NEUROPHYSIOLOGICAL STUDY IN CEREBROTENDINOUS XANTHOMATOSIS

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ABSTRACT: *Introduction*: Cerebrotendinous xanthomatosis (CTX) is a rare autosomal-recessive disease due to mutations of the 27α-hydroxylase. It is characterized by cataracts, xanthomas, and neurological manifestations. Polyneuropathy has been reported, although it is unclear whether it is axonal or demyelinating. *Methods*: We report clinical and neurophysiological results of 13 patients with CTX diagnosed in Spain. *Results*: In 8 patients (62%), peripheral neuropathy was demonstrated (4 demyelinating, 3 axonal, and 1 mixed; 3 predominantly motor and 5 sensorimotor). All patients had clinical signs/symptoms of peripheral neuropathy. Upper limb somatosensory evoked potentials (SSEPs) were affected in 38% of patients, and lower limb SSEPs in 67%. Fifty percent of patients had delayed brainstem auditory evoked potentials, and 43% had affected visual evoked potentials. *Discussion*: In this series, polyneuropathy was predominantly sensorimotor and demyelinating. Neurophysiological studies correlated only partially with clinical follow-up. Therefore, we recommend neurophysiological follow-up studies only if clinical symptoms are present.

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Cerebrotendinous xanthomatosis (CTX) is a rare autosomal-recessive metabolic disorder. It was first described by van Bogaert et al. in 1937,[1] and it is caused by a defect of mitochondrial sterol 27α-hydroxylase. This deficiency leads to impaired oxidation of the cholesterol side chain, with reduced synthesis of cholic acid and chenodeoxycholic acid (CDCA) and increased formation of intermediates, such as cholestanol and 27-carbon bile alcohols.[2] Cholestanol deposition on tendons, the ocular lens, and nervous system causes a variety of symptoms, beginning with chronic diarrhea in childhood and juvenile cataracts. Progressive neurological dysfunction usually appears in the third decade of life and includes cerebellar symptoms, pyramidal signs, mental retardation, dementia, epilepsy, psychiatric disturbances, and parkinsonism.[3–5] Tendinous xanthomas, although very suggestive, are not mandatory for the diagnosis.[6]

The primary laboratory finding is a marked elevation in the concentration of cholestanol in plasma.[2] Magnetic resonance imaging (MRI) typically shows bilateral hyperintensity in the cerebellar dentate nuclei and pyramidal tracts on T_2-weighted images.[7] Somatosensory evoked potentials (SSEPs), visual evoked potentials (VEPs), and brainstem auditory evoked potentials (BAEPs) usually show prolonged central conduction times.[8] Replacement therapy with chenodeoxycholic acid (CDCA), which inhibits abnormal cholestanol synthesis, is effective in reducing plasma cholestanol.[9] Combined treatment with CDCA and a 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitor has been proposed, because it further increases the reduction of serum cholestanol and cholesterol.[10]

Polyneuropathy is a frequent presentation,[11–14] but controversies exist regarding whether it is demyelinating or axonal in origin.[15] In 2000, Wang et al.[16] proposed, based on a review of different reports, that polyneuropathy in CTX could be classified into three pathological types: axonal (with axonal degeneration and regeneration)[12]; demyelinating (with profuse demyelination, thin myelin sheaths and onion bulbs of myelinated fibers)[17–19]; and mixed.[20]

The aim of this work was to describe the neurophysiological findings in patients with CTX and their clinical–neurophysiological correlations.

METHODS

Patients. We analyzed the clinical, laboratory, and electrophysiological data of 13 patients with a diagnosis of CTX. The patients had received a genetic diagnosis at one of the main reference centers for CTX (Fundación Pública Galega de Medicina

Abbreviations: BAEP, brainstem auditory evoked potential; CDCA, chenodeoxycholic acid; CTX, cerebrotendinous xanthomatosis; DTI, diffusion tensor imaging; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-A, LDL-apheresis; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; MUAP, motor unit action potential; NCS, nerve conduction studies; NCV, nerve conduction velocity; PCR, polymerase chain reaction; SSEP, somatosensory evoked potential; VEP, visual evoked potential

Key words: cerebrotendinous xanthomatosis, chenodeoxycholic acid, evoked potentials, neurophysiological study, polyneuropathy

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Table 1. Clinical, biochemical, and mutational findings in 13 patients with CTX.

