QUEBEC COOPERATIVE STUDY
OF FRIEDREICH'S ATAXIA

Visual Evoked Potentials and Brain Stem Auditory Potentials in Friedreich's Ataxia — A Longitudinal Study

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ABSTRACT: Six patients with Friedreich's ataxia, 4 males and 2 females, their ages ranging from 13 to 33 years, were studied. The early manifestations started between age 7 and 13 with an evolution time between 6 and 20 years. Serial visual and brain stem auditory evoked potential recordings were made. A progressive increase in latency, reduction in amplitude and in latency inter-ocular difference of *P100* were observed. The pattern of the reversal checker-board visual evoked potential was preserved. A disorganized BAEP pattern, a well defined potential I, a very small potential V and a delay in the interpeak latency were constant findings. The assumption is made of a progressive involvement of both visual and central auditory pathways. Pathophysiological mechanisms are discussed.

RÉSUMÉ: Six patients avec ataxie de Friedreich, 4 hommes et 2 femmes, âgés de 13 à 33 ans, furent étudiés. Les premiers signes débutent de 7 à 13 ans avec une période d'évolution de 6 à 20 ans. Des potentiels évoqués visuels et auditifs du tronc cérébral furent faits en série. Nous avons noté une augmentation progressive dans la latence, une réduction de l'amplitude et de la différence de latence inter-oculaire du *P100*. Le pattern du potentiel évoqué visuel fut cependant conservé. De façon constante nous avons retrouvé un pattern BAEP désorganisé, un potentiel I bien défini, un très petit potentiel V et un retard dans la latence interpics. Nous croyons donc à une atteinte progressive des voies visuelles et auditives centrales dans cette maladie. Nous en discutons la pathophysiologie.

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For many years there was no agreement on the diagnostic criteria and classification of Friedreich's ataxia as well as the other hereditary spinocerebellar degenerations. The Quebec Cooperative Study on Friedreich's ataxia established the clinical criteria for a more precise definition of Friedreich's ataxia and its different clinical patterns: group Ia, typical complete form; group Ib typical incomplete form and group IIa, atypical form.

Recently, several authors (Caroll et al., 1980; Noel and Desmedt, 1980; Pedersen and Trojaborg, 1981) have shown that evoked potentials could provide evidence of subclinical dysfunction in specific sensory pathways in Friedreich's ataxia and other hereditary spinocerebellar degenerations. Electrophysiologic findings support the assumption of the involvement of the central somatosensory pathways in the ataxia of Friedreich's (Desmedt and Noel, 1973; Noel and Desmedt, 1980). On a subclinical basis, there is the possibility that other sensory modalities, ie, the visual and the auditory pathways, could also be disturbed by the neurochemical dysfunctions which probably are responsible for triggering the demyelination of the nervous

pathways and fibres and neuronal loss in the ataxia of Friedreich's. The aim of this report is to present data which evidence nerve conduction disturbances of the visual and auditory pathways.

SUBJECTS

Six patients with Friedreich's ataxia, 4 males and 2 females, their ages ranging from 13 to 33 years, were studied. Four cases showed a typical complete picture (cases 1, 2, 3, 4); one case a typical incomplete picture (case 5), the last case an atypical picture (case 6). Cases 2, 3 and 4 are siblings of consanguinous matings. The early manifestations started between 7 and 13 years of age with an evolution of 6 to 20 years.

Case 1: M.B. - Male, 33 years old. The disease started at age 13. Dysarthria of speech, nystagmus, + amyotrophia and paresis in both lower limbs, areflexia, bilateral Babinski, severe cerebellar ataxia and incoordination, loss of deep sensibility, kyphoscoliosis and bilateral pes cavus.
Typical complete form (Ia).

