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Neurophysiological assessment of disease severity in Friedreich's Ataxia: a study of brainstem auditory and visual evoked potentials

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ABSTRACT

Objective: To evaluate a multimodal assessment including clinical rating scales, brainstem auditory evoked potentials (BAEPs), pattern reversal visual evoked potentials (p-VEPs), and serum biomarkers as candidate measures of disease severity in longstanding Friedreich's ataxia (FRDA).

Methods: In a prospective, monocentric cohort, we conducted a cross-sectional baseline assessment of 29 genetically confirmed adult FRDA patients. Disease severity was rated with modified Friedreich Ataxia Rating Scale (mFARS). All underwent BAEPs and/or p-VEPs; available serum markers (NfL, NfH, GFAP, IL-6) were assayed. Associations with mFARS were tested using correlations and multiple linear regression adjusted for age and disease duration.

Results: Neurophysiological abnormalities were frequent (p-VEPs 96.3% [26/27]; BAEPs 85.7% [24/28]). mFARS correlated with BAEP wave III latency ($R = 0.70$, $p < 0.0001$) and p-VEP N75 latency ($R = 0.56$, $p = 0.002$). A BAEP model predicted mFARS ($F(4,13) = 13.70$, $p = 0.00014$; adjusted $R^2 = 0.75$), with disease duration ($\beta = 0.64$, $p = 0.001$) and wave III latency ($\beta = 0.42$, $p = 0.007$) as significant contributors. A p-VEP model also predicted mFARS ($F(4,12) = 20.35$, $p = 0.0003$; adjusted $R^2 = 0.83$), with disease duration ($\beta = 0.62$, $p = 0.001$) and N75 latency ($\beta = 0.45$, $p = 0.005$). Patients with abnormal BAEPs had higher mFARS than those with normal BAEPs ($U = 35.0$, $p = 0.03$). mFARS differed across BAEP grades ($H(4,N = 28) = 10.22$, $p = 0.04$) and p-VEP grades ($H(4,N = 27) = 11.39$, $p = 0.02$). Serum biomarkers showed no consistent association with mFARS.

Conclusions: BAEPs and p-VEPs are highly prevalent and closely associated with clinical severity in chronic FRDA, outperforming tested serum biomarkers.

Significance: Evoked potentials provide accessible, non-invasive, quantitative candidate biomarkers for severity assessment and longitudinal monitoring in FRDA, supporting their use in clinical practice and trial design when fluid markers are inconclusive.

1. Introduction

Friedreich's ataxia (FRDA) is a rare autosomal recessive disease, primarily characterized by progressive axial and limb incoordination due to dysfunction of cerebellum and sensory system from the posterior columns to dorsal roots and nerves. In 96% of cases, it is due to homozygous GAA expansion in intron 1 of the frataxin (FXN) gene, located in chromosome 9 and leading to reduced expression of frataxin (Campuzano et al., 1996). Frataxin is a mitochondrial protein implicated in essential biochemical pathways, including iron–sulfur cluster biogenesis, heme biosynthesis, and the regulation of mitochondrial redox homeostasis. Its deficiency disrupts iron homeostasis, leading to mitochondrial iron overload and elevated oxidative stress (Campuzano et al., 1997; Adamec et al., 2000).

According to European Friedreich's Ataxia Consortium for Translational Studies (EFACTS), age at onset is usually before 25 years with

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most cases (60%) occurring before puberty while late-onset (>25 years) FRDA cases are less frequent; earlier onset is linked to more severe disability, more rapid disease progression and is associated with higher number of GAA repeats on the smaller repeat allele (Reetz et al., 2015; Reetz et al., 2016). Ataxia is the main neurological manifestation but abnormal eye movements, dysarthria, dysphagia, and sensory complaints due to polyneuropathy are very common while spasticity is more prevalent in late-onset FRDA (Reetz et al., 2018). Non-neurological manifestations lead to significant morbidity and mortality and include cardiomyopathy, scoliosis and foot deformities, increased risk of diabetes (Pousset et al., 2015; Reetz et al., 2018; Tamaroff et al., 2022). Hearing disturbances can be quite frequent, especially in typical-onset FRDA patients (Reetz et al., 2018). Vision loss or reduced visual acuity has been reported in 3% of patients (Reetz et al., 2018), and may present either as a sudden onset resembling Leber's hereditary optic neuropathy, or more commonly as a slowly progressive and subclinical condition, as indicated by abnormal visual evoked responses observed in nearly half of the patients (Fortuna et al., 2009, Damásio et al., 2021). Clinical heterogeneity in FRDA is still matter of debate since it is not fully understood by current knowledge of genetics, and variability in age at onset or clinical presentations is only partially explained by GAA repeat size, underlying the role of unknown genetic and epigenetic factors (Reetz et al., 2025).

Moreover, with the advent of omaveloxolone (Lynch et al., 2018) and the emergence of new ongoing clinical trials, there is a growing need to identify and validate novel clinical or fluid biomarkers to deepen our understanding of disease pathophysiology and to support the development of targeted therapeutic and disease modifying strategies. For instance, neurofilament light chain (NfL) and other biomarkers such as glial fibrillary acidic protein (GFAP) have been proposed as potential biomarkers in FRDA (Zeitlberger et al., 2018; Hayer et al., 2020) but no clear associations with age, disease severity and progression were detected (Zeitlberger et al., 2018). Recent real-world data supported a role for serum IL-6 in FRDA patients treated with omaveloxolone (Lima et al., 2025), but there is still a lack of neurophysiological data on FRDA apart from single observations on sensory nerve action potentials (Rotar and Leonardis, 2025).

Neurophysiological assessment using evoked potentials has long been used to investigate sensory pathway involvement in Friedreich's ataxia. Brainstem Evoked Potentials (BAEPs) are abnormal in at least half of patients, ranging from prolonged wave latencies and interpeak intervals to complete absence of waves, reflecting both peripheral and central auditory dysfunction (Amantini et al., 1984; De Pablos et al., 1991; Zeigelboim et al., 2018). Visual Evoked Potentials (VEPs) are also frequently altered, typically showing bilateral delays of N75 and P100 latencies with reduced P100 amplitude (Carroll et al., 1980; Kirkham and Coupland, 1981; Pelosi et al., 1984; Pinto et al., 1988; Fortuna et al., 2009). These abnormalities often occur subclinically, highlighting early central sensory involvement even in the absence of overt symptoms. Building on this rationale, we conducted a monocentric study to investigate the potential of VEPs, BAEPs, and serum biomarkers as complementary tools to probe disease severity in FRDA.

2. Materials and methods

This is a prospective observational study on FRDA patients conducted at the tertiary center of neuromuscular disorders at Policlinico Paolo Giaccone, Palermo (Italy), for which the present analysis is a baseline cross-sectional assessment. The inclusion criterion was genetic confirmation of FRDA and age >18 years and informed consent for study participation. From January 2024 to June 2025, consecutive patients with a FRDA diagnosis were asked to participate in the study protocol which included clinical, neurophysiological assessment and blood sample. Patients willing to participate signed an informed consent to be enrolled. Institute Ethics Committee approval was obtained for the on 10th December 2024 (V n.28/2024, "Comitato Etico Locale Palermo 1") and was conducted in accordance with the Declaration of Helsinki World Medical Association (2013).

