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Nerve ultrasound in Friedreich's Ataxia: enlarged nerves as a biomarker of disease severity

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HIGHLIGHTS

- Nerve Ultrasound reveals enlarged nerves in Friedreich's Ataxia.
- Nerve abnormalities correlate with clinical disability scales.
- Nerve ultrasound can provide useful information where nerve conduction study is no longer informative.

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ABSTRACT

Objective: In Friedreich's ataxia research, the focus is on discovering treatments and biomarkers to assess disease severity and treatment effects. Our study examines high-resolution nerve ultrasound in these patients, seeking correlations with established clinical markers of disease severity.
Method: Ten patients with Friedreich's Ataxia underwent a comprehensive clinical assessment with established scales (SARA, FARS, mFARS, INCAT, ADL 0-36, IADL). Additionally, they underwent nerve conduction studies and high-resolution nerve ultrasound. Quantitative evaluation of nerve cross-sectional area, conducted at 24 nerve sites using high-resolution nerve ultrasound, was compared with data obtained from 20 healthy volunteers.
Results: All the patients had a severe sensory axonal neuropathy. High-resolution nerve ultrasound showed significant increase, in cross sectional area, of median and ulnar nerves at the axilla and arm. The cumulative count of affected nerve sites was directly associated with clinical disability, as determined by SARA, FARS, mFARS, ADL 0-36, and INCAT score, while displaying an inverse correlation with IADL.
Conclusions: Our study shows that high-resolution ultrasound reveals notable nerve abnormalities, primarily in the upper limbs of patients diagnosed with Friedreich's Ataxia. The observed correlation between these nerve abnormalities and clinical disability scales indicates the potential use of this technique as a biomarker for evaluating disease severity and treatment effects.
Significance: Nerve Ultrasound is a potential biomarker of disease severity in Friedreich's Ataxia.

1. Introduction

Friedreich's ataxia caused by GAA expansions within the FXN gene, stands as the most prevalent form of hereditary ataxia, inherited in an autosomal recessive manner. *FXN* encodes for Frataxin, a pivotal mitochondrial protein involved in iron methabolism. Longer trinucleotide expansions have been linked to more severe phenotypes, with early onset (<25 years), and a higher risk of mortality (Bürk, 2017; Rummey et al., 2022).

Friedreich's ataxia is a multisystem disorder, affecting Central and Peripheral Nervous Systems as well as the heart, skeleton, and endocrine pancreas. Mutations in *FXN* gene particularly result in damage to the Peripheral Nervous System, leading to sensory

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neuropathy, a primary hallmark of Friedreich's ataxia (Koeppen, 2011).

Clinical research is actively pursuing potential treatments to advance patient care significantly. Therefore, there is a growing emphasis on identifying potential biomarkers to effectively evaluate disease severity and treatment effects. While nerve conduction studies can effectively identify sensory neuropathy in Friedreich's ataxia, sensory nerve action potentials are often significantly reduced or completely absent. This occurrence suggests a floor effect, thus limiting the ability of nerve conduction study to measure disease severity or treatment effects, thus diminishing its potential as a biomarker in patients with Friedreich's ataxia (Creigh et al., 2019).

Having a readily available and reliable biomarker capable of highlighting and measuring disease severity or treatment effects would significantly enhance our ability to identify effective therapeutic strategies for this rare condition (Gavriilaki et al., 2023). In the process of identifying a reliable biomarker in Friedreich's ataxia, a critical step involves validating how the potential biomarker correlates with clinically established variables.

High-resolution nerve ultrasound is increasingly used as tool for investigating conditions affecting the peripheral nervous system. This technique provides useful structural and anatomic information in different peripheral nervous system diseases (Walker, 2017). However, its usefulness in assessing peripheral neuropathy associated with Friedreich's ataxia remains a largely unexplored research area. Accordingly, the reliability of high-resolution ultrasound examination in reflecting clinical variables and its potential use as a biomarker in Friedreich's ataxia remain unclear.

In this study, our aim was to investigate whether high-resolution nerve ultrasound might serve as a potential biomarker in patients with Friedreich's ataxia. To do so, we examined the nerve Cross-Sectional Area (CSA) using high-resolution nerve ultrasound in patients with Friedreich's ataxia and investigated its correlation with disease severity as assessed with clinically established variables.

