Longitudinal Multimodal Evoked Potential Studies in Abetalipoproteinaemia

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ABSTRACT: Recent studies have reported that in abetalipoproteinaemia patients high dose vitamin E therapy may arrest or improve the neurological syndrome. Five patients with abetalipoproteinaemia have been followed since 1982, when all were started on high dose vitamin E therapy. Auditory brainstem responses (ABR), visual evoked potentials (VEP), and sensory evoked potentials (SEP) were recorded every six to twelve months. The vitamin E levels stayed below normal range in all patients; the neurological status remained relatively stable in most of the patients over the four years. The ABRs were consistently normal in all patients over the period of study. The VEPs improved in one patient with introduction of vitamin E therapy, and remained stable in the others, one of whom always had abnormal VEPs. The cortical SEPs were abnormal in all but the least affected patient and fluctuated in the two patients who also demonstrated some deterioration in neurological status. These results suggest that serial assessments combining neurological and neurophysiological studies provide important information in the follow-up of patients with abetalipoproteinaemia and that the SEP is the evoked potential best suited for the detection of the neurological changes in this disorder.

RÉSUMÉ: Etudes longitudinales des potentiels évoqués multimodes dans l'abêta lipoprotéinémie. Il a été rapporté dans des études récentes que le traitement par la vitamine E à hautes doses peut arrête ou améliorer le syndrome neurologique chez les patients souffrant d'abêtalipoprotéinémie. Cinq patients atteints d'abêtalipoprotéinémie ont été soumis à un traitement par la vitamine E à hautes doses et suivis depuis 1982. Les potentiels évoqués auditifs (PEA) les potentiels évoqués visuels (PEV) et les potentiels évoqués sensitifs (PES) étaient enregistrés à tous les six à douze mois. Les niveaux de vitamine E sont demeurés sous la normale chez tous les patients; l'état neurologique est demeuré relativement stable chez la plupart des patients pendant les quatre ans. Les PEA sont demeurés normaux chez tous les patients pendant toute la durée de l'étude. Les PEV se sont améliorés chez un patient avec l'introduction du traitement par la vitamine E et sont demeurés stables chez les autres, dont un qui avait toujours eu des PEV anormaux. Les PES corticaux étaient anormaux chez tous, sauf chez les patients les moins affectés et fluctuaient chez les deux patients qui manifestaient aussi une certaine détérioration de leur état neurologique. Ces résultats suggèrent que des évaluations en série comprenant des études neurologiques et neurophysiologiques fournissent des renseignements importants pour le suivi des patients atteints d'abêtalipoprotéinémie et que les PES est le potentiel évoqué qui est le plus approprié pour la détection des changements neurologiques dans cette maladie.

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Abetalipoproteinaemia was first described in 1950 by Bassen and Kornzweig[1] in an 18 year old girl with a neurological picture consistent with Freidreich's ataxia, an atypical retinitis pigmentosa and malformation of the erythrocytes. Since the original description of abetalipoproteinaemia, or Bassen-Kornzweig syndrome, it has been recognized that the disorder is an inherited lipoprotein deficiency state. The manifestations include fat malabsorption, atypical retinitis pigmentosa, acanthocytosis and a neurological syndrome characterised by ataxia and areflexia. There may also be skeletal abnormalities such as scoliosis and pes cavus, features which further emphasize the similarity to Friedreich's ataxia.[2] It is thought that the neurological abnormalities in the disorder are due, at least in part, to the malabsorption of the fat soluble vitamins, particularly vitamin E. High dose therapy with this vitamin, may arrest or even improve the neurological syndrome.[3,4]

We report the results of longitudinal multimodal evoked potential (EP) studies on a group of 5 patients with abetalipoproteinaemia after the commencement of high dose vitamin E therapy and comment on the role of EPs in the follow-up of these patients. The initial EP studies and brief clinical histories have been previously reported.[5]

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Table 1: Summary of Clinical Data of Five Patients with Abetalipoproteinaemia

PT	Age at Diagnosis	Presenting Symptoms	Consanguinity	High Dose Vitamin E & Serial EPS Begun
1	16 mths	Failure to thrive, steatorrhoea	No	9 yrs
2	5 yrs	Diarrhoea for 3 yrs, misdiagnosed as coeliac disease	Yes	17 yrs
3	11 yrs	Poor growth, malabsorption, misdiagnosed as coeliac disease	No	13 yrs
4	7 mths	Failure to thrive, steatorrhoea, rickets	No	12 yrs
5	12 yrs	Admitted for surgical correction of congenital ptosis	Yes	21 yrs

METHODS

Five patients with abetalipoproteinaemia have been followed with multimodal EP studies since 1982. Their clinical data are summarised in Table 1. Case histories and findings on initial neurological examinations were obtained from a review of the medical charts. Neurological examinations were performed by one of the authors (EF) at the time of the most recent EP studies. Vitamin E determinations in blood were performed regularly over the four year period.

