

Vestibular, saccadic and fixation abnormalities in genetically confirmed Friedreich ataxia

Michael C. Fahey,^{1,2} Phillip D. Cremer,³ Swee T. Aw,⁴ Lynette Millist,⁵ Michael J. Todd,³ Owen B. White,⁵ Michael Halmagyi,⁴ Louise A. Corben,¹ Veronica Collins,¹ Andrew J. Churchyard,⁶ Kim Tan,³ Lionel Kowal⁷ and Martin B. Delatycki^{1,2}

¹Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, ²Department of Paediatrics, University of Melbourne, Victoria, ³Department of Neurology, Royal North Shore Hospital, ⁴Department of Neurology, Royal Prince Alfred Hospital, New South Wales, ⁵Department of Neurology, Royal Melbourne Hospital, ⁶Monash Neurology, Monash Medical Centre and ⁷Department of Ophthalmology, Royal Victorian Eye and Ear Hospital, Victoria, Australia

Correspondence to: Associate Professor Martin Delatycki, Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Flemington Road, Parkville, Victoria 3052, Australia

E-mail: martin.delatycki@ghsv.org.au

Friedreich ataxia (FRDA), the commonest of the inherited ataxias, is a multisystem neurodegenerative condition that affects ocular motor function. We assessed eye movement abnormalities in 20 individuals with genetically confirmed FRDA and compared these results to clinical measures. All subjects were assessed with infrared oculography. Fifteen individuals underwent a full protocol of eye movement recordings. Ten subjects were analysed using two-dimensional scleral coil equipment and five using three-dimensional scleral coil recording equipment. We also recorded visual quality of life, Sloan low contrast letter acuity and Friedreich Ataxia Rating Scale scores to compare to the visual measures. Whilst saccadic velocity was essentially normal, saccadic latency was prolonged. The latency correlated with clinical measures of disease severity, including the scores for the Friedreich Ataxia Rating Scale and the Sloan low contrast letter acuity tests. Fixation abnormalities consisting of square wave jerks and ocular flutter were common, and included rare examples of vertical square wave jerks. Vestibular abnormalities were also evident in the group, with markedly reduced vestibulo-ocular reflex gain and prolonged latency. The range of eye movement abnormalities suggest that neurological dysfunction in FRDA includes brainstem, cortical and vestibular pathways. Severe vestibulopathy with essentially normal saccadic velocity are hallmarks of FRDA and differentiate it from a number of the dominant spinocerebellar ataxias. The correlation of saccadic latency with FARS score raises the possibility of its use as a biomarker for FRDA clinical trials.

Keywords: Friedreich ataxia; ocular-motor; vision; saccades; biomarker

Abbreviations: FRDA = Friedreich ataxia; SLCLC = Sloan Low Contrast Letter Chart; SWJ = square wave jerks

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Introduction

Friedreich ataxia (FRDA), an autosomal recessive disorder, is the commonest of the inherited ataxias. Studies based on molecular data estimate a carrier frequency of 1:60–1:90 (Epplen *et al.*, 1997), with a disease incidence of 1:29 000 (Cossee *et al.*, 1997). Pathology within the brain, spinal cord and peripheral nerves results in progressive ataxia, weakness, absent deep tendon reflexes and upgoing plantar responses (Durr *et al.*, 1996). In addition, hypertrophic cardiomyopathy is commonly present. Symptoms typically manifest in teenage years (Harding, 1981; Durr *et al.*, 1996).

The natural history of FRDA is one of slow progression of symptoms over decades with increasing dependence on assistance with activities of daily living.

FRDA is due to mutations in the *FXN* gene. In 98% of mutant alleles an unstable GAA repeat expansion is present within intron 1 of *FXN*, the other 2% being point mutations (Campuzano *et al.*, 1996).

FRDA is a slowly progressive disease but the rate of progression is neither constant nor linear. Furthermore, multiple areas of the central and peripheral nervous system are affected. FRDA therefore provides a challenge in the

development of tools to measure clinical progression. There is currently no gold standard for evaluation of neurological status in FRDA.

The ocular motor system represents a model motor system which can only generate a limited range of output possibilities. Furthermore there are minimal problems with inertia and plasticity, such that motor output closely reflects both input stimulus and the influence of motor processing. The resultant ocular movements are highly reproducible, yield a continuous outcome and can be measured with a high level of accuracy. In other disease processes, ocular motor findings have been validated as reflecting progression of disease (Golding *et al.*, 2006). Anatomical pathways which mediate the ocular motor system have been identified in the brainstem and cerebellum (Ramat *et al.*, 2007).

Ocular motor and visual involvement in FRDA

Previous studies examining visual function in FRDA indicate that optic atrophy is present in up to 30% (Harding, 1981). Visual and auditory evoked potentials are abnormal in the majority (Carroll *et al.*, 1980; Ell *et al.*, 1984; Pinto *et al.*, 1988; Lopez-Diaz-de-Leon *et al.*, 2003). Other reported findings include fixation instability manifesting as square wave jerks (SWJ) and ocular flutter. Saccadic abnormalities include both hypo and hypermetria, and slowed smooth pursuit with superimposed fixation instability (Kirkham *et al.*, 1979; Furman *et al.*, 1983; Moschner *et al.*, 1994). A number of studies have found impaired vestibulo-ocular reflexes (VOR) and impaired visual-vestibular interaction when measured by oculography (Kirkham *et al.*, 1979; Monday *et al.*, 1984). Caloric testing is abnormal in the majority (Furman *et al.*, 1983; Ell *et al.*, 1984; Moschner *et al.*, 1994).

Many of these studies predate genetic diagnosis in FRDA and therefore may have been contaminated by inclusion of individuals with other diagnoses. Furthermore, they did not use scleral search coils, considered the 'gold standard' eye movement recording technique (Cremer *et al.*, 1998). Previous studies did not attempt to quantify the eye movement abnormalities to explore their use as measures of disease progress, nor compare the ocular motor dysfunction to other measures. These studies did not rigorously measure the VOR using the high-frequency head impulse test and therefore potentially under-diagnosed vestibular failure in these individuals (Monday *et al.*, 1978; Ell *et al.*, 1984; Monday *et al.*, 1984; Spieker *et al.*, 1995; Wessel *et al.*, 1998).