2. Methods

2.1. Study cohort and design

Between January 1, 2022, and December 31, 2022, we conducted a prospective enrolment of a consecutive series of patients at the Rare Neurological Diseases Unit (Department of Medico-Surgical Sciences and Biotechnologies, University Sapienza, Latina) who were genetically confirmed to have Friedreich's Ataxia. The study took place at the Peripheral Neuropathy and Neuropathic Pain Unit within the Department of Human Neuroscience at Sapienza University, Rome. On the same day, all patients underwent a comprehensive neurological examination, nerve conduction study, and high-resolution nerve ultrasound examination.

Data collection was meticulously carried out using structured forms and standardized protocols, with the involvement of dedicated staff members. The clinical examination was performed by AT, CC, and EC, the nerve conduction study by EG and GDS, and the high-resolution nerve ultrasound examination by GDP and PF.

Prior to their participation, all patients provided written informed consent. The research adhered to the principles outlined in the Declaration of Helsinki and its later amendments, and it received approval from the institutional ethics committee.

2.2. Clinical evaluation

Demographic and clinical data, including age, gender, comorbidities, and disease duration, were systematically collected. Each patient also underwent a comprehensive neurological examination, which included the assessment of clinical and functional scales, including the Scale for the Assessment and Rating of Ataxia (SARA), Friedreich's Ataxia Rating Scale (FARS), modified FARS (mFARS), the Inflammatory Neuropathy Cause and Treatment Disability Score (INCAT), the Activities of Daily Living (ADL 0-36 score) and the Instrumental Activities of Daily Living (IADL).

SARA is an 8-items scale providing a total score ranging from 0 (no ataxia) to 40 (severe ataxia) (Yabe et al., 2008). FARS and mFARS are neurological scales where higher scores correspond to higher severity; the total score (maximum score: 125 for FARS and 93 for mFARS) is obtained by the sum of five subscales (bulbar function, upper limb coordination, lower limb coordination, peripheral nervous system, and upright stability) (Rummey et al., 2022). INCAT was assessed at the upper limb ranging from 0 (not affected) to 5 (prevented to perform specific tasks) and at the lower limb ranging from 0 (walks without difficulty) to 5 (confined to wheelchair). The overall INCAT disability score sums the upper and lower limb scores (Merkies et al., 2000). Quantification of daily life activities was estimated by the ADL, score ranging from 0 (normal function) to 36 (severe functional disability) (Lynch et al., 2006). IADL is an 8-items questionnaires that measure the degree of independence and the ability to perform the skills of daily living, the final score ranges from 8 (high function) to 0 (low function) (Edemekong et al., 2022).

2.3. Nerve conduction study

Nerve conduction study was performed using surface recording electrodes following the recommendations of the International Federation of Clinical Neurophysiology (Kimura, 2006). We studied sensory nerve action potentials and conduction velocities of sural, median, ulnar, and superficial radial nerves; compound muscle action potentials and conduction velocities of peroneal, tibial, median and ulnar nerves. Skin temperature was kept between 32 °C and 34 °C. Nerve conduction study data were compared with the age-matched normative ranges established in our laboratory.

2.4. High-resolution nerve ultrasound

High-resolution nerve ultrasound examination (MyLabX8, Esaote, Genova, Italy) was performed with a broadband linear transducer (frequency band 5–15 MHz). Median, ulnar, peroneal, tibial and sural nerves were followed along their anatomical course bilaterally. For each patient we evaluated a total of 24 nerve sites. The CSA of each nerve segment was measured at the most enlarged nerve point using the ellipse technique or the area tracing, when the nerve had an irregular shape, at: axilla, arm, forearm, wrist, popliteal fossa, fibular head and calf. High-resolution nerve ultrasound findings in patients with Friedreich's ataxia were compared with a control group of 20 healthy subjects.

For each patient we calculated a total number of altered nerve sites as the numerical sum of the detected abnormal sites considering axilla, arm, forearm, popliteal fossa, and calf bilaterally. Nerve segments with a nerve CSA within our laboratory range values were considered normal. In the assessment of the total number of altered nerve sites we excluded common entrapment sites, to avoid a possible bias due to entrapment neuropathies.

