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Case Report

Peripheral Neuropathy in Cerebrotendinous Xanthomatosis: A Case report and Literature Review

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Abstract

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive disorder characterized by the accumulation of cholestanol and cholesterol in most tissues. Clinical manifestations include tendon xanthoma, premature cataracts, juvenile atherosclerosis and a progressive neurological syndrome including mental retardation, cerebellar ataxia, pyramidal tract signs, myelopathy and peripheral neuropathy which appear later in the progression of the disease. The authors report the case of a 24-year-old man presenting with gait difficulty. The diagnosis of Cerebrotendinous xanthomatosis with severe peripheral neuropathy was retained. Nerve biopsy showed evidence of axonal degeneration. In this work we discuss clinical, electric and biopsy features of the neuropathy associated to this disease.

ABBREVIATIONS

CTX: Cerebrotendinous Xanthomatosis

INTRODUCTION

Cerebrotendinousxanthomatosis (CTX) is an autosomal recessive disease characterized by an increase of cholestanol concentrations in plasma and storage of sterols in all tissues, especially in the tendons and the nervous system. It is characterized by progressive neurological dysfunction (cerebellar ataxia beginning after puberty, systemic spinal cord involvement, and a pseudo bulbar phase leading to death), premature atherosclerosis and cataracts [1,2]. Mutations in the sterol 27-hydroxylase gene cause this disease [3-6]. Substantial elevation of serum cholestanol and urinary bile alcohols with low to normal plasma cholesterol concentrations establishes the diagnosis. Peripheral neuropathy in CTX is not rare and usually occurs in a tardive stage of the disease but many mechanisms were described. Early diagnosis of CTX is crucial because early treatment with chenodeoxycholic acid (CDCA) may stop or even reverse the progression of the disease.

CASE PRESENTATION

A 24-year-old man was admitted at Fattouma Bourguiba hospital in Tunisia with a slowly progressive muscle weakness. His medical history revealed difficulty in standing and walking since the age of 12. He could not finish his education because of mental retardation. His parents were not related. He has two asymptomatic siblings aged respectively 40 and 36 years. Physical examination showed a dysmorphic face with severe mandibular retrognathia, bilateral cavusequinovarus foot with claw toes and 3 tendon xanthomas in elbows. Yellowish papules of 2 to 3 mm in diameter in the superior eyelid compatible with xanthelasmas were observed. Neurologic examination revealed a deficit in all muscle strength essentially in distal muscles, mental retardation, spastic-ataxic gait, bilateral Babinski sign, symmetric amyotrophy in inferior extremities, and hyperactive deep tendon reflexes with associated left Achilles clonus. Ligamentous hyperlaxity was also observed. Laboratory findings, including those of blood tests cell count, coagulation tests, biochemistry, and cholesterol, triglyceride tests were normal. A tendon biopsy specimen obtained from one lesion on the left knee showed an infiltrate of foam cells surrounded by fibrous tracts. Inflammatory cells such as lymphocytes, histiocytes, and neutrophils were observed around the foam cells in some areas and one cholesterol cleft was found. The electromyogram showed reduced motor and sensitive velocities in all limbs with increased latencies and signs of degeneration. Nerve biopsy showed reduction in the myelinic fiber number, suggesting axonal degeneration without onion bulbs or clusters (Figure 1). Magnetic resonance imaging revealed cerebral and cerebellar atrophy and hyper intense signals in mesencephalic

peduncles, protuberance and cerebellar hemispheres (Figure 2). Ophthalmologic examination showed bilateral dense cataracts. Later, our suspected diagnosis was confirmed by the determination of plasma cholestanol concentration which was equal to 66,5 µmol/L(normal<12,5µmol/L).Once the diagnosis had been confirmed, we continued the treatment with CDCA, 750 mg daily. After a follow-up period of 3 years, only mild improvement of spasticity was observed.All data of our patient were included in Table 1.

DISCUSSION

CTX is a rare, recessive, lipid-storage disease that was first described as affecting two cousins in 1937 by Van Bogaert [7]. Diagnosis of CTX is difficult to establish during the first decade of life because symptoms and findings may be absent or vague in the early stages of the disease. The characteristic findings of CTX typically do not appear until the late teens or early twenties. Early detection is necessary as untreated CTX results in progressive neurological dysfunction and atherosclerotic disease. Peripheral neuropathy occurs frequently but in a late stage of the disease [8,9]. The literature review revealed different types and a variable frequency of peripheral neuropathy in CTX. Many authors found a predominantly demyelinating type. Actually, Pilo B et al. [10] found that 62% of patients had peripheral neuropathy with clinical signs/symptoms in all cases. In this series, polyneuropathy was essentially demyelinating and sensory-motor. Besides, Mondelli et al. [11], used electro physiologic studies including nerve conduction study (NCS), and they found that eight CTX patients had a moderate sensory-motor neuropathy of demyelinating type, but this finding was not further confirmed by pathological study of nerve. Argov et al. [12] also noted a demyelinating process in a study of peripheral neuropathy in three CTX patients. However, Verrips et al. [4] concluded that the most predominant neuromuscular abnormality is sensory-motor axonal polyneuropathy. These results were confirmed by Lionnet et al. [1] in that sensory-motor axonal neuropathy was found in 40%. Besides, Shu-fang Chen et al. [2] noted different degrees of axonal sensory-motor polyneuropathy in three cases and mixed axonal and demyelinating sensory-motor polyneuropathy in one case. In these patients, Peripheral neuropathy should be detected even in asymptomatic patient. Ohnishi et al. [13] found demyelinating peripheral neuropathy with onion bulbs in an asymptomatic patient. In another morphological peripheral nerve study, Katz et al. [14] found loss in myelinating fibers and suggested an ischemic mechanism as a possible cause of the peripheral neuropathy. These features were not found in our patient where signs of demyelination and remyelination were noted with no cluster or

Table 1: Clinical data and diagnostic test of our patient.