We have undertaken studies on ocular motor and visual function in FRDA using a combination of methods including scleral search coils, infrared oculography and clinical measures, in a cohort of individuals with genetically confirmed FRDA. The aim of this study was to document and quantify abnormalities, and their clinical impact.

We also aimed to determine whether non-invasive infrared oculography gave a good representation of ocular motor function in FRDA patients, when compared with the more invasive and less accessible scleral search coil testing.

Methods

Subjects

We studied 20 individuals with FRDA (mean age 35.3 ± 12.8 years) due to homozygosity for a GAA expansion within intron 1 of the *FXN* gene. Clinical assessments included the Friedreich Ataxia Rating Scale (FARS) (15 subjects), Sloan Low Contrast Letter Chart (SLCLC) (20 subjects) and Visual Quality of Life (VF14 and VFQ36) (20 subjects). All underwent full ophthalmic examination including Snellen visual acuity, corrective refraction, ocular motility examination, examination for motor fusion, stereo examination, slit lamp examination, retinal examination and Humphrey computerised perimetry.

Participants underwent a series of ocular motor studies using infrared oculography and scleral coils. Fifteen of the 20 participants with FRDA were tested with the scleral coil. Four could not be tested due to an inability to sit on the wooden chair inside the recording apparatus. One participant could not be tested with the scleral coil due to markedly diminished vision ($<6/60$) meaning he could not see the visual targets. Ten subjects were analysed using two-dimensional recording equipment in Melbourne and five using three-dimensional equipment in Sydney. All 20 participants were studied with infrared oculography.

The protocol was approved by the Royal Prince Alfred Hospital Human Research Ethics Committee and the Royal Melbourne Hospital Human Research Ethics Committee and was in accordance with the Declaration of Helsinki.

Controls

Sex-matched controls without neurological disease (12 males and 8 females, mean age 46.5 years, range 30–61 years) were obtained from the Melbourne eye laboratory, whose scleral search coil data were used for establishing normal values for saccadic latency and velocity.

Recording systems

Scleral search coils

Scleral coil testing involved the insertion of scleral coils embedded in a contact lens under local anaesthetic as described previously (Robinson, 1963; Aw *et al.*, 1996; Cremer *et al.*, 1998). This technique provides accurate measurement of head and eye position with a resolution of 0.017° and with a sampling rate of 0.001 s. In this way, the exact position of the head and eye can be recorded 1000 times each second. The coils were in place for a maximum of 30 min. Two-dimensional scleral coils (2DSC) were used to record data on the 10 subjects tested in Melbourne and three-dimensional scleral coils (3DSC) were used for the five subjects tested in Sydney.

Recording set-up

Head and left eye position were recorded with dual-search coils (Skalar, Delft, The Netherlands) which were precalibrated before each recording with output sampled at 1 kHz and data relayed

directly to a computer. A computer-controlled illuminated target was presented at a distance of 1.5 m. The recording system had a 16-bit resolution and minimum spatial resolution of 0.1 min of arc with maximum errors and cross-coupling at 2%. Participants were seated and the head was fixed with a bite bar.

Infrared oculography

Left eye recording was undertaken using a commercially available infrared pupil tracking system (Micromedical Technologies, Illinois, USA). Participants were seated 1 m from a digitally controlled LED light bar. Simultaneous video and infrared data acquisition at 30 Hz was made directly to a coupled computer. Infrared studies were undertaken to assess the validity of this readily available, non-invasive technique as a means of recording the ocular motor biomarkers of disease progression in FRDA.

Experimental protocols

Saccades

Saccades are rapid re-fixation eye movements. The participants were asked to follow a target with their eyes while their head was fixed. The target jumped in a sequence of 10, 30 and 60° steps in the horizontal plane. Sequences were programmed using software from Micromedical Technologies (Illinois, USA) for infrared oculography, Matlab (Mathworks, Massachusetts, USA) for 2DSC and Labview (National Instruments Inc., Texas, USA) for 3DSC.

Fixation

In an otherwise darkened room, a central fixation target was presented for 60 s, followed by a target-off period of 60 s. A refixation flash of 100 ms duration was shown at 10 s intervals. Participants were instructed to look directly at the target, or at the remembered target. This sequence was repeated for the central position, 30° left and right, and 15° up and down.

Smooth pursuit

The participants were asked to follow a moving target with their eyes while their head was fixed. The target moved horizontally in a sinusoidal waveform with maximum amplitude of 20°, at a frequency of 0.2 and 0.4 Hz. During infrared recording the target moved horizontally in a sinusoidal waveform with maximum amplitude of 15°, at a frequency of 0.1, 0.2 and 0.4 Hz.

Vestibulo-ocular reflex

The vestibulo-ocular reflex maintains steady vision during head movement. To assess VOR, the participants were instructed to stare at a target, while their head was rapidly moved by the operator. Ten passive, unpredictable, low-amplitude (10–20°), high-acceleration (3000–4000°/s) head rotations, approximately in the plane of the SCC pairs were delivered (Cremer *et al.*, 1998). There are three orthogonal SCCs in each ear. Each SCC is paired with a coplanar SCC in the opposite ear. In the 2DSC, head movements were delivered in the yaw plane only, corresponding to the horizontal SCCs. In the 3DSC additional diagonal head movements in the plane of the left-anterior and right-posterior SCC pair (LARP pair), and in the plane of the right-anterior and left-posterior SCC pair (RALP pair) were delivered. A computer-generated profile of the head trajectory was projected after each

head movement, to allow the operator to deliver uniform head rotations.

Sloan low-contrast letter chart

The Sloan Low-Contrast Letter Chart (SLCLC) is a quantitative assessment of visual dysfunction used in clinical trials in diabetes (Regan and Neima, 1984), multiple sclerosis (Balcer, 2001) and FRDA (Lynch *et al.*, 2006). Contrast acuity was assessed using a front-lit SLCLC at 1 m in a brightly lit room according to manufacturer's instructions. 100, 5, 2.5 and 0.6% charts were utilized. There are 60 letters on each chart, and scores were added to give a total score out of a maximum of 240.