Visual, auditory and somatosensory evoked potentials were recorded at six to twelve monthly intervals using the techniques described in the initial report.[5] The first studies were performed prior to the commencement of high dose vitamin E therapy. The EPs were recorded and scored by one of the authors (MJT) who was blinded to the patients' clinical status. ERGs were not recorded.

RESULTS

Clinical Features

Patients were numbered 1-5 according to their neurological status, Patient 1 having the least neurological involvement. The clinical examination of Patient 1 was unchanged throughout the four year study period. He had no retinopathy, no ataxia but mild generalized hyporeflexia was present. Patient 2 had mild retinopathy, minimal ataxia and absent reflexes at the commencement of high dose vitamin E therapy. On his most recent assessment biceps jerks were present, but depressed, bilaterally and the remainder of his clinical examination was unchanged. Patients 3 and 4 had mild retinopathy, mild ataxia, areflexia and reduced proprioception and vibration sense. Minimal weakness and wasting of the small muscles of the hands, not previously documented, were present. In addition, Patient 4 had developed significant scoliosis. Patient 5 had the most marked neurological signs with retinopathy, moderate ataxia, areflexia and moderate sensory loss. The neurological status of this patient has remained stable over the last four years.

Vitamin E Levels

Vitamin E levels were measured at outpatient visits prior to the initiation of high dose vitamin E therapy and yearly thereafter. All results were less than 3 μmol/l, well below the normal range (7-12 μmol/l). Patients 1 and 2 showed a slight increase in their vitamin E levels while on high dose vitamin E therapy but patients 3, 4 and 5 had consistently low levels (less than 1 μmol/l) before and during high dose treatment.

Evoked Potentials

ABRs Absolute latencies and interpeak latencies for the ABRs were within normal limits in all cases; no changes were observed over the course of the study.

VEPs The VEPs were of normal amplitude in all patients. Patient 1 had delayed VEPs on the initial study, subsequently showing some improvement, but remaining at the upper limit of normal. In patient 2 the VEPs were consistently delayed over the period of study; in patients 3 and 4 the latency values were at the upper limits of normal and patient 5 had consistently normal responses. Apart from patient 1, there was only the usual test-retest variability affecting the stability of the VEPs over the four years.

SEPs The results of serial SEPs are presented in Table 2. The spinal responses were normal in all patients. Patient 1 always had normal cortical SEPs with the amplitude, morphology and latency of the waveforms being well within normal limits. Patient 2 had consistently prolonged latency of cortical SEPs with normal morphology and amplitude. The SEPs remained stable throughout the study period. In patient 3 the initial SEP study showed cortical responses with a mild increase in latency but with low amplitude waveforms. At first follow-up study, no reproducible cortical responses were obtained on right median nerve stimulation and only very low amplitude responses were obtained on the left. Subsequent studies demonstrated a slight improvement and usually low amplitude responses could be obtained. The most recent study showed a low amplitude response with only the N20 and P22 components being present and both demonstrating a slight latency shift. The initial responses of patient 4 were of low amplitude and poorly defined. Again, at the first follow-up, no reproducible cortical SEPs were obtained

Table 2: Serial SEPs — Cortical Responses

	1982 R - L	1983 R - L	1984 R - L	1985 R - L	1986 R - L
Pt 1	N N	N N	N N	N N	N N
Pt 2	↑ ↑	↑ ↑	↑ ↑	↑ ↑	↑ ↑
Pt 3	↓ ↓	NR NR	NR PR	PR PR	↓ ↓
Pt 4	↓ ↓↑	PR NR	PR PR	↓ ↓	↓ ↓
Pt 5	↑ ↑	↑ ↑	↑ ↑	↑ ↑	↑ ↑

↓ — decreased amplitude
↑ — increased latency
N — normal
PR — poorly defined response
NR — no recognizable response

