Different phenotypes in identical twins with Cerebrotendinous Xanthomatosis: case series

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Acknowledgement

This study was funded by Hungarian Brain Research Program – Grant No. KTIA_NAP_13-A_II/18. Dénes Zádori was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences. The linguistic corrections were made by a native English reader, Jennifer Tusz from Canada.

Conflict of interest

The authors declare that they have no conflict of interest.

Abstract

Cerebrotendinous Xanthomatosis (CTX) is a rare genetically determined error of metabolism. The characteristic clinical symptoms are diarrhea, juvenile cataracts, tendon xanthomas and neuropsychiatric alterations. The aim of this study is to present a pair of identical adult twins with considerable differences in the severity of phenotype. With regards to neuropsychiatric symptoms, the predominant features were severe Parkinsonism and moderate cognitive dysfunctions in the more affected individual, whereas these alterations in the less affected patient were only very mild and mild, respectively. The characteristic increase in the concentrations of serum cholestanol and the lesion volumes in dentate nuclei in the brain assessed with magnetic resonance imaging were quite similar in both cases. The lifestyle conditions, including eating habits of the twin pair, were quite similar as well, therefore currently unknown genetic modifiers or certain epigenetic factors may be responsible for the differences in severity of phenotype. This case series serves as the first description of an identical twin pair with CTX presenting heterogeneous clinical features.

Keywords: Cerebrotendinous Xanthomatosis, Parkinsonism, cognitive dysfunction, identical twins, heterogeneous phenotype

Introduction

Cerebrotendinous Xanthomatosis (CTX) is an autosomal recessively inherited condition belonging to the group of inborn errors of metabolism [1]. It affects approximately 1 to 2 out of 100,000 individuals. The pathogenic mutations are located in the *CYP27A1* gene mapped to 2q35 [2,3]. The gene product, sterol 27-hydroxylase, which is expressed in the central nervous system, liver, lungs, duodenum and endothelial cells, takes part in the appropriate production of bile acids from cholesterol [4]. Sterol 27-hydroxylase deficiency results in the accumulation of 7α-hydroxy-4-cholesten-3-one and its metabolites, including cholestanol, and also results in the insufficient production of chenodeoxycholic acid [1]. The main characteristic signs and symptoms of CTX are diarrhea, juvenile cataracts, tendon xanthomas and neuropsychiatric alterations, including cognitive and psychiatric disturbances, pyramidal and/or cerebellar signs, seizures and Parkinsonism [3]. Although there is a marked heterogeneity of signs and symptoms in CTX patients, even in intrafamilial cases [2], no phenotypic variability has yet been reported in twins or triplets, [5]. The aim of the current study is to present the considerably different phenotypes of a pair of identical adult twins diagnosed with CTX.

Case reports

One member of a 40-year-old female twin pair was first admitted to our neurology department in 2016 with the aim of a diagnostic work-up on her movement disorder. She had already had cataracts and glaucoma in childhood, but her movement and speech only began to worsen progressively from 2013. Additionally, she complained of an episode of pronounced diarrhea and gastrointestinal discomfort in 2015, and her parents mentioned memory problems, anxiety and impatience as well. On neurological examination, she presented signs of a movement disorder with dominating Parkinsonism (moderate symmetric hypo- and bradykinesia, rigor,

mainly right-sided occasional limb rest tremor, severe postural instability, freezing of gait, antecollis, hypomimia, severe dysarthria and mild seborrhea; Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III: 75 points in OFF state; Suppl. video 1) showing some levodopa response (MDS-UPDRS part III: 56 points in ON state, i.e., 25.3% improvement; Suppl. video 2). Furthermore, the patient had mild cerebellar ataxia and pyramidal signs (brisk patellar reflex and ankle clonus on the right side with bilateral Babinski sign) as well. The unaided stance and gait could not be implemented. The neuropsychological assessment demonstrated moderate cognitive dysfunctions in light of 65/100 points in Addenbrooke's Cognitive Examination (ACE) and 24/30 points in the Mini-Mental State Examination (MMSE). The skull MRI revealed T2 and FLAIR abnormal signals in the dentate nuclei and some supratentorial white matter alterations (Figures 1A, B, C and D). The clinical picture raised the possibility of CTX which was supported by elevated serum cholestanol levels (31 µM; normal range: 2-12.6 µM). The genetic testing for a disease-causing mutation in the *CYP27A1* gene revealed a known pathogenic homozygous frameshift mutation in exon 4 (c.819delT, p.D273EfsTer13).

