Neuro-otological abnormalities in Friedreich's ataxia

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SUMMARY Ten patients with an accepted diagnosis of Friedreich's ataxia have been examined neuro-otologically, and oculomotor, vestibular and auditory function assessed. Brainstem auditory evoked potentials (BAEPs) were also recorded. A high incidence of various eye movement disorders was noted. Some of these were indicative of cerebellar dysfunction. Reduced vestibular function and impaired hearing were common to most of the patients. BAEPs were also abnormal in the majority; reasons underlying these abnormalities are discussed. Neuro-otologically, the patients did not constitute an homogeneous group. The findings cast doubt upon the accuracy and validity of the currently accepted criteria for the diagnosis and classification of the spinocerebellar degenerations.

Since Nicholas Friedreich's initial description in 1863¹ of the disease which was by 1882 to become known as Friedreich's ataxia, there have been many attempts to define the condition as both a clinical entity in its own right and also to establish its place within the broader context of the other hereditary ataxic syndromes. Friedreich's ataxia remains one of the few eponymous ataxic syndromes that is confidently diagnosed in modern neurological practice. The most recent classifications by Barbeau and his group² and Harding³ have relied upon common phenotypic expressions of the condition as the principal features essential for diagnosis. We have examined ten cases neuro-otologically to ascertain whether, from that point of view, they constitute a homogeneous population.

Patients and methods

Ten patients with Friedreich's ataxia, (six male, four female), all definite cases according to the criteria of Harding³ and eight definite and two probable according to the criteria of Barbeau² were examined. Their ages ranged from 12 to 36 years. The range of duration of symptoms was 3 to 19 years. Oculomotor, vestibular and auditory functions were assessed and brainstem auditory evoked potentials were recorded.

Oculomotor function

Eye movements were recorded using conventional DC-

coupled electro-oculography. Separate eye recordings were made in the horizontal and vertical planes. An electrostatic ink jet recorder print out was used for qualitative assessments and manual measurements. Saccade velocities were assessed for target jumps of 30 degrees. Smooth pursuit was judged to be impaired when the patient could not follow a sinusoidal target moving at 20 degrees/s (at a frequency of 0.2 Hz) or less without saccadic intrusions. Optokinetic responses were assessed by whole field stimulation using a cylindrical curtain rotating at 40 degrees/s constant angular velocity. Optokinetic nystagmus was judged to be normal if the gain of the slow phase was near unity at that velocity and the pattern of insertion of the fast phases was orderly. The target used for assessment of pursuit and saccades was the projected beam of a Helium-neon laser reflected from a servo-controlled rotating mirror on to a tangent screen. The target subtended 0.002 radians at a distance from the subject of 3 metres. Ability to suppress the vestibulo-ocular reflex was assessed by observation of the EOG for the presence of nystagmus during impulsive rotational stimulation at up to 40 degrees/s constant angular velocity with the patient fixating on a target rotating with him in a Barany chair.

Vestibular function

The patients underwent caloric testing (method of Fitzgerald and Hallpike⁴). The threshold of nystagmus to angular acceleration was measured. Each patient was given an impulsive starting and stopping rotational stimulus to and from 40 degrees/s constant angular velocity (trapezoidal wave form) in a rotating chair. The maximum slow phase velocity generated was measured manually from the traces.

Auditory function

Pure tone audiometry, loudness discomfort levels and, in some cases, tone decay and speech audiometry were

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performed using a Peters AP 5 audiometer and MRC 25 word lists recorded by a BBC announcer from the overseas service in a sound proof booth.

Brainstem auditory evoked potentials

BAEPs were recorded with standard EEG electrodes placed over the vertex and the mastoid processes. The earth electrode was placed on the chin. Monaural and binaural recordings were obtained using a 100 microsecond click of peak SPL 90 dB (alternating rarefaction and compression phase) at a rate of 10 Hz. Signal averaging was carried out by a minicomputer (CAI Alpha LSI 2:20) with an analysis window of 10 ms duration comprising 1024 sampling points. The test was repeated twice to check the reliability of the response.

Results

OCULOMOTOR FUNCTION

The oculomotor abnormalities are listed in table 1. Saccades were dysmetric in nine of the subjects but maximal velocities were within normal limits. In seven patients square wave jerks were seen throughout the records and five patients had brief episodes of ocular flutter. Examples of these two latter abnor-

malities are shown in fig 1. The square wave jerks varied in duration from 80 ms (seen in all 7 patients) to 250 ms.

