Electrophysiological Studies in Five Cases of Abetalipoproteinemia

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SUMMARY: Auditory brainstem responses (ABRs), visual and somatosensory evoked responses (VEPs and SEPs) and nerve conduction studies were conducted in 5 patients with abetalipoproteinemia. The ABRs were normal in all cases. The VEPs were of normal amplitude but of increased latencies in two patients. The four eldest patients had delayed cortical SEPs but normal peripheral sensory nerve conduction studies. The peripheral motor conduction velocities were normal in all cases. The peripheral sensory studies showed normal velocity when a response was seen; however, the amplitude of the response was often reduced or it was absent. The electrophysiological studies reported here support a model of axonal loss of large myelinated fibres with secondary demyelination in abetalipoproteinemia.

RÉSUMÉ: Nous avons étudié 5 patients avec abetalipoprotéinémie quant aux potentiels évoqués auditifs du tronc (ABR), et aux réponses évoquées visuelles (VEP) et somato-sensitives (SEP). Les ABR étaient normaux dans tous les cas. Les VEP étaient d'amplitude normale mais de latence augmentée chez 2 patients. Les 4 plus vieux patients avaient des SEP ralentis mais des conductions sensitives périphériques normales. Les conductions motrices étaient toutes normales. Les études périphériques montraient une vélocité normale lorsqu'une réponse était obtenue, mais une amplitude diminuée ou absente. Ces résultats sont compatibles avec une perte axonale des grosses fibres myélinisées et une démyélinisation secondaire dans l'abétalipoprotéinémie.

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Abetalipoproteinemia was first described by Bassen and Kornzweig in 1950. Since then more than 50 cases have been reported. The typical presentation is fat malabsorption with diarrhea and failure to thrive in infancy (Muller et al., 1977). Significant laboratory findings include the presence of acanthocytes in the blood smear and a low level of serum cholesterol. On lipoprotein electrophoresis the betalipoprotein fraction is absent (Salt et al., 1960). The disease is inherited in an autosomal recessive fashion.

Signs and symptoms of nervous system involvement appear within the first decade. The classic findings are ataxia of gait associated with a loss of tendon reflexes. Eventually there is distal loss of sensation involving mainly modalities carried by the posterior columns (Miller et al., 1980). Pes cavus and scoliosis may occur and the clinical picture can be indistinguishable from cases of Freidreich's ataxia. Retinitis pigmentosa develops later in the disease. Recent workers have suggested that the neurological and ophthalmologic problems in abetalipoproteinemia may be prevented by early treatment with large doses of oral vitamin E (Muller and Lloyd, 1982; Aziz et al., 1978).

Recently a number of investigators have reported evoked potential abnormalities in several of the hereditary degenerative disorders (Pedersen and Trojaborg, 1981; Livingstone et al., 1981; Bird and Crill, 1981). The present study investigates nerve conduction and multimodal evoked potentials in five abetalipoproteinemia patients. The results are discussed and compared to those found in Freidreich's ataxia patients.

Methods

Subjects

Five patients (2 female) with abetalipoproteinemia were studied. Their ages ranged from 6-21 years (mean 14). Their clinical data are summarized in Table 1. Twenty neurologically normal children (12 female) served as controls; their ages ranged from 5-17 years (mean 12).

Procedure

Visual, auditory and somatosensory evoked responses were completed in one session. A Nicolet CA-1000 clinical signal averager was used to collect the data; automatic artefact reject was used throughout to remove unwanted signal due to movement of the patient. Visual evoked potentials (VEPs) were recorded with a bandpass of .5-100 Hz, a gain of 20k and a sweep of 200 msec. They were elicited by reversing checkerboard pattern stimulation; the visual display subtended 12° and the checks 30′ of arc and reversed at a rate of 1.88/sec. VEPs were recorded over left and right occipital lobes (01 and 02) referenced to Fz. Sixty-four trials per average were recorded in response to monocular stimulation. For all evoked resonse studies Grass gold cup electrodes were used; electrode impedance was always below 5kOhms.

Auditory brainstem responses (ABRs) were recorded using the same equipment but with a bandpass of 150-3k Hz, a gain of 100k and a sweep of 10 msec. The stimuli were 100 μsec rarefaction, monaural click stimuli, presented at 70 or 80 dBHL (70 or 80 dB above the average hearing threshold of 10 adults with normal hearing in the lab) and a rate of 11/sec. The ABRs were recorded between Cz and stimulated ear; contralateral masking (-30dB) was used to prevent cross-stimulation. Two averages of 1024 trials were obtained at each intensity level tested for each year.

