An Electroretinal and Visual Evoked Potential Study in Friedreich's Ataxia

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SUMMARY: *We made an electroretinographic (ERG) and visual evoked potential (VEP) study of 12 patients with Friedreich's ataxia whose diagnosis was established using the Quebec diagnostic criteria. ERGs and VEPs were elicited to the same stimulating conditions. Flash evoked luminance changes and pattern-specific evoked potentials to check and diamond stimuli were used. Statistical analysis of the data was made using independent sample t-tests. Significant VEP delays were present under all test conditions. The presence of significant interocular and interhemispheric delays as well as evidence of abnormal temporal dispersion of the VEP response suggest there to be both diffuse anterior visual system disease and retrochiasmal involvement in Friedreich's ataxia. The implicit times of the ERG b-waves were statistically within normal limits but the waveforms were of low amplitude and deformed and there were significant interocular implicit time differences. These ERG results suggest there are retinal conduction abnormalities in Friedreich's ataxia which possibly play a role in the genesis of the abnormal VEPs.*

RÉSUMÉ: *Une étude a été réalisée sur des électrorétinograms (ERG) et des potentiels évoqués visuels (PEV) chez 12 patients souffrant de l'ataxie de Friedreich. Les ERGs et PEVs ont été enregistrés suivant les mêmes stimulations. On a utilisé comme stimulations des éclairs et des renversements de patrons de carreaux et de losanges. Une analyse statistique des données a été accomplie utilisant les tests "t". Nous avons trouvé des délais du PEV significatifs sous chaque condition examinée. Les prolongations de différences significatives du PEV suivant la stimulation des deux yeux, les délais interhémisphériques ainsi que la dispersion anormale temporale des pics majeurs du PEV nous portent à croire que la dégénération dans l'ataxie de Friedreich affecte non seulement les voies visuelles antérieures, mais aussi les voies visuelles rétrochiasmatiques. Statistiquement, la latence de l'onde "b" des ERGs a été dans les limites de la normale; cependant les ondes étaient déformées et de basse amplitude et il y avait des différences significatives entre les deux yeux. Il se peut que les anomalies de l'ERG impliquent la rétine dans la génèse des délais du PEV dans l'ataxie de Friedreich.*

INTRODUCTION

In the 100 years since his death no precise clinical or biochemical criteria for the diagnosis of the ataxia described by Friedreich have been established. The Quebec Cooperative Study of Friedreich's Ataxia gave obligatory features for the diagnosis of typical Friedreich's ataxia (Geoffroy et al., 1976). These features were the onset of progressive ataxia before age 20 years, dysarthria, decreased position and vibration sense, muscle weakness and deep tendon areflexia in the lower limbs and an autosomal recessive mode of inheritance. Even using these criteria it is evident that there is phenotypic heterogeneity within the group and there are difficulties in classification of the patients particularly in sporadic cases. Optic atrophy was described by Friedreich in one of his patients and has been reported in the literature as a manifestation of Friedreich's ataxia but careful review shows that the majority of such cases would not qualify for the diagnosis of typical Friedreich's ataxia as defined by the Quebec Study and in most cases no criteria were given as to how the optic atrophy was diagnosed.

We initially studied 14 patients with Friedreich's ataxia and did not find any evidence of clinical visual dysfunction (Kirkham et al., 1979). Recent studies of visual evoked potentials (VEP) in Friedreich's ataxia using the Quebec criteria showed significant abnormalities even when clinical visual function was normal (Carroll et al., 1980; Livingstone et al., 1981; Bird and Crill, 1981). We now report upon a group of patients with Friedreich's ataxia who underwent simultaneous recordings of electroretinal and visual evoked cortical potentials. Our object was to document any possible retinal

contribution to the visual evoked potential delay and to more extensively categorize the electroretinographic (ERG) and VEP abnormalities in this disease.

MATERIALS AND METHODS

Thirty-one subjects (19 females, 12 males) who had no history of ophthalmological or neurological disease and who underwent complete neuro-ophthalmological examination were used as normal control subjects. Their ages ranged from 12 to 53 years (mean age = 29). Twelve patients with typical Friedreich's ataxia were examined. There were 4 females and 8 males whose ages ranged between 18 to 40 years (mean age = 25). Acuity for distant and near vision, and Ishihara colour vision was determined for all patients. Pupillary reactions were assessed. Goldmann visual field examination was possible in 8 cases. Fundus examination was made after pupillary dilatation.

