ARTICLE

Nonataxia symptoms in Friedreich Ataxia

Report from the Registry of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS)

Kathrin Reetz, MD,* Imis Dogan, PhD,* Christian Hohenfeld, Claire Didszun, PhD, Paola Giunti, MD, Caterina Mariotti, MD, Alexandra Durr, MD, PhD, Sylvia Boesch, MD, Thomas Klopstock, MD, Francisco Javier Rodríguez de Rivera Garrido, MD, Ludger Schöls, MD, Ilaria Giordano, MD, Katrin Bürk, MD, Massimo Pandolfo, MD, and Jörg B. Schulz, MD, the EFACTS Study Group

Correspondence
Dr. Schulz
jschulz@ukaachen.de

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Abstract

Objective

To provide a systematic evaluation of the broad clinical variability in Friedreich ataxia (FRDA), a multisystem disorder presenting mainly with afferent ataxia but also a complex phenotype of nonataxia symptoms.

Methods

From the large database of the European Friedreich's Ataxia Consortium for Translational Studies, 650 patients with genetically confirmed FRDA were included. Detailed data of medical history documentation, questionnaires, and reports on clinical features were analyzed to provide in-depth description of the clinical profile and frequency rates of phenotypical features with a focus on differences between typical-onset and late-onset FRDA. Logistic regression modeling was used to identify predictors for the presence of the most common clinical features.

Results

The most frequent clinical features beyond afferent ataxia were abnormal eye movements (90.5%), scoliosis (73.5%), deformities of the feet (58.8%), urinary dysfunction (42.8%), cardiomyopathy and cardiac hypertrophy (40.3%), followed by decreased visual acuity (36.8%); less frequent features were, among others, depression (14.1%) and diabetes (7.1%). Most of these features were more common in the typical-onset group compared to the late-onset group. Logistic regression models for the presence of these symptoms demonstrated the predictive value of GAA repeat length on the shorter allele and age at onset, but also severity of ataxia signs, sex, and presence of neonatal problems.

Conclusions

This joint European effort demonstrates the multisystem nature of this neurodegenerative disease encompassing most the central nervous, neuromuscular, cardiologic, and sensory systems. A distinct and deeper knowledge of this rare and chronic disease is highly relevant for clinical practice and designs of clinical trials.

*These authors contributed equally to this work.

From the Department of Neurology (K.R., I.D., C.H., C.D., J.B.S.), RWTH Aachen University; JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging (K.R., I.D., C.H., C.D., J.B.S.), Forschungszentrum Jülich GmbH and RWTH Aachen University, Germany; Department of Molecular Neuroscience (P.G.), Ataxia Center, UCL Institute of Neurology, London, UK; Unit of Genetics of Neurodegenerative and Metabolic Diseases (C.M.), Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; ICM (Brain and Spine Institute) Sorbonne Universités (A.D.), UPMC Univ Paris 06 UMR S 1127, and INSERM U 1127, CNRS UMR 7225 and APHP, Pitié-Salpêtrière University Hospital, Genetic Department, Paris, France; Department of Neurology (S.B.), Medical University Innsbruck, Austria; Department of Neurology (T.K.), Friedrich Baur Institute, University Hospