Evoked Potential Studies in Friedreich's Ataxia and Progressive Early Onset Cerebellar Ataxia

M. Vanasse, L. Garcia-Larrea, Ph. Neuschwander, P. Trouillas and F. Mauguière

ABSTRACT: We recorded somatosensory evoked potentials (SEP) in 15 patients affected by Friedreich's ataxia (FA) and in 9 patients with progressive early onset cerebellar ataxia (PEOCA). Brainstem auditory evoked potentials (BAEP) were also recorded in 14 FA patients and in five PEOCA patients. SEP results showed clear differences between groups of FA, evidence of peripheral involvement was seen in all patients, with absence of the N9 potential or a major reduction of its amplitude. In patients in whom central responses could be recorded, conduction velocity was normal or near normal up to the brainstem but was reduced from brainstem to cerebral cortex. Four patients with PEOCA had SEP abnormalities similar to those seen in FA. In the five other patients, the amplitude and latency of N9 were normal but conduction velocity was reduced from brainstem to cerebral cortex. In FA, BAEP were abnormal in all patients with a disease duration of four years or more but were normal in four of the five PEOCA patients. Systematic evoked potential recording is useful in the investigation of hereditary ataxias.

RÉSUMÉ: Des études de potentiels évoqués dans l'ataxie de Friedreich et dans l'ataxie cérébelleuse progressive à début précoce. Nous avons procédé à l'enregistrement de potentiels évoqués somesthésiques (PES) chez 14 patients atteints d'ataxie de Friedreich (AF) et chez neuf patients présentant une ataxie cérébelleuse évolutive à début précoce (ACEDP). De plus, nous avons étudié les potentiels évoqués auditifs précoces (PEAp) chez 14 cas d'AF et cinq d'ACEDP. Les PES ont montré des anomalies de nature différente chez ces patients. Chez tous les patients atteints d'AF, il existe une atteinte périphérique avec absence du potentiel N9 ou diminution importante de son amplitude. Chez les patients chez qui des potentiels P4 ou N20 ont pu être enregistrés, on note que la vitesse de conduction est normale ou près de la normale jusqu'au tronc cérébral mais ralentie entre le tronc et le cortex. Chez quatre patients présentant une ACEDP, les PES ont révélé des anomalies semblables à celles retrouvées dans l'AF. Chez les cinq autres cas, l'amplitude et la latence de N9 étaient normales mais la vitesse de conduction était ralentie entre le tronc cérébral et le cortex. Dans l'AF, les PEAp étaient anormaux chez tous les patients dont la maladie évoluait depuis quatre ans ou plus mais étaient normaux chez quatre des cinq patients avec ACEDP. Des enregistrements systématiques des potentiels évoqués sont utiles dans l'investigation des ataxies héréditaires.

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Inherited ataxias have received much attention over the last decade and at least three new classifications have been proposed recently.[1,2,3] These classifications have several points in common being largely based on age of onset, mode of inheritance, specific clinical features (in particular the presence or absence of deep tendon reflexes in the lower limbs) and known (such as metabolic disorders or defective DNA repair) or unknown etiology. The extensive works of Harding[1,4,5,6] and of the Québec Cooperative Study on Friedreich's Ataxia[7] have led to the identification of specific clinical entities which are either variants of Friedreich's ataxia[8,9,10] or distinct disease entities such as the autosomal recessive spastic ataxia of Charlevoix-Saguenay[11] and early onset cerebellar ataxia with retained tendon reflexes.[4]

Several authors have studied visual evoked potentials (VEP);[12,13,14,15,16] brainstem auditory evoked potentials (BAEP);[17,18,19,20,21,22] somatosensory evoked potentials (SEP)[23,24,25,26] or multimodality evoked potentials[27,28,29,30,31,32] and have described several characteristic electrophysiological abnormalities in Friedreich's ataxia (FA). Evoked potentials (EP) have also been recorded in ataxia telengiectasia,[32] olivo-pontocerebellar ataxias (OPCA) and various, mostly adult onset, cerebellar ataxias.[13,14,16,27,28,30]

Apart from FA, progressive early onset cerebellar ataxias (PEOCA) have never been specifically studied from an EP point of view. We report here SEP recordings carried out in nine patients with PEOCA and compare the results obtained in these patients to those observed in 15 patients affected by FA. In addition five of the nine patients with PEOCA and 14 FA patients also had BAEP recordings.