Electrophysiological Methods

Electroretinograms (ERGs) and visual evoked potentials were simultaneously recorded to the same stimuli. ERGs were recorded from infraorbital sites using Ag-AgCl electrodes secured by hypoallergenic adhesive tape. VEPs to flash and pattern stimuli were recorded from O_1 and O_2 referenced to linked mastoids. Monocular and binocular flash stimulation was given from a Grass PS-22 photic stimulator (Grass Instruments, Quincy, Mass.) with intensity = 16 through a Wratten 47B filter masked to provide a 6.5 degree field flickering at 4 Hz. The checkerboard and diamond pattern stimulation were generated by an Apple II+ (Apple Computer Inc., Cupertino, Calif.) on a TV display masked to provide a 12 degree circular field (check size = 30′) and for the diamond condition the CRT display was rotated through 45 degrees. The simultaneously sampled ERG and VEP responses were recorded with Grass P511-J preamplifiers (0.1 - 300 Hz. bandwidth) and 128 samples were signal averaged using an LSI-11 microprocessor-based multichannel analyzer (TN-1710, Tracor-Northern

Ltd., Wisconsin) and the averaged waveforms were stored on floppy disk.

It was noted that several of the patients had some difficulty in controlling body and head posture throughout the tests and some had short attention span. The ERG and VEP records were therefore somewhat contaminated by eye movement artefact, so each test condition was performed twice. The ERG and VEP records were scored visually and the latencies of the ERG b-wave and early negative and major positive peaks of the VEP were determined for each test condition. From our normal sample mean and standard deviation we determined a latency delay criterion exceeding 99% of normal control subjects. The results for each condition studied were statistically analyzed using independent sample t-tests (Tables 1-4) and chi-square statistics.

RESULTS

Two of our 12 patients had definite clinical visual dysfunction in that they had reduced visual acuity, absent Ishihara colour vision, central scotomata on visual field examination and definite ophthalmoscopic evidence of optic atrophy with retinal nerve fibre layer loss. The other 10 patients had normal visual function on all the parameters studied.

Figure 1 shows a typical pattern-reversal VEP to check stimulation. It is apparent that there are marked interhemispheric and interocular differences in waveform morphology in association with grossly delayed latencies of the major positive components in this case. Table 1 shows the results of the VEPs which were monocularly recorded from the pattern reversal and binocular flash conditions. For the pattern reversal conditions the results are given for the early negative (N70) and major positive (P98) peak latencies and also for the N70-P98 interpeak period. For flash stimulation the mean peak latencies of the early negative (N70) and later positive (P110) as well as the N70-P110 interpeak period are reported.
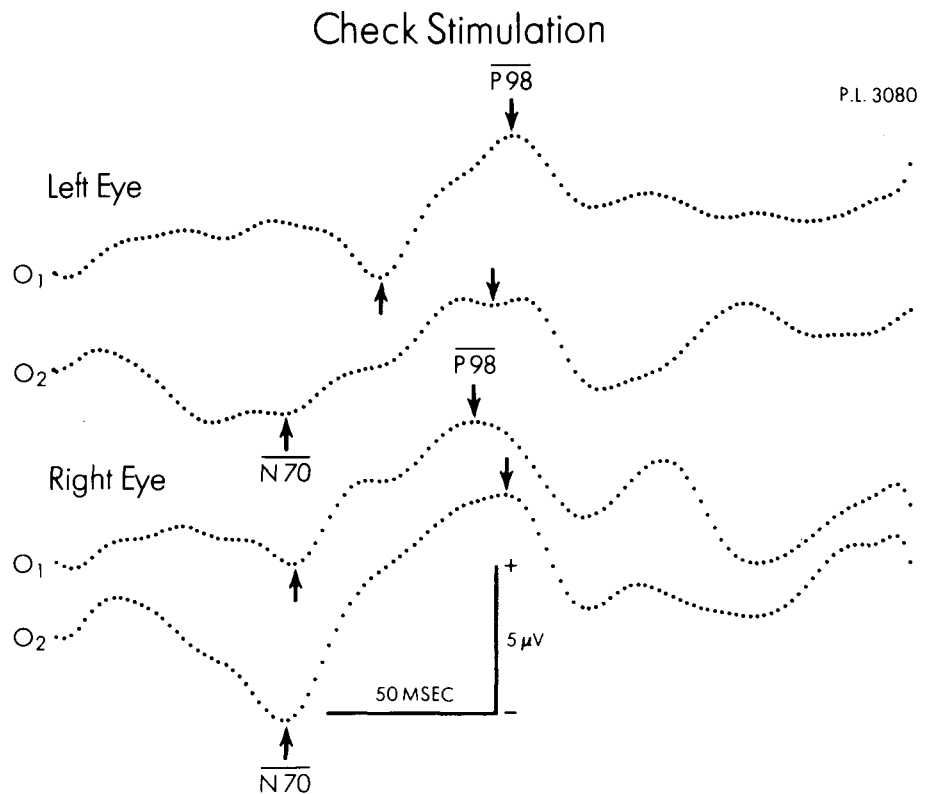