Case 2: A.S. - Female, 28 years old. Parents with consanguinity, 2 other siblings with the same disease (cases 3 and 4). The disease started at age 12. Dysarthria of speech, nystagmus + + +, amyotrophia, hypotonia and paresis in the 4 limbs predominantly in the lower limbs, areflexia, bilateral Babinski, severe cerebellar ataxia and incoordination, severe deficit of deep sensibility, scoliosis. Great handicap.
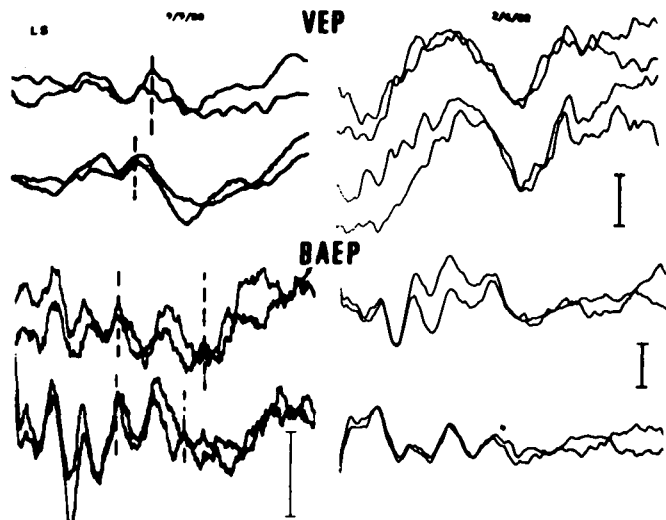
Typical complete form (1a).

Case 3: L.S. - Male, 24 years old. The disease started at age 11. Dysarthria, nystagmus +, amyotrophia and paresis predominantly in lower limbs, areflexia, bilateral Babinski, severe cerebellar incoordination, severe deep sensibility deficit, kyphoscoliosis and bilateral pes cavus.

Typical complete form (1a).

Case 4: D.S. - Male, 27 years old. Symptoms started at 11 years old. Dysarthria, nystagmus +, amyotrophia, spasticity and paresis in lower limbs, areflexia, bilateral Babinski, severe staggering and severe cerebellar incoordination, urinary incontinence, kyphoscoliosis, bilateral pes cavus with tropic lesions.

Typical complete form (1a).

Case 5: D.V. Male, 13 years old. The disease started at age 7. Heart failure, dyspnea, paresis of the 4 limbs with generalized hypotonia and areflexia, Babinski at right, cerebellar incoordination with severe staggering, moderate deficit of deep sensibility, kyphoscoliosis. Severe cardiopathy.

Typical incomplete form (1b).

Figure 1 — Case 1 M.B. — A 34 year old male whose symptoms of Friedreich's started at the age of 13. Complete typical form (1a). VEP: visual pattern reversal evoked potential. Upper and lower trace: Left and right eye. CAL: 2 mV: BAEP: Brain-stem auditory evoked potentials. Upper and lower trace: Left and right ear (C₂-M ipsilateral). P 100 component latencies increased from 112 (left) -107 (right) to 122-124 ms in the 2nd recording, without changing the normal waveform and amplitude. CAL: 2 mV. Potential I was the only one which could be identified in BAEP.
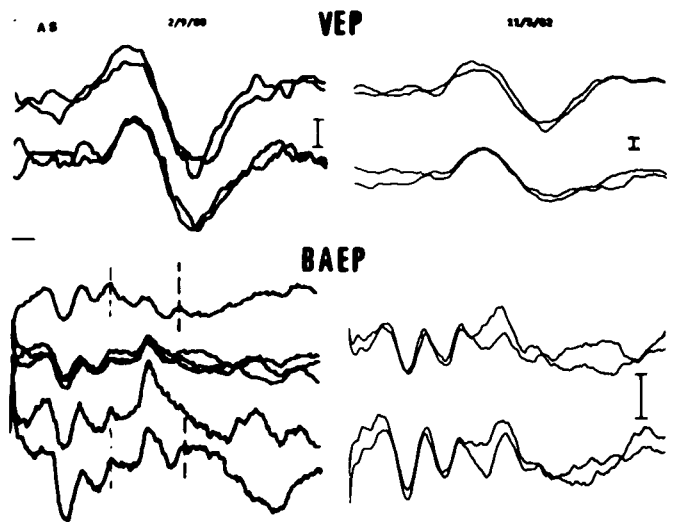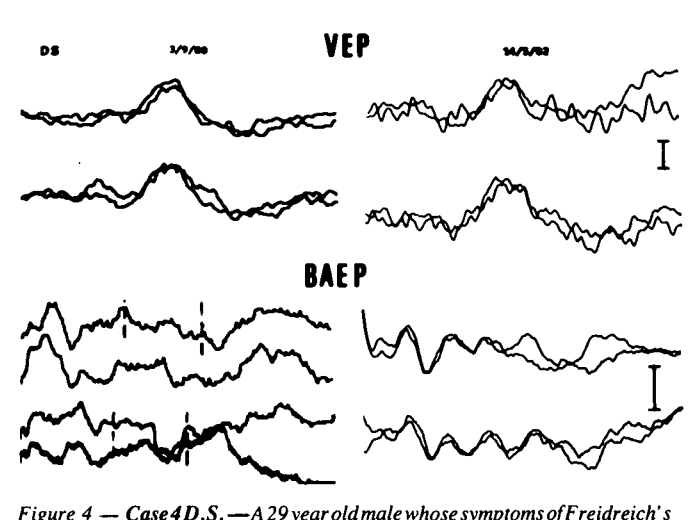