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Table 1: Clinical and Laboratory Data in 9 Patients with Progressive Early Onset Cerebellar Ataxia (PEOCA)

Patient #	1	2	3	4	5	6	7	8	9
Heredity	Dominant	Dominant	Dominant	Sporadic	Sporadic	Sporadic	Sporadic	Sporadic	Recessive
Age of onset (yrs)	1	10	12	1	5	8	11	13	20
Duration (yrs)	9	21	23	26	9	8	8.5	18	1
Limb ataxia	Present	Present	Present	Present	Present	Present	Present	Present	Present
Knee jerks	Abs	Abs	Abs	Inc	Inc	Inc	Inc	Inc	Inc
Vibration — position sense	Affected	Normal	Normal	Normal	Normal	Affected	Normal	Normal	Normal
Fundoscopic abnormalities	None	None	None	None	None	None	None	Optic atrophy	None
CT scan findings	Cerebellar atrophy	Diffuse atrophy	Normal	Diffuse atrophy	Normal	N.A.	N.A.	Diffuse atrophy	Normal
Neurography									
Motor	Normal	↓CV ↓A	Normal	Normal	Normal	Normal	Normal	↓CV ↓A	Normal
Sensory	↓CV ↓A	Abs	↓A	Normal	Normal	Normal	Normal	↓CV ↓A	Normal
Type of EP recorded	SEP	SEP	SEP	SEP BAEP	SEP BAEP	SEP	SEP BAEP	SEP BAEP	SEP BAEP

↓A = Decreased Amplitude
↓CV = Decreased Conduction Velocity
Abs = Absent
Inc = Increased
N.A. = Not Available

PATIENTS

Friedreich's ataxia (FA)

This group includes 16 patients which satisfied all the major criteria defined by the Québec Cooperative Study on Friedreich's Ataxia.[33] The mean age at the time of the recording was 28.5 years (range 14 to 53) and the mean duration of their disease 15.4 years (range 2 to 38 years). Fifteen had SEPs and 14 BAEPs.

Progressive early onset cerebellar ataxia (PEOCA)

All nine patients presented with a progressive cerebellar ataxia. The main clinical features are summarized in Table 1. One patient (case #8) had ophthalmologic abnormalities consisting of a slight optic atrophy associated with increased pigmentation of the retina. In addition five patients had pes cavus (patients #2, 5, 6, 8, 9) and three patients were mentally retarded (patients #4, 6, 9). In patients #1, 2 and 3, the family history was suggestive of an autosomal dominant inheritance. In each case, one parent and other relatives in the two previous generations presented similar symptoms. Patient #9 had a brother affected by a similar condition and this suggested an autosomal recessive inheritance, both parents being asymptomatic. The other cases were considered as sporadic. All nine had SEPs and five had BAEPs recorded.

METHODS

SEP

SEP were elicited by 0.2 msec electrical square pulses delivered percutaneous to the median nerve at the wrist through silver disk electrodes and were recorded using either a 4- or 8-channel montage of disk electrodes. In all patients this montage included electrodes located in the ipsi- and contralateral parietal regions (P'3 and P'4, 3 cm behind C2 and 7 cm from the midline), at supraclavicular Erb's point and at Cv 6 spinal process. In addition, electrodes located on the contralateral frontal (F7, F8), on the mid-frontal (Fz) region and an anterior cervical (located in the neck over the cricoid bone) were also used for the 8-channel montage. A non cephalic reference situated on the shoulder on the non-stimulation side was used for all the derivations with the exception of Erb's point for which the reference was placed over the mid-frontal region (Fz). Averaging was performed on 2000 responses with an analysis time of 66 msec and a bin width of 236 µsec (filter bandpass 1.6-3200 Hz, 6 dB down per octave). The stimuli were delivered at motor threshold for abductor pollicis brevis at a rate of 2/sec. At least two sets of averaged responses were obtained in the same session.