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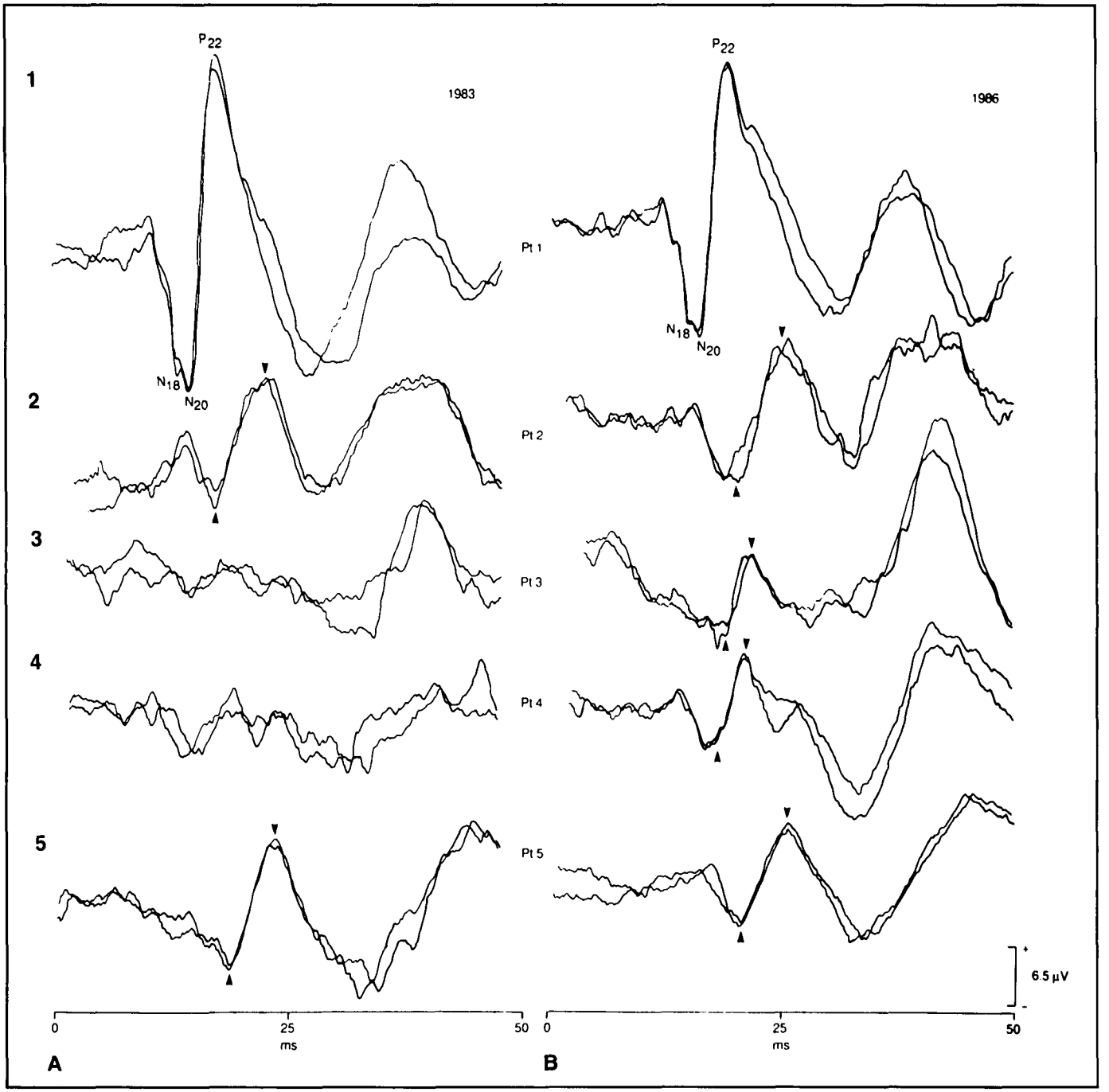

Figure 1 — Cortical SEPs recorded in the 5 patients in 1983 (A) and in 1986 (B) showing the normal SEPs in Pt. 1 and the abnormal, but stable SEPs in Pts. 2 and 5. The SEPs in Pts. 3 and 4 varied over the course of the studies (see text and Table 2) with no clearly identifiable components in 1983, but improved although still abnormal SEPs in 1986.

and subsequent studies showed low amplitude, poorly defined, delayed waves with a mild asymmetry, the response over the right cortex being worse than that over the left. Patient 5 demonstrated well defined cortical responses but always with a marked latency shift (Figure 1).

Discussion

Abetalipoproteinaemia is a genetically determined disorder in which the plasma lipoproteins containing apoprotein B (apo B) are deficient, either due to a defect in the synthesis of apo B or failure of the intracellular assembly of apo B with lipid. As a result of this deficiency there is fat malabsorption including the fat soluble vitamins A, D, E and K.[6] There is a relationship between the neurologic abnormalities associated with the disorder and the deficiency of these fat soluble vitamins. Patients with abetalipoproteinaemia have been demonstrated to arrest their retinal deterioration with a combined therapy of vitamin A and E. ERGs show an improvement after vitamin A replacement, however, vitamin A alone is not sufficient to prevent retinal degeneration and adequate vitamin E is also required.[7] Neuro-