2.1. Clinical data

The baseline demographic and clinical details including age at presentation, classification according to age at onset (typical onset <25 years; late onset >25 years), disease duration, initial symptom/s, presence or absence of gait ataxia, limb ataxia, dysarthria, dysphagia, diabetes, cardiopathy, pes cavus, loss of ambulation with wheelchair dependency, scoliosis, abnormal eye movements, deep tendon reflexes, spasticity, polyneuropathy defined by previous nerve conduction study, proprioception, self-reported visual and auditory symptoms were collected at the time of study inclusion. At the screening visit clinical assessment as well as clinical scales were administered by experienced neurologists to evaluate disease severity and functional status: modified Friedreich Ataxia Rating Scale (mFARS) and Friedreich Ataxia Rating Scale – Activities of Daily Living (FA-ADL) (Rummey et al., 2019; Traschütz et al., 2024).

Data from 29 patients with FRDA were prospectively collected for this study. All demographical and clinical data are displayed in Table 1.

2.2. Neurophysiological data

Neurophysiological assessment included p-VEPs and BAEPs.

For brainstem evoked potentials, we used a two channels registration (Cz-A1, Cz-A2) with a click stimulus at 90 dBHL, alternate polarity with a presentation frequency of 21.1 cycles per second, window of 15 ms, 10 Hz to 3 kHz filter and at least 2,000 stimuli, and at least two rounds of repetition, ground electrodes on the forehead. Clicks were presented via 3A insert earphones. In patients with hearing loss, it was necessary to increase the intensity of the click stimulus to 100 dBHL. Wave latencies I, III and V and interpeak intervals I-III, III-V, I-V were analyzed according to Hall's criteria (Hall, 1992). We also considered any side-to-side difference. Upper normal limits latencies (mean ± 2 SD) were 1.82 ms for wave I, 3.87 ms for wave III, and 6.02 ms for wave V, with side-to-side differences > 0.10, >0.24, and > 0.41 ms respectively. For interpeak intervals, limits were 2.44 ms (I–III, >0.22 ms), 2.30 ms (III–V, >0.26 ms), and 4.56 ms (I–V, >0.21 ms). According to these values, BAEP findings were classified in 0 – normal; 1 – unilateral abnormalities (prolonged latencies and/or interpeak intervals); 2 – bilateral abnormalities (prolonged latencies and/or interpeak intervals); 3 – absent unilateral response and abnormal response in the other; 4 – bilaterally absent responses.

p-VEPs were recorded in a semi-dark, sound-isolated room with subjects seated in front of a display presenting a checkerboard visual stimulus (80% contrast, mean luminance 110 cd/m^2). The checkerboard pattern was generated on a television monitor and reversed in contrast at a rate of 2 reversals per second (1 Hz). A central fixation target, subtending approximately 0.5° of visual angle, was positioned at the center of the stimulus. At a viewing distance of 114 cm, the monitor subtended a visual angle of 23°, with check edges subtending 15 arcminutes (15′) and 60 arcminutes (60′) of visual angle. For this study, only data from the 60′ condition were analyzed. Recordings were obtained using cup-shaped Ag/AgCl electrodes affixed with conductive paste. The active electrode was placed at Oz, the reference at Fpz, and the ground at Cz. Electrode impedance was maintained below 3 kΩ. Recording parameters followed the International Society for Clinical Electrophysiology of Vision standards (Odom et al., 2010; Šuštar Habjan et al., 2025), including monocular stimulation, a bandwidth of 1–250 Hz, an analysis time of 250 ms, and two averages of at least 100 responses per condition to ensure reproducibility. We assessed the latencies of the N75, P100, and N145 components, as well as the amplitude of the P100 wave, for both eyes. For p-VEPs (60′), upper normal limits (mean + 2 SD) latencies were 83 ms for N75, 112 ms for P100, and 160 ms for N145; the lower limit for P100 amplitude (mean –

Table 1
Demographic and clinical features of FRDA patients.

Demographical and clinical characteristics	Cohort (n = 29)
Sex (females)	18 (62%)
Age (mean ± SD, years)	42.5 ± 12.4
Age at onset (mean ± SD, years)	16.9 ± 9.8
Classification according to age at onset	
Typical onset	24 (83%)
Late Onset	5 (17%)
Disease duration in years (mean ± SD, years)	25.3 ± 11.0
Clinical onset:	
- Gait ataxia n (%)	28 (96.5%)
- Dysarthria n (%)	4 (13.8%)
- Scoliosis n (%)	4 (13.8%)
- Cardiomyopathy	1 (3.4%)
Neurological and extra-neurological abnormality at the time of the evaluation:	
−Gait ataxia n (%)	29 (100%)
−Limb ataxia n (%)	29 (100%)
−Reduced or absent deep tendon reflexes in the lower limbs n (%)	28 (96.5%)
–Non-ambulatory without assistance n (%)	26 (89.7%)
−Polyneuropathy n (%)	13/18 (72.2%)
−Dysarthria n (%)	23 (79.3%)
−Proprioception abnormalities n (%)	14 (48.3%)
−Abnormal eye movements n (%)	13 (44.8%)
−Titubation n (%)	10 (34.5%)
−Dysphagia n (%)	8 (27.5%)
−Scoliosis n (%)	7 (24.1%)
−Cardiomyopathy n (%)	6 (20.7%)
−Pes cavus n (%)	5 (17.2%)
−Diabetes n (%)	3 (10.3%)
−Self-reported visual symptoms n (%)	3 (10.3%)
−Self-reported auditory symptoms n (%)	2 (6.9%)
−Spasticity n (%)	2 (6.9%)
mFARS median (IQR)*	66.25 (55.25–81)
FA-ADL median (IQR)*	15.5 (12.25–23.5)

Abbreviations. FA-ADL: Friedreich Ataxia-Activities of Daily Living; FRDA: Friedreich's ataxia; IQR: interquartile range; mFARS: modified Friedreich Ataxia Rating Scale; SD: standard deviation. *mFARS and FA-ADL scores were assessed in 28 and 14 patients respectively.

2 SD) was 2.1 μV. For the latency components N75, P100, and N145, differences between the two eyes exceeding 10 ms were considered abnormal. For the P100 amplitude, an interocular asymmetry greater than 50% was regarded as indicative of altered responses. Based on these parameters, p-VEP responses were classified into five categories: 0 – normal; 1 – unilateral abnormalities (prolonged latencies and/or reduced amplitude); 2 – bilateral abnormalities (prolonged latencies and/or reduced amplitude); 3 – absent response in one eye with abnormal response in the other; 4 – bilaterally absent responses.

For both BAEP and p-VEPs, limits for normal latencies and amplitude were derived from a normative dataset collected in our laboratory following the recording standards described above. The dataset comprised 35 healthy adults, aged 20–72 years, with no history of auditory, visual, or neurological disorders. Although the sample size is limited, these normative data provide a consistent internal reference for comparison with FRDA patients. These comparative data were used exclusively for this study and are shown in Supplementary Table S1.

2.3. Laboratory biomarkers

Blood samples of FRDA patients were processed and analyzed at the Institute of Clinical Biochemistry, Clinical Molecular Medicine, and Clinical Laboratory Medicine.