BAEP

Responses to monaural stimulation were recorded with a one-channel montage between Cz and the mastoid on the stimulated side. The ground electrode was situated on the ear lobe contralateral to the stimulated ear. The filter bandpass of the amplifiers was set up at 160-1600 Hz (6 dB down). Unfiltered alternating clicks of 100 usec were delivered at a rate of 20/sec

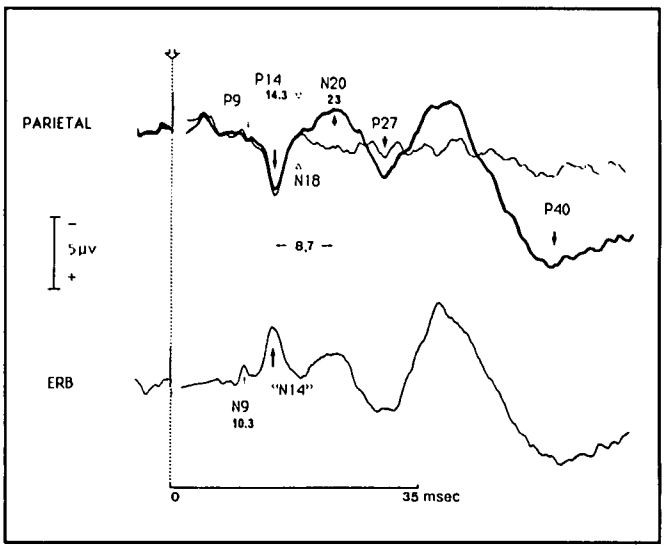

*Figure 1 — **SEP findings in a case of Friedreich Ataxia.** A N9 potential of very low amplitude but normal latency is recorded at Erb's point (cephalic reference at Fz). With a parietal electrode (non-cephalic reference at the shoulder) a normal P14 and a delayed N20 are seen. N9-P14 IPL (4 msec.) is within normal limits but P14-N20 IPL (8.7 msec.) is markedly increased, thus indicating a conduction slowing at rostral brainstem or thalamo-cortical radiations. Notice that due to the cephalic reference in the bottom trace an inverted P14 (labelled "N14" in the figure) is also present which is the mirror image of the P14 picked by the parietal electrode.*

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Table 2: SEP and BAEP Latencies and IPL in 16 Patients with Typical F.A.

		SEP						BAEP		
Patient #	Disease Duration (yrs)	N9	P14	N20	N9-P14	N9-N20	P14-N20	I	V	I-V
1	2	N	Abs/N (1)	Abs	–/N	—	—	ND	ND	ND
2	2	N	↑	N	N	N	N	N	N	N
3	4	N	N	↑	N	↑	↑	N	↑	↑
4	5	Abs	Abs	Abs	—	—	—	N	↑	↑
5	6	Abs	Abs	Abs	—	—	—	N	Abs/N (2)	–/N
6	9	ND	ND	ND	—	—	—	Abs	Abs	—
7	10	Abs	Abs	Abs	—	—	—	↑	↑	N
8	12	Abs	↑Ab (3)	↑Abs (3)	—	—	↑/–	N	N	↑
9	13	Abs	Abs	Abs	—	—	—	Abs	Abs	—
10	14	↑	↑	Abs	N	—	—	Abs	Abs	—
11	16	Abs	Abs	Abs	—	—	—	N	Abs	—
12	17	↑	↑	Abs	N	—	—	Abs	Abs	—
13	18	Abs	Abs	Abs	—	—	—	Abs	Abs	—
14	32	Abs	Abs	Abs	—	—	—	N	Abs	—
15	33	Abs	N	↑	—	—	↑	ND	ND	ND
16	38	Abs	Abs	Abs	—	—	—	Abs	Abs	—

Abs = Bilateral absence of response; N = Bilateral normal latency or IPL; ND = Not done; ↑ = Latency or IPL ≥ 2.5 SD bilaterally as compared to normal controls. (1) In patient #1 no P14 was obtained after right median nerve stimulation (2). In patient #5, wave V was absent on the right side (3). In patient #8 P14 and N20 were absent after left median nerve stimulation.

