Four novel CYP27A1 mutations in seven Italian patients with CTX

G. N. Gallus*, M. T. Dotti*, A. Mignarri, A. Rufa, P. Da Pozzo, E. Cardaioli and A. Federico
Department of Neurological, Neurosurgical and Behavioural Sciences, Medical School, University of Siena, Siena, Italy

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Background and purpose: Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive disease, because of sterol 27-hydroxylase deficiency. Clinical manifestations of CTX are tendon xanthomas, juvenile cataracts, osteoporosis, diarrhoea and multiple progressive neurological dysfunctions. More than 300 patients with CTX have been reported to date worldwide and about fifty different mutations identified in *CYP27A1* gene. This study describes the clinical and laboratory findings of seven new patients.
Methods: We report the molecular and clinical characterization of seven new Italian patients with CTX carrying four novel mutations.
Results: We identified four novel mutations located in different exons, in particular in the region of exons 2–5 of the *CYP27A1* gene. Phenotypical expression did not differ from classical CTX presentation except for absence of tendon xanthomas in two patients.

Introduction

Cerebrotendinous xanthomatosis (CTX; OMIM 213700) is a rare autosomal recessive disease because of mutations in the *CYP27A1* gene encoding for the mitochondrial enzyme sterol 27-hydroxylase that catalyses the cholesterol oxidation in the bile acid pathway [1] Main clinical manifestations are tendon xanthomas, juvenile cataracts, osteoporosis, diarrhoea and multiple progressive neurological dysfunctions [2].

CYP27A1 deficiency leads to impaired bile acid synthesis and increased production of cholesterol metabolites such as cholestanol that accumulates in many tissues leading to clinical manifestations of the disease. Chenodeoxycholic acid treatment may prevent the progression of neurological and systemic complications of the disease [3].

CYP27A1 gene consists of nine exons and eight introns and spans 18.6 kb of DNA [4]. Forty-nine different mutations within the *CYP27A1* gene have been reported worldwide [5].

Materials and methods

We investigated seven new Italian patients, with CTX phenotypic presentation, four of them deriving from two families. Ethics committee approval is not necessary in Italy for this kind of research. Written informed consent was obtained from patients. Serum cholestanol was measured by gas-liquid chromatography as previously described [6]. The clinical and biochemical characteristics are summarized in Table 1.

Description of the patients

Patient-1
Thirty-six-year-old Italian woman. Symptoms include diarrhoea since childhood, cataracts diagnosed at age of 5–6 and extracted at the age of 20, progressive walking difficulties and dysarthria since 30 years. Clinical evaluation revealed bilateral 'pes cavus', hypotonia, gait ataxia, dysarthria and mild cognitive impairment mini mental state examination (MMSE) = 23; intelligence scale (IQ) = 70). Tendinous xanthomas were absent. Serum cholestanol levels were elevated (3.14 mg/dl; normal value (n.v.) < 1 mg/dl). Brain MRI showed hyperintense T2-W lesions of dentate nuclei and cerebellar white matter. Electromyography (EMG) and electroneurography (ENG) were normal. Motor evoked potentials (MEP) showed increased central motor conduction times (CMCTs). Bone mineral densitometry (BMD) revealed osteoporosis.

Patient – 2
Twenty-two-year-old Italian man (the older brother of patient 3). Clinical history showed chronic refractory neonatal-onset diarrhoea, bilateral cataracts at the age of 7, left Achilles tendon xanthomas at 11 years of age which were subsequenly removed, progressive gait

Correspondence: Prof A. Federico, Department of Neurological, Neurosurgical and Behavioural Sciences, University of Siena, Viale Bracci 2, 53100 Siena, Italy (tel.: 39 577 585763; fax: 39 577 40327; e-mail: federico@unisi.it).

*These authors contributed equally to this article.