2.5. Statistical analysis

Since most variables had a non-normal distribution as assessed by Kolmogorov-Smirnov test we used nonparametric tests. Fisher's exact test was used to test the association between categorical variables. For the statistical analysis we considered each nerve on its own; CSA values between Friedreich's ataxia and controls were

compared with the Kruskal-Wallis test with Dunn's multiple comparison test for nerves with multiple scanning sites (median, ulnar, peroneal nerves) and Mann-Whitney test for nerves with a single scanning point (tibial and sural nerves). The association between clinical and high-resolution nerve ultrasound findings was assessed by Spearman correlation. Statistical analyses were performed with GraphPad Prism 9.5 (GraphPad Software, Inc., San Diego, CA).

3. Results

Ten patients with Friedreich's ataxia (Table 1) and twenty healthy controls were enrolled. None of these participants had possible causes of acquired peripheral neuropathy. All the patients had a sensory axonal neuropathy, while one patient had severe reduction of all sensory action potentials, the other nine patients had absent sensory nerve action potentials. Motor nerve compound muscle action potentials and motor conduction velocities were within normal ranges in all patients.

In the comparison between patients with Friedreich's ataxia and healthy participants, high-resolution nerve ultrasound examination showed statistically significant enlargement of the median ($p < 0.001$, using the Kruskal-Wallis Test with Dunn's multiple comparisons test) and ulnar ($p < 0.001$, using the Kruskal-Wallis Test with Dunn's multiple comparisons test) nerves, both at the axilla and arm locations (Table 2, Fig. 1, Fig. 2, Fig. 3). High-resolution nerve ultrasound findings are summarized in Table 2.

The total number of abnormal nerve sites positively correlated with SARA, FARS, mFARS, INCAT and ADL scores, and inversely correlated with IADL (the more severe the clinical and functional symptoms, the more extensive the nerve damage) (Table 3). Conversely, GAA repeats in the shorter of the two alleles and the disease duration did not correlate with the total number of altered nerve sites ($p = 0.75$ and $p = 0.072$, respectively).

4. Discussion

In the present study, we showed that high-resolution ultrasound examination detected specific nerve abnormalities in patients with Friedreich's ataxia. These abnormalities correlated with clinically established variables thus indicating the potential of high-resolution nerve ultrasound as a sensitive biomarker in Friedreich's ataxia.

In our patients with Friedreich's ataxia, high-resolution nerve ultrasound examination showed an increased CSA in multiple

Table 1
Clinical data in patients with Friedreich's ataxia.

	Patients, n = 10
Age (years)	40 (29–44.8)
Sex (M:F)	2:8
Disease Duration (years)	21 (8.8–27.8)
Trinucleotide Repeat Length (GAA1)	598 (415–795)
Clinical Scales	
SARA	28.5 (10.8–30.5)
FARS	68.75 (48.1–73.4)
mFARS	62.25 (43.9–65.1)
INCAT Arm	3 (2–4)
INCAT Leg	4 (1–5)
INCAT Total	8 (3–8.2)
ADL	28.5 (11.3–30)
IADL	3 (2–8)

Values are expressed as median (IQR).
GAA1: the shorter of the two alleles.
SARA: Scale for the Assessment and Rating of Ataxia.
FARS: Friedreich's Ataxia Rating Scale.
mFARS: modified Friedreich's Ataxia Rating Scale.
INCAT: Inflammatory Neuropathy Cause and Treatment Disability Score.
ADL: Activities of Daily Living 0–36 score.
IADL: Instrumental Activities of Daily Living.

Table 2
Nerve Cross Sectional Area (mm^2) as assessed with high-resolution ultrasound.

	Patients, n = 10	Controls, n = 20	p*
Median Nerve			
Axilla	14.5 (12.5–22.75)	7 (7–9)	**0.0007**
Arm	16 (11.25–30.25)	7 (6–8)	**<0.0001**
Forearm	7 (6–8)	6 (5–7)	0.32
Wrist	7 (5–9.75)	7 (6–8)	0.1
Ulnar Nerve			
Axilla	10 (8–13)	7 (7–9)	**0.0002**
Arm	13 (8.25–15.5)	7 (6–8)	**<0.0001**
Forearm	6 (5–7.75)	5 (5–6)	0.604
Wrist	4 (3–4.75)	3 (2.25–3)	0.1
Peroneal Nerve			
Popliteal fossa	12.5 (9–15)	10 (8–10)	0.109
Caput fibulae	12 (9.25–14)	10 (9–10)	0.202
Tibial Nerve			
Popliteal fossa	24 (16–29.25)	22 (19.25–25)	0.545
Sural Nerve			
Calf	4 (3–6)	4 (3–4)	0.125

Values are expressed as median (IQR).
CSA Cross Sectional Area.
* by Kruskal-Wallis test with Dunn's multiple comparison test for Median, Ulnar and Peroneal nerves; by Mann-Whitney test for Tibial and Sural nerves.