Table 3: SEP and BAEP Latencies and IPL in 9 Patients with PEOCA

	SEP						BAEP		
Patient #	N9	P14	N20	N9-P14	N9-N20	P14-N20	I	V	I-V
1	Abs	Abs	Abs	—	—	—	ND	ND	ND
2	Abs	Abs	Abs	—	—	—	ND	ND	ND
3	N	N	Abs	N	—	—	ND	ND	ND
4	N	N	↑	N	↑	↑	N/Abs (1)	Abs	Abs
5	N	Abs/N (2)	Abs/↑(2)	-/N	-/↑	-/↑	N	N	N
6	N	N	↑	N	↑	↑	ND	ND	ND
7	N	N	N	N	↑	↑	N	N	N
8	N	N	Abs	N	–	–	N	N	N
9	N	N	N	N	↑	↑	N	N	N

Abs = Bilateral absence of response; ND = Not done; N = Bilateral normal latency or IPL; ↑ = Latency or IPL ≥ 2.5 SD bilaterally as compared to normal controls; (1) In patient #4, wave I was present on right side but absent on left side (2). In patient #5, P14 and N20 were absent after right side stimulation.

successively to each ear. The non-stimulated ear was masked by white noise at 20 dB lower intensity than the stimulus. Each trial consisted of an average of 2560 sweeps. Time of analysis was 10 msec with a bin width of 19.5 usec (512 sampling points). In all patients "complete" BAEP audiometry was performed by gradually decreasing the stimulus from 100 dBHL to wave V threshold. At least two trials were repeated at 100 dB for each patient and for each stimulated ear.

Results

For SEPs we measured the amplitude and latency of N9 (brachial plexus potential obtained at Erb's point), the latencies of the scalp far-field P14 and contralateral parietal N20 potentials, as well as the N9-P14, N9-N20 and P14-N20 interpeak latencies (IPL). For BAEPs we measured the latencies of waves I and V and the I-V IPL. Results were considered as abnormal when exceeding the mean +2.5 S.D. of values obtained in normal controls. Recording conditions were the same in controls as those described above. For BAEPs, 25 normal subjects (mean age 33.3 years, s.d. 12 years) were recorded; for SEPs, normative data were based on results obtained in 22 subjects (mean age 29 years s.d. 3.7 years).

Results are summarized in Tables 2 and 3. In FA, no patient had entirely normal SEP (Table 2). In eight of the 15 patients no potential could be recognized. Of the seven remaining patients, two had no N9 potential and in the five others N9 was decreased in amplitude. N9 latency was normal in three and slightly increased in two. The P14 potential could be identified at least on one side in these seven patients including the five in whom N9 was recorded (Figure 1). P14 latency was normal in three patients and increased in four patients. N20 was obtained at least unilaterally in four patients and was normal in only one being desynchronized and of prolonged latency in the three others. The N9-P14 IPL could be measured in five patients and was normal in all of them. N9-N20 IPL was measurable in only two

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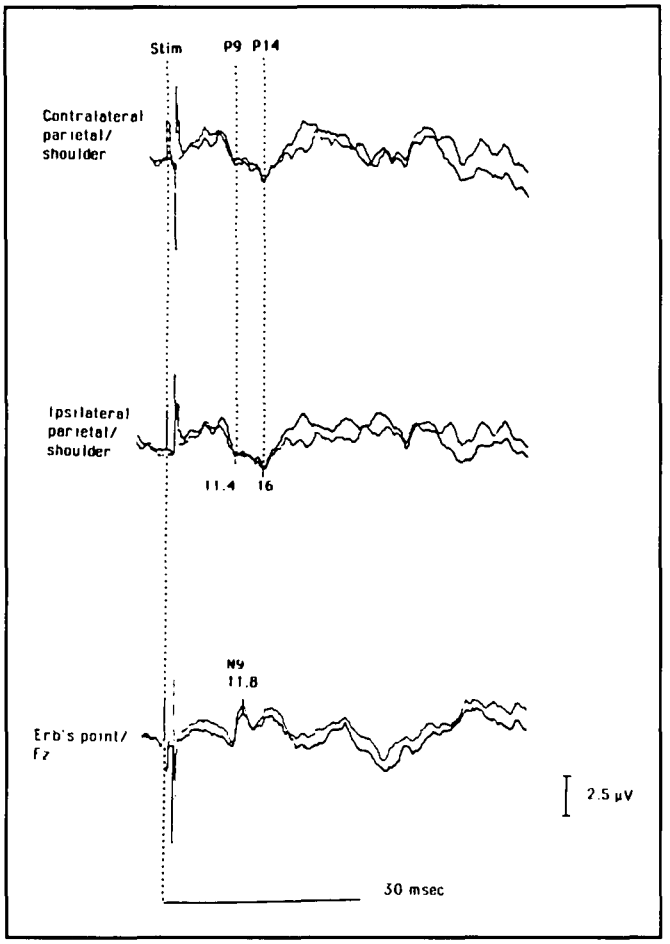

*Figure 2 — **SEP findings in a patient with a dominant PEOCA** (case #3). N9 is of reduced amplitude, P14 is normal and N20 is absent. N9-P14 IPL is within normal limits.*

patients and was normal in one and increased in the other. Finally, the P14-N20 IPL was found to be prolonged in three of the four patients in whom it could be measured.