Friedreich ataxia rating scale

The FARS is a clinical neurological scale specifically developed for FRDA (Subramony *et al.*, 2005). It comprises a general measure of ataxia, an activity of daily living (ADL) subscale and a neurological subscale yielding a maximum score of 159. A higher score indicates worse disease severity. It has good face and content validity, and interrater reliability has been shown to be acceptable (Subramony *et al.*, 2005). Clinical assessment utilizing the FARS scale was undertaken within 6 months of the eye examination in 15 subjects.

VF 14 and VFQ39

Visual quality of life was measured by the VF14 and VFQ39. The VF 14 is a questionnaire developed to assess functional visual impairment (Steinberg *et al.*, 1994). A result is expressed as a single number scored out of 100 with higher values representing greater function. The VFQ39 is an extended version of the VFQ25 which includes optional items (Mangione *et al.*, 2001). Data presented in this study relate to the following subscale items as we considered these to be the most pertinent to morbidity in FRDA: general vision, near activities and distance activities.

Data analysis

Eye movements recorded using scleral coils were analysed offline. Fixation instability and saccade analysis utilized Matlab customized software (Mathworks, Massachusetts, USA) and VOR was analysed using Labview customized software (National Instruments Inc., Texas, USA).

Saccade analysis

Analysis of latency, velocity and accuracy was undertaken for all saccades. Latency to the initiation of the saccade was defined as the time (ms) from target presentation until the eye speed exceeded a threshold of 30°/s for scleral coils, and 100°/s for infrared oculography. The infrared threshold was the default setting in the Micromedical system. Maximum velocity (°/s) was analysed for 10° and 30° saccades. The end of the saccade was defined as the point where eye speed was below 30°/s for scleral coils and 100°/s for infrared oculography. Following automated analysis, the results were visually examined to exclude inappropriate waveforms and artefacts, such as blinks. Extreme outliers (saccades with velocity slower than 2SD from mean velocity) were excluded manually, following examination of scatter-plot data. Saccades with latencies of <120 ms were deemed anticipatory and were also excluded from the analysis. Saccadic accuracy was

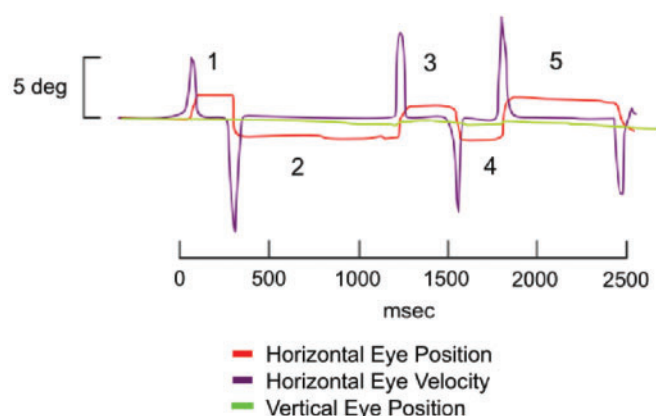


Fig. 1 Analysis of fixation instability indicating the method of counting square wave jerks. Here five square wave jerks are shown. Three sequential eye movements are designated as two square wave jerks.

defined as the percentage error in the initial saccade compared with the target amplitude (Leigh and Zee, 2006).

Fixation instability analysis

Gaze evoked nystagmus was analysed at horizontal gaze 30° left and right. SWJ were analysed with target-on and target-off in the central position. Counting of SWJ was automated using Matlab software (Mathworks, Massachusetts, USA). Three sequential eye movements were designated as two SWJs (Fig. 1). SWJ were classified as micro SWJ (<0.5°), SWJ (0.5–3°) and macro SWJ (3–30°).

The automated analysis program searched for a saccade in one direction (threshold velocity 10°/s) followed by a saccade in the opposite direction, separated by a duration of 60–900 ms. Ocular flutter was defined as to and fro saccades, without a fixation period (Leigh and Zee, 2006). Importantly, automated analysis was validated by visual inspection of all records. The benefits of automated analysis are improved consistency of detection and definition and improved efficiency of analysis. This will facilitate analysis in future studies.

Smooth pursuit analysis

Smooth pursuit was analysed quantitatively using the infrared recording system software (Micromedical Technologies, Illinois, USA), and qualitatively by visual inspection of the scleral coil data.

VOR analysis

We measured function in each of the six individual SCC using rapid head movements in the plane of each SCC pair (Cremer *et al.*, 1998). Three-dimensional head, gaze and eye position were expressed as rotation vectors. Head and eye position were expressed in head-fixed coordinates. Head and eye velocity were calculated from rotation vectors and expressed in degrees per second (Aw *et al.*, 1996; Cremer *et al.*, 1998).

VOR gain was defined as the ratio of eye velocity to head velocity in SCC coordinates, at close to peak head velocity. For each head impulse direction, the mean head and eye velocity in SCC coordinates were determined from approximately 10 trials.

Table 1 Demographic characteristics and disease parameters of participants

	Mean \pm SD	Range
Age at review (years)	35.3 \pm 12.8	21–64
Age at disease onset (years)	15.7 \pm 4.9	6–26
Disease duration (years)	19.5 \pm 11.7	6–45
Longer GAA repeat	970.1 \pm 178.4	707–1345
Shorter GAA repeat	648.7 \pm 171.4	318–1005
FARS	92.3 \pm 24.7	47.8–129.5
SLCLC	165.1 \pm 57.6	0–222
VF I4	3.6 \pm 0.8	0.3–4.0

VOR latency was calculated automatically, using established criteria (Aw *et al.*, 2003).

Statistical analysis

Statistical analysis was undertaken using SPSS 12.0.1 (SPSS Inc., Illinois, USA) and Excel (Microsoft, Washington, USA). Pearson correlation coefficients were calculated for parametric data, and Spearman correlation coefficients were calculated where the data was not parametric.

Results

Demographic details of the participants are presented in Table 1. Twelve participants were male and nine were ambulant, which we defined as being able to walk at least 25 feet (with or without a walking aid).

Ophthalmological examination

Nineteen of the twenty subjects had normal visual acuity. Only one participant had optic atrophy (acuity <6/60) and he also had peripheral retinopathy. Four subjects identified oscillopsia as a symptom. Visual field testing was normal in 14/15 with the remaining subject being unable to see the target. Motor fusion and slit lamp examination was normal in all fifteen subjects tested.

