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Electrophysiological studies in cerebrotendinous xanthomatosis

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Abstract

Seven patients with cerebrotendinous xanthomatosis (CTX) were studied by electrophysiological techniques. The percentages of abnormalities detected in nerve conduction studies and electroencephalograms were 28·6% (two patients) and 100%, respectively. All patients showed prolonged central conduction times in short latency somatosensory evoked potentials (SSEPs) by tibial nerve stimulation but normal SSEPs by median nerve stimulation. Brain stem auditory evoked potentials and visual evoked potentials were abnormal in three (42·9%) and four patients (57·1%), respectively. These electrophysiological parameters were correlated with the ratio of serum cholestanol to cholesterol concentration. The results of SSEPs suggest that the polyneuropathy in CTX is caused by distal axonopathy affecting longer axons before shorter axons (central-peripheral distal axonopathy).

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive disorder first described by van Bogaert *et al* in 1937.[1] Its main clinical manifestatons include tendon xanthomas, cataracts, intellectual disturbance, spastic paraparesis, cerebellar ataxia, peripheral neuropathy, and premature atherosclerosis.[2] Psychiatric disorders and osteoporosis have also been reported.[3 4] CTX is a lipid storage disease with an increase in cholestanol (the 5-α-dihydro derivative of cholesterol) concentration in both plasma and tissues.[5 6] Biochemical studies have shown that patients with CTX have abnormal bile acid synthesis due to a defect in hepatic 26-hydroxylase.[7] Biochemical, clinical, and electroencephalographic (EEG) improvements have been obtained after oral administraton of chenodeoxycholic acid.[8 9] Pedley *et al* reported on one patient with CTX who showed abnormalities in evoked potentials and improvement after treatment with chenodeoxycholic acid.[10] We performed electrophysiological studies in seven patients with CTX (*a*) to determine the correlation between serum cholestanol concentrations and the extent and severity of nervous system involvement and (*b*) to clarify the pathogensis of neuronal dysfunction in CTX.

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Patients and methods

Electrophysiological studies were performed in seven patients (six men and one woman) whose ages ranged from 35 to 50 (mean 40·3 years). The diagnosis of CTX was established from clinical manifestations and biochemical abnormalities. The subjects in cases 3 and 4 were siblings; the others were sporadic cases. The clinical features of and laboratory findings in patients will be described in detail in a separate report.[11] We also examined two heterozygote subjects (the mothers of the patients in cases 3 and 4 and in case 5), who showed no clinical manifestations. Serum cholesterol and cholestanol concentrations were determined by high performance liquid chromatography,[12] and the ratio of cholestanol to cholesterol concentration (%) was calculated. The ratio was raised in patients with CTX (1·93 (0·78)) compared with normal controls (0·15 (0·06)) and two carriers (0·13 and 0·15).

Motor nerve conduction velocities (MCVs) were measured in the median, posterior tibial, and common peroneal nerves. Sensory nerve conduction velocities (SCVs) were measured in the median, sural, and superficial peroneal nerves.

We investigated the short latency somatosensory evoked potentials (SSEPs). The median nerve was stimulated at the wrist (MN–SSEPs) and peak latencies of N_9 and N_{13} and interpeak latencies (IPLs) of N_{13}–N_{20} were recorded. To obtain lower limb SSEPs the posterior tibial nerve was stimulated at the ankle (TN–SSEPs). Peak latencies of N_{20} and

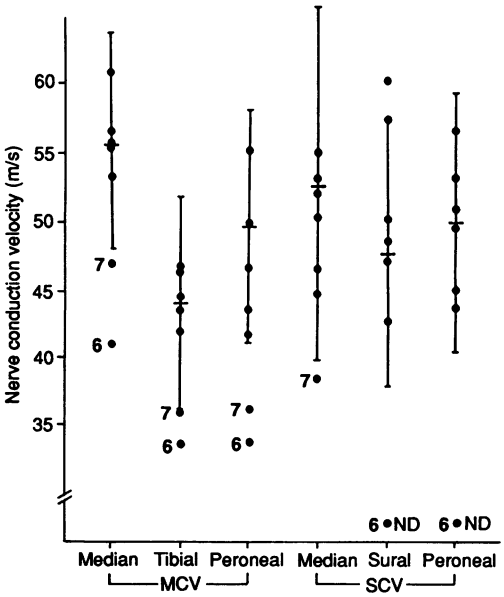

Figure 1 Nerve conduction velocities in seven patients with cerebrotendinous xanthomatosis (CTX); ND = not detected.