The following serum biomarkers were collected: creatinkinase (CK, normal range 0–192 U/L), alpha-fetoprotein (AFP, normal range 0–7 μg/L), N-Terminal pro–Brain Natriuretic Peptide (NT-proBNP, normal range <125 ng/L), Aspartate Aminotransferase (AST, normal range 0–35 U/L), Alanine Aminotransferase (ALT, normal range 0–35 U/L), Gamma-Glutamyl Transferase (GGT, normal range 5–36 U/L), triglycerides (normal range <150 mg/dl), total cholesterol (optimal range <200 mg/dl), high density level (HDL, optimal range >60 mg/dl) cholesterol, low density level (LDL, total <200 mg/dl) cholesterol, hemoglobin glycate (HBA1C, normal range 20–41 mmol/mol), C reactive protein (CRP, normal range <5 mg/L), interleukin 6 (IL-6, normal range <7.0 pg/mL), NfH (normal range <0.17 ng/ml).

Moreover, for each participant, serum was collected by drawing whole blood into dry tubes, followed by centrifugation at room temperature for 10 min at 1,800g. The separated serum was then immediately aliquoted into 500 μL portions using 2 mL polypropylene tubes and stored at − 80 °C until further analysis. Serum concentrations of neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) were quantified using the fully automated Lumipulse G1200 platform (FUJIREBIO Inc., Tokyo, Japan), with the Lumipulse G NfL and GFAP assay kits, following the manufacturer's protocols. The Lumipulse platform provides high sensitivity and specificity for detecting both GFAP and NfL. For GFAP, the limit of detection (LoD) is 1.8 pg/mL, with a limit of quantification (LoQ) defined at a 10% coefficient of variation (CV), and an overall precision of less than 5% CV. As a reference standard, the assay employs full-length recombinant human GFAP protein (LS Bio, Shirley, MA, USA). The detection range for GFAP spans from 4.0 to 5,000.0 pg/mL. For NfL, the manufacturer reports a limit of detection (LoD) of 1.99 pg/mL and a limit of quantification (LoQ) of 3.25 pg/mL. The intra-assay coefficient of variation (CV) is below 5%. All controls and calibrators were run in duplicate, and the average of the duplicate measurements was used as the result. No sample dilution was necessary prior to analysis.

2.4. Statistical analysis

Continuous variables were expressed as mean/median with standard deviation/interquartile range (IQR) while categorical variables were expressed as frequencies and percentages. Side-to-side differences in BAEPs and p-VEPs findings were assessed using a paired *t*-test, but only when responses were recordable from both sides. Differences in the frequency of identifiable responses were compared using Fisher's exact test. To explore associations between clinical, functional, and biochemical measures in FRDA, we performed correlation analyses using either Pearson's or Spearman's correlation coefficients, selected based on the distribution and scale of each variable. Spearman's rank correlation was used for variables with non-normal distributions or ordinal characteristics, including disease duration, clinical rating scales (FA-ADL and mFARS), and biomarker levels typically showing skewed distributions (NT-pro-BNP, NfL, NfH, IL-6 and GFAP). Unilateral BAEP and p-VEP findings and type of BAEP or p-VEP alteration were also analyzed using Spearman's correlation.

To explore the impact of neurophysiological measures on disease severity, two separate multiple regression models were conducted with mFARS as the dependent variable given the limited sample size. Both models included age and disease duration as covariates. The first model included wave III latency from BAEP as an independent variable, while the second model included the latency of the N75 component from p-VEP. This approach allowed the evaluation of distinct neurophysiological predictors while limiting the number of regressors per model.

Moreover, the Mann–Whitney *U* test was used to evaluate differences

between continuous variables in typical and late-onset FRDA patients, and between patients with normal or altered BAEPs and normal or altered p-VEPs. An additional Kruskal–Wallis test was applied to assess differences between groups based on the type of BAEP or p-VEP alteration. For significant Kruskal–Wallis results, pairwise comparisons were performed using Mann–Whitney U tests between all relevant groups, with Bonferroni correction applied to adjust for multiple testing. This approach provides a conservative control for multiple comparisons and is widely accepted for non-parametric data, ensuring the reliability of the reported differences. Statistical analysis was performed using Statistica software 8.0 and only $p < 0.05$ was accepted as statistically significant.

3. Results

3.1. Clinical, laboratory and neurophysiological findings

Our cohort is mainly constituted by typical onset FRDA patients (n = 24; 83%) with a long disease duration (25.3 ± 11.0 years). Frequency of different clinical features is shown in Fig. 1.

Gait ataxia was the most frequent clinical onset except for one patient who reported scoliosis as isolated first manifestation. During the initial course of the disease, 4 patients also reported dysarthria and one reported cardiomyopathy. Overall, scoliosis was reported as initial symptom in 4 patients.

Gait and limb ataxia were present in all patients (100%) at the evaluation time, followed by reduced/absent deep tendon reflexes in lower limbs (n. = 27; 96.6%), loss of independent ambulation (n = 25;89.7%) and dysarthria (n. = 22;79.3%). Polyneuropathy defined by a previous nerve conduction study was evaluated in only 18 patients and was present in 13 patients. Scoliosis (n = 7;24.1%) and pes cavus (n. = 5;17.2%) were also reported. Cardiomyopathy was present in (n = 6; 20.7%) and diabetes in 3 patients (10.3%). Self-reported visual symptoms were uncommon (n = 3, 10.3%) and consisted of bilateral reduction of visual acuity with sudden onset in one patient. Self-reported auditory symptoms were present in 2 patients (6.9%): both patients reported tinnitus and hearing loss in the right ear.

Disability and disease severity have been assessed by mFARS and FA-ADL showing moderately-severe disability. AFP, ALT, CPK, AST, GGT, cholesterol levels, triglycerides, HbA1c, NT-pro-BNP, IL-6, NfH were available for 25 patients (see Table 2), while 19 patients completed the assessment by NfL and GFAP assessment.

BAEP and p-VEP results are displayed in Table 3. Twenty-eight patients completed the BAEP and 27p-VEP assessment. Based on our reference values, only 4 patients had normal BAEPs and one patient had normal p-VEP findings.

The most frequently encountered BAEP abnormality was absence of bilateral response in more than a half of the sample (53.6%), followed by the combination unilateral abnormal responses/absent unilateral responses (type 3). In case of identifiable response, we frequently observed an increased III latency.

As regards to p-VEP findings (60′), the most common alteration was bilateral abnormal responses (40.7%), characterized by increased N75, P100, N145 latencies and reduced P100 amplitude, followed by bilaterally absent p-VEPs (29.6%). Side-to-side comparisons didn't show any difference. According to our abnormality grading, main BAEP and p-VEP findings are illustrated in Fig. 2A and 3A.

Table 2
Laboratory findings in FRDA patients.