Case no.	S, AO/AD	C	X	A	P	PC	M	H	CH	Allele 1	Allele 2	T
1	M, 18/54	+	−	+	+	−	−	−	57	c.845-1G→A	c.845-1G→A	Co
2	F, 37/44	+	+	+	+	+	+	−	238	c.1213C→T (p.R405W)	c.1213C→T (p.R405W)	Co
3	F, 12/46	+	−	−	+	+	+	−		c.1183C→T (p.R395C)	c.1414-1421delGGGGTCCG	Co
4	F, 12/46	+	−	−	+	+	+	−		c.1183C→T (p.R395C)	c.1414-1421delGGGGTCCG	Co
5	M, 30/32	+	+	−	+	+	−	−		c.1183C→T (p.R395C)	c.1183C→T (p.R395C)	CDCA
6	F, 12/46	+	−	+	+	+	+	−	82	c.804G→T (p.W268C)	c.804G→T (p.W268C)	Co
7	M, 12/51	−	−	+	+	−	−	−	57	c.1043-1054delTGTACCACCTCT	c.1043-1054delTGTACCACCTCT	
8	F, 14/36	+	+	+	+	+	+	−	102	c.1183C→T (p.R395C)	c.1183C→T (p.R395C)	CDCA
9	M, 12/31	+	+	+	+	+	+	−		c.1016C→T (p.T339M)	c.1473C→T (p.Q525X)	CDCA
10	M, 12/36	+	+	+	−	+	+	−	104	c.1184+1G→A	c.1184+1G→A	Co
11	F, 12/41	+	+	+	+	−	−	−				Co, LDL-A
12	M, 12/14	+	−	+	+	+	+	−	97	c.1213C→T (p.R405W)	c.1183C→T (p.R395C)	Co
13	F, 10/30	+	−	+	+	+	+	+	66	c.1183C→T (p.R395C)	c.688C→T (p.Q230X)	Co

G, gender; AO, age at onset; AD, age at diagnosis; C, cataracts; X, xanthomas; A, ataxia; P, pyramidalism; LDL-A, LDL-apheresis; PC, pes cavus; M, muscular atrophy; H, hypoaesthesia; CH, serum cholestanol (μmol/L); T, therapy; Co, combined; CDCA, only chenodeoxycholic acid.

Xenómica in Santiago de Compostela or Hospital Ramón y Cajal in Madrid) between 1990 and 2008. CTX diagnosis was established by the clinical features, together with mutational analysis, and, in some cases, plasma cholestanol testing.

Data Collection and Evaluation. Information was registered using a standard data form. The following items were recorded: gender; geographical origin; mutations; age at appearance of first neurological symptoms; age at diagnosis; presence of xanthomas; myopathy; peripheral neuropathy; serum cholestanol and cholesterol; electromyography; evoked potentials; therapies; and response to treatment.

Motor nerve conduction velocities (NCVs) were carried out on median, ulnar, posterior tibial, and peroneal nerves using standard techniques. Sensory orthodromic NCVs were measured in the median, ulnar, and sural nerves. BAEPs and VEPs were recorded by conventional proceedings. To obtain upper limb SSEPs, the median nerve was stimulated at the wrist and peak latencies of N9, and N13 and interpeak latencies of N13–N20 were recorded. For lower limb SSEPs, the posterior tibial nerve was stimulated at the ankle. Peak latencies of N35 and P40 and interpeak latencies of N35–P40 were registered.

Genetic Analysis. DNA was extracted from peripheral blood leukocytes using QIAmp Mini-kit DNA blood (Qiagen, Valencia, California). *CYP27A1* gene exons and intronic adjacent regions were amplified by polymerase chain reaction (PCR) using primers and protocols as reported by Leitersdorf et al.[21] The purified PCR products were sequenced using an automated sequencer (ABI 3730XL) using the BigDye 3.1 terminator cycle sequencing kit. DNA sequences were analyzed using Generunner v3.05 (Hastings Software, Inc., Chatsworth, California) and Chromas v2.0 (Technelsyum Pty, Ltd., Queensland, Australia).