Check Stimulation

P98

P.L. 3080

Left Eye

O_1

O_2

P98

N70

Right Eye

O_1

O_2

+

5 μV

50 MSEC

−

N70

Figure 1 — VEPs to check pattern recorded from monocular stimulation of right and left eyes show gross bilateral delay of major positive (P98) components. Marked increase in the temporal dispersion of the N70-P98 intercomponent period is also evident.

The abnormality which proved consistantly present throughout the pattern stimulation were the delays in N70 and P98 peaks which were significant beyond the p < .05 level (Table 1) for all check and diamond pattern conditions. For the flash stimulation also there was significant delay in the peak latency of the early negative (N70) and major positive (P110) VEP components. In addition, the N70-P98 and N70-P110 interpeak periods were significantly greater in the Friedreich's ataxia patients than in normal controls (Table 1) suggesting an abnormal degree of temporal dispersion of the visual evoked response (Fig. 1).

Within the Friedreich's ataxia group the relative frequencies of occurrence of VEP delay under check and diamond conditions were tabulated into bivariate contingency tables. Chi-square analysis showed no significant difference in the relative frequencies of VEP delay specific to pattern orientation (chi² = 2.0 p < .95).

Table 2 shows the VEP interhemispheric latency difference in the N70 and P98 components measured over the left (O₁) and right (O₂) hemispheres from monocular pattern and binocular flash stimulation. Significant interhemispheric peak latency differences were found for all recording sites and for both components. There were significant asymmetrical prolongations of the N70-P98 interpeak period in pattern conditions and the N70-P110

period in flash conditions suggesting that the VEP delay was in part a manifestation of retrochiasmal disease (Figure 2).

Table 3 shows the interocular differences in the early negative and major positive components of the VEP under flash and pattern stimulation. Significant interocular latency differences associated with abnormal waveform morphology were found at the p<.01 level for all conditions suggesting that some of the observed VEP delay is also due to prechiasmal disease (Fig. 3).

Flash ERGs were of very variable amplitude and often abnormal in waveform. Table 4 shows the results of the flash ERG in terms of b-wave implicit time and while there was no statistically significant difference in the mean b-wave implicit time in the Friedreich's ataxia group, the variability was substantially greater than that found in the normal sample. Interestingly, we observed that 6 of the 12 patients had interocular peak implicit times which exceeded 99% of the normal control values even though the b-wave implicit time in each eye fell well within normal limits. While the ERG waveform in Figure 4 is somewhat atypical for the group since it retains a normal morphology and amplitude there is still a statistically significant interocular difference in b-wave implicit time.

DISCUSSION

The nature and incidence of visual system dysfunction in Friedreich's ataxia is difficult to ascertain from the older literature. The impetus given to accurate classification of ataxic patients by the Quebec Study has provoked three groups to examine the visual evoked potentials (VEPs) of well defined populations of Friedreich's ataxia patients (Carroll et al, 1980; Livingstone et al, 1981; Bird and Crill, 1981). There has been no previous systematic study of ERGs and VEPs in Friedreich's ataxia.

Carroll et al (1980) mentioned that 3 of their patients had ERGs which were considered to be "mildly abnormal" with reduced amplitude and thought to indicate defective cone function. We

TABLE 1

VISUAL EVOKED POTENTIAL LATENCIES

Means and standard deviations for normal and Friedreich's subjects in milliseconds for major negative (N70) and positive (P98) VEP peaks and the N70-P98 intercomponent latency.