Smooth pursuit was severely impaired in two patients (duration of symptoms was 10 years in both). In one patient (duration of symptoms 8 years) pursuit was normal and in the remaining seven patients pursuit was mildly impaired. Inability to suppress the vestibulo-ocular reflex corresponded approximately with the pursuit deficit. The patterns of nystagmus were highly variable. Gaze-evoked nystagmus (of "gaze paretic" wave form) in the horizontal plane was seen in eight patients, and in the vertical plane in two patients. Rebound nystagmus was recorded in five patients. Optokinetic responses to whole field stimulation (passive OKN) were within normal limits in eight patients and severely deranged in the two patients with marked deficit of smooth pursuit.

VESTIBULAR FUNCTION

Results of caloric and rotational testing and assessments of thresholds to angular acceleration are shown in table 2. In general, the durations of nystagmus induced by caloric stimulation were within

Table 1 Oculomotor function in Friedreich's ataxia

Patient name and sex and age	Duration of symptoms (years)	Saccades		Pursuit	VOR suppression	Nystagmus	Square waves and flutter	OKN (40°/s)
		V max (deg/s)	Dysmetria					
MB M 23	7	540	+	+	N	H 1°	+ F	N
SC F 21	4	610	+++	+	++	H 1°	+++ F	N
DG M 27	10	440	+++	+++	+++	H 1° U 2°, D 1° Rebound	0	+++ 5°/s
MB F 35	19	690	++	+	+	H 1° Rebound	0	N
MH M 17	8	480	+	N	N	H 1° Rebound	++ F	N
SW M 36	10	610	+++	+++	—	H 2° U 3° Rebound	0	+++ 5°/s
LB F 23	5	350	++	+	+	Nil	++	N
EB F 18	6	500	+	++	+	H 1°	++ F	N
CD M 12	3	320	N	+	N	Nil	++ F	N
RB M 37	14	540	++	+	++	H 1° Rebound	++	N

Vmax = maximum velocity. H = horizontal, U = upbeat, D = downbeat. N = normal, F = flutter +, ++, +++ = degree of abnormality :- mild, moderate, severe, 0 = Absent, °/s in OKN column indicates max. slow phase velocity generated for 40°/s stimulus

Fig 1 Square wave jerks and brief episodes of ocular flutter in three Friedreich's ataxia patients. (C = centre, R = right, L = left)

Table 2 Vestibular function in Friedreich's ataxia

Patient name and sex and age	Duration of symptoms (years)	Threshold to angular acceleration (deg/s ²)	Caloric response 44°C (min-s)		Starting		Rotation (40°/s) Duration (s) Stopping		Slow phase V max (deg/s)
			R	L	R	L	L	R	
MB M 23	7	0.5	2-25	2-25	25	23	14	10	13
SC F 21	4	0.5	2-10	2-10	22	30	20	20	20
DG M 27	10	0.5	2-10	2-10	16	14	32	17	40
MB F 35	19	1.0	1-55	2-25	120	54	41	56	30
MH M 17	8	0.5	1-40	1-40	19 SR	19	9	22	10
SW M 36	10	0.5	2-35 SR	2-25 SR	33	36	64	61	40
LB F 23	5	0.5	Nil	Nil	20 SR	19	18	17	20
EB F 18	6	0.5	Nil	Nil	38	20	25	23	27
CD M 12	3	1.5	Not Done		10	16	17	14	22
RB M 37	14	0.5	2-20	2-10	15	17	14	15	24

V max = maximum velocity. SR = spontaneous reversal

Fig 2 Deranged vestibular responses of two Friedreich's ataxia patients following a stopping stimulus from rightwards 40 deg/s constant angular velocity rotation.

normal limits apart from two patients in whom no responses were obtained. Both had narrow external auditory canals. Otherwise, the responses appeared disorganised. The responses to rotational stimuli were of generally reduced duration. There was a high degree of variability in the amplitudes and irregularity of insertion of the fast phases of nystagmus. Two representative traces are illustrated in fig 2. Maximum slow phase velocities generated were reduced in eight of the patients. Abnormal spontaneous reversal of rotational or caloric induced nystagmus was observed in two patients. Thresholds to angular acceleration with eyes open in the dark were elevated

in all 10 patients, ranging between 0.5 deg/s² and 1.5 deg/s² (N = 0.1–0.2 deg/s²).

AUDITORY FUNCTION

Although no patient complained of deafness only one had a completely normal audiogram in both ears. As a group there was a significant decrease in acuity (Mann Whitney test $p < 0.04$) at 0.25, 1 and 2 kHz in the left ear and 0.25, 0.5 and 1 kHz in the right ear, compared with 44 neurological control subjects (fig 3). There was no significant tone decay in any patient and the speech audiograms were normal in all tested.