Statistical Analysis. Statistical analysis was performed using SPSS v15.0 for Windows (SPSS, Inc., Chicago, Illinois). Group comparisons of categorical variables were performed with Fisher's exact test. Correlations of numerical characteristics between groups were established with Pearson's correlation. Categorical and numerical variables were compared by *t*-test. All reported *P*-values were two-sided. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics. Thirteen adult CTX patients (7 females, 6 males) from 12 families were investigated (Table 1). The average age of the first neurological symptom was 15.8 years (range 10–37 years). The average age at diagnosis was 39 years (range 14–54 years). In 12 patients (92.3%) cataracts were present. Only 6 patients (46%) had tendon xanthomas. The most frequent neurological symptoms/signs were: pyramidalism (92.3%); ataxia (77%); polyneuropathy (62%); mental retardation (61.5%); psychiatric disorders (61.5%); dementia (46.2%), parkinsonism (31%); and epilepsy (15.4%).

All patients with peripheral neuropathy (8 patients) had mild to moderate clinical manifestations of peripheral neuropathy consisting of lower limb calf atrophy, distal weakness, and pes cavus. None had sensory symptoms. In the group of patients without polyneuropathy (5 patients), 2 had clinical signs or symptoms of peripheral neuropathy (1 had distal hypesthesia and pes cavus and the other pes cavus). No association was found

Table 2. Neurophysiological data for 13 patients with CTX.

		Average	SD	Affected case nos.
Peroneal amplitude (mV), $N \geq 2$		2.51	2.02	2, 3, 8, 10
Peroneal NCV (m/s), $N \geq 40$		36.1	5.41	2, 3,4, 6, 8, 9
Tibial amplitude (mV), $N \geq 4$		5.99	3.88	3, 4
Tibial NCV (m/s), $N \geq 40$		39.2	4.71	3, 4, 9, 12
Sural amplitude (μV), $N \geq 6$		12.99	8.93	3, 5, 6, 9
Sural NCV (m/s), $N \geq 40$		45.1	8.15	2, 3, 4, 7
Median motor amplitude (mV), $N \geq 4$		9.86	5.23	
Median motor NCV (m/s), $N \geq 49$		50.2	4.82	2, 4, 8, 9
Median sensory amplitude (μV), $N \geq 10$		27.34	33.29	5, 6
Median sensory NCV (m/s), $N \geq 50$		52.5	3.18	7
Neuropathy	Not present		5	
	Sensorimotor demyelinating		3	
	Sensorimotor axonal		2	
	Motor demyelinating		1	
	Motor axonal		1	
	Motor (peroneal) mixed		1	
Electromyography	Normal		7	
	Increased duration and high amplitude MUAPs		1	
	Decreased recruitment		3	

CTX, cerebrotendinous xanthomatosis; NCV, nerve conduction velocity; MUAPs, motor unit action potentials.

between the presence of neuropathy and any other neurological symptoms/signs.

Laboratory Tests. No other metabolic or genetic causes of neuropathy were detected by screening of serum abnormalities or familial history. Cholestanol levels were measured in 6 patients. All patients had high cholestanol levels, with an average of 100.4 μmol/L and a range of 57–238 μmol/L (normal: 2–12.6 μmol/L). The group of patients with neuropathy had higher cholestanol levels in plasma (114.9 μmol/L) compared to the group of patients without neuropathy (57 μmol/L), although this difference was not statistically significant, probably due to the small size of the sample. Cholesterol levels were similar in both groups (4.53 mmol/L).

Mutation Analysis. Mutation analysis revealed mutations on both alleles of the 27-hydroxylase gene in all tested patients (all patients except patient 11). The most frequent mutation was c.1183C→T (p.R395C) (33.3% of the alleles), followed by c.1213C→T (p.R405W) (12.5%), c.804G→T (p.W268C) (8.3%), c1043–1054delTGTACCACCTCT (8.3%), c.1414–1421delGGGGTCCG (8.3%), c.1184+1G→A (8.3%), c.845-1G→A (8.3%), c.1016C→T (p.T339M) (4.2%), c.688C→T (p.Q230X) (4.2%), and c.1473C→T (p.Q525X) (4.2%). No association was found between a certain mutation and the presence or type of polyneuropathy.