Age (years)	24
Clinical manifestation	Tendinous xanthmatosis cataracts Mental retardation
	Cerebellar sign Pyramidal sign Foot muscle atrophy
Cholestanol level	66,5µmol/L
Cholesterol level	4.58mmol/L
MRI	hyperintense signals
EMG	Mixed axonal and demyelinating sensory-motor polyneuropathy
Nerve biopsy	axonal degeneration

Table 2: Clinical and laboratory data of the reported cerebrotendinous xanthomatosis patients with peripheral neuropathy [1-2].

year	Total case No/ gene mutation/ age or range of age (y/r)	Described type of neuropathy	Nerve conduction study	Sural nerve biopsy	Muscle biopsy
1079	4/ND/12-27	S-M pnp	D	ND	ND
1979	1/ND/25	ND	D	D	ND
1984	4/ND/35-43	S-M pnp	D	D	D
1985	1/ND/50	S-M pnp	D	D	ND
1986	3/ND/14-30	demyelinated S-M pnp	D	D	ND
1987	1/ND/29	S-M pnp	D	D	D
1990	1/ND/30	S-M pnp	D	D	ND
1991	1/ND/22	Axonal pnp	D	D	ND
1992	10/ND/26-44	Mixed S-M pnp (2) and demyelinating S-M pnp (8)	D	ND	ND
1995	1/ND/34	Mixed	D	ND	ND
2000	10/D[a]/24-54	Axonal pnp (5), mixed pnp (1), pnp (1)	D	D	D
2007	1/D[b]/47	Polyneuropathy	D	ND	ND
2007	1/D[c]/42	S-M polyneuropathy	D	D	ND
2011	4/ND/29-54	Mixed S-M pnp (2) and axonal S-M pnp (3)	D	D	D
2014	15/D[d]/27-65	axonal S-M pnp (4),axonal sensory (1),demyelinating pnp(3), mixed pnp (1), pnp (6)	D	ND	ND

Abbreviations: No: Number; ND: Not Determined; D: Determined; SM: Sensori-Motor; PNP: Peripheral Neuropathy
[a] = mutations on both alleles of the *CYP 27* gene in all 10 patients
[b] = mutations 1016C > T (T339M) and 1183C > T (R395C) in the *CYP21A2* gene
[c] = mutations 379C > T (R94W) and 1420 C > T (R441W) in the *CYP27A1* gene
[d]== mutations 1183C > T,1184+1G>A, 1017G>C and 1198G>T in the *CYP27A1* gene

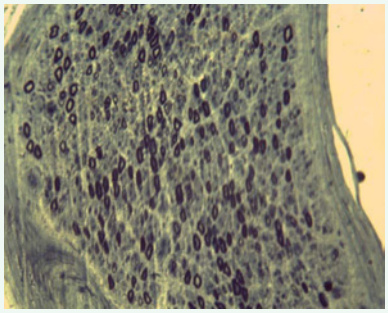

Figure 1 Nerve biopsy showed reduction in the myelinic fiber number, suggesting axonal degeneration without onion bulbs or clusters.

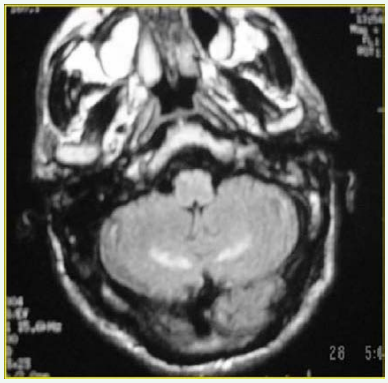

Figure 2 Magnetic resonance imaging revealed hyper intense signals in mesencephalic peduncles, protuberance and cerebellar hemispheres.

evidence of onion bulbs. We also noted a loss of the myelinic fiber with a wide diameter and increased amyelinic wide diameter fiber number as it was seen in the case described by Ben Hamida et al. [9]. Ultrastructural study of the nerve showed an increase in the endoneuronal collagen with hypertrophy of swanien nucleus cells with no endoneuronal inclusion and axonal degeneration. Voiculescu et al. [15], Donaghy et al. [16] and Wang et al. [17] found the deposition of lipid in Schwann cells in CTX patients with neuropathy, while this pathologic change was not noted in the studies of Katz et al. [14], Argov et al. [12] and Verrips A et al. [4]. The hypothegenis is until now hypothetical. Several authors have suggested demyelination as the primary pathological. [9] lesion where as others have suggested primary neuro axonal pathology with secondary myelin loss [18]. Genetic studies showed also a huge variability. In the study of Shu-fang Chen et al another 12 CTX patients [2] with a peripheral neuropathy had a genetic analysis, but different mutation patterns were noted. This lack of correlation between the genotype and pathogenesis of peripheral neuropathy or other phenotypes was also noted in the studies of Verrips et al. [4]. For a better delineation of peripheral neuropathy, features in CTX patients were included in Table 2.

CONCLUSION

The physiopathology of peripheral neuropathy in Cerebrotendinous Xanthomatosis is still not understood. Demyelination, remyelination and features of axonal degeneration, can be found in these patients and genetic analysis wasn't contributory. Therefore, more studies must be lead in order to have more explanations.

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