P_{40} and IPLs of N_{20}–P_{40} were also recorded.

Brain stem auditory evoked potentials (BAEPs) and pattern reversal visual evoked potentials (VEPs) were recorded in conventional ways. In all cases except case 2 subjects had cataracts, but in cases 1, 4, 5, and 6 the lenses had been removed and visual acuities were corrected by glasses. In cases 3 and 7 cataracts were very mild and visual acuities were not reduced.

Nerve conduction velocities and the evoked potentials were studied using an electromyograph (Mystro MS 25, Medelec, England). Values in excess of 2 SD or 2·5 SD from the mean value for the control subjects were judged to be abnormal.

Electroencephalograms (EEGs) were recorded using the international 10–20 system. Abnormalities were graded mild, moderate, or severe.

All subjects except in case 3 were treated with oral chenodeoxycholic acid for about a year. Electrophysiological studies were repeated after the treatment.

Results

Nerve conduction study

Results are shown in fig 1. MCVs were normal in cases 1, 2, 3, 4, and 5 but slow in cases 6 and 7. No SCVs for the sural and superficial peroneal nerves were detected in case 6 and the median SCV was slow in case 7. Two heterozygotes were normal.

SSEPs

For the MN–SSEPs the N_9 latency was recorded at Erb's point, the N_{13} latency at Cv2, and the N_{20} at the hand somatosensory area (fig 2, A). All these latencies were prolonged only in case 6. The N_{13-20} IPLs, however, were normal in all patients (fig 2, B).

For the TN–SSEPs (fig 3) the N_{20} latencies recorded at T12 were normal in five patients but were not detected in case 6 and were markedly prolonged in case 7; both of these patients had peripheral neuropathy. The P_{40} latencies recorded in the foot somatosensory area were all delayed except in case 3. The N_{20}–P_{40} IPLs were prolonged in all six subjects. We examined the TN–SSEPs in two heterozygotes for CTX as the N_{20}–P_{40} IPL may be a sensitive and suitable parameter for detecting the subclinical lesions. However, no abnormal findings were found in either heterozygote.

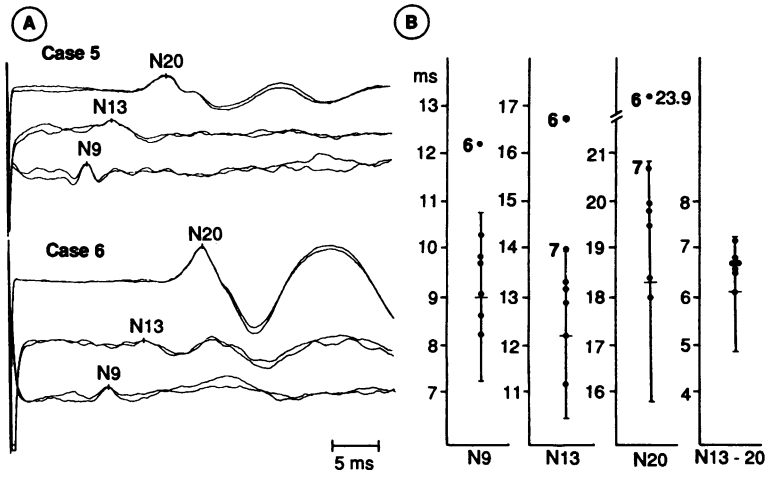

Figure 2 (a) Short latency somatosensory evoked potentials by median nerve stimulation (MN–SSEPs). (b) Peak and interpeak latencies of MN–SSEPs in seven patients with CTX.