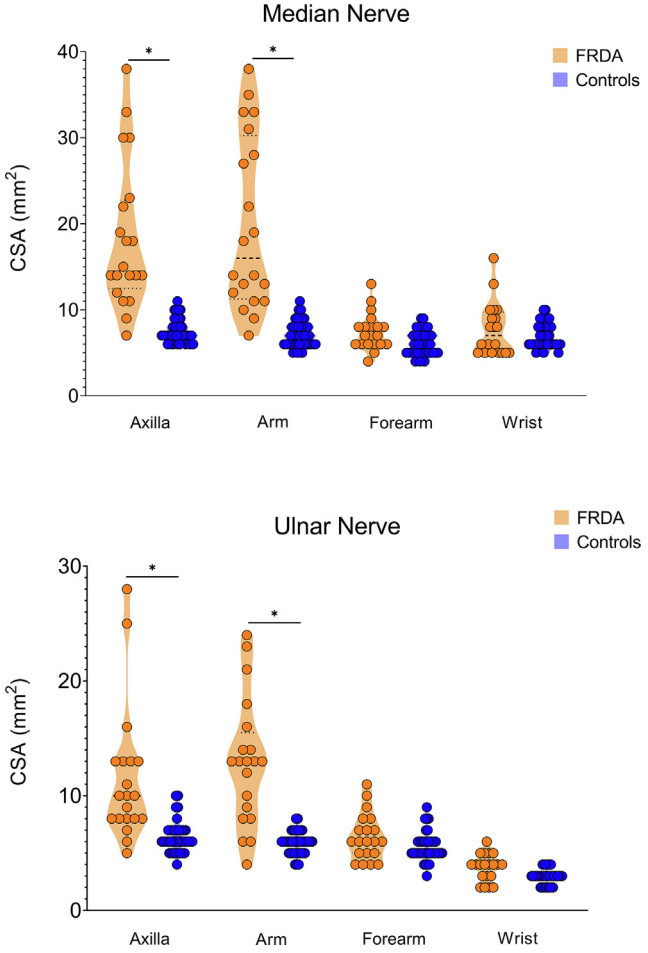

Fig. 1. Cross Sectional Area of median and ulnar nerves as assessed with high-resolution nerve ultrasound examination in patients with Friedreich's ataxia (FRDA, orange) and control participants (blue).

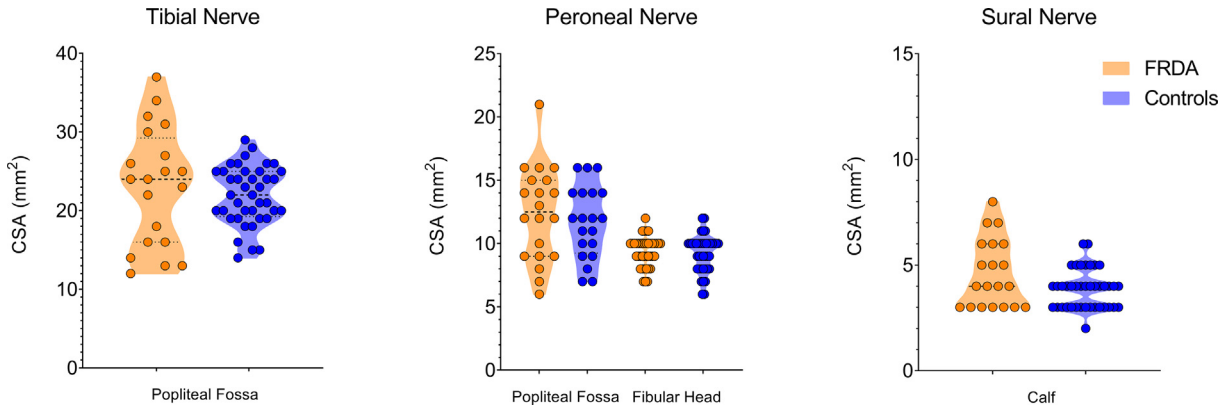

Fig. 2. Cross Sectional Area of tibial, peroneal and sural nerves as assessed with high-resolution nerve ultrasound examination in patients with Friedreich's ataxia (FRDA, orange) and control participants (blue).