Laboratory findings	
AFP mean ± SD (μg/L)	2.5 ± 1.8
ALT mean ± SD (U/L)	29.3 ± 27.3
AST mean ± SD (U/L)	23.2 ± 9.3
GGT mean ± SD (U/L)	18.5 ± 18.4
CK U/L mean ± SD (U/L)	68.7 ± 36.6
Total cholesterol mean ± SD (mg/dl)	186.4 ± 34.1
HDL cholesterol mean ± SD (mg/dl)	53 ± 12.2
LDL cholesterol mean ± SD (mg/dl)	119.8 ± 31.6
Triglycerides mean ± SD (mg/dl)	118.6 ± 56
Hba1c mean ± SD (mmol/mol)	37.7 ± 6.5
NT-pro-BNP mean ± SD (ng/L)	116.8 ± 158.4
IL-6 mean ± SD (pg/ml)	4.3 ± 1.9
CRP mean ± SD (mg/L)	2.5 ± 2.3
NfH mean ± SD (ng/ml)	0.01 ± 0.02
NfL mean ± SD (pg/ml)	20.2 ± 6.7
GFAP mean ± SD (pg/ml)	17.5 ± 19.8

Abbreviations. AFP: alphafetoprotein; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; CK: Creatine Kinase; FRDA: Friedreich's ataxia; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; Hba1c: Hemoglobin A1c or Glycated Hemoglobin; NT-pro-BNP: N-terminal pro B-type Natriuretic Peptide; IL-6: Interleukin-6; CRP: C-Reactive Protein; NfH: Neurofilament Heavy chain.

3.2. Correlation and regression analysis

Pearson's coefficient was used to assess any correlation between age, disease duration, mFARS and FA-ADL. Age moderately correlated with disease duration ($r = 0.59$, $p = 0.02$), but not with mFARS and FA-ADL. Disease duration strongly correlated with mFARS ($r = 0.83$, $p < 0.0001$) and FA-ADL ($r = 0.81$, $p < 0.0001$); mFARS and FA-ADL were strongly correlated ($r = 0.92$, $p < 0.0001$).

Correlation analysis by Spearman's test is shown in Table 4. Age moderately correlates with GFAP ($R = 0.55$, $p = 0.01$), NfL ($R = 0.52$, $p = 0.02$) and mFARS ($R = 0.44$, $p = 0.02$). Disease duration moderately correlates with GFAP ($R = 0.48$, $p = 0.04$), III wave latency ($R = 0.56$, $p = 0.002$), N75 latency ($R = 0.43$, $p = 0.03$). Disease severity as assessed

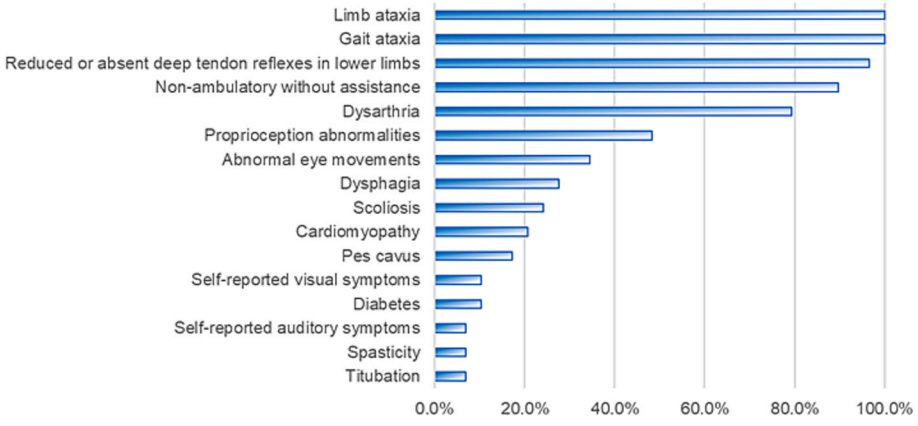

Fig. 1. Frequency of clinical features of our cohort.

Table 3
Neurophysiological assessment by BAEP and p-VEP.

Neurophysiological findings			
Normal BAEP n (%)		4 (14.3%)	
BAEP findings (n = 28)	**Right**	**Left**	**Side-to-side comparisons**
Identifiable response n (%)	12 (42.8%)	10 (35.7%)	p = 0.39 (Fisher)
I wave latency mean ± SD	1.53 ± 0.10	1.57 ± 0.07	p = 0.42 (t-student)
III wave latency mean ± SD	3.74 ± 0.27	3.73 ± 0.15	p = 0.49 (t-student)
V wave latency mean ± SD	5.34 ± 0.38	5.35 ± 0.3	p = 0.41 (t-student)
I-III interpeak mean ± SD	2.21 ± 0.16	2.17 ± 0.2	p = 0.59 (t-student)
III-V interpeak mean ± SD	1.55 ± 0.29	1.63 ± 0.26	p = 0.49 (t-student)
I-V interpeak mean ± SD	3.71 ± 0.19	3.95 ± 0.54	p = 0.41 (t-student)
Normal p-VEP n (%)		1 (3.7%)	
p-VEP findings 60′ (n = 27)	**Right**	**Left**	**Side-to-side comparisons**
Identifiable response n (%)	17 (63%)	17 (63%)	p = 0.58 (Fisher)
N75 latency mean ± SD	90.4 ± 9.7	90.3 ± 8.4	p = 0.64 (t-student)
P100 latency mean ± SD	112.5 ± 7.4	112.4 ± 5.5	p = 1.00 (t-student)
N145 latency mean ± SD	140.5 ± 10.8	140.1 ± 9.0	p = 0.89 (t-student)
P100 amplitude mean ± SD	1.76 ± 0.87	1.63 ± 0.86	p = 0.45 (t-student)

Abbreviations. BAEP: Brainstem Evoked Potential; p-VEP: pattern reversal-Visual Evoked Potential.
Upper limits of latencies and interpeaks (mean, 2 SD): I wave 1.82 (side-to-side difference > 0.10 msec), III wave 3.87 (side-to-side difference > 0.24), V wave 6.02 (side-to-side difference > 0.41), I-III interpeak 2.44 (side-to-side difference > 0.22), III-V interpeak 2.30 (side-to-side difference > 0.26), I-V interpeak 4.56 (side-to-side difference > 0.21). Upper limits for p-VEPs (60′) of latencies and lower limit for P100 amplitude (mean, 2 SD): N75 83 msec, P100 112 msec, N145 160 msec, P100 amplitude 2.1 μV.

by mFARS is strongly correlated with III latency (R = 0.70, p < 0.0001) and moderately with I latency (r = 0.59, p = 0.0001), III-V interpeak (R = 0.59, p = 0.0009), V latency (R = 0.58, p = 0.001), I-V interpeak (R = 0.58, p = 0.0001), N75 latency (R = 0.56, p = 0.002), type of p-VEP alteration (R = 0.52, p = 0.005), GFAP (R = 0.49, p = 0.03) and type of BAEP abnormality (R = 0.48, p = 0.009), negatively with age at onset (R = -0.49, p = 0.009). Scatterplots illustrating the relationships between the latencies of the principal BAEP and p-VEP components are shown in Fig. 4. Analyses include only patients with recordable and identifiable BAEP or p-VEP responses.