Somatosensory evoked potentials (SEPs) were recorded with a bandpass of 30-3K Hz, a gain of 40k and a sweep of 50 msec. Electrical pulse stimulation to the median nerve at the wrist

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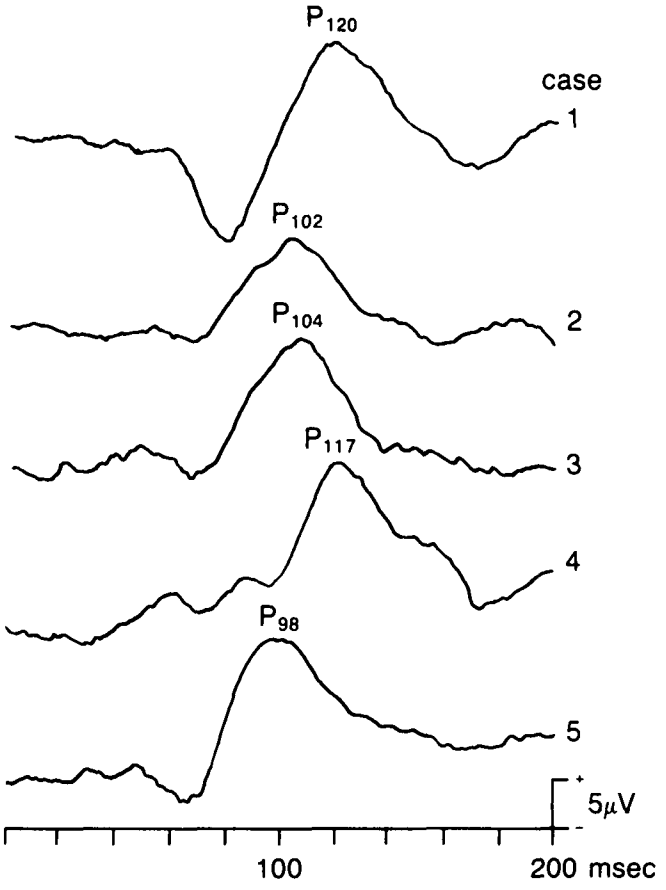

Figure 1 — VEP's from five abetalipoproteinemia patients showing increased P100 latencies in patients 1 and 4. These patients had no clinically apparent visual abnormalities.

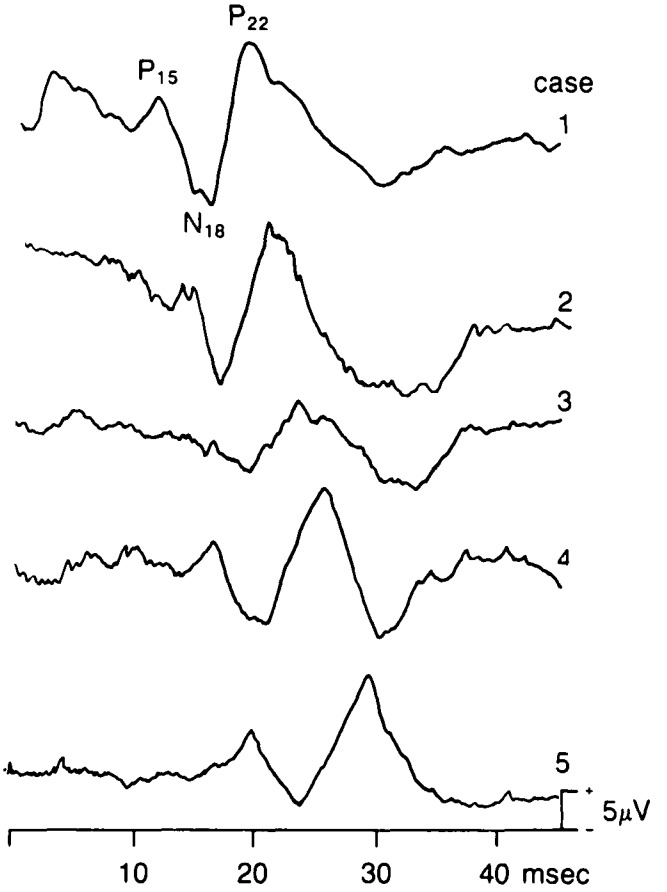

Figure 2 — SEPs from five abetalipoproteinemia patients. The SEPs were normal in case 1, but both the absolute latencies (corrected for arm length) and interpeak latencies were increased in the four older patients. This was particularly marked with the cortical components (N18 and P22).