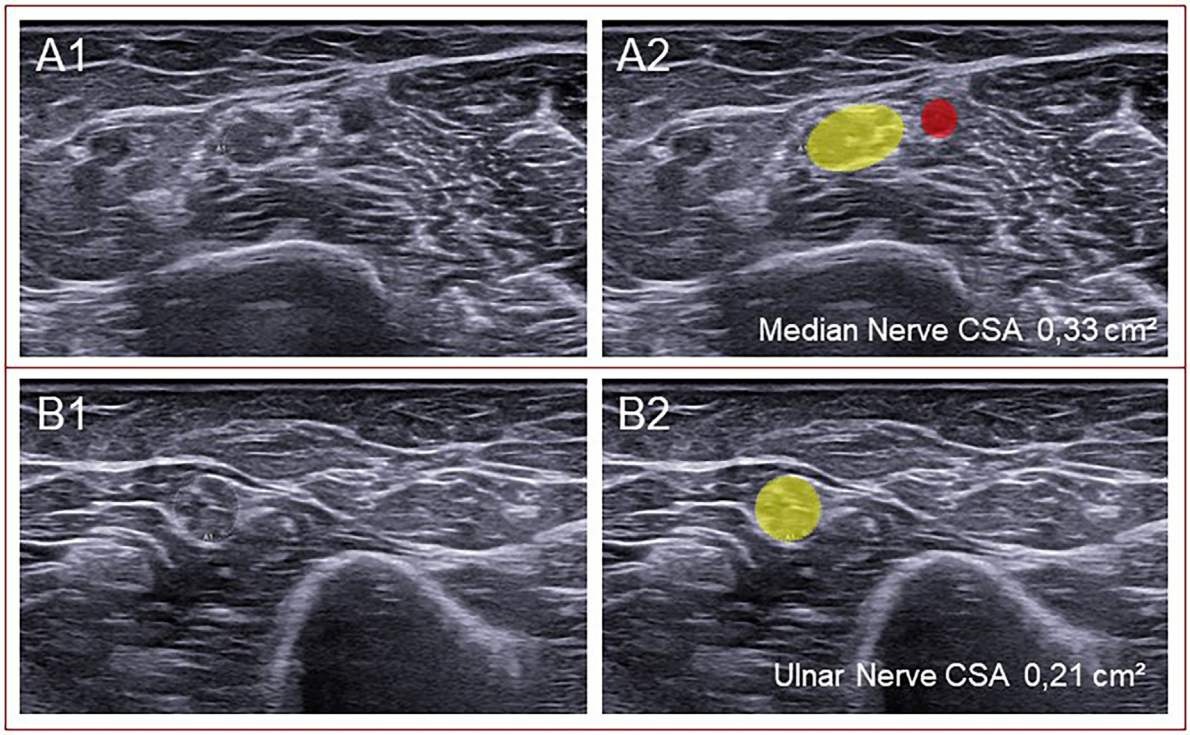

Fig. 3. High-resolution nerve ultrasound examination showing an enlarged median (A) and ulnar (B) nerves at the arm in Friedreich's ataxia. Yellow circles indicate the nerves and red circle indicate the artery.

Table 3
Correlations between the Total Number of Altered nerve Sites and clinical scales.

	Spearman r	p
TNAS vs SARA	0.709	0.026
TNAS vs FARS	0.740	0.018
TNAS vs mFARS	0.758	0.014
TNAS vs INCAT	0.648	0.048
TNAS vs ADL	0.674	0.038
TNAS vs IADL	−0.758	0.015

TNAS: Total Number of Altered nerve Sites (median nerve at axilla, arm and forearm; ulnar nerve at axilla, arm and forearm; peroneal and tibial nerves at popliteal fossa and sural nerve at calf bilaterally).
SARA: Scale for the Assessment and Rating of Ataxia.
FARS: Friedreich's Ataxia Rating Scale.
mFARS: modified Friedreich's Ataxia Rating Scale.
INCAT: Inflammatory Neuropathy Cause and Treatment Disability Score.
ADL: Activities of Daily Living 0–36 score.
IADL: Instrumental Activities of Daily Living.