Figure 3 — Case 3 L.S. — A 25 year old male whose symptoms of Friedreich's ataxia started at the age of 11. Complete typical form (1a). P 100 component latencies increased from 117 (left) 121 ms (right) to 124 ms on both sides in the 2nd recording with a greater temporal dispersion (from around 50 ms to close to 80 ms). CAL: 2 mV. BAEP — 1st recording: I-V pattern with a very small potential V (left 0.10 mV, right 0.03 uV). 2nd recording: Potential V was not preserved on both sides. Potential I was the most clearly defined wavelet. CAL: 0.2 uV.

Figure 2 — Case 2 A.S. — A 30 year old female whose symptoms of Friedreich's ataxia started at the age 12. Complete typical form (1a). P 100 component latencies increased from 1st to 2nd recording to become almost symmetrical, with a reduction in the interocular latency difference (from 5 to 2 ms). A clear amplitude reduction was shown in the 2nd recording. CAL: 2 mV. BAEP — 1st recording: pattern I-V (IPL: left 4.4 ms, right 4.28 ms) with a very small potential V (left 0.04 uV, right 0.11 uV). 2nd recording: potential V was not recorded and potential I became the best defined wavelet. CAL: 0.2 uV.

Figure 4 — Case 4 D.S. — A 29 year old male whose symptoms of Friedreich's ataxia started at the age of 11. Complete typical form (1a). P 100 component latencies did not show an important change from 1st to 2nd recording (131 ms and 132 ms respectively) on right eye inverted checkerboard stimulation but increased from 122 to 134 on left eye stimulation. Amplitude (P100 - N2) decreased almost 1 mV in right eye. Normal waveform was preserved. BAEP — 1st recording the pattern (I-V) was preserved with a very small potential V (uV 0.09 and 0.06 left and right). IPL (I-V) 4.28 ms (left) 4.64 ms (right). 2nd recording: potential V was abolished on both sides. CAL: 0.2 uV.
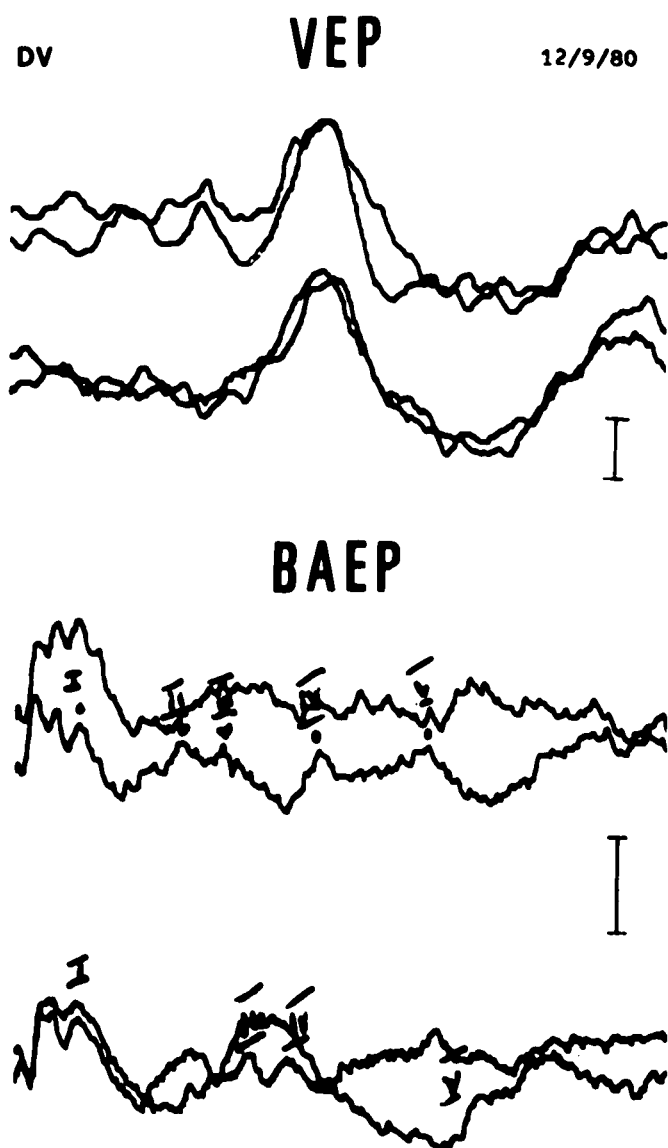
DV **VEP** 12/9/80