Table 1: Summary of clinical data from 5 patients with abetalipoproteinemia

	Age At Diagnosis	Presenting Symptoms	Age at Study	CNS
1.	16 months	Diarrhea x 4 months	9 years	Normal
2.	6 months	Vomiting Failure to thrive	12 years	Poor co-ordination Areflexia Position sense Ataxic gait I.Q. 70
3.	11 years	Diarrhea Failure to thrive Misdiagnosed as coeliac	13 years	Poor co-ordination Areflexia I.Q. 81
4.	5 years	Diarrhea x 3 years Misdaignosed as coeliac	17 years	Mild ataxia of gait Areflexia Position sense I.Q. 72
5.	12 years	Poor weight gain Acanthocytes on routine blood smear	21 years	Ataxic gait Areflexia Position sense Sensation to touch

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Table 2: Latencies (msec) of P100 component of VEPs in abetalipoproteinemia patients

		O1	O2
1.	o.d.	117*	100
	o.s.	123*	100*
2.	o.d.	104	103
	o.s.	102	103
3.	o.d.	104	108
	o.s.	106	109
4.	o.d.	119*	120*
	o.s.	121*	120*
5.	o.d.	95	96
	o.s.	99	95

Normal Values; mean: 97; s.d.: 5.1; upper limit: 110
*Increased latency

was used. The duration of the pulses was 200 μsec and they were presented at a rate of 4.1/sec. Stimulation intensity was gradually increased until a slight thumb movement was observed, and the studies were then run at the level of stimulation. The motor threshold was determined separately for left and right median nerve stimulation. The SEPs were recorded over the postcentral contralateral cortex (C3′ and C4′) referenced to Fpz. The SEP latencies were all standardized to age-matched controls; the latencies were divided by the ratio of the patient's arm length to the mean arm length for the normal controls of the same age. It was then determined whether the standardized latencies fell within the normal range (mean ± 2.5 s.d.). This procedure allowed the latencies to be assessed, independent of arm length, with age-matched controls.

Motor conduction velocities were determined using conventional techniques. Sensory nerve action potentials were recorded orthodromically with surface electrodes over the median nerve at the wrist. The sensory action potentials in the sural nerve were recorded antidromically with surface electrodes behind the lateral malleolus at the ankle.

Results

The data are summarized in Tables 2-4. Absolute latencies and interpeak latencies for the ABRs were within normal limits in all cases. There was no suggestion of hearing impairment or damage within the auditory brainstem pathway.

The VEPs were of normal amplitude in all five patients but of increased latency ($p < .01$) in patients 1 and 4 (Figure 1, Table 2). Neither patient had any clinical evidence of opthalmic disease. SEP abnormalities were found in the four oldest patients; both absolute wave latencies (adjusted for arm length) and the interpeak latencies (reflecting central conduction) were prolonged compared to age matched controls (Figure 2, Table 3). Clinically, three of these patients had impaired position sense and the eldest had decreased sensation to touch. Abnormal SEPs are most often associated with posterior column abnormalities but one patient with delayed SEPs had no clinical evidence of sensory loss.

The motor conduction velocities were within normal limits in all patients. The sensory studies, however, showed potentials of decreased amplitude or absent responses (Table 4). Patient 3 had an abnormal median nerve SEP with a normal peripheral sensory response. As with the SEPs the degree of abnormality in the nerve conduction studies was more pronounced in the older patients.

Table 4: Results of nerve conduction studies

		Maximum motor velocity m/sec	Amplitude of sensory response μv
1.	Median	58.6 (N48-66)	Median 14.2 (N>8)
	Post. Tibial	48.9 (N38-60)	Sural 7.0 (N>8)
2.	Ulnar	55.9 (N52-66)	Median 4.0
	Peroneal	50.4 (N38-60)	Sural -absent response
3.	Median	70.0	Median 10.0
	Peroneal	43.4	Sural -absent response
4.	Median	58.3	Median -absent response
	Post. Tibial	39.7	Sural 2.0
5.	Ulnar	66.2	Median 7.3
	Post. Tibial	52.3	Sural -absent response

Discussion

This is the first report of central conduction abnormalities in abetalipoproteinemia. VEP and SEP abnormalities were found in patients both with and without clinical evidence of sensory involvement.