nerves. This finding appears to contradict the common assumption that sensory neuropathy, in Friedreich's ataxia, is primarily a ganglionopathy. Considering that sensory axons constitute more than 90% of the total axons in a mixed nerve (Gesslbauer et al., 2017), a pure sensory neuronopathy would typically result in a reduction in nerve size (Leadbetter et al., 2019; van Alfen, 2019). However, frataxin is expressed in Schwann cells and its deficiency leads to cell death by activating inflammatory pathways, thus leading to peripheral nerve oedema and inflammation potentially resulting in the observed nerve enlargement (Lu et al., 2009; McLeod, 1971).

The detection of nerve enlargement, in combination with severe sensory axonal loss at nerve conduction study, is a peculiar finding. Conventionally, nerve enlargement is a characteristic feature in acquired and genetic demyelinating neuropathies (Grimm et al., 2017; Lucchetta et al., 2011), while axonal neuropathies typically show minimal or no nerve swelling (Grimm et al., 2014). Limited

research has highlighted increased nerve CSA in specific axonal neuropathies (Leonardi et al., 2022; Salvalaggio et al., 2020). This emphasizes the significance of our findings in the context of Friedreich's ataxia.

We found an increased nerve CSA, especially at the upper limbs. This finding may reflect a differential involvement of upper and lower limb sensory neurons in patients with Friedreich's ataxia, as observed at the spinal cord level, where the gracile fasciculus is more severely affected (Koeppen, 2011). Accordingly, the lack of detectable high-resolution nerve ultrasound alterations at the lower limbs may be the consequence of a long-standing nerve damage where atrophy and regeneration phenomena coexist (Caruso et al., 1983; Koeppen, 2011).

In our cohort, an observed increase in CSA using nerve ultrasound aligns with both clinical severity and functional disability. Notably, high-resolution nerve ultrasound examination proves to be valuable in situations where nerve conduction studies might lack meaningful insights. As novel disease-modifying drugs for Friedreich's ataxia are under exploration (Lynch et al., 2006; Zesiewicz et al., 2020), high-resolution nerve ultrasound examination emerges as a promising and reliable biomarker for assessing treatment effects. Future longitudinal studies in patients with Friedreich's ataxia could explore the potential of nerve CSA as assessed with high-resolution ultrasound as a valid surrogate endpoint, objectively reflecting changes in patient outcomes or condition.

Our study strengthens the significance of high-resolution nerve ultrasound as a complementary tool to nerve conduction studies, offering support in investigating peripheral nervous system diseases. Building upon and expanding previous research using high-resolution nerve ultrasound in small Friedreich's ataxia patient groups, our study presents a comprehensive analysis of clinical, neurophysiological, and ultrasound findings within a larger patient cohort. Notably, we employed a more detailed ultrasound protocol compared to earlier studies (Mulroy et al., 2018; Salvalaggio et al., 2015).

4.1. Limitations

We examined the correlation between nerve CSA and clinical variables in a cohort of ten patients. It follows that our findings might have a limited generalizability due to the small sample size. Nevertheless, among these ten patients, we observed a consistent correlation between nerve CSA and all the different clinical variables we assessed.

Given that high-resolution nerve ultrasound examination is operator-dependent, the reproducibility of this technique remains an open issue, potentially impacting our findings. Nonetheless, our study implemented a standardized ultrasound protocol, leading to improved reproducibility (Di Pietro et al., 2023).

In our study, we focused primarily on a nerve parameter—namely, the nerve CSA—due to its high reproducibility and reliability in nerve high-resolution ultrasound measures (Fisse et al., 2021). However, it is worth noting that the inclusion of additional parameters, such as nerve echogenicity and vascularity, cannot be ruled out and might enhance the diagnostic utility of high-resolution nerve ultrasound.

5. Conclusions

Our study now shows that high-resolution nerve ultrasound examination can detect nerve enlargements in patients with Friedreich's ataxia (mostly at the level of upper limbs).

Neve ultrasound abnormalities correlate with clinically established variables in patients with Friedreich's ataxia. This technique, therefore, might be a promising biomarker for measuring disease severity and treatment effects in this rare and severely disabling condition.

Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed. The author(s) received no financial support for the research.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.01.004.

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