BAEPs and VEPs

BAEP and VEP results are shown in fig 4. The I–V IPLs in the BAEPs were markedly prolonged in cases 5, 6, and 7. This was due to delayed I–III and III–V IPLs in cases 5 and 7 and to delayed I–III IPL in case 6. The P_{100} peak latencies of the VEPs were prolonged in cases 2, 4, 6, and 7 (fig 4, C).

EEG study

The EEGs of six subjects were examined. Cases 1, 2, and 4 showed increased slow waves which were judged to be mildly abnormal. In case 5 predominant activity at a frequency of 5–6 Hz was seen and judged to be severely abnormal. Cases 6 and 7 showed the presence of theta and delta waves and were judged to be severely abnormal.

Correlations between electrophysiological abnormalities and serum cholestanol to cholsterol ratio

All the patients had raised serum cholestanol concentrations and ratios of cholestanol to cholesterol concentration (%).

There were significant correlations between the serum cholestanol to cholesterol ratio and the MCVs, the N_{20}–P_{40} IPLs in the TN–SSEPs, and the I–V IPLs in the BAEPs (fig 5). No significant correlations were found between the ratio and the P_{100} peak latencies in the VEPs or SCVs.

Electrophysiological parameters after treatment

The six subjects who had extensive treatment for about a year showed a 60–80% reduction on the serum cholestanol concentration and the ratio of cholestanol to cholesterol. Some patients showed an improvement in EEG findings after short term treatment. However, each parameter of the electrophysiological examinations, including the EEG findings presented, did not improve and none of them were normal after a year's treatment.

Discussion

Central nervous system signs that include intellectual disturbances, cerebellar ataxia, pyramidal tract signs, sometimes convulsions, and peripheral neuropathies have been observed in patients with CTX.[2] Our study, which used multimodal electrophysiological examinations, detected the subclinical involvement of the central and peripheral nervous systems. The TN–SSEPs, BAEPs, and VEPs showed high percentages of abnormalities (100%, 42·9%, and 57·1%, respectively), whereas there were no abnormalities in any of the MN–SSEPs. Nerve conduction velocities were delayed in two cases (28·6%),

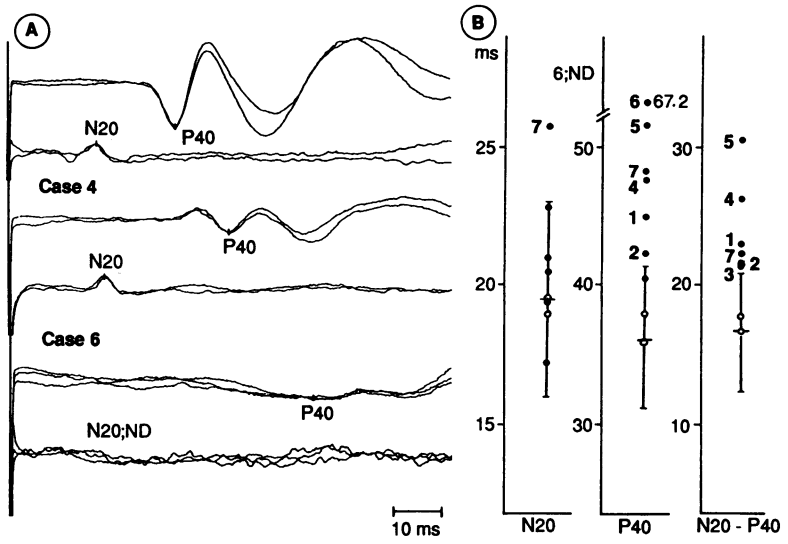

Figure 3 (a) Short latency somatosensory evoked potentials by tibial nerve stimulation (TN-SSEPs). (b) Peak and interpeak latencies of TN-SSEPs. Solid circles indicate patients with CTX (n = 7), open circles heterozygotes for CTX (n = 2); ND = not detected.