BAEP

Figure 5 — Case 5 D.V. —A 13 year old male whose symptoms of Freidreich's ataxia started at the age of 7. Incomplete typical form (1b). P100 component latencies were 125 (left) - 123 (right) ms. CAL: 2 mV. BAEP: the pattern was very disorganized, potential I was the best defined. CAL: 0.2 mV.

Case 6: M.M. - Female, 27 years old. The disease started at age 13. Moderate dysarthria, ocular dyskinesia, moderate hypotonia and paresis in lower limbs, areflexia, bilateral Babinski, ataxia, moderate cerebellar incoordination, hypopallesthesia, bilateral pes cavus.
Atypical form (11a).

METHODS

Evoked potentials were recorded with standard silver electrodes for EEG. Electrode impedance was maintained below 2000 ohms. The signal averager employed was the Nicolet CA-1000 system. Analysis time was 250 msec for visual and 10 msec for brain-stem auditory evoked potentials (BAEP). The traces were written on a X-Y Hewlett-Packard pen plotter. Serial evoked potentials recordings were made. Visual evoked potentials (VEP) were recorded via electrodes placed at Oz using a reference
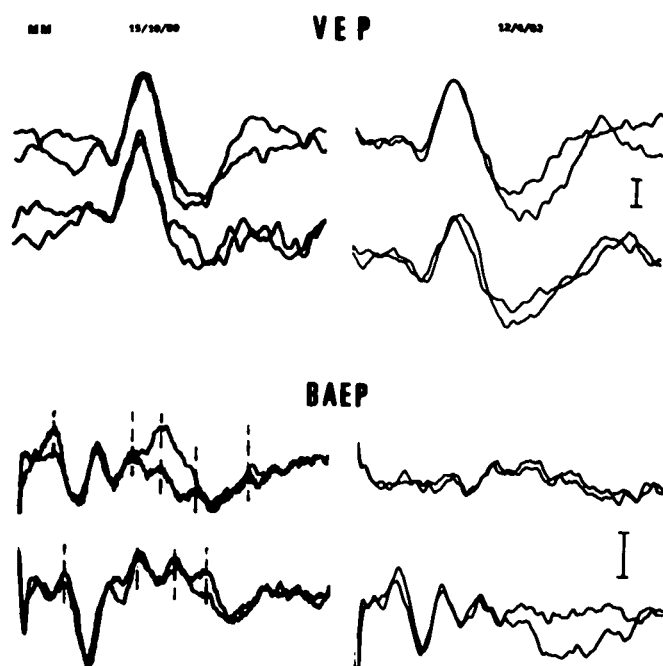
VEP

BAEP

Figure 6 — Case 6 M.M. — A 29 year old female whose symptoms of Freidreich's ataxia started at the age of 13. Atypical form (11a). P100 component latencies increased from 99 (left) -102 (right) ms to 105-111 ms in the 2nd recording without changing the normal wave form and amplitude. BAEP: 1st recording: the pattern was preserved; 2nd recording potential V was almost abolished. In both recordings potentials I showed an amplitude greater than the other wavelets. CAL: 0.2 uV. Details as in case M.B.