Recording site and Component	Left eye stimulation			Right eye stimulation		
	Normal	Friedreich's	t	Normal	Friedreich's	t
CHECKERBOARD STIMULATION						
O₁ N70	70.8 ± 5.7	78.0 ± 24.7	#	69.6 ± 4.8	83.1 ± 18.6	+
O₁ P98	98.5 ± 4.4	120.6 ± 21.1	*	97.3 ± 5.3	122.6 ± 23.1	*
O₁ N70-P98	27.6 ± 4.8	42.7 ± 18.2	*	27.6 ± 5.5	39.4 ± 14.2	*
O₂ N70	70.1 ± 6.0	83.3 ± 23.6	+	70.1 ± 5.8	82.5 ± 19.1	+
O₂ P98	98.3 ± 5.2	123.4 ± 21.2	*	97.7 ± 5.9	121.3 ± 25.3	*
O₂ N70-P98	28.1 ± 5.0	40.1 ± 21.8	+	27.6 ± 6.3	38.8 ± 10.3	*
DIAMOND STIMULATION						
O₁ N70	69.5 ± 6.5	82.8 ± 23.8	+	69.6 ± 4.8	84.4 ± 21.5	+
O₁ P98	100.3 ± 3.8	124.8 ± 24.1	*	100.3 ± 4.5	119.3 ± 17.9	*
O₁ N70-P98	30.7 ± 6.9	42.0 ± 17.0	+	30.7 ± 4.8	34.8 ± 8.1	$
O₂ N70	69.4 ± 6.3	83.3 ± 23.6	+	69.3 ± 4.8	81.2 ± 15.3	*
O₂ P98	98.6 ± 5.0	123.6 ± 21.4	*	100.0 ± 5.3	121.5 ± 15.9	*
O₂ N70-P98	29.2 ± 6.8	40.3 ± 13.9	+	30.7 ± 4.4	40.3 ± 11.6	+

BINOCULAR FLASH STIMULATION

	Normal	Friedreich's	t
O₁ N70	72.5 ± 6.8	86.5 ± 21.0	+
O₁ P110	108.4 ± 5.6	128.8 ± 21.0	$
O₁ N70-P110	35.8 ± 6.5	42.2 ± 9.5	+
O₂ N70	74.3 ± 6.2	86.0 ± 25.0	+
O₂ P110	109.1 ± 5.6	130.1 ± 22.5	+
O₂ N70-P110	34.8 ± 5.4	50.8 ± 14.3	*

t-test results: * = p < .001   + = p < .01 $ = p < .05   # = p < .10

are not aware of any other report in the literature of ERGs in Friedreich's ataxia. We found grossly abnormal waveforms of low amplitude in 5 of our cases and in one subject the ERGs were not distinguishable from the background noise. While the b-wave implicit times of the ERGs were within normal limits in 23 of the 24 eyes studied, there were marked interocular implicit time differences which proved to be statistically significant for the group as a whole (Table 4; Figure 4). Pattern ERGs were recorded from skin electrodes in this study and, where recognizable, appeared to have normal positive peak (q-wave) latencies, but the majority of the skin recordings were of such small amplitude that these results were not included in this statistical analysis. The electroretinal abnormalities observed in the flash ERGs may suggest a functional defect of transport of a retinal neurotrasmitter such as taurine which has been shown to have defective transport in other tissues in this disease (Barbeau, 1978).