In PEOCA (Table 3), two patients (#1 and 2) had no recognizable potentials either at Erb's point or further centrally. N9 could be recorded in the seven other patients, being of normal latency in all and of reduced amplitude in two (#3 and 8). P14 was present and of normal latency bilaterally in six patients as was the N9-P14 IPL. In patient #5, P14 was normal with left side stimulation but absent with right median nerve stimulation. On the contrary, N20 was absent in two patients (cases #3 and 8, Figure 2) or delayed in three (cases #4, 5, 6) and the P14-N20 IPL was increased in the five patients in whom it could be recorded (Figure 3).

As can be seen in Table 2, BAEP were abnormal in 13 of 14 FA patients in whom this test was done. Clearly, the abnormalities were more important in patients with a disease of longer duration and always affected wave V (Figure 4). In PEOCA (Table 3), only one of the five patients in whom it was done showed BAEP abnormalities with a disappearance of wave V.

Discussion

Our goal in carrying this study was to determine if EPs could be of some use in differentiating PEOCA cases from one another and from FA patients and try to gain information about the pathophysiology of these disorders.

As can be seen by our results, there are clear differences in SEPs between FA and PEOCA patients. Our SEP findings in FA are in agreement with what has been previously described[23,24,25,26,27,28,30,31,32] and showed two types and locations of abnormalities. In all our patients we found evidence of peripheral involvement suggested by the absence or decreased amplitude of N9, which when present appeared at a normal or near normal latency. When measurable, central conduction was abnormal in all patients except one whose illness was of short duration (#2), indicated by N20 being either desynchronized (of lower amplitude and longer duration) and of prolonged latency (with increased N9-N20 and P14-N20 IPL (Figure 1) or unobtainable.

In previous studies[25,27,31] N13 or N14 potentials recorded at the cervical level were shown to be present in most patients and of normal or near normal latency. However, these recordings were done with an Fz reference electrode which may create some problems in localization, since the waveform complex obtained at the cervical level with this cephalic reference is the resultant of activity from a spinal cord generator (N13) and a brainstem generator (P14); this latter component is picked up by the reference electrode and appears as an 'N14' potential with inverse polarity (see Figure 1).[34,35] Although the precise generator of P14 is not yet known, its brainstem origin has been demonstrated conclusively by EP studies and anatomical correlates.[34,35,36,37] When present the P14 potential was of normal or