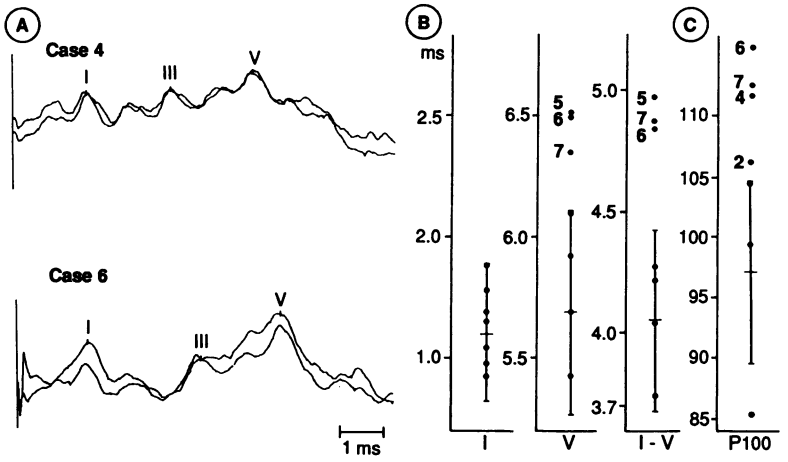

Figure 4 (a) Brain stem auditory evoked potentials (BAEPs). (b) Peak and interpeak latencies of BAEPs in seven patients with CTX. (c) P_{100} peak latencies of visual evoked potentials (VEPs) in seven patients with CTX.

and EEGs showed that there were mild to severe abnormalities in all the subjects examined. On the other hand, the MCVs, SCVs, and TN-SSEPs for two carriers of CTX were normal.

An increase in serum cholestanol concentration is diagnotic for CTX but the cholestanol to cholesterol ratio is a better biochemical parameter for the diagnosis and severity of CTX.[11] This ratio showed a positive correlation with the thickness of the Achilles' tendon.[13] We analysed the correlations between the ratio of cholestanol to cholesterol and certain electrophysiological parameters. The MCVs, N_{20}–P_{40} IPLs in the TN-SSEPs, and I–V IPLs in the BAEPs correlated significantly with this ratio. In addition, severely affected patients who had high ratios showed multiple abnormalities in these parameters; therefore, these parameters may prove useful indicators of the severity of neuronal dysfunction and may reflect the metabolic imbalance in patients with CTX.

These parameters did not show remarkable change after the oral administration of chenodeoxycholic acid for a year. Berginer *et al* and Pedley *et al* described marked improvement in EEG findings and evoked potentials after the treatment with chenodeoxycholic acid.[9 10] Our data suggest that the nervous function in our patients may be irreversibly damaged and that such patients should be treated in the early stages of the disease. Pop *et al*[14] and Ugawa *et al*[15] reported electrophysiological studies in patients with CTX but did not comment on the relation between their electrophysiological abnormalities and biochemical data, or report the effect of the treatment.[14 15]

Peripheral neuropathy occasionally occurs in CTX. Kuritzky *et al* described four cases with polyneuropathy and reported that the degree of peripheral nerve damage seemed to parallel the degree of involvement of the central nervous system.[16] In our study two of the seven patients (28·6%) had peripheral neuropathy. Both also showed severe abnormalities in their TN-