electrode placed in F_z (international 10-20 electrode system). The frequency bandpass was 1-100 H_z. The responses were obtained from each eye to wide-field stimulation with the subject sitting 1 m 20 in front of a TV set. The visual stimulus was a wide-field black-and-white checkerboard reversal pattern, 1.88/sec. The amplitude (P-N peak-to-peak), latency of P 100 recorded from O_z, the duration of the potential (difference between the negative wave following and preceding P 100) and interocular differences in P 100 latency were determined.

Brain-stem auditory evoked potentials (BAEP) were provoked by monoaural stimulation 0.1 msec rarefaction clicks delivered through 10 ohm TDH-39 transducers mounted in acoustically shielded audio-caps at 80db HL at a rate of 10.9/sec. An internal white noise source was delivered to the unstimulated ear. Recordings were derived from a bipolar montage of C_z to the ipsilateral mastoid (M), using a bandpass of 150 to 3000 H_z, Two thousand auditory responses and one hundred visual responses series, repeated twice on each side, were stored in memory providing 256 data points for each 10.24 msec average.

For the purpose of this longitudinal study, two sets of recordings were made (with the exception of D.V. who died in the interval), the second around 18 and 20 months after the first.

RESULTS

In the first recording in three cases (cases 3, 4, 5) wide-field P 100 component of VEP, was delayed on both sides, only in *I*

Table 1: Latencies in ms. of Checkerboard Reversal Pattern Visual Evoked Potentials.

CASE	1				2				3				4				5		6			
	M. B.				A. S.				L. S.				D. S.				D. V.		M. M.			
	1		2		1		2		1		2		1		2		1		1		2	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
N_1	87	87	92	91	86	54	86	78	98	104	89	90	101	85	111	104	93	94	77	75	88	82
P 100	107	112	124	122	112	107	114	112	121	117	124	124	131	122	132	134	123	125	102	99	111	105
N_2	152	156	183	174	158	159	162	157	150	155	167	170	151	152	153	179	161	147	128	126	146	139

1. - First recording. 2. - Second recording.
R. - Right stimulation. L. - Left stimulation.

(case 5) with values in the same range. In the other 3 cases (cases 1, 2, 6) P 100 had a latency below 115 ms. In the second recording, taken 18-20 months after the first in the 5 cases which survived (cases 1, 2, 3, 4, 6) the P 100 latency increased with values in the same range on both sides. The mean value went from 115 ms to 120 ms (right side) and from 111 ms to 119 ms (left side) (Table 1).

In the first VEP recording, only in 2 cases (cases 3, 4) was the interocular latency difference higher than 6 ms. In the second recording the interocular difference was reduced, the mean from 5.8 ms went down to 3.0 ms. The interval between the negative peaks preceding and following the P 100 component, taken as an index of temporal dispersion of response, increased from 58 to 68 ms (right and left sides) to 69 and 75 ms (right and left sides). The amplitude (P 100 - N2 mV) was below normal (5 mV) in two cases (cases 3, 4) in the first recording and in 3 cases (1, 2, 6) in the second recording. However there was a decrement of the amplitude in all cases, even in those in which the amplitude persisted in the normal range (Table 2). In the first recording the 6 cases showed a disorganized BAEP pattern. In all cases the first four waves were clearly identified. Potential I remains with the highest amplitude of all the wavelets on the left and right sides in both studies. In one case (case 1) the potential I was the only one preserved. Potential V was very small, less than 0.1 uV and the coefficient of amplitude (V/l) was 0.5 or less. In the second study (18-20 months after the first one) potential V was not recorded in four cases (cases 1, 2, 3, 4), with the reference in the ipsilateral or in the contralateral mastoid. (Table 3).

Table 2: Amplitudes (mV) of P 100 - N_2 (peak- to peak).

		M. B.	A. S.	L. S.	D. S.	D. V.	M. M.
Left eye	1	16.8	11.9	3.1	3.8	7.6	10.5
	2	15.0	4.3	3.2	3.5		9.3
Right eye	1	12.0	10.2	4.5	4.1	7.1	11.5
	2	13.0	4.0	3.4	3.4		9.5

1 - First recording. 2 - Second recording.