With regards to family history, the other member of the twin pair also had juvenile cataracts and glaucoma and was suspected to have some kind of immunological disorder. Furthermore, her parents also reported less expressed memory problems, anxiety and impatience. Otherwise, the family history of the assessed patient was irrelevant. Despite the absence of pronounced neurological features, this second patient was also screened for possible signs of CTX. The examination revealed signs of slight Parkinsonism (mainly left-sided slight hypo- and bradykinesia and rigor on provocation in the left upper limb, and moderate postural instability; MDS-UPDRS part III: 8 points in OFF state; Suppl. video 3) and mild sensory ataxia with a slightly broad-based gait. With regards to cognitive function, the neuropsychological assessment demonstrated mild alterations in light of 72/100 points in

ACE and 27/30 points in the MMSE. The abnormal signals in the dentate nuclei were present as well (Figures 1E and F). Furthermore, the MRI revealed asymptomatic mega cisterna magna (Figures 1E, F and H) and a small tentorial meningeoma (Figures 1G and H). Despite the less expressed clinical alterations when compared to her twin sister, similarly elevated serum cholestanol levels were detected (36.8 μM). The genetic testing identified the same disease-causing mutation in the *CYP27A1* gene.

The considerably different phenotypes raised the question of whether the twin pair is identical or not. The following 15 short tandem repeat markers were analyzed for that purpose: D8S1179, D21S11, D7S820, CSF1PO, D3S1358, TC11, D13S317, D16S539, D2S1338, D19S433, VWA, TPOX, D18S51, D5S818 and FGA. The DNA profile of the 2 subjects was completely identical, so they are confirmed to be identical twins. The parents were heterozygous for the assessed mutation and they did not show any sign or symptom of CTX.

Discussion

Although the role of *CYP27A1* gene mutations in the pathogenesis of CTX is well-established, no genotype-phenotype correlation can be determined. When compared with previously reported CTX patients, the clinical features of our identical twin pair were slightly different from typical cases (including those with the same pathogenic mutation [6]), lacking tendon xanthomas and seizures, and presenting a predominant Parkinsonian syndrome, especially in the more severely affected patient. However, the Parkinsonian features were similar to that of a previously published case [7]. Nevertheless, the major aim of this case series is not only the simple demonstration of signs and symptoms in this identical twin pair, but to draw attention to the considerable differences in the severity of their clinical features and the identification of possible underlying factors. Biochemical testing revealed similar alterations in cholestanol concentrations, but it is known that the levels of this metabolite have

no correlation with clinical phenomena [8]. Although the role of environmental factors has been suggested to be possibly responsible for the clinical differences [2], the fact that our twin pair has been continuously living together with their parents and their eating habits are similar as well, makes this theory questionable. However, currently unknown genetic modifiers of certain epigenetic factors may play a role in clinical heterogeneity. The clarification needs further studies.

In conclusion this case series study serves as the first report of identical twins diagnosed with CTX demonstrating remarkably different phenotypes.

Ethical approval

Written informed consent was obtained from the patients for video recording and the publication of this study (institutional research committee registration numbers are 150/2014. and 44/2016., respectively). All procedures applied during the assessment of patients were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figure Legend

Figure 1. The main characteristic magnetic resonance imaging (1.5 Tesla) features of our patients with Cerebrotendinous Xanthomatosis. The lesion of the dentate nuclei is prominent in the more affected member (black arrows; T2-wheighted images: A; FLAIR images: B) and the less affected member (black arrows; T2-wheighted images: E; FLAIR images: F) of the identical twin pair. Furthermore, the more affected member demonstrated supratentorial white matter alterations (black arrows; T2-wheighted images: C; FLAIR images: D). In the less affected member the MRI revealed asymptomatic mega cisterna magna (grey arrows; axial

T2-wheighted images: E; axial FLAIR images: F; coronal T1-wheighted images: H) and a small contrast-enhancing tentorial meningeoma (black arrows; sagittal T1-wheighted images: G; coronal T1-wheighted images: H)

Video legends for supplementary materials

Supplementary video 1. The Parkinsonian features of the more affected member of the identical twin pair in OFF state.

Supplementary video 2. The Parkinsonian features of the more affected member of the identical twin pair in ON state following levodopa challenge.

Supplementary video 3. The very slight Parkinsonian features of the less affected member of the identical twin pair.

Figure 1

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