Neurophysiological Studies. Table 2 summarizes the main neurophysiological findings. In 5 patients, nerve conduction studies (NCSs) were normal. In 7 patients, the peroneal conduction velocity was decreased, and in 4 the amplitude was diminished. Four patients had decreased conduction velocity in the tibial nerve. One patient had absent sural sensory nerve action potentials. Median nerve sensory conduction was normal in 9 patients. Median nerve motor conduction velocities were slowed in 4 cases, with normal amplitudes. Prolonged duration and high amplitudes of motor unit action potentials (MUAPs) were observed in 2 patients. Decreased recruitment was found in 4 patients. These NCS findings established a demyelinating peripheral neuropathy in 4 patients (1 predominantly motor and 3 sensorimotor), axonal in 3 (1 predominantly motor and 2 sensorimotor), and mixed in 1 patient.

Five patients had normal median nerve SSEPs, whereas 3 had delayed N9, N13, N20, and N13–20 interpeak latencies with irregular morphology. After lower limb stimulation, 2 patients had normal SSEPs, whereas 4 patients had delayed P40 latencies. However, due to the presence of polyneuropathy, in 3 of these 4 patients, the interpretation of affected lower limb SSEPs was limited. The I–V interpeak latencies in the BAEPs were significantly prolonged in 4 cases, but they were within the normal range in 4 cases. The P100 peak latencies of the VEPs were prolonged in 3 cases, whereas they were normal in 4 cases. The study of the central motor conduction time, performed in cases 9 and 11, showed delayed responses in both cases.

Treatment and Follow-Up. Two patients received treatment exclusively with CDCA. Nine patients received a combination of CDCA and a statin. In 1 patient low-density lipoprotein (LDL)-apheresis

was performed biweekly for 6 months and then monthly for 4 years. Despite treatment, 6 patients continued to deteriorate, and 3 patients died during follow-up. Only 4 patients stabilized clinically. The evolution did not correlate with the treatment. In the group of patients who died, 2 received CDCA and a statin (the third patient died only some months after diagnosis). In the group of patients who continued to deteriorate, 1 patient received LDL-apheresis, CDCA, and a statin; 4 patients received CDCA and a statin; and 1 patient was treated exclusively with CDCA. In the group of patients who stabilized, 3 received the combined therapy and 1 received CDCA.

A second neurophysiological study was performed in 6 patients during follow-up to establish response to treatment (Fig. 1). Two of the patients continued to deteriorate despite treatment with CDCA and a statin during 6 years (cases 3 and 4). Two of them stabilized (cases 5 and 8) at 2 years after treatment (1 of them exclusively with CDCA and the other with the combination). In cases 2 and 12, neurophysiological improvement (predominantly of the NCVs) was observed after treatment with CDCA and a statin (patient 2 at 1 year after treatment and patient 12 at 3 years after treatment).

