. (9) and include the measurement of plasma cholestanol levels. However, because of increased opportunities for genetic testing, a diagnosis of the disease can now be made without measuring plasma cholestanol levels. In our case, although we planned to assess plasma cholestanol levels during the diagnostic process, the inability to measure cholestanol levels at our hospital and the ability to perform genetic testing allowed us to establish a diagnosis without measuring cholestanol levels. Chenodeoxycholic acid treatment normalizes cholestanol concentrations, halting disease progression and preventing permanent neurological damage, thereby stabilizing the disease. In addition to CDCA, treatments such as HMG-CoA reductase inhibitors, cholestyramine, and ursodeoxycholic acid have been used in these patients but have not shown significant clinical differences. Early initiation of therapy can reverse or even prevent the progression of neurological symptoms in CTX. Studies have shown that patients starting treatment after the age of 25 years have worse outcomes than those starting therapy at younger ages (10). Age at diagnosis and treatment initiation, brain magnetic resonance imaging findings, and response to CDCA treatment are prognostic factors (1).

In conclusion, we described a 55-year-old adult female patient with CTX who had a CDCA treatment response verified through gait analysis. CTX should be considered among hereditary neurometabolic diseases in patients with a history of juvenile cataracts, pyramidal-cerebellar system signs, ataxia, dystonia/parkinsonism, and/or cognitive impairment, along with observed tendon xanthomas. CDCA treatment should commence as early as possible. Our case demonstrates that CDCA treatment led to an improvement in disease symptoms and prevented irreversible neurological damage.

Footnote

Informed Consent: Informed consent form the patient has been obtained.

Authorship Contributions

Surgical and Medical Practices: E.B., S.U., S.A., F.F.O., Concept: E.B., S.U., F.F.O., Design: E.B., S.U., F.F.O., Data Collection or Processing: E.B., S.U., S.A., F.F.O., Analysis or Interpretation: E.B., S.A., F.F.O., Literature Search: E.B., S.U., Writing: E.B., S.U., S.A., F.F.O.

Conflict of Interest: No conflicts of interest were declared by the authors.

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