In the pattern-reversal VEPs we found evidence of delay of the N70 or P98 peak latencies in 11 of our 12 Friedreich's ataxia patients. Carroll et al (1980) and Livingstone et al (1981) examined the clinical visual function of their Friedreich's ataxia patients and found abnormalities of visual acuity, colour vision or overt optic atrophy in some cases. They remarked that the severity of the visual evoked potential abnormalities which they found in their patients appeared to correlate with the clinically observed visual status. Both studies showed that over 66% of their patients had abnormally delayed VEPs indicating that the visual pathways are frequently involved in Friedreich's ataxia and that such involvement is often subclinical. Carroll et al (1980) considered that the amplitude of the VEP response was reduced in their patients even when the latencies of the major postive peaks were just within their criterion latency. Livingstone et al (1981) found the amplitudes of all their patients responses were within the normal range and that there was a tendency for amplitude diminution to occur with increasingly abnormal major positive peak latency. The range
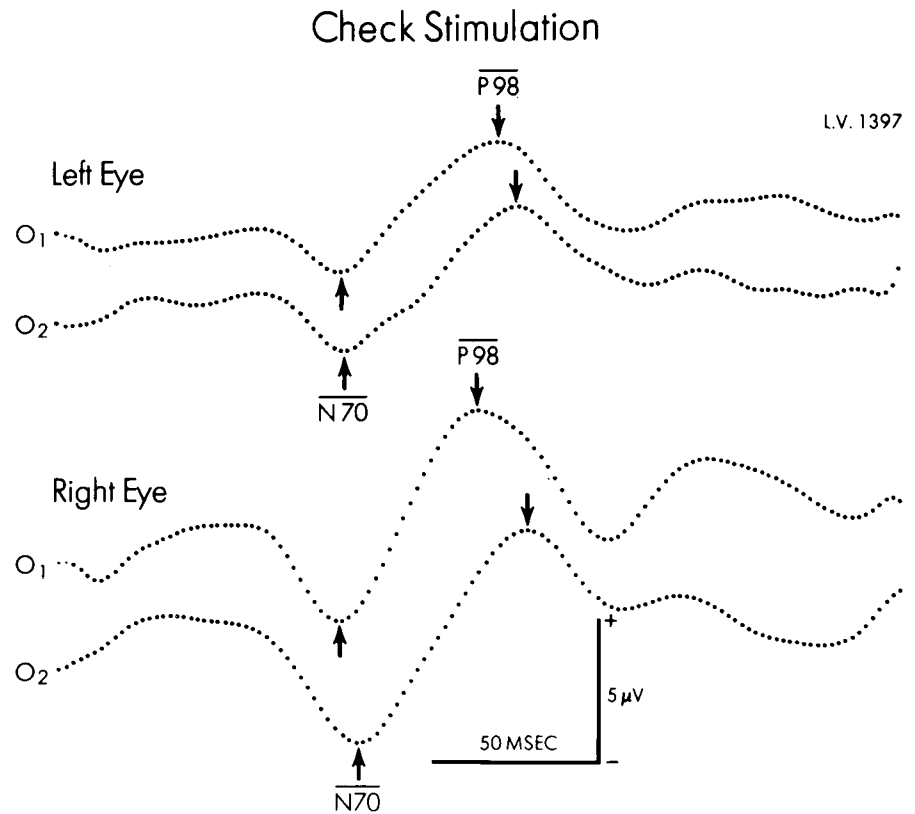

Figure 2 — Monocular pattern VEPs to check stimulation reveal significant, asymmetrical, delay of N70 and P98 components. These consistent interhemispheric latency differences provide evidence of retrochiasmal disease.

TABLE 2

VISUAL EVOKED POTENTIAL LATENCIES
Means and standard deviations for normal and Friedreich's subjects in milliseconds for interhemispheric (O_1 and O_2) latency differences of the major negative (N70) and positive (P98) components of the pattern VEP.

VEP Component	Left eye stimulation			Right eye stimulation		
	Normal	Friedreich's	t	Normal	Friedreich's	t
CHECKERBOARD STIMULATION						
N70	1.8 ± 1.8	11.0 ± 10.5	*	1.5 ± 2.2	9.7 ± 8.1	*
P98	1.3 ± 1.1	6.8 ± 6.4	*	1.4 ± 1.1	7.8 ± 6.1	*
N70-P98	1.9 ± 1.8	9.1 ± 7.9	*	2.3 ± 6.5	8.4 ± 6.8	*
DIAMOND STIMULATION						
N70	1.6 ± 1.9	13.1 ± 10.6	*	1.3 ± 1.5	13.1 ± 10.6	*
P98	2.3 ± 2.2	8.3 ± 5.2	*	1.1 ± 1.5	5.9 ± 6.7	*
N70-P98	2.4 ± 2.4	6.5 ± 4.3	*	1.8 ± 2.2	9.3 ± 8.9	*