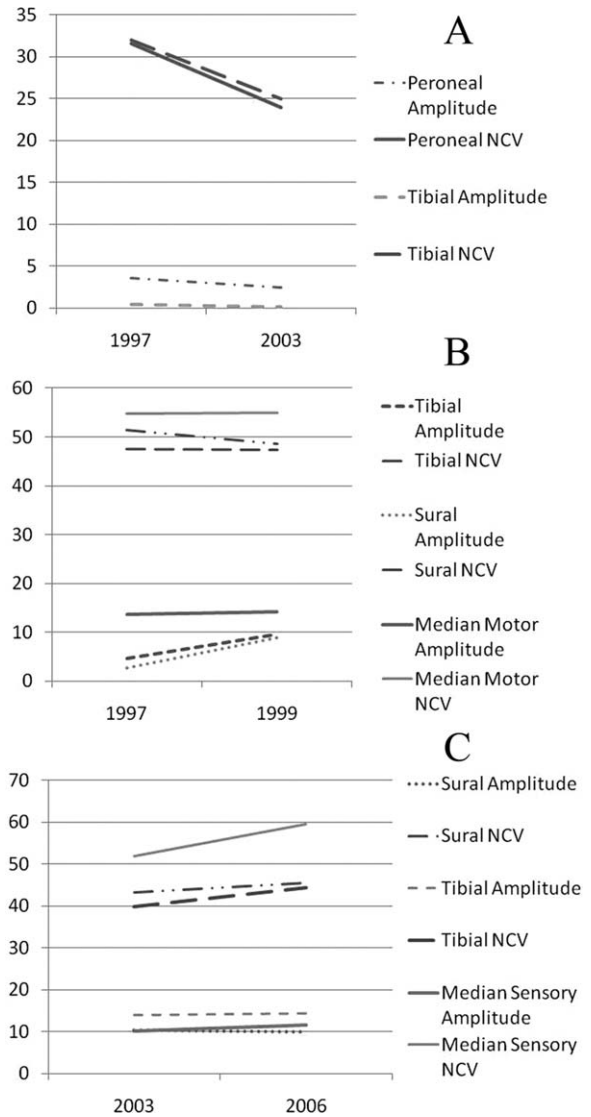

FIGURE 1. Follow-up of the disease after treatment. **(A)** Patient 4 (neurophysiological deterioration). **(B)** Patient 5 (stabilization). **(C)** Patient 12 (neurophysiological improvement).

DISCUSSION

Peripheral neuropathy is a recognized feature of CTX. In our series, all patients with demonstrated neuropathy had pes cavus and muscle atrophy, although deep tendon reflexes were not hypoactive, because of concurrent pyramidal signs. No clinical sensory abnormalities were noted. Two patients with normal neurophysiological studies had pes cavus, and 1 of them had distal hypesthesia as well. The limited correlation between clinical signs/symptoms and neurophysiological results has been described by Argov et al.[18]

When Kuritzky et al.[11] described in 1979 the presence of a peripheral neuropathy in CTX, it was suggested that the degree of peripheral nerve abnormality paralleled the central nervous system involvement. It was concluded that the study of peripheral nerve conduction could not facilitate an early diagnosis, because these changes seemed to occur relatively late. Our series questions this theory. Patient 7 was diagnosed at 51 years of age in a very advanced stage of the disease and died only some months after diagnosis. His neurophysiological study was normal. On the other hand, patient 12 was diagnosed at the age of 14 years. The first NCS was done at 17 years of age and showed mixed demyelinating polyneuropathy. Therefore, peripheral neuropathy seems to be an independent process (not related to the central nervous involvement). The main question remains as to why cholestanol deposits occur in dentate nuclei in some patients to produce ataxia, in the spinal cord in other patients to produce chronic myelopathy, and why some patients have peripheral neuropathy.

Higher cholestanol levels were found in the group of patients with neuropathy, although these results were not statistically significant. These levels did not correlate with severity of the disease, because they were lower in the 3 patients who died during follow-up (cases 1, 6, and 7; average of 65.3 μmol/L cholestanol in this group). Cholestanol levels were measured at diagnosis, which was at a different time in the natural course of the disease in each case. Because the natural evolution of cholestanol levels is unknown, the interpretation of these results is quite limited.

In this series, 38% of upper limb SSEPs and 67% of lower limb SSEPs were affected (although 75% of patients with delayed lower limb SSEPs had polyneuropathy). In 1992, Tokimura et al.[8] noted that predominant lower limb involvement was evidence of pathological changes in the posterior column. It was suggested that central–peripheral distal axonopathy may play a role in the pathogenesis of lesions of the central and peripheral nervous systems in CTX. BAEP and VEP abnormalities in CTX have been described by many investigators and, in some cases, used in the follow-up of the disease.[22–24] In our series, BAEPs and VEPs were affected in 50% and 43% of patients, respectively. In case 8, BAEPs were repeated 2 years after treatment with CDCA and pravastatin, and there was clear deterioration (in the first study, interpeak latencies were delayed and irregular; in the second study, normal peaks were unrecognizable).

The study of central motor conduction time, which was performed in cases 8 and 11, showed delayed responses in both instances. In 1992, Mondelli et al.[23] described delayed central motor conduction time, especially in the lower limbs. In case 8, central motor conduction time was repeated 2 years after treatment. An increased latency was observed, despite therapy. This neurophysiological worsening correlated with the clinical deterioration that was observed.