Saccadic abnormalities

Fifteen individuals were analysed with a scleral coil and infrared oculography, and five were analysed using infrared oculography alone. Group mean horizontal latency was 289 ms using the scleral coil (range 176–390 ms, SD 76.5 ms) and 337 ms using the IR (range 229–467 ms, SD 71.8 ms). The apparent discrepancy is due to differences in sampling rate and predefined threshold for saccadic onset between the scleral coil and infrared recording systems. It is not due to differing patient groups. A very high correlation was present between the results from the two systems (Pearson correlation = 0.94; $P < 0.001$). There was a significant correlation between the saccadic latency and the variability of latency (Pearson correlation = 0.84; $P < 0.001$). That is, those who had longer mean latencies also demonstrated the greatest variation in the latencies.

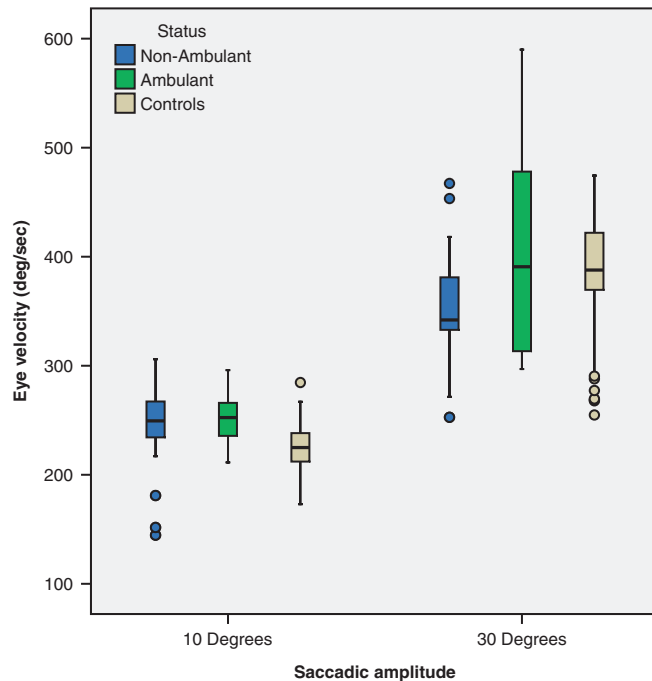


Fig. 2 Boxplot comparing the saccadic velocity of ambulant participants, non-ambulant participants and control participants for saccades of 10° and 30°. Non-ambulant participants had significantly slower saccades at 30° compared to both ambulant and control participants.

With scleral coils, the mean saccadic latency for non-ambulant participants was 339 ms (95% CI 320–342) which was significantly longer than for ambulant participants [243 ms (95% CI 233–252), $P < 0.001$] and both were significantly longer than control subjects [196 ms (95% CI 192–201), $P < 0.001$].

Group analysis of saccadic accuracy demonstrated that 54% of saccades were accurate to within 10% of the saccadic amplitude, 37% were hypermetric and 9% hypometric. Hypermetria and hypometria were often evident in the same individual.

Velocity

Peak velocity for 10 and 30° saccades was examined. For 30° saccades the mean velocity in the non-ambulant group (352°/s) was significantly slower than for ambulant participants (411°/s; $P = 0.04$) and controls (382°/s; $P < 0.001$) (Fig. 2). There was no significant difference in velocity between ambulant participants and control subjects ($P = 0.19$).

Fixation

Nystagmus

Horizontal gaze evoked nystagmus was present in 12/20 (60%) subjects. There was no significant correlation between the presence of nystagmus and other ocular

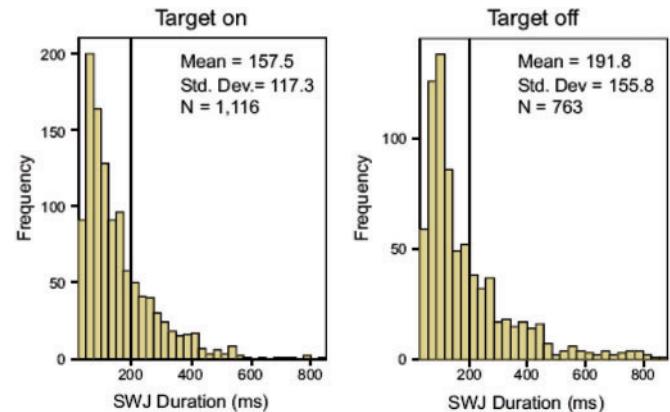


Fig. 3 Histograms of SWJ duration with target-on and target-off. The reference line indicates 200 ms, the historical cutoff for SWJ duration.

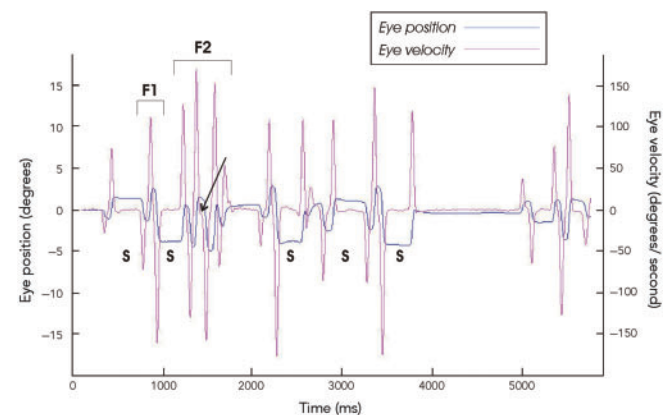


Fig. 4 Three-dimensional scleral coil recording of ocular flutter blending with square wave jerks. The blue trace represents horizontal eye position and the pink trace represents horizontal eye velocity. S = Square wave jerk. F = Ocular flutter with a saccade frequency of approximately 13 Hz. F1 identifies three back-to-back saccades with no intersaccadic interval. F2 is seven back to back saccades with slowing between saccades three and four (arrow) but the eye does not completely come to rest.

motor abnormalities or with the clinical parameters measured. In contrast, spontaneous downbeat vertical nystagmus in the dark, present in 9/20 participants, correlated with disease duration (Spearman $\rho = 0.59$; $P = 0.012$).