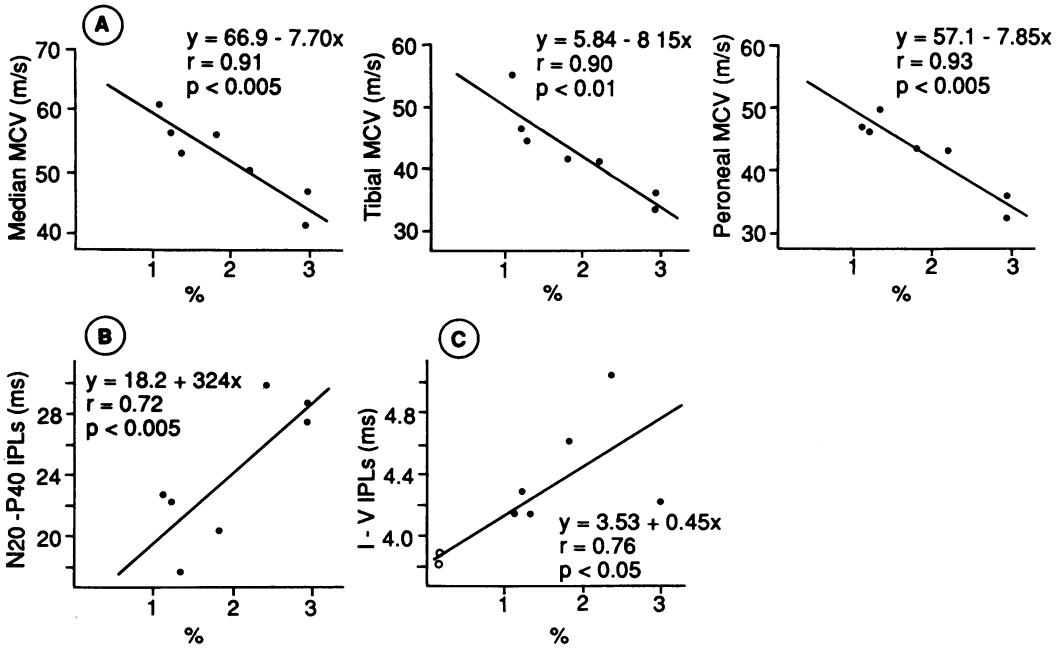

Figure 5 Correlation between electrophysiological parameters and serum cholestanol to cholesterol ratio (%)—A-1 median MCV; A-2, tibial MCV; A-3, common peroneal MCV, B, N_{20}–P_{40} interpeak latencies of TN-SSEPs (solid circles indicate patients with CTX (n = 6), open circles heterozygotes for CTX (n = 2)); C, I-V interpeak latencies of BAEPs.

SSEPs, BAEPs, VEPs, and EEGs and had remarkably high ratios of cholestanol to cholesterol concentration in their serum compared with the five others who had normal MCVs and SCVs. We conclude that peripheral nerves are involved in severe cases of CTX.

The pathogenesis of peripheral neuropathy in CTX is still in doubt. Ohnishi *et al* emphasised the demyelination process and Argov *et al* supported it.[17 18] Pop *et al* reported that biopsy specimens of sural nerve showed moderate axonal degeneration mixed with slight segmental demyelination and remyelination and that in one case at necropsy the dorsal columns of the spinal cord were more prominently involved proximally than distally; however, the pyramidal tracts were involved distally more than proximally.[14] They concluded that neuroaxonal factors were more important than segmental demyelination on the pathogenesis of neurological manifestations in both the central and the peripheral nervous systems. By contrast, Katz *et al* speculated that peripheral nerve lesions could be induced by mechanically compressive and ischaemic process on a nerve by tendon xanthoma.[19] Recently, Voiculescu *et al* and Donaghy *et al* reported polyneuropathy with axonal degeneration and lipid deposits in Schwann cells.[20 21] Our study showed normal N_{13-20} IPLs in the MN–SSEPs and delayed N_{20}–P_{40} IPLs in the TN–SSEPs in all the subjects examined. These SSEP findings may be evidence of pathological changes in the posterior column as has been reported by Pop *et al*.[14] Two of the seven subjects in our study had prolonged MVCs and SCVs. Pathological findings in biopsy specimens of the sural nerves in cases 6 and 7 showed marked decreases of large myelinated fibres and demyelination, which suggests chronic axonal degeneration (unpublished data). Taken together, these findings suggest that central-peripheral distal axonopathy plays a part in the pathogenesis of lesions of the central and peripheral nervous systems in CTX.

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