BINOCULAR FLASH STIMULATION

	Normal	Friedreich's	t
N70	2.2 ± 2.0	7.0 ± 8.9	+
P110	1.4 ± 1.2	8.9 ± 8.9	*
N70-P110	2.1 ± 2.9	10.7 ± 10.0	*

t-test results: * = p < .001   + = p < .01

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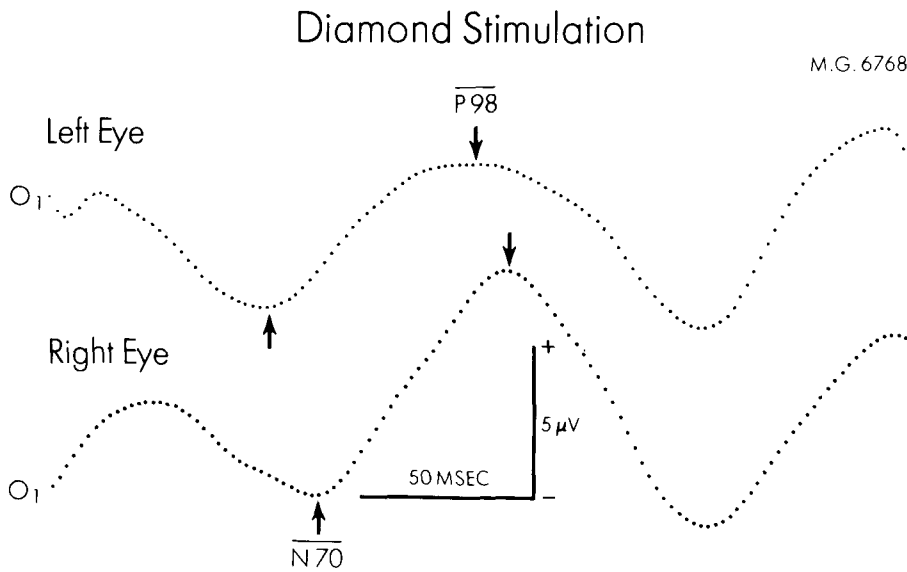
Diamond Stimulation

M.G. 6768

Figure 3—Monocular pattern VEPs to diamond stimulation recorded over the left hemisphere (O_1) reveal a marked interocular latency difference in both the N70 and P98 components suggesting prechiasmal disease.

TABLE 3

VISUAL EVOKED POTENTIAL LATENCIES
Means and standard deviations for normal and Friedreich's subjects
in milliseconds for interocular (O.S. - O.D.) latency differences
of the major negative (N70) and positive (P98) components of the pattern
and flash VEPs.

VEP Component	CHECKERBOARD STIMULATION			DIAMOND STIMULATION		
	Normal	Friedreich's	t	Normal	Friedreich's	t
N70	3.8 ± 4.0	12.8 ± 13.5	+	3.0 ± 5.0	10.0 ± 8.5	+
P98	2.8 ± 2.1	9.7 ± 10.8	+	1.5 ± 1.3	9.6 ± 6.7	*
N70-P98	4.2 ± 4.0	15.0 ± 10.2	*	3.5 ± 4.7	7.8 ± 9.7	*

t-test results: * = p < .001   + = p < .01
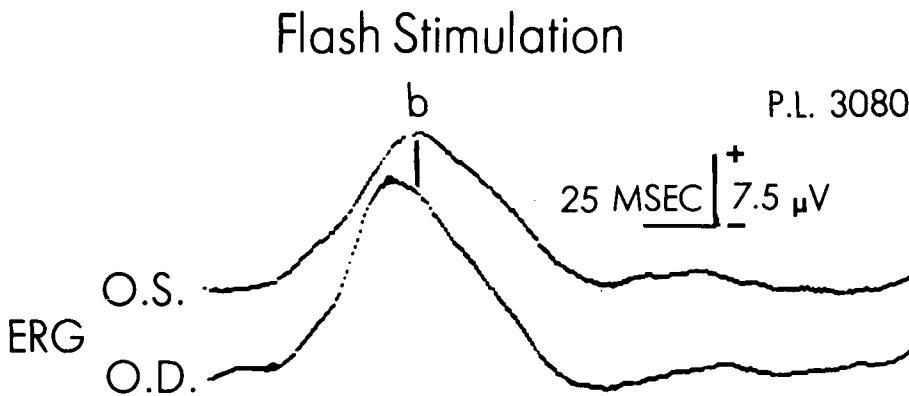
Flash Stimulation

P.L. 3080

Figure 4—Binocular flash ERGs with normal b-wave implicit times but with a significant interocular difference suggest a possible retinal contribution to the VEP abnormalities in Friedreich's ataxia.