The first multiple regression model evaluating BAEP significantly predicted mFARS scores (F(4,13) = 13.70, p = 0.00014, R^2 = 0.80; adjusted R^2 = 0.75). Among the predictors, disease duration (β = 0.64, p = 0.001) and III latency (β = 0.42, p = 0.007) showed a significant positive association with mFARS. The second multiple regression model evaluating p-VEP also predicted mFARS (F(4,12) = 20.35, p = 0.0003, R^2 = 0.87; adjusted R^2 = 0.83) showed a significant positive association with mFARS. Among the predictors, disease duration (β = 0.62, p = 0.001) and N75 latency (β = 0.45, p = 0.005) showed a significant positive association with mFARS. Age and GFAP levels were included in both models but did not reach statistical significance.

NfL moderately correlated with age and GFAP (for both, R = 0.52, p = 0.02), but not with other variables. GFAP also moderately correlated with age (R = 0.55, p = 0.01). NfH, IL-6, CRP and NT-pro-BNP didn't correlate with any clinical or neurophysiological feature described in this study.

3.3. *Differences between groups*

No significant difference was detected between typical onset and late onset FRDA.

Patients with BAEP alterations significantly differed from patients

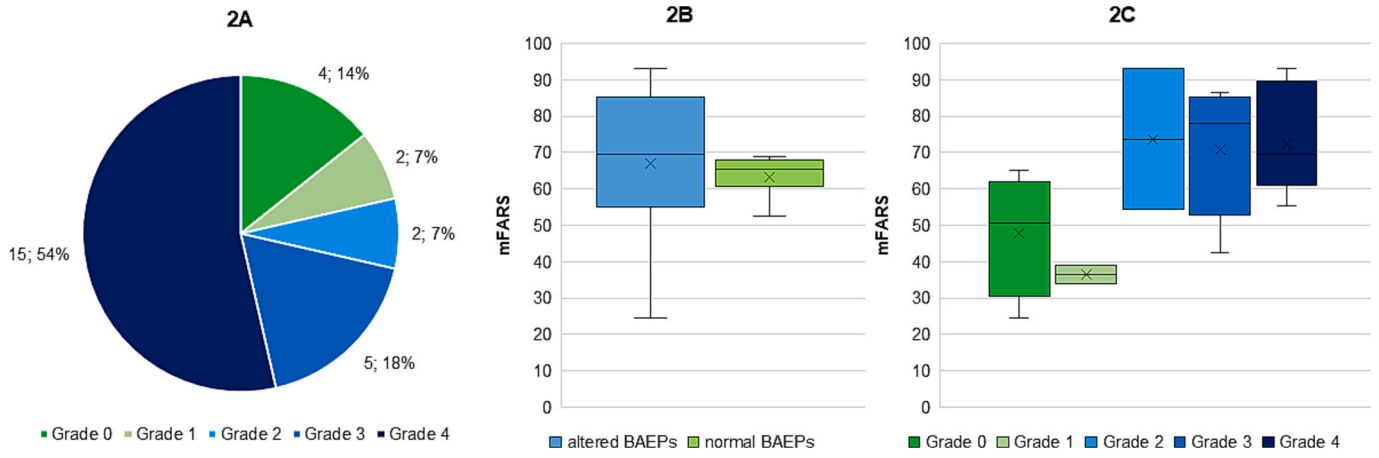

Fig. 2. BAEP findings. Fig. 2A: BAEP findings with absolute values and frequencies according to our grading classification. Grading: 0: normal; 1: unilateral abnormal response/unilateral normal response; 2: bilaterally abnormal response; 3: unilateral abnormal response/unilateral absent response; 4: bilaterally absent response. Fig. 2B: Box-and-whisker plot illustrating differences in mFARS scores according to the presence or absence of BAEP abnormalities. Fig. 2C: Box-and-whisker plot illustrating differences in mFARS scores across grades of BAEP abnormalities. In both Fig. 2B and 2C, the box represents the interquartile range (IQR, 25th–75th percentile), with the horizontal line inside the box indicating the median and the cross inside the box represents the mean. The whiskers extend to the minimum and maximum values within 1.5 × IQR from the lower and upper quartiles, respectively. Individual data points outside this range represent outliers. Abbreviations. BAEP: Brainstem Evoked Potentials; IQR: interquartile range; mFARS: modified Friedreich Ataxia Rating Scale.

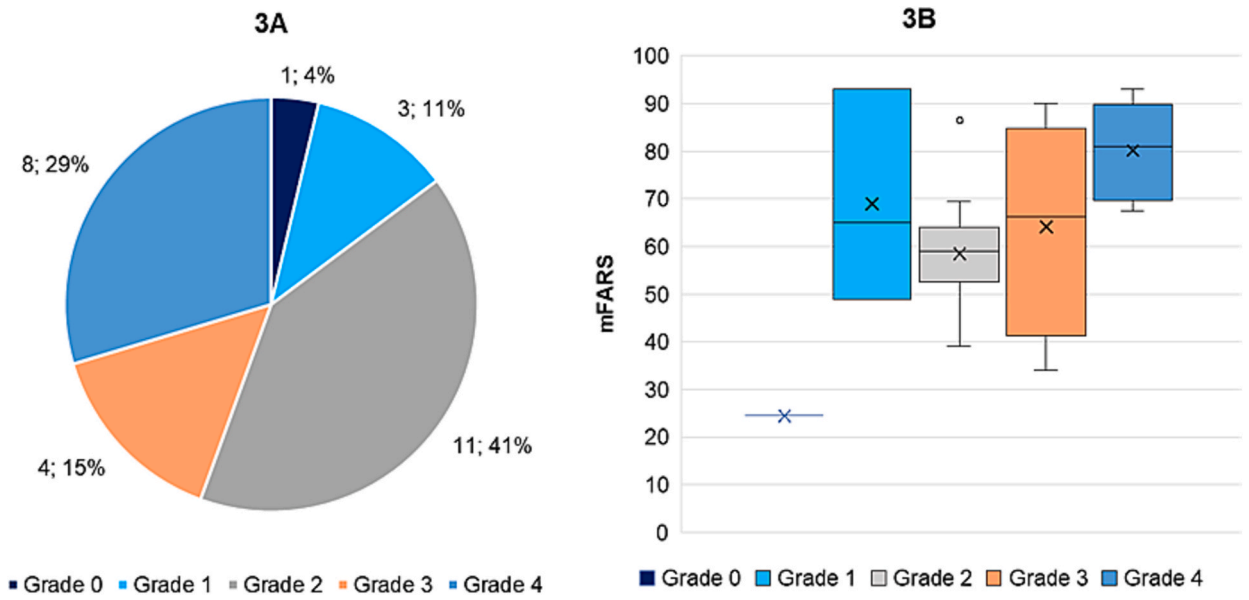

Fig. 3. P-vep findings. fig. 3a: p-vep findings with absolute values and frequencies according to our grading classification. grading: 0: normal; 1: unilateral abnormal response/unilateral normal response; 2: bilaterally abnormal response; grade 3: unilateral abnormal response/unilateral absent response; 4: bilaterally absent response. fig. 3b: box and whiskers plot showing differences between groups based on mFARS scores and p-VEP anomalies. The box represents the interquartile range (IQR, 25th–75th percentile), with the horizontal line inside the box indicating the median and the cross inside the box represents the mean. The whiskers extend to the minimum and maximum values within 1.5 × IQR from the lower and upper quartiles, respectively. Individual data points outside this range represent outliers. Abbreviations. p-VEP: pattern reversal Visual Evoked Potentials; mFARS: modified Friedreich Ataxia Rating Scale.

with normal BAEPs for higher values at mFARS ($U = 35.0$, $Z = 2.1$, $p = 0.03$) (Fig. 2B). Bonferroni correction confirmed this difference (adjusted $p = 0.028$).