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logical syndromes similar to that seen in abetalipoproteinaemia are observed in patients with vitamin E deficiency, which may be either idiopathic or secondary to liver dysfunction or malabsorption.[8,9,10] The efficacy of vitamin E therapy in patients with abetalipoproteinaemia has been widely reported. Accumulating evidence supports the role that vitamin E deficiency has in the development of the neurological syndrome associated with abetalipoproteinaemia, although the pathophysiology remains uncertain. Since the introduction of high dose vitamin E therapy the neurological outlook for these patients has improved.[3,4,11,12]

Pathological studies in patients and animals have shown that vitamin E deficiency produces loss of sensory axons in posterior column and nerve roots, loss of large caliber myelinated fibres, spheroids and mild degenerative changes in the spinocerebellar tracts.[13,14,15] Neuropathological reports on patients with abetalipoproteinaemia are relatively scarce. Studies on peripheral nerves have demonstrated either a modest degree of segmental demyelination comparable to a chronic primary axonal neuropathy or patchy demyelination. Marked demyelination of the posterior columns with less marked changes in the dorsal and ventral spinocerebellar tracts is described. Loss of nuclei in the anterior horn cells, cerebellar molecular layer and Betz cell layer with slight demyelination in the corticospinal tract may also be present.[16,17,18,19]

Lowry et al[5] were the first to report multimodal EPs in these same patients with abetalipoproteinaemia. In these initial studies the ABRs were normal, the VEPs showed a slight latency shift in one patient while the SEPs demonstrated both loss of amplitude and latency increases. In a report of multimodal EPs in one patient with abetalipoproteinaemia, only serial SEPs demonstrated any abnormalities and their stability correlated well with the stability of the neurological examination.[20] Brin et al[12] also found normal ABRs in all ten of their patients. Three patients had prolonged VEP latencies all of whom had an abnormal ERG; however, not all patients with an abnormal ERG had prolonged VEPs. Nine of the ten patients had abnormal SEPs with the abnormality being in central conduction time. In the 5 patients who had more than one study, there was either an improvement or no change in the follow-up studies.

In our group of patients with abetalipoproteinaemia, all had normal ABRs and no clinical abnormality of hearing was detected. This is consistent not only with the available neuropathology, which to date has not demonstrated any involvement in the pons or midbrain, but also with the other published reports.

In the one patient (patient 2), who had consistently prolonged VEPs, there was evidence of a mild retinopathy while in the 3 who had latencies at the upper limits of normal, only one had clinical evidence of retinopathy. Patient 5 who has a definite retinopathy has consistently normal VEPs. Hence a retinopathy of its own does not necessarily prolong the latency of the VEP and other mechanisms may need to be invoked; e.g., involvement of the visual pathway in a demyelinating process. Without the benefit of ERGs it is difficult to be sure of the significance of the latency prolongation. In future studies, it would be important to incorporate ERGs into routine electrophysiological monitoring of patients with abetalipoproteinaemia. This would facilitate detection of early retinopathy and the assessment of treatment response. ERGs could also assist in the differentiation of peripheral from central disturbances of the visual pathways.

The SEPs demonstrated the most significant abnormalities. The peripheral response was normal in all patients but the central response was frequently abnormal. In patients 1, 2 and 5 the cortical response of the SEP remained fairly stable over the study period and this coincided with the stability of their neurological status. Patient 1 had an almost normal examination correlating with his normal SEPs. Patient 2 whose neurological findings were minimal had a significantly prolonged latency on his cortical response suggesting that the SEP is able to detect neurological abnormalities which are not clinically apparent. Patients 3 and 4 demonstrated some fluctuations in their SEPs, but the most recent studies were only minimally worse than the initial ones. These 2 patients had findings on their neurological examinations which had not been documented previously: slight weakness and wasting of the small muscles of the hand but no increase in the degree of ataxia and incoordination. The patients most involved neurologically (patients 3, 4 and 5) also demonstrated the most marked SEP abnormalities and the lowest vitamin E levels. The changes in the SEPs are consistent with both a loss of axons (low amplitude) and demyelination (prolonged latency) in sensory pathways; the neuropathological data previously reported in patients with abetalipoproteinaemia and vitamin E deficiency[13-19] suggests that both these processes may be present. It is interesting to note that patient 5, who had the most severe neurological involvement had SEPs with good morphology but prolonged latencies. Patients 3 and 4, both of whom had relatively mild neurological signs, had SEPs where the most striking abnormality was low amplitude, poorly formed cortical responses. One could postulate that this may be due to differences in the predominant underlying pathology, demyelination versus axonal loss.

These results indicate that serial assessments combining neurological and neurophysiological studies provide important information in the follow up of patients with abetalipoproteinaemia and that the SEP is the evoked potential best suited for the detection of the neurological changes in this disorder. The SEPs detected neurological dysfunction not clinically apparent and demonstrated the most marked abnormalities in patients with the most significant clinical findings, but without directly paralleling the neurological status of these patients.

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