Although there are a series of similarities in presentation, in electrophysiology and in pathology between abetalipoproteinemia and the more extensively studied Friedreich's ataxia, there are also pathognomonic differences. The neuropathy in Friedreich's

Table 3: Latencies (msec) of SEP components in abetalipoproteinemia patients, standardized for arm length with age-matched controls

	Erb/s pt.	P15	N18	P22	P15-N18	N18-P22	P15-P22
1. r.m.n.	—	11.6	15.2	19.2	3.6	4.0	7.6
l.m.n.	—	11.6	15.3	18.8	3.7	3.5	7.2
2. r.m.n.	8.9	18.0*	15.2*	19.2*	4.2	5.7*	9.9*
l.m.n.	8.9	15.1	18.9	24.8*	3.8	5.9*	9.7*
3. r.m.n.	—	15.0	20.4*	23.8*	5.4*	3.4	8.8*
l.m.n.	—	15.4*	18.8	24.4*	3.4	5.6*	9.0*
4. r.m.n.	9.0	17.7*	21.5*	27.5*	3.8	6.0*	9.8*
l.m.n.	—	16.8	21.5*	27.4*	4.7	5.9*	10.6*
5. r.m.n.	8.8	20.3*	23.4*	29.4*	3.1	6.0*	9.1
l.m.n.	8.6	20.2*	23.5*	28.5*	3.3	5.0	8.0

— not tested
* increased latency
r.m.n. right median nerve stimulation
l.m.n. left median nerve stimulation

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ataxia is felt to be due to a professive loss of large myelinated fibres (Dyck et al., 1971; McLeod, 1979; Peyronnard et al., 1976). The typical electrophysiological findings in those studies consisted of normal motor conduction with reduced or absent sensory action potentials. Miller et al. (1980) demonstrated similar findings in the peripheral nervous system of three patients with abetalipoproteinemia. He examined sural nerve biopsies on the three patients and found a loss of fibres in the large diameter range. Our findings of normal motor conduction velocities and reduced or absent sensory potentials are in agreement with those of Miller et al. (1980) and support the concept that the primary pathological mechanism in abetalipoproteinemia is loss of large myelinated axons.

The SEP abnormalities in our patients — delayed cortical responses — are similar to those found in Friedreich's ataxia. Jones et al. (1980), discussed four possible mechanisms for the SEP abnormalities in Friedreich's ataxia: 1) loss of large diameter axons in the peripheral nerve and posterior columns, 2) segmental or paranodal demyelination, 3) abnormal synaptic transmission in the gracile and cuneate nuclei and 4) abnormal formation of myelin in the central nervous system. He concluded that the most likely explanation was an axonal type of dying back neuropathy affecting the dorsal columns. Because of the similarities in the results of the SEPS and nerve conduction studies, we believe that the pathology in abetalipoproteinemia is also that of an axonal neuropathy. The relative preservation of SEP amplitudes in this study may be explained by the more slowly progressive nature of abetalipoproteinemia compared to Friedreich's ataxia. The findings of increasing SEP abnormalities with duration of disease may be a method of quantitatively evaluating the effect of such therapies as high dose vitamin E on the natural progression of abetalipoproteinemia.

In the two patients with abnormal VEPs, the P100 latencies were increased but the amplitudes were normal. This finding is most likely attributable to the same process that affects the somatosensory system — axonal neuropathy with paranodal demyelination. This is in line with the pathophysiological models of the degenerative process in Friedrich's ataxia proposed by several groups investigating VEPs in that disorder (Halliday, 1981; Carroll et al., 1980; Kirkham and Coupland, 1981). There is considerable variability, however, in the VEP abnormalities described in the reports. A clear answer as to the pathophysiology in both the visual and somatosensory systems in abetalipoproteinemia will only be provided by careful neuropathological examinations of the sensory pathways. Future electrophysiological studies with these patients, however, should include electroretinograms as well as VEPs, as these patients can develop retinitis pigmentosa and it would be important to differentiate between peripheral and central abnormalities in this pathway.

The normal ABRs in abetalipoproteinemia clearly differentiate these patients electrophysiologically from Friedreich's ataxia. Several groups have found abnormal ABRs in Friedreich's ataxia (Pederson and Trojaborg, 1981; Satya-Murti et al., 1980). Taylor et al. (1982) have shown the progressive loss of ABR waveforms with increasing duration of the disease. There is also pathological evidence of involvement of the auditory pathway in the periphery, pons and midbrain in Friedreich's ataxia (Oppenheimer, 1979). The limited autopsies of abetalipoproteinemia reported in the literature (Brin, 1983; Sobrevilla et al., 1964; Dische et al., 1970) mention the predominance of abnormalities in the posterior columns, spinocerebellar tracts and peripheral nerves. The pons and midbrain did not appear to be involved in the disease. This conclusion is supported by the preservation of the ABR waveforms in all our patients.

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