If we considered BAEP alterations grading used in this study, there were significant differences between groups in mFARS scoring ($H(4,N = 28) = 10.22$, $p = 0.04$). Pairwise comparison revealed only significant differences between grade 1 (unilateral abnormal BAEP) and grade 4 (bilaterally absent BAEPs) (adjusted $p = 0.04$) but not between the other groups (Fig. 2C). No significant difference was detected for age, age at onset, disease duration, FA-ADL, GFAP or NfL.

Patients with abnormal p-VEPs didn't differ from patients with normal p-VEPs in terms of age, age at onset, disease duration, FA-ADL, GFAP, NfL.

However, if we considered p-VEPs abnormality grading, there were significant differences only considering the mFARS ($H(4,N = 27) = 11.39$, $p = 0.02$); pairwise comparisons confirmed significant differences of mFARS between grade 0 and 2 abnormality (adjusted $p = 0.02$) but not with other groups (Fig. 3B). We have included representative BAEP (Fig. 5) and p-VEP (Fig. 6) recordings from one healthy control and three representative FRDA patients across different stages of disease severity to exemplify the spectrum of electrophysiological alterations observed in this condition.

4. Discussion

The objective of this study was to characterize the clinical, neurophysiological, and serological profiles of a cohort of genetically confirmed FRDA patients managed at a tertiary care center in Sicily. Our cohort ($n = 29$) consisted of adult patients with typical onset disease (83%) and less frequently (17%) by late-onset patients, with mean age at onset of 16.9 years. Moreover, our patients had a long disease course with a mean disease duration of 25 years. Clinical features were similar to those observed in other cohort studies with gait and limb ataxia present in all patients, followed by deep tendon areflexia in lower limbs, polyneuropathy and dysarthria (Harding, 1981; Dürr et al., 1996; Schöls et al., 1997). Abnormal eye movements, dysphagia, scoliosis, foot deformities and cardiomyopathy were less frequent compared to other cohorts while spasticity and diabetes frequency was similar (Reetz et al., 2018; Indelicato et al., 2020; Rummey et al., 2021). Self-reported visual and auditory symptoms were uncommon. In this study, disease severity was assessed by mFARS, which has been previously used in clinical trials (Lynch et al., 2019) and seems to be more sensitive to detect sensory ataxia than other scales such as Scale for the Assessment and Rating of Ataxia (SARA) or International Cooperative Ataxia Rating Scale (ICARS) (Schwabova et al., 2014; Pandolfo, 2019; Rummey et al., 2022). Our cohort has a mean mFARS score of 66, meaning that motor disability is quite high and is related to long disease duration as shown by correlation analysis.

Neurophysiological assessment included BAEPs and p-VEPs, performed in 28 and 27 patients, respectively. Although hearing complaints such as unilateral hearing loss and tinnitus were infrequent in our cohort ($n = 2$), BAEPs revealed abnormalities in most cases (24/28). Bilateral responses were often absent, with identifiable waveforms observed in only 43% of right-side and 36% of left-side recordings. The most frequent abnormality, found in 53.6% of patients, was the complete bilateral absence of early BAEP components, a prevalence notably higher than previously reported (Amantini et al., 1984; De Pablos et al., 1991; Lanzillo et al., 1994; Zeigelboim et al., 2018; Mahale et al., 2024). However, our cohort had a disease duration 5 to 15 years longer than in those earlier studies, which may account for the more advanced electrophysiological alterations observed. As such, we likely missed earlier-stage findings reported by others, including the isolated loss of wave V (Amantini et al., 1984; De Pablos et al., 1991; Pelosi et al., 1984) or the prolongation of absolute latencies and interpeak intervals of waves I, III, and V (Zeigelboim et al., 2018), both of which point to progressive central auditory pathway involvement and auditory neuropathy. These alterations are consistent with the high prevalence of speech perception deficits described in Friedreich's ataxia (Rance et al., 2010). Our findings are also in line with those of Maudoux et al. (2020), who documented similar abnormalities in auditory, vestibulo-ocular, and gaze stability testing in younger FRDA patients (<24 years), suggesting their potential as biomarkers of disease severity or progression. The present study extends these observations to individuals with a longer disease course, supporting the relevance of neurophysiological markers across

Table 4
Spearman's rank correlation analysis.

	Age (R, p-value)	Age at onset (R, p-value)	Disease duration (R, p-value)	mFARS (R, p-value)	NfL (R, p-value)	GFAP (R, p-value)	I latency (R, p-value)	III latency (R, p-value)	V latency (R, p-value)	I-III interpeak (R, p-value)	III-V interpeak (R, p-value)	I-V interpeak (R, p-value)	Type of BAEP alteration (R, p-value)	N75 latency (R, p-value)	P100 latency (R, p-value)	N145 latency (R, p-value)	P100 amplitude latency (R, p-value)	Type of VEP alteration (R, p-value)
Age		0.38, 0.04	**0.69** **<0.0001**	**0.44** **0.02**	**0.52** **0.02**	**0.55** **0.01**	0.13 0.51	0.28 0.14	0.18 0.34	0.14 0.48	0.21 0.29	0.13 0.49	0.11 0.58	0.35 0.07	0.14 0.94	0.09 0.65	0.16 0.42	0.11 0.59
Age at onset	0.38, 0.04		−0.32 0.09	**−0.49** **0.009**	0.29 0.23	0.11 0.65	−0.38 0.05	**−0.47** **0.01**	−0.36 0.06	**−0.39** **0.04**	−0.33 0.09	−0.32 0.1	**−0.42** **0.03**	−0.16 0.43	−0.01 0.93	0.08 0.68	−0.17 0.41	−0.37 0.06
Disease duration	0.69 <0.0001	−0.32 0.09		**0.76** **<0.0001**	0.29 0.13	**0.48** **0.04**	0.13 0.61	**0.56** **0.002**	0.38 0.05	0.36 0.06	0.38 0.05	0.28 0.15	0.27 0.16	**0.43** **0.03**	0.03 0.86	−0.1 0.61	0.23 0.26	0.33 0.09
mFARS	**0.44** **0.02**	**−0.49** **0.009**	**0.76** **<0.0001**		0.27 0.25	**0.49** **0.03**	**0.45** **0.01**	**0.7** **<0.0001**	**0.58** **0.001**	**0.55** **0.002**	**0.59** **0.0009**	**0.49** **0.007**	**0.48** **0.009**	**0.55** **0.002**	−0.08 0.67	−0.21 0.29	0.32 0.1	**0.52** **0.005**
NfL	**0.52** **0.02**	0.29 0.23	0.13 0.61	0.27 0.25		**0.52** **0.02**	0.19 0.43	0.24 0.31	0.20 0.41	0.28 0.24	0.21 0.37	0.25 0.29	0.16 0.51	0.34 0.16	0.13 0.61	0.05 0.82	−0.16 0.52	0.002 0.99
GFAP	**0.55** **0.01**	0.11 0.65	**0.48** **0.04**	**0.49** **0.03**	**0.52** **0.02**		−0.05 0.82	0.17 0.48	0.23 0.33	0.03 0.9	0.26 0.27	0.002 0.99	−0.07 0.98	0.42 0.08	−0.31 0.21	−0.37 0.13	0.26 0.29	0.07 0.78.