Fig 3 Mean thresholds at different frequencies for 44 neurological control subjects (■ Right ear, □ Left ear) and 10 Friedreich's ataxia patients (● Right ear, ★ Left ear).

Loudness discomfort levels were elevated in three patients at 0.5, 1 and 2 kHz.

BAEP

Only one of the patients had an unequivocally normal BAEP (DG) and one a clear delay of component V (SW). The remaining five patients had BAEPs in which the IV/V complex was of unusual form in which it appears that the component IV was dominant rather than V (fig 4). The fact that the III-IV/V interval in these five patients was about 1.30 ms rather than 1.85 ms favours the major component of the IV/V complex being component IV. Unfortunately no BAEP was obtained at high stimulation rates, a technique that degrades component IV but to which component V is relatively resistant. Another striking feature of the IV/V complex was the lack of increase in amplitude of the wave form to binaural compared with unilateral stimulation (compare normal subject with MBM, SC and MBF fig 4). The earlier components were not always clearly defined and component I could only be identified with confidence in two patients (RB and MH). The mean latency of component III was 4.02 ms compared with 3.82 ms for control subjects.

Fig 4 BAEP from 7 Friedreich's ataxia patients. At left unilateral stimulation (right ear), at right binaural stimulation. A normal response shown for comparison. Bar = 1 μ V. A positive potential at the vertex relative to the mastoid gives a downward deflection. Latencies for control subject I = 1.70 $\pm$ 0.12, III = 3.82 $\pm$ 0.71, V = 5.68 $\pm$ 0.19 ms.

Discussion

OCULOMOTOR ABNORMALITIES

All 10 patients showed abnormalities of oculomotor function of varying severity. No definite correlation between length of history and extent of oculomotor dysfunction could be made. Previous surveys in the literature quote differing types and frequencies of abnormalities but all the abnormalities seen in this series have been reported before.

Concerning the incidence of abnormal smooth pursuit and nystagmus, Harding³ states values of 12.2% and 20% respectively. Baloh *et al*⁶ found broken pursuit and nystagmus in 100% and 80% of their patients. Kirkham *et al*⁷ cite incidences of 85% and 64%, Rossi *et al*⁸ 100% and 50%. Geoffroy *et al*⁹ found nystagmus in 42.2% of their cases. The disparity between these values may well reflect varying levels of threshold of detection of oculomotor dysfunction by clinical examination as opposed to EOG. A further problem is the exact method employed for EOG examination. Only two of our patients had abnormal OKN by our method of testing. Kirkham *et al*⁷, using a hand held drum (that is eliciting mainly "active" OKN), found abnormal OKN in all their subjects when more than one stimulus velocity was used, there being an abnormal pattern of increase in slow phase velocity with increasing drum speeds. Baloh *et al*⁶ found abnormal OKN in two of the three patients tested. In our patients there was often a disparity between the degree of impairment of pursuit as compared with the optokinetic response suggesting relative preservation of that part of the optokinetic system mediated through peripheral retinal input.

From our results and surveying the literature the pattern of gaze evoked nystagmus, whether in the horizontal or vertical planes, seems highly variable and therefore unhelpful with respect to diagnosis and classification. The observation of rebound nystagmus in the context of Friedreich's ataxia is of particular interest. This unusual form of nystagmus has been reported previously in Friedreich's ataxia patients.^{6, 7, 9} Rebound nystagmus is thought to be characteristic of cerebellar system disease.^{10, 11} As such, this finding is at variance with the usually accepted neuropathology of Friedreich's ataxia, the major abnormality being in the spinal cord (dorsal columns and posterior spinocerebellar tracts) and the low brainstem, the cerebellum often being normal.^{12, 13} The common finding of square wave jerks (Gegenrucke) again points to cerebellar system disease.^{11, 14, 15} In the six patients affected, square wave jerks of short duration (80 ms) were recorded. These are particularly suggestive of cerebellar dysfunction as they cannot be mediated by retinal feedback.¹⁶ The

longer duration square wave jerks recorded (up to 250 ms) can occur with cerebellar, brainstem or cerebral hemispheric disease.¹⁷

Saccadic dysmetria was seen in most of the patients although saccade velocities were normal. Baloh *et al.*,⁵ however, found two out of their five Friedreich's ataxia patients to have slowed saccades. The diagnosis in one of their cases must be questioned as the patient also had epilepsy. Whether the presence of slowed saccades precludes a diagnosis of Friedreich's ataxia and points more to an illness of the olivopontocerebellar atrophy group requires appropriate examination of further cases.