Square wave jerks

Analysis of fixation instability revealed variation in the morphology and duration of SWJ. Using traditional definitions, 29% of square waves would not be defined as SWJ because their duration was >200 ms (Dell'Osso *et al.*, 1975) (Fig. 3). Square wave jerks were found to blend with ocular flutter in some instances (Fig. 4). When the waveforms were examined, there was no qualitative

difference between SWJ of duration shorter or longer than the arbitrary definition of 200 ms, and individual participants exhibited both long and short SWJ. We therefore defined SWJ as any waveform with square wave morphology for inclusion in the analysis, in keeping with more recent data (Abadi and Gowen, 2004).

SWJ were significantly longer and larger in the dark (target-off) compared to target-on (mean duration 192 ms versus 158 ms, $P < 0.001$, mean amplitude 2.1° versus 1.8° , $P < 0.001$). The frequency of SWJ with target-on (Pearson correlation = -0.57 ; $P = 0.03$) and target-off (Pearson's correlation = -0.58 ; $P = 0.03$) inversely correlated with age of onset, but not with disease duration. Age at onset also correlated with shorter SWJ duration (Pearson correlation = 0.83 ; $P < 0.001$). That is, those with an earlier age of onset had more frequent shorter SWJ (more fixation instability). The total number of SWJ per 60 s with the target on, was not significantly different in ambulant compared to non-ambulant participants (ambulant = 298, non-ambulant = 327; one-way ANOVA, $P = 0.10$). Macro SWJ ($3\text{--}30^\circ$) on the other hand were significantly more frequent in non-ambulant participants (mean for ambulant = 7.4, mean for non-ambulant = 45.6; $P = 0.02$). It should be noted however, that macro SWJ are rare, and that 99% of SWJ had amplitudes $< 10^\circ$. The mean amplitude of all SWJ was 2.3° .

Vertical components of SWJ were identified in 7/15 participants, but their presence did not correlate with other eye movement abnormalities, including the presence of vertical nystagmus. The vertical components of the SWJ were usually associated with horizontal SWJ but independent vertical SWJ were also demonstrated (Fig. 5).

Smooth pursuit

Smooth pursuit was qualitatively abnormal in all individuals, with frequent saccadic interruptions, low pursuit gain and catch-up saccades (Fig. 6). This made automated analysis impossible using the software available with scleral coils. Automated pursuit analysis on the IIR system demonstrated reduced smooth pursuit gain, especially at higher target oscillation frequencies.

VOR

VOR analysis demonstrated abnormalities in VOR latency and gain affecting each SCC (Fig. 7). The VOR latency was prolonged for each SCC (Lateral canal 26 ms, SD 0.5, Anterior canal 27 ms, SD 9.7, Posterior canal 35 ms SD 13.1. Normal is < 10 ms) and the gain was reduced (Lateral canal 0.48, SD 0.2, Anterior canal 0.44, SD 0.2, Posterior canal 0.40 ms SD 0.2. Normal = 1) (Aw *et al.*, 1996). The deficiency in yaw gain and the prolonged latency correlated with increased horizontal saccadic latency (Pearson correlation = 0.79 ; $P < 0.01$).

Correlations between ocular motor measures, clinical measures and visual function scales are presented

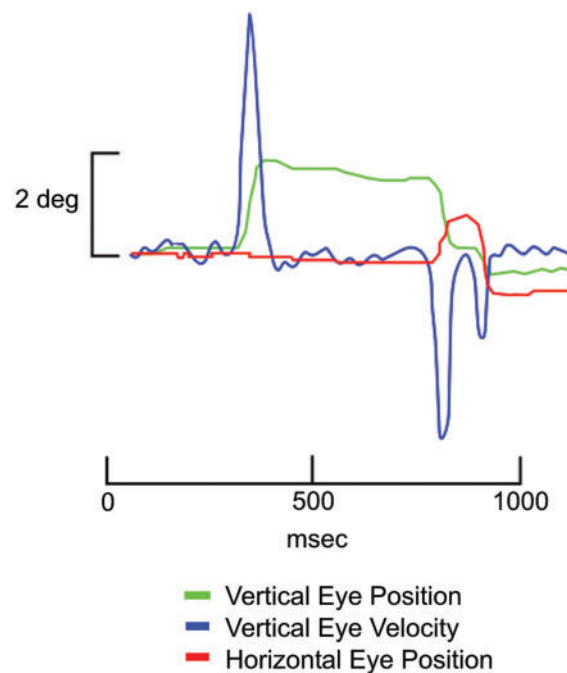


Fig. 5 Independent vertical square wave (green) followed by a horizontal square wave (red).

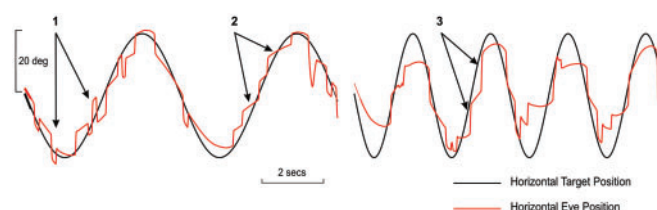


Fig. 6 Smooth pursuit at 0.2 and 0.4 Hz. At 0.2 Hz, frequent saccadic interruptions are demonstrated with occasional catch-up saccades. At 0.4 Hz, smooth pursuit was more severely affected than at 0.2 Hz. Arrows point to key features. 1. SWJ interrupting smooth pursuit, 2. Smooth pursuit with 3. Catch-up saccades.

in Table 2. A correlation was demonstrated between the mean horizontal saccadic latency and both the FARS score and the SLCLC score (FARS: Pearson correlation = 0.66 ; $P = 0.03$, SLCLC: Pearson correlation = 0.78 ; $P < 0.01$) (Fig. 8). Macro SWJ (amplitude of $> 3^\circ$) correlated with scores on the SLCLC (Pearson correlation = 0.88 , $P < 0.001$). Six subjects complained of oscillopsia or visual blur. One way ANOVA did not demonstrate a correlation of this symptom with other clinical measures, or with scores on the VF14.