of amplitude for their control group was from 1 - 21 uv and 5 of their subjects had non-recordable responses. This huge variation in normal subjects in VEP amplitude renders it a poor criterion for determining abnormality in our experience and we have therefore not used it in the statistical analysis of our data. Bird and Crill (1981) did not find any clinical visual abnormalities in their patients, but 3 of their 5 cases had abnormally delayed major positive peaks of the VEP. In our present study we confirm these significant delays of the major negative and positive VEP peaks under checkerboard and diamond pattern stimulation as well as to flash stimulation, suggesting that there are abnormalities both in the channels for pattern as well as luminance detection in the visual system. We were unable to find any evidence of meridional-specific VEP delay as tested by changing pattern orientation. There was no statistically significant difference in the relative frequency of VEP abnormalities elicited by check or diamond stimulation. This provides further support that the pathology in Friedreich's ataxia is widely disseminated throughout the visual system.

We also found significant inter-hemispheric latency differences which we interpret as evidence for asymmetrical involvement of the retrochiasmal visual pathways by the disease process. This was not apparently noted by the

TABLE 4

FLASH ELECTRORETINOGRAM
Means and standard deviations for normal
and Friedreich's subjects in milliseconds
for the b-wave implicit time of the ERG to
4 Hz. flicker stimulation of the right (O.D.)
and left (O.S.) eyes. Interocular implicit
time (OD-OS) is expressed as the absolute
difference in milliseconds.

ERG b-wave	Normal	Friedreich's	t
O.D.	69.0 ± 7.3	64.6 ± 16.6	ns
O.S.	69.5 ± 7.7	62.5 ± 9.2	ns
OD-OS	1.9 ± 1.8	4.7 ± 4.8	*

t-test results: * = p < .001   ns = not significant at p < .10

other groups who did not report on this aspect. Abnormal temporal dispersion of the response was not detected by Carroll et al (1980) who measured the difference between the first and second major negative peaks as their measure for afferent volley dispersion. However Livingstone et al (1981) using the same criterion found significantly abnormal temporal dispersion in 6 of their patients. Further, Bird and Crill (1981) used the difference between the first major positive peak and the following major negative peak as a measure of dispersion and found it to be significantly abnormal. We used the difference between the N70 and the P98 peak as our temporal dispersion measure and it was found to be abnormally increased in 9 of our 12 Friedreich's ataxia patients.

Finally interocular latency differences were not detected by Carroll et al (1980) or by Bird and Crill (1981), but Livingstone et al (1981) noted abnormal interocular latency differences for the major positive peak in two of their cases. In our present study we detected significant interocular differences under both checkerboard and diamond stimulation for both major negative and positive peaks. Additionally, we detected significant interocular differences in the N70-P98 intercomponent period.

The results of our study confirm the previous reports of significant abnormalities of the VEP in visually asymptomatic patients with Friedreich's ataxia. We have added data concerning possible retinal involvement in Friedreich's ataxia in addition to documenting the VEP abnormalities which included significant interocular latency differences, interhemispheric differences and evidence of abnormal temporal dispersion of the VEP under pattern and flash stimulating conditions. We believe that our results are consistent with the idea that in Friedreich's ataxia there is diffuse and possibly progressive loss of nerve fibers associated with slowing and abnormal spread of conduction in the visual pathways. These results suggest strongly that the disease process is not limited just to the anterior visual system, but also involves the retrochiasmal pathways. The distribution of neuronal loss or dysfunction is fairly symmetrical but sufficiently diffuse such that significant interocular and interhemispheric delays in the VEP occur.

Some of the disparate results from the other reports of VEP abnormalities are most probably a result of the small sample sizes used as well as methodological differences in stimulation and recording techniques and the different criteria for defining latency abnormalities. Further, it is obvious that despite the consistant use of the Quebec criteria (Geoffroy et al, 1976) for the definition of typical Friedreich's ataxia there are interfamilial and intersubject differences in genetic expression and it may be that future studies of visual electrophysiology combined with the Quebec criteria may lead to further subdivisions of cases currently diagnosed as Friedreich's ataxia. Other evoked potential studies such as sensory evoked potentials have been found abnormal in the patients of Carroll et al (1980) and Jones et al (1981), and also, abnormal brainstem auditory evoked potential abnormalities occur in Friedreich's ataxia (Satya-Murti et al., 1980).

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