In segment I - III, the only portion which could be reliably identified, the interpeak latency (IPL) was increased in the four cases. In case 6 potential V was preserved, and the III - V IPL also showed an important delay.

DISCUSSION

No difference was found in the present study between the typical and non-typical Friedreich's ataxia. The results of this longitudinal study with an interval of 18-20 months between recordings showed a progressive dynamic involvement of both visual and auditory pathways, suggesting a slow build up of a nervous multisystem malfunction process.

In a general way, our results of abnormal VEP and BAEP are similar to those of Caroll et al. (1980), Pedersen and Trojaborg (1981). However, unlike Caroll et al. (1980), the increment of

Table 3: Interpeak Latencies of the Brain Stem Auditory Potentials.

	A. S.				L. S.				D. S.				M. M.			
	1		2		1		2		1		2		1		2	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
I-V	4.28	4.40	—	—	4.68	4.08	—	—	4.64	4.28	—	—	4.40	4.52	5.16	4.84
I-III	2.04	2.12	2.08	2.12	2.0	2.0	2.08	2.0	2.24	1.72	2.28	2.16	2.48	2.32	2.36	2.42
III-V	2.24	2.28	—	—	2.68	2.08	—	—	2.40	2.56	—	—	1.92	2.20	2.80	2.42

1. - First recording. 2. - Second recording.
R. - Right stimulation. L. - Left stimulation.

the latency of P 100 was not regularly associated with a progressive reduction in the amplitude (from peak of P 100 to the next negative wave). The checkerboard reversal VEP pattern was preserved in all cases and P 100 could be easily identified. Instead the BAEP patterns were disorganized from the beginning showing a high degree of deterioration; potential V or the complex IV/V which was very small, even with the contralateral mastoid as a reference, disappeared afterward. So, it could be assumed that there is a brainstem pathology, particularly in the pontorostral mesencephalic segment.

It seems, at least in our cases, that auditory pathways are less affected in the peripheral portion (potential I showed normal latency and amplitude) while the proximal portion of the visual pathway (optic nerve) is subclinically involved.

Pathophysiological mechanisms for the increase in latency of VEP and BAEP in hereditary ataxias are not well understood. Although there is a tendency to accept axonal degeneration as a main neuropathological feature (Greenfield, 1974) some degree of demyelination of the central gross (myelinated) sensory axons and loss of sensory fibres could be a reasonable anatomical basis for the well-demonstrated slowing of central nervous conduction along the visual and auditory pathways.

Satya-Murti et al. (1980) suggested that the probable, although non-demonstrated, degeneration of spiral ganglion neurons, could be the anatomical ground for BAEP abnormalities. These would be the homologous phenomena of what is going on with the dorsal root ganglion cells and their axonal process and the related abnormalities of the peripheral sensory action potentials. However, our findings do not support such assumption. In all cases, potential I, which is in close relation with the VIII nerve is well organized, with latency and amplitude in the normal range. Neuronal degeneration in spiral ganglia with a significant damage of a massive number of the axons of the auditory nerve would imply a loss of potential I or an increase in latency and a reduction in amplitude. However in our 5 cases potential I was the wave most easily identified. In our cases, a primary intra-axial central sensory dysfunction mechanism is a suitable hypothesis. Unfortunately, to our knowledge, systematic neuropathological studies on the central auditory pathways in Friedreich's ataxia are unknown. In central somatosensory pathways,loss of neurons in the dorsal column nuclei (Greenfield, 1954; Balckwood and Consellis, 1976) and atrophy of the medial lemniscus (Van Bogaert and Martin, 1974) were recorded. In visual pathways gliosis of the optic nerves, chiasm (Urich et al., 1957) and optic tracts (Urich et al., 1957; Boudin et al., 1972) were observed. Nerve fibre loss in the optic tracts and neuron loss in the lateral geniculate nucleus were also described (Oppenheimer, 1976). Based on the electrophysiological findings, it is reasonable to assume that it is possible to find similar neuropathological anomalies (fibre and neuronal loss) along the central auditory pathways.

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