Discussion

In this study, we demonstrated widespread dysfunction in the ocular motor system in FRDA, including abnormalities in saccades, fixation and vestibular function.

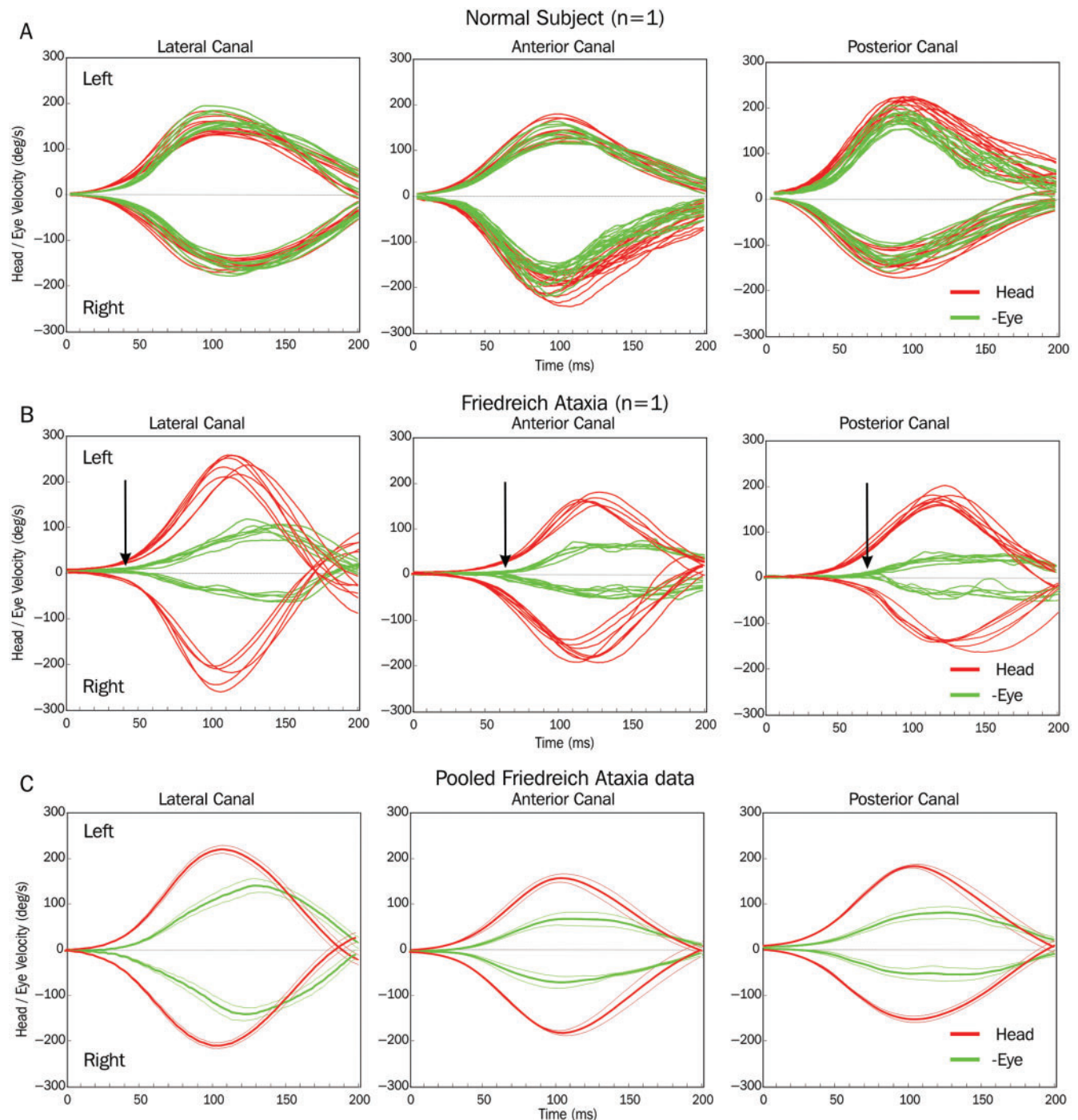


Fig. 7 VOR analysis across three semicircular canals. **(A)** Data from a single control participant showing individual head rotations in the plane of each lateral, anterior and posterior SCC. Head velocity (red) is equal to the inverse of the eye velocity (green), which are plotted against time (MS). **(B)** Data from a single FRDA participant showing individual head rotations. The vertical arrow demonstrates prolonged latency of the eye movement. The velocity of the eye movement is deficient compared to the head velocity stimulus reflecting reduced VOR gain from all six SCC. **(C)** Pooled data from 15 FRDA participants (lateral canal) and five FRDA participants (anterior and posterior canal). The average head and eye velocity \pm 1 SD are plotted against time.

Saccadic function

Saccadic latency was prolonged in FRDA. We demonstrated that those participants with prolonged latencies also have a greater variation in their latencies. In addition, there was a correlation between mean latency for the individual and

their total FARS score. This is also seen in other neurodegenerative conditions such as Huntington disease, where this observation was postulated to be due to disruption of the projections from frontal areas to the superior colliculus, via the caudate and the substantia nigra

Table 2 Pearson correlations between ocular motor measures, clinical measures and visual function measures