In spite of the fact that BAEPs and central motor conduction showed the best clinical–neurophysiological correlation, we could not find any correlation between these parameters and the MRI findings. Recently, diffusion tensor imaging (DTI) MRI findings in patients with CTX have been reported.[25] This technique allows further insights about white matter tract pathology, because it is sensitive to water diffusion. According to that study, white matter changes in patients with CTX in axial and radial diffusivity suggested the presence of both demyelinating and axonopathic lesions in CTX. DTI showed improved sensitivity in detecting white matter changes.

In this series, despite receiving a standard therapy, 6 patients continued to deteriorate, and 3 patients died. Only 4 patients stabilized clinically. EMG follow-up was done in 6 patients. No correlation was found between progression and cholestanol levels or mutational analysis. Cases 3 and 4 had NCS deterioration after 6 years of treatment. They had an axonal sensorimotor neuropathy. Clinically, patient 4 stabilized, whereas, in patient 3, disease was progressive (predominantly the chronic myelopathy). NCV stabilization was observed in cases 5 and 8 at 2 years after treatment. Clinically, patient 5 remained stable, whereas patient 8 progressed (predominantly the ataxia and cognitive decline). As previously described, BAEPs and central motor conduction time were correlated with this clinical decline.[8] In cases 2 and 12 neurophysiological improvement was recorded. Patient 2 had a sensorimotor demyelinating polyneuropathy. She received CDCA and simvastatin for 1 year. Although amplitudes and nerve conduction velocities improved, the patient continued to experience progressive ataxia, paraparesis, and cognitive decline. Patient 12 was diagnosed at 14 years of age and received CDCA and simvastatin. He had a sensorimotor demyelinating polyneuropathy. A neurophysiological study 3 years later demonstrated a near normalization of nerve conduction velocities and amplitudes. Clinically, the patient stabilized. In this case, the early diagnosis and treatment may have accounted for the favorable evolution.

To conclude, polyneuropathy in CTX can be demyelinating, axonal, or mixed, although in this series it was predominantly sensorimotor and demyelinating. Therefore, CTX should be included in the differential diagnosis of any type of neuropathy of unknown etiology. Despite standard therapy, no clinical improvement was observed in this series. Only 4 patients stabilized clinically, and early diagnosis was an important prognostic factor. Neurophysiological studies correlated only partially with clinical evolution, and BAEPs and central motor conduction showed the best clinical–neurophysiological correlation. This was probably due to the fact that neuropathy only accounted for mild symptoms compared with the central nervous system symptoms, which were predominant in most cases (ataxia, myelopathy, and cognitive decline among the most prevalent). Therefore, we recommend using neurophysiological follow-up studies, depending on clinical symptoms.

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REFERENCES

1. van Bogaert L, Scherer HJ, Epstein E. Une forme cérébrale de la cholesterinose généralisée. Paris: Mason et Cie; 1937.
2. Moghadasian MH. Cerebrotendinous xanthomatosis: clinical course, genotypes and metabolic backgrounds. Clin Invest Med 2004;27: 42–50.
3. Verrips A, Hoefsloot LH, Steenbergen GC, Theelen JP, Wevers RA, Gabreels FJ, et al. Clinical and molecular genetic characteristics of patients with cerebrotendinous xanthomatosis. Brain 2000;123: 908–919.
4. Gallus GN, Dotti MT, Federico A. Clinical and molecular diagnosis of cerebrotendinous xanthomatosis with a review of the mutations in the CYP27A1 gene. Neurol Sci 2006;27:143–149.
5. Grandas F, Martin-Moro M, Garcia-Munozguren S, Anaya F. Early-onset Parkinsonism in cerebrotendinous xanthomatosis. Mov Disord 2002;17:1396–1397.
6. Verrips A, van Engelen BG, Wevers RA, van Geel BM, Cruysberg JR, van den Heuvel LP, et al. Presence of diarrhea and absence of tendon xanthomas in patients with cerebrotendinous xanthomatosis. Arch Neurol 2000;57:520–524.