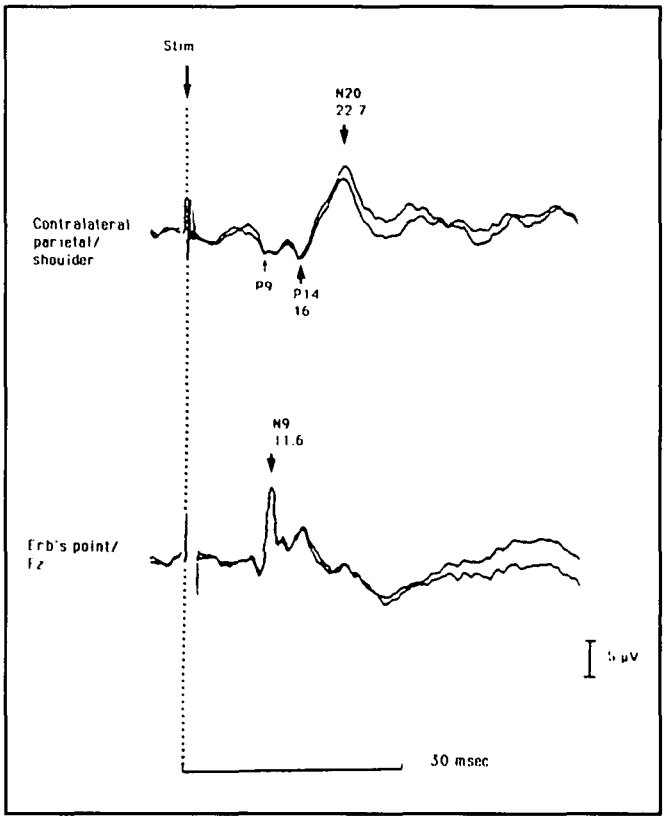

*Figure 3 — **SEP findings in a patient with a recessive PEOCA.** Erb's point potential (N9) and brainstem P14 are of normal latency and amplitude. Conversely, N20 is delayed with an abnormal P14-N20 IPL.*

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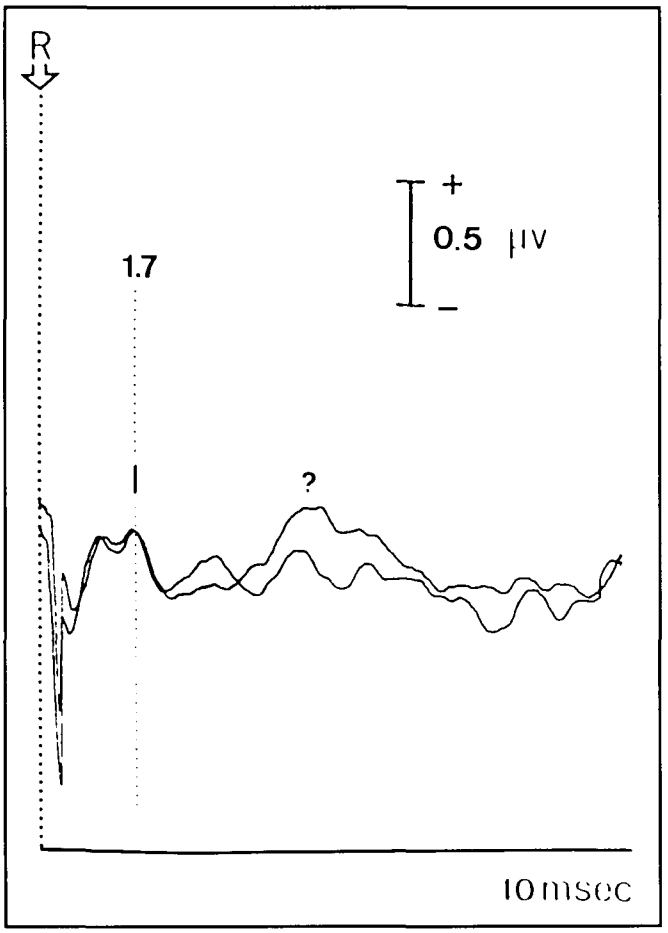

*Figure 4 — **BAEP findings in FA**. This patient illustrates a typical BAEP finding in cases of FA. Only wave I is present in two consecutive trials; all subsequent components have disappeared or are markedly reduced in amplitude.*

near normal latency in our FA patients and was associated with a normal N9-P14 IPL (Figure 1). This suggests that conduction velocity in somatosensory pathways serving upper limbs is unaffected up to the level of the brainstem in this disease.

In PEOCA, five of the nine patients could be distinguished from the FA group since none of them had any peripheral or brainstem involvement, N9 amplitude and latency, P14 latency and N9-P14 IPL being normal in these patients. They showed however, abnormalities indicative of central dysfunction with a prolonged N9-N20 and P14-N20 IPL seen in all patients. In the remaining four PEOCA patients the abnormalities were reminiscent of those observed in FA: in two (cases #1 and 2) no SEP could be obtained. Both of these patients had a dominant form of ataxia and both had abnormal sensory nerve conduction velocities. In the two others, one dominant and one sporadic (cases #3 and 8), we found a N9 potential of reduced amplitude but of normal latency; P14 latency and N9-P14 IPL were normal but N20 was absent bilaterally (Figure 2). One of them (case #8) also had slightly decreased motor and sensory nerve conduction velocities with low amplitude sensory nerve action potentials.