	SLCLC	FARS	VOR yaw peak gain	VOR yaw peak latency	Saccadic mean horizontal latency	Total SWJ target-on	SWJ target-on >3°	Total SWJ target-off	SWJ target-off 0–0.5°	SWJ target-off 0.5–3°	SWJ target-off >3°
Age of symptom onset	0.55*	–0.51	0.49	–0.24	–0.38	–0.57*	–0.55*	–0.58*	–0.26	–0.32	–0.63*
Disease duration	–0.42	0.71**	–0.27	0.26	0.38	0.33	0.56*	–0.04	–0.49	–0.29	0.45
Age at review	–0.15	0.39	0.00	0.11	0.12	–0.10	0.16	–0.51	–0.76**	–0.59*	0.01
Shorter GAA repeat	0.09	0.32	–0.15	0.04	0.26	0.37	0.31	0.15	0.09	0.02	0.23
Longer GAA repeat	–0.26	–0.05	–0.17	0.08	–0.07	0.27	0.08	0.48	0.64**	0.39	0.23
SLCLC	1.00	–0.70**	0.59*	–0.41	–0.78**	–0.55*	–0.82**	–0.61*	–0.09	–0.32	–0.73**
FARS	–0.70**	1.00	–0.34	0.63*	0.66*	0.52	0.68*	0.17	–0.41	–0.21	0.60
VF-14	0.73**	–0.46	–0.09	0.02	–0.19	–0.20	–0.55*	–0.35	–0.17	–0.02	–0.59*
VFQ-39 General vision	0.55**	–0.32	–0.06	0.23	0.05	0.01	–0.38	–0.15	0.06	0.10	–0.43
VFQ-39 Near activities	0.83**	–0.53	0.45	–0.21	–0.47	–0.35	–0.60*	–0.45	–0.28	–0.20	–0.53
VFQ-39 Distance activities	0.42	–0.47	–0.05	–0.03	0.39	–0.11	–0.53*	–0.07	0.05	0.28	–0.51

Figures in bold are significant, $P < 0.05$. General vision, near activities and distance activities are subcomponents of the visual function questionnaire (VFQ39) scale.

* $P \leq 0.05$, ** $P \leq 0.01$.

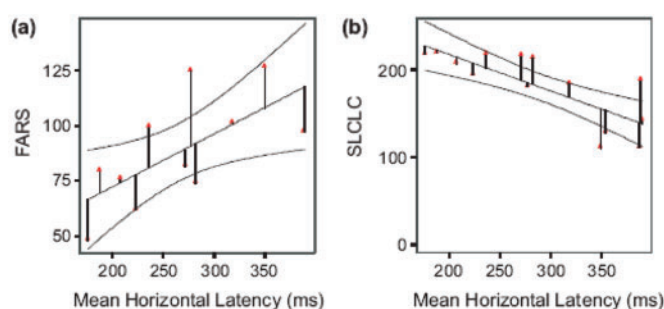


Fig. 8 Linear regression analysis with 95% mean prediction interval, comparing mean horizontal saccadic latency with (a) FARS ($R^2 = 0.44$) and (b) SLCLC ($R^2 = 0.61$).

pars reticulata (Blekher *et al.*, 2006). This explanation is plausible in FRDA, although it is also possible that dysfunction in the brainstem or burst and pause cell interaction may contribute to this phenomenon. It would be of interest to examine different saccadic paradigms in subjects with FRDA to further localize the site of the lesion.

We demonstrated only a slight reduction in saccadic velocity, which was restricted to non-ambulant participants making larger saccades. This suggests that saccadic velocity is affected as disease progresses. Some larger saccades in participants with FRDA were faster than in controls, a finding reported in a different recessive ataxia also associated with saccadic intrusions and peripheral neuropathy (Swartz *et al.*, 2003). This is different from some autosomal dominant cerebellar ataxias, including SCA1, SCA2, SCA7 and SCA28, where saccades are markedly slowed (Velazquez-Perez *et al.*, 2004).

Saccadic accuracy was within 10% of the target in the majority of saccades, however both hypometria and hypermetria were also seen. There was an overall tendency

to hypermetria (39%), which is the opposite pattern to normal subjects, who have a tendency to hypometria (Irving *et al.*, 2006).

Models of saccadic generation imply that the cerebellum has a role in saccadic accuracy, by modulating burst neuron function (Optican and Quaiá, 2002). The presence of hypometria and hypermetria in the same patients raises the possibility of cerebellar pathology generating saccadic instability, although it remains possible that the pathogenesis of abnormality derives from the superior colliculus or pontine reticular formation, or may even be a result of higher influences on these structures. There is evidence from pathological and radiological studies that the cerebellum and, in particular, the dentate nucleus is affected by FRDA (Waldvogel *et al.*, 1999).

Fixation abnormalities

The historical literature on ocular motor pathology presents strict definitions regarding SWJ duration (Dell'Osso *et al.*, 1975). The current data supports previous studies in both FRDA (Dale *et al.*, 1978; Furman *et al.*, 1983; Spieker *et al.*, 1995) and neurologically normal individuals (Abadi and Gowen, 2004) that indicate traditional definitions of SWJ duration are too narrow. As shown in Fig. 3, there was no clear distinction between SWJ with duration shorter or longer than 200 ms. We therefore decided to include all eye movements with square wave morphology for analysis. Some authors suggest that ocular flutter may represent more advanced dysfunction of the ocular fixation mechanisms that are failing when SWJ are generated (Hotson, 1982). Our research is consistent with that view but does not provide sufficient data to support a common pathogenesis (Fig. 4). Ramat and colleagues have suggested that oscillations may be generated entirely within the brainstem circuits and are not dependent on cerebellar

influences (Ramat *et al.*, 2005). This however, does not exclude the possible involvement of cerebellar pathology producing saccadic system instability through its connection with the brainstem or by a different mechanism. If that were the case then SWJ and ocular flutter may be different manifestations of the same pathological process. The presence of ocular flutter in an individual with progressive ataxia is suggestive of FRDA (Moschner *et al.*, 1994) but both can also occur in demyelination, infection, as a paraneoplastic phenomenon and as a consequence of drug or toxin exposure (Leigh and Zee, 2006). The rate of progression of ataxia may however provide further clues as to the aetiology.

SWJ are traditionally defined as occurring in the horizontal plane (Hotson, 1982). Although pure horizontal SWJ were far more common in all participants, 7/15 subjects exhibited oblique SWJ with a prominent vertical component, in addition to the horizontal component. Occasionally the SWJ were purely vertical (Fig. 5). In contrast, vertical flutter was not observed. SWJ with a vertical component have been reported in previous studies where lesions were introduced into the superior colliculus as well as in normal participants (Fukazawa *et al.*, 1986; Abadi and Gowen, 2004). Our data confirms that they occur in FRDA.