7. Vanrietvelde F, Lemmerling M, Mespreuve M, Crevits L, De Reuck J, Kunnen M. MRI of the brain in cerebrotendinous xanthomatosis (van Bogaert–Scherer–Epstein disease). Eur Radiol 2000;10:576–578.
8. Tokimura Y, Kuriyama M, Arimura K, Fujiyama J, Osame M. Electrophysiological studies in cerebrotendinous xanthomatosis. J Neurol Neurosurg Psychiatry 1992;55:52–55.
9. Berginer VM, Salen G, Shefer S. Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. N Engl J Med 1984;311:1649–1652.
10. Kuriyama M, Tokimura Y, Fujiyama J, Utatsu Y, Osame M. Treatment of cerebrotendinous xanthomatosis: effects of chenodeoxycholic acid, pravastatin, and combined use. J Neurol Sci 1994;125:22–28.
11. Kuritzky A, Berginer VM, Korczyn AD. Peripheral neuropathy in cerebrotendinous xanthomatosis. Neurology 1979;29:880–881.
12. Pop PH, Joosten E, Van Spreeken A, Gabreels-Festen A, Jaspar H, ter Laak H, et al. Neuroaxonal pathology of central and peripheral nervous systems in cerebrotendinous xanthomatosis (CTX). Acta Neuropathol (Berl) 1984;64:259–264.
13. Ben Hamida M, Chabbi N, Ben Hamida C, Mhiri C, Kallel R. Peripheral neuropathy in a sporadic case of cerebrotendinous xanthomatosis [in French]. Rev Neurol (Paris) 1991;147:385–388.
14. Geraldes R, Santos-Bento M, de Carvalho M. Cerebrotendinous xanthomatosis: no involvement of the autonomic nervous system in a case with severe neuropathy. Neurophysiol Clin 2007;37:47–49.
15. Verrips A, van Engelen BG, ter Laak H, Gabreels-Festen A, Janssen A, Zwarts M, et al. Cerebrotendinous xanthomatosis. Controversies about nerve and muscle: observations in ten patients. Neuromuscul Disord 2000;10:407–414.
16. Wang Z, Yuan Y, Zhang W, Zhang Y, Feng L. Cerebrotendinous xanthomatosis with a compound heterozygote mutation and severe polyneuropathy. Neuropathology 2007;27:62–66.
17. Ohnishi A, Yamashita Y, Goto I, Kuroiwa Y, Murakami S, Ikeda M. De- and remyelination and onion bulb in cerebrotendinous xanthomatosis. Acta Neuropathol (Berl) 1979;45:43–45.
18. Argov Z, Soffer D, Eisenberg S, Zimmerman Y. Chronic demyelinating peripheral neuropathy in cerebrotendinous xanthomatosis. Ann Neurol 1986;20:89–91.
19. Voiculescu V, Alexianu M, Popescu-Tismana G, Pastia M, Petrovici A, Dan A. Polyneuropathy with lipid deposits in Schwann cells and axonal degeneration in cerebrotendinous xanthomatosis. J Neurol Sci 1987;82:89–99.
20. Donaghy M, King RH, McKeran RO, Schwartz MS, Thomas PK. Cerebrotendinous xanthomatosis: clinical, electrophysiological and nerve biopsy findings, and response to treatment with chenodeoxycholic acid. J Neurol 1990;237:216–219.
21. Leitersdorf E, Reshef A, Meiner V, Levitzki R, Schwartz SP, Dann EJ, et al. Frameshift and splice-junction mutations in the sterol 27-hydroxylase gene cause cerebrotendinous xanthomatosis in Jews or Moroccan origin. J Clin Invest 1993;91:2488–2496.
22. Pedley TA, Emerson RG, Warner CL, Rowland LP, Salen G. Treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. Ann Neurol 1985;18:517–518.
23. Mondelli M, Rossi A, Scarpini C, Dotti MT, Federico A. Evoked potentials in cerebrotendinous xanthomatosis and effect induced by chenodeoxycholic acid. Arch Neurol 1992;49:469–475.
24. Mondelli M, Sicurelli F, Scarpini C, Dotti MT, Federico A. Cerebrotendinous xanthomatosis: 11-year treatment with chenodeoxycholic acid in five patients. An electrophysiological study. J Neurol Sci 2001;190:29–33.
25. Chang CC, Lui CC, Wang JJ, Huang SH, Lu CH, Chen C, et al. Multi-parametric neuroimaging evaluation of cerebrotendinous xanthomatosis and its correlation with neuropsychological presentations. BMC Neurol 2010;10:59.