The observation of brief episodes of ocular flutter in five patients is in agreement with previous studies.⁵⁻⁹ If the hypothesis of Zee and Robinson¹⁸ that an abnormality of the "pause" cells of the pontine paramedian reticular formation is the defect responsible for ocular flutter is correct, then this is a confirmatory sign of brainstem involvement.

In summary, disordered pursuit (and vestibulo-ocular reflex suppression), dysmetric saccades, gaze evoked nystagmus, rebound nystagmus, square wave jerks and ocular flutter were all observed amongst our patients. However, no single abnormality was common to all 10 patients and clustering of abnormalities was variable.

VESTIBULAR ABNORMALITIES

Durations of responses to caloric stimulation were within normal limits in seven of the nine patients tested. In the two patients with no response the external auditory canals were very narrow and accordingly the results of the tests are dubious. However, the findings of reduction in the duration of the response and maximum slow phase velocity generated on rotational testing, in conjunction with elevated thresholds to angular acceleration, indicate reduced vestibular function. Spoendlin¹⁹ examined pathologically the temporal bones of two sisters with Friedreich's ataxia and found vestibular nerve degeneration with relative preservation of the saccular and utricular branches. The labyrinthine end organs were preserved. Igarishi *et al.*²⁰ found similar changes. Other authors have reported reduced or absent caloric responses in Friedreich's ataxia.^{5-7,9} The appearance of derangement or irregularity of vestibular responses is due to an abnormal pattern of insertion of fast phases of nystagmus. This probably indicates disturbed function of neurons in the reticular formation involved in the generation of vestibular saccades.²¹ The spontaneous reversal of vestibular nystagmus, and also the rebound nystagmus, suggest a faulty brainstem velocity-storage integrator²² possibly situated in the perihypoglossal nuclei. Reduced vestibular function, whether it be

due to degeneration in the vestibular nuclei, vestibular nerves, Scarpa's ganglion or any combination of these, appears to be a consistent feature in Friedreich's ataxia.

AUDITORY ABNORMALITIES

Symptomatic hearing loss is rare in Friedreich's ataxia but it has occasionally been reported. Spoendlin¹⁹ studied two patients with Friedreich's ataxia who had deafness and commented upon the dome shaped audiogram in which there was relative preservation of the middle frequencies. In our study none of the patients complained of deafness but as a group they did have significantly raised thresholds at low frequencies. It is possible that the dome shaped audiograms obtained by Spoendlin reflect superimposition of the normal decline of acuity with age at high frequencies and the low frequency loss although in general patients with Friedreich's ataxia do not survive beyond 50 years of age.

The site of the lesion causing deafness in Spoendlin's two cases was the spiral ganglia, and those neurons innervating the inner hair cells were especially involved. Whether this also applies to other patients is not known. It might be supposed that the BAEP would be helpful in elucidating this problem but published data on the BAEP in Friedreich's ataxia are inconsistent, reports ranging from normality in 20 patients²⁴ to complete absence of all components in the three patients studied by Satya-Murti *et al.*²³ The present study shows that a variety of abnormalities of the BAEP occur in some but not all patients with Friedreich's ataxia. It appears that component V is the most vulnerable, a result in agreement with the work of Rossi *et al.*⁷ and that a loss of normal morphology rather than simple delay occurs. The cause of the abnormalities of the BAEP could lie in the spiral ganglion cells. Although it is tempting to suggest that since component V is abnormal, and component I when recorded, normal, there is additional damage to the brainstem structures, such an interpretation is unwise. We have no way of knowing how perverted input as a result of VIII nerve dysfunction might affect later components of a serial train. The marked effect on component V might well originate at the spiral ganglia and cannot be taken as evidence of a more central disturbance.

Concluding remarks

The neuro-otological abnormalities in Friedreich's ataxia are extensive but do not form a consistent pattern. In this small series there is no obvious correlation between the type or severity of the abnormalities found and the duration of the disease suggesting that these patients constitute a *hetero-*

geneous group. Of particular interest is the high proportion of patients with vestibular and oculomotor abnormalities generally associated with cerebellar disease despite the absence of pathology at a gross level in that structure. This may reflect subtle physiological dysfunction of the cerebellum consequent upon congenital absence or deficiency of normal sensory input, for example from somatosensory afferent pathways, and, if this is so, provides further evidence for plasticity of cerebellar function.

It appears from these data that a diagnosis of Friedreich's ataxia based upon a constellation of physical signs and pattern of inheritance does not result in the selection of a homogeneous group. Further, more accurate classification of the spinocerebellar degenerations must await the development of new biochemical techniques.

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