SWJ are thought to be caused by dysfunction of omnipause neurons in the PPRF (Zee and Robinson, 1979; Schon *et al.*, 2001). Omnipause neurons exert tonic inhibitory tone on saccade premotor burst neurons, to keep the eye on target. Primate studies show that lesions of the omnipause neurons cause slow horizontal and vertical saccades, not fixation instability (Kaneko, 1996). In the monkey, omnipause neurons receive projections from the superior colliculus (Buttner-Ennever *et al.*, 1999). Experimental inactivation of superior colliculus neurons by lignocaine or muscimol can cause saccadic intrusions, as well as prolonged saccadic latency (Hikosaka and Wurtz, 1985, 1986). Both saccadic intrusions and prolonged saccadic latency were features seen in FRDA in this study. It has been suggested that the superior colliculus supplies bilateral tonic inhibitory tone to the PPRF via the omnipause neurons, and pathology in the superior colliculus may thus result in loss of inhibition on the PPRF which results in SWJ (Fukazawa *et al.*, 1986).

The present research has also demonstrated that there was a significant difference in the quality of the SWJ with fixation target-on and off. Without a fixation target, SWJ were of longer duration and larger amplitude than SWJ with a fixation target present. This implies a feed forward effect of fixation on the tonic inhibitory effects from the omnipause neurons. Previous studies following pallidotomy have also demonstrated that removal of a fixation target had a similar effect on SWJ (Averbuch-Heller *et al.*, 1999). This supports the concept that fixation provides extra stimulus to suppress saccades, the so-called 'task demand' concept (Shaffer *et al.*, 2003).

The saccade and fixation data in this study are consistent with dysfunction of the superior colliculus—omnipause neuron pathway. Furthermore, the cerebellum, frontal and parietal eye fields, which have direct connections with the superior colliculus, might therefore be implicated in ocular motor pathology in FRDA (Hotson, 1982; Leigh and Zee, 2006).

A correlation between the total number of SWJ and age of disease onset was demonstrated. Those with earlier disease onset have more frequent, shorter duration SWJ. Significantly there was no such correlation with disease duration. These findings may implicate the effect of FRDA on the developing brain rather than the effect of disease progression. SWJ number may also be a maker of FRDA severity, as suggested by the significant correlation between the FARS score and the presence of macro SWJ.

VOR

VOR was abnormal in latency and gain. A consistent, severe, bilateral vestibulopathy was demonstrated. Previous studies have largely failed to identify this deficit because they used low frequency stimuli, such as caloric testing and rotation chairs (Monday *et al.*, 1978; Ell *et al.*, 1984; Monday *et al.*, 1984; Spieker *et al.*, 1995; Wessel *et al.*, 1998). These methods of testing are inferior to head impulse testing, because the stimuli are not rapid enough to eliminate interference from other (slower) ocular motor systems (Halmagyi *et al.*, 1990). Furthermore we have found that all six SCCs are similarly affected, and previous studies have only attempted to examine the lateral SCCs. The rapid head rotations we employed are not affected by cortical influences, and they reflect the short latency three-neuron brainstem reflex (Aw *et al.*, 1996; Cremer *et al.*, 1998). Our findings are consistent with damage to the vestibular end organ, the vestibular nerve or the vestibular brainstem nucleus. These findings are similar to the increased latency found in individuals with pure vestibular hypofunction (Tabak *et al.*, 1997). Histopathological studies in FRDA have demonstrated gliosis in the vestibular nucleus (Oppenheimer, 1979) and abnormalities of the spiral ganglion (Satya-Murti *et al.*, 1980) and vestibular nerve (Spoendlin, 1974). Abnormal auditory nerve function has been demonstrated in FRDA through auditory brainstem evoked responses (Satya-Murti *et al.*, 1980; Jabbari *et al.*, 1983; Ell *et al.*, 1984). However, cochlear function has been shown to be normal as judged by preserved otoacoustic emissions (Oppenheimer, 1979; Satya-Murti *et al.*, 1980; Jabbari *et al.*, 1983; Ell *et al.*, 1984; Lopez-Diaz-de-Leon *et al.*, 2003). Other forms of cerebellar ataxia, especially when associated with cerebellar atrophy, may be associated with VOR gain of greater than one (Wessel *et al.*, 1998), which contrasts with the findings in the current study where all subjects had a markedly reduced VOR gain. The marked vestibulopathy in FRDA differentiates FRDA

from most other cerebellar ataxias where a normal or increased VOR gain is observed (Moschner *et al.*, 1994).

Oscillopsia is the apparent movement of the visual world that occurs when the head or whole body moves quickly. It is due to bilateral loss of VOR (Bronstein, 2004). However, only 4/15 subjects in the present study complained of this symptom. One possible explanation is that individuals with FRDA may not move quickly enough to experience this symptom. An alternative explanation is that the vestibular impairment develops over years in FRDA and therefore there may be an alteration in perception. The vestibular dysfunction however, is likely to contribute to the ataxia.

Clinical utility

This study demonstrated severe bilateral VOR deficit and essentially normal saccadic velocity in FRDA, which differentiates it clinically from a number of the dominantly inherited spinocerebellar ataxias. We also sought to examine the possibility of using eye movements as a biomarker in FRDA. Significant correlation between various ocular motor parameters and the FARS and the SLCLC supports the validity of the eye movement measures (Table 2). The FARS is a general examination that includes no tests of visual function, while the SLCLC specifically examines visual function. This is the likely explanation for the higher correlation of eye movement measures with the SLCLC. From this study the best candidates for use in the clinical, and possibly trial, setting are saccadic latency and VOR testing.

Regression analysis of saccadic latency implies that it progresses from within the normal range to pathological as the disease progresses. Saccadic latency was easily measured with non-invasive infra red oculography and could be undertaken in an outpatient setting with minimal training. Vestibular function was abnormal in all subjects tested and may also be an early biomarker.

In conclusion, FRDA is characterized by severe and widespread abnormalities in the ocular motor system, which is an important source of disease morbidity, as evidenced by the decreased visual quality of life. Ocular motor abnormalities can be measured accurately and reliably. They show progressive change which correlates with other markers of disease severity. They therefore show promise as measures for use in monitoring disease progress and clinical trials that might overcome some of the issues with scales or continuous measures (Biglan and Halmagyi, 2006; Pulst, 2007).

This report documents significant ocular motor abnormalities in FRDA, not well explained by the documented pathology. Further systematic studies of histopathology may further elucidate the pathogenesis of these deficits.

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