BAEP abnormalities have been extensively documented in FA.[17,18,19,21,22,27,28,29,30,31,32] They were found to be abnormal in most cases with the exception of Nuwer et al[28] who reported normal results in all of the 20 FA patients they studied. BAEP are of special interest in FA since their degree of abnormality is related to the duration and severity of the disease.[18,19,21,29,31,32] These potentials can be normal in younger patients but then become gradually abnormal, showing a rostro-caudal pattern of deterioration with wave V and I-V IPL always being affected first. Our results are again in concordance with these observations since we found abnormal BAEPs in 13 of the 14 FA patients in whom these tests were done (Figure 4). These abnormalities were of increasing severity with increasing duration of the disease. Furthermore, as can be seen in Table 2, when BAEPs were abnormal, wave V was always affected (frequently absent) even though wave I was still present and of normal latency in five patients. On the contrary BAEPs were normal in four of the five PEOCA patients in whom this test was done, even though the duration of the disease was from one to 18 years in these particular patients. BAEPs were abnormal in only one patient with a PEOCA of 26 years duration.

The pathophysiology of the various EP abnormalities seen in FA is not completely understood. The decreased amplitude of N9 is probably due to a loss of nerve fibres. Degeneration of large neurons in the posterior root ganglia and the resulting disappearance of large myelinated fibres in the peripheral nerves has been well documented.[38,39,40,41] Since this process is mostly one of axonal degeneration, it may explain why N9 latency is normal or near normal. However, fibre loss can not account for the increase of P14-N20 IPL. Such an increase could be more easily explained by demyelination but no significant demyelination of the thalamo-cortical projections has been found in FA patient autopsies.[42,43,44] A slight to severe loss of thalamic neurons was seen in several FA patients[43,44] affecting particularly the ventroposterolateral nucleus in one single case.[42] Although these changes could explain the disappearance of N20, they could not account for the increased conduction time between the brainstem and the parietal cortex. Diffuse gliosis of the cerebral white matter and myelin pallor or a slight degeneration of the median lemniscus have been reported at autopsies of FA patients by Oppenheimer[43] and Lamarche et al.[44] These abnormalities could explain the increased P4-N20 interval seen in our patients since the sensory stimulations which generate SEPs are conducted by the median lemniscus to the thalamus (VPL nucleus) and the cerebral cortex.

BAEP abnormalities were first thought to be secondary to spiral ganglion degeneration since no potential could be obtained in the first patients recorded.[17] This hypothesis was dismissed by several further studies showing a rostro-caudal deterioration with persisting wave I in many patients in whom other waves had disappeared.[18,19,29,32] Jabbari et al[19] suggested that there is a primary brainstem dysfunction in FA. Again, the nature of this dysfunction has not been clarified and is certainly not restricted to the brainstem since cortical auditory EP have also been found to be abnormal in FA, and these abnormalities were at least partially independent from those BAEPs in the same patients.[18,22]

On clinical grounds, our six sporadic or recessive PEOCA patients could be classified as early onset cerebellar ataxia with retained tendon reflexes as defined by Harding.[4] From an electrophysiological point of view however, one patient (case #8) was different from the others since he had clear evidence of

peripheral involvement with decreased sensory and motor nerve conduction velocities and an N9 potential of low amplitude. In this same patient central involvement was also more severe than in other patients since N20 was absent bilaterally. This patient should thus be considered as belonging to a different category of ataxia than the other five.

The three patients with a dominant ataxia were very similar to FA patients and had definite signs of central and peripheral involvement. In two of them no peripheral or central SEP could be obtained, while in the third N9 was of decreased amplitude, P14 was normal and N20 was absent (see Figure 3). These patients are difficult to classify: a form of OPCA with peripheral neuropathy and slow ocular saccades have recently been described by Wadia[45] but the very early age of onset in one patient (case #1) and the absence of slow saccades in all three seem to differentiate our cases from theirs. Almost identical cases (except for the very early age of onset of our patient #1) of dominant ataxia with large fibre sensory neuropathy have been recently reported by Bennett et al[46] and this may represent a specific type of inherited ataxia.

The number of patients in our study is too small to enable us to make any useful contribution to the complex task of classifying inherited ataxias. We feel however that systematic electrophysiological studies of ataxic patients could be useful in such a classification in combination with clinical, biochemical and molecular genetics data. Furthermore EPs could be of value in monitoring the response to eventual drug treatment, since they may give quantifiable measurements of the disease and of its evolution. For FA, BAEPs may be of particular value since they appear to reflect the severity of the disease.

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