Significant correlations ($p < 0.05$) are highlighted in bold. Abbreviations. mFARS: modified Friedreich Ataxia Rating Scale; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein.

disease stages.

p-VEP abnormalities were observed in the majority of patients, with only one individual showing normal P100 latency and amplitude, confirming the high prevalence of VEP alterations previously reported by Pinto et al. (1988). Notably, these electrophysiological abnormalities were frequently subclinical, as suggested by the low rate of self-reported visual symptoms in our cohort (10.3%). Consistent with earlier findings (Carroll et al., 1980; Kirkham and Coupland, 1981; Pelosi et al., 1984), the most common alteration was a bilateral delay of N75 and P100 latencies, often accompanied by a reduction in P100 amplitude. Although other cohorts have reported a lower prevalence of p-VEP abnormalities (Fortuna et al., 2009; Mahale et al., 2024), our findings may reflect the longer disease duration in our population, paralleling observations made for BAEPs. The visual pathway involvement likely reflects a progressive degenerative process affecting the central visual system, characterized by reduced cortical excitability (Brighina et al., 2005), relative sparing of the retina in early stages (Pinto et al., 1988), and dysfunction of the optic nerve and occipital radiations (Fortuna et al., 2009; Rojas et al., 2021).

Our neurophysiological findings and subsequent correlation analysis show a promising role of BAEPs and p-VEPs as disease-severity biomarkers as all BAEP measures and some of p-VEP findings (N75, type of p-VEP alteration) were correlated with disease severity evaluated by mFARS. These results are corroborated by the regression analysis showing that increased III wave and N75 latencies can predict disease severity, together with disease duration. Visual and auditory central pathways are damaged in FRDA patients contributing to disease severity, suggesting the potential role of BAEP and p-VEP in follow-up and/or as treatment biomarkers. Our findings align with those of a recent study by Visani et al. (2025), which employed neuromagnetic recordings across different sensory modalities and identified altered visual and auditory responses rather than tactile or somatosensory, as potential biomarkers of disease severity in FRDA. While their work provides important mechanistic insights, it relies on advanced and less widely available magnetoencephalographic techniques. In contrast, our study supports similar conclusions using more accessible, non-invasive, and clinically applicable neurophysiological tools (BAEPs and p-VEPs) making their use feasible in routine clinical settings and multicenter trials.

Neurophysiological assessment appears to play a meaningful role in FRDA management, as suggested by the reappearance of sensory nerve action potentials in two patients treated with omaveloxolone (Rotar and Leonardis, 2025). Larger, longitudinal studies are needed to validate these findings. Complementary audiological and ophthalmological evaluations, including visual acuity testing, ERG, and OCT, will also be essential to draw more definitive conclusions.

Both NfL and GFAP levels showed an age-related increase in our cohort, consistent with previous findings (Rodero-Romero et al., 2024; Arslan et al., 2025; Agnello et al., 2025). Although a moderate correlation was observed between mFARS and GFAP, regression analysis confirmed the results reported by Zeitlberger et al. (2018), indicating that GFAP lacks sufficient sensitivity to serve as a reliable biomarker of disease severity. Our findings confirm that neither NfH nor NfL are dependable indicators of disease severity in FRDA, and their utility as biomarkers in therapeutic trials remains unclear (Hayer et al., 2020; Johnsson et al., 2023).

We didn't observe any significant difference of BAEP and p-VEPs findings between typical and late-onset FRDA patients, probably due to long-standing disease and small sample size.

4.1. Limitations

The diagnosis of FRDA in our cohort was confirmed by Southern Blot, although GAA repeat size was unavailable in most cases, preventing a genotype–phenotype correlation. As a monocentric study with a relatively small sample size, not all patients completed the full

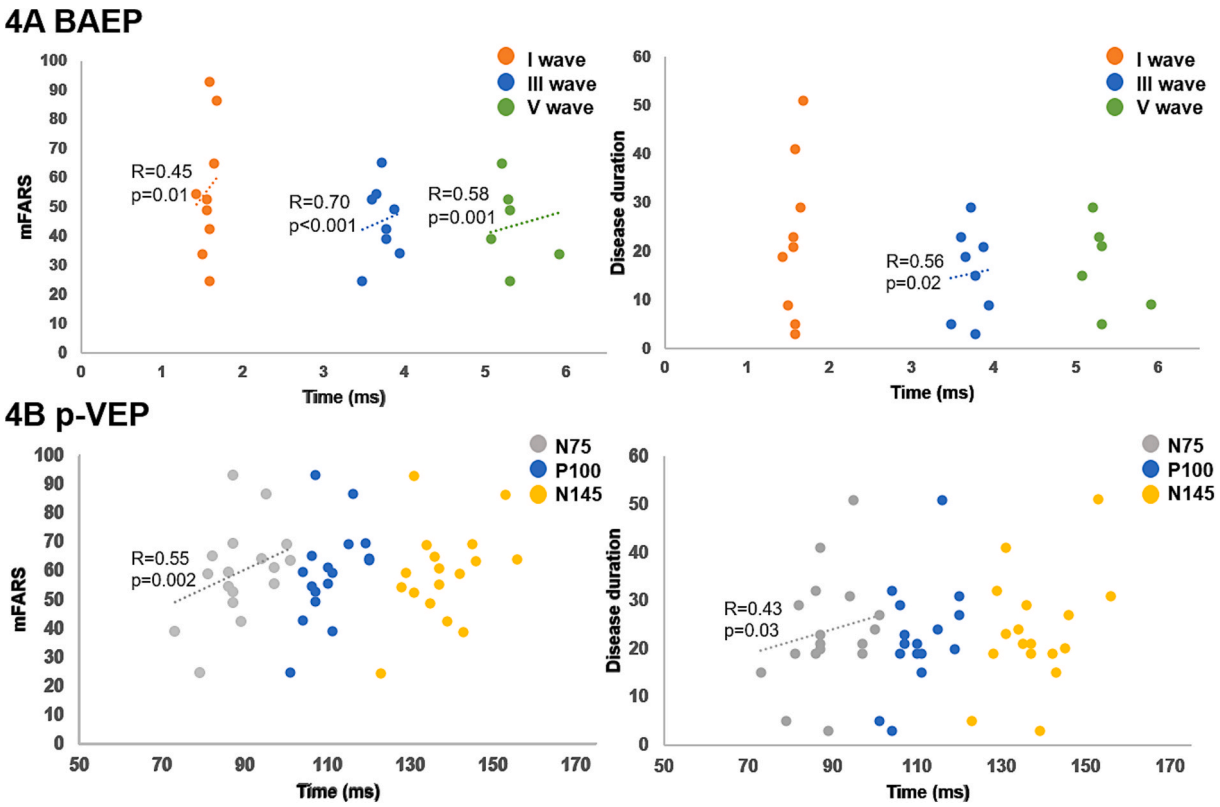

Fig. 4. Scatterplots illustrating the relationship between evoked potential latencies, disease severity, and disease duration. Fig. 6A: BAEP latencies of waves I, III, and V (ms) plotted against mFARS score and disease duration. Fig. 6B: p-VEP latencies of N75, P100, and N145 components (ms) plotted against mFARS score and disease duration. Each point represents an individual patient. Some patients are not displayed in the scatterplots due to unrecordable traces or unidentifiable wave components. Only statistically significant correlations identified through Spearman's rank correlation analysis are shown with a trend line, including the corresponding correlation coefficient (R) and p-value. Abbreviations. BAEP: brainstem auditory evoked potential; p-VEP: pattern visual evoked potential; mFARS, modified Friedreich's Ataxia Rating Scale; ms: milliseconds.

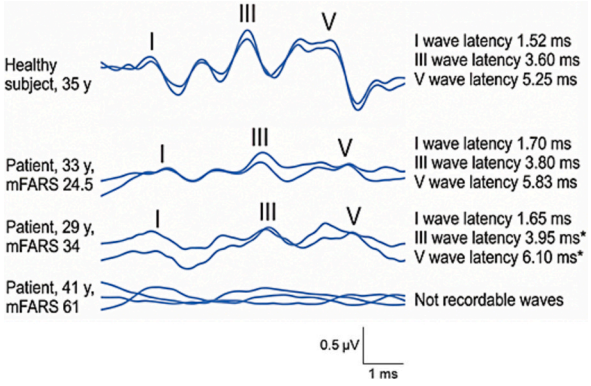

Fig. 5. Representative BAEPs in a healthy subject and three FRDA patients assessed by mFARS. The healthy subject shows clearly identifiable waves I, III, and V with normal absolute latencies. FRDA patients demonstrate progressive prolongation of wave III and V latencies with relative preservation of wave I, up to absence of recordable responses in the most severely affected patient. Abbreviations. BAEP: Brainstem Evoked Potentials; FRDA: Friedreich's ataxia; mFARS: modified Friedreich Ataxia Rating Scale. *Asterisk marks altered absolute latencies.

neurophysiological assessment, and potential limitations due to selection bias or convenience sampling cannot be excluded. Additionally, the absence of ophthalmological testing (e.g., electroretinogram or optical coherence tomography), neuroimaging, and audiological evaluations may have limited our ability to detect other relevant findings. These limitations underscore the need for larger, multicentric, and longitudinal studies to further explore the role of BAEPs and p-VEPs as biomarkers of disease progression and their potential responsiveness to therapeutic interventions.

5. Conclusions

This study provides a comprehensive characterization of a cohort of genetically confirmed FRDA patients with exceptionally long disease duration, offering valuable insights into the advanced stages of the disorder. The mean disease duration of 25 years distinguishes our population from those described in previous studies and allows us to capture electrophysiological and clinical features that emerge over time. Although self-reported visual and auditory symptoms were infrequent, neurophysiological testing revealed widespread subclinical involvement of central sensory pathways. Alterations in BAEPs and p-VEPs were highly prevalent, with findings such as bilateral absence of early auditory components and delayed N75 and P100 latencies indicating progressive neurodegeneration. These abnormalities correlated significantly with disease severity, and, in regression models, certain latency measures (III latency, N75 latency) emerged as independent predictors. In contrast, blood-based biomarkers such as NfL, NfH, and GFAP failed to show a consistent relationship with clinical status, limiting their reliability as indicators in chronic FRDA. Overall, our

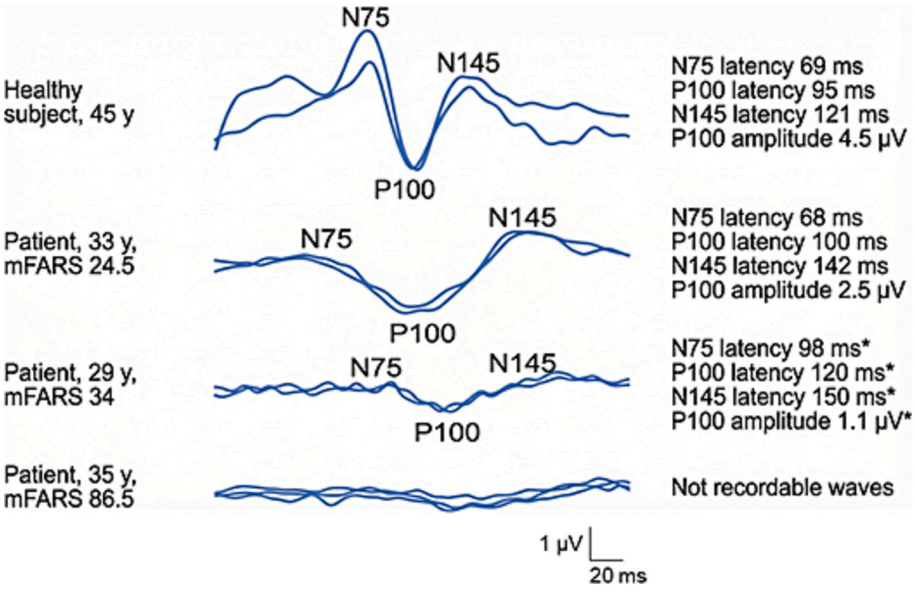

Fig. 6. Representative p-VEPs obtained from a healthy subject and three representative FRDA patients assessed by mFARS. The healthy individual shows clearly identifiable N75, P100, and N145 components with normal latencies and P100 amplitude. FRDA patients demonstrate progressive prolongation of N75, P100, and N145 latencies and reduction of P100 amplitude, up to absence of recordable responses in the most severely affected patient. Abbreviations. FRDA: Friedreich's ataxia; mFARS: modified Friedreich Ataxia Rating Scale; p-VEP: pattern reversal-Visual Evoked Potentials. *Asterisk marks altered absolute latencies and amplitudes.

findings highlight the utility of multimodal neurophysiological assessments in monitoring disease progression, especially in patients with long-standing FRDA. Longitudinal studies, coupled with detailed audiological and ophthalmological evaluation, are needed to validate these measures and define their role in future therapeutic strategies.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the University of Palermo.

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Data Availability Statement

The data presented in this study are available upon request from the corresponding author (the data are not publicly available due to privacy restrictions).

CRediT authorship contribution statement

Simona Maccora: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Investigation, Data curation, Conceptualization. **Umberto Quartetti:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Salvatore Maria Lima:** Data curation, Investigation, Writing – review & editing. **Nicasio Rini:** Data curation, Investigation, Writing – review & editing. **Marco Cucchiara:** Investigation, Resources. **Luisa Agnello:** Methodology, Writing – review & editing. **Caterina Maria Gambino:** Methodology, Writing – review & editing. **Filippo Brighina:** Writing – review & editing, Supervision, Resources, Validation. **Marcello Ciaccio:** Writing – review & editing, Methodology, Supervision, Validation, Project administration. **Vincenzo Di Stefano:** Writing – review & editing, Visualization, Project administration, Formal analysis, Investigation, Validation, Supervision, Methodology, Data curation, Conceptualization.

Informed consent

Informed consent was obtained from all subjects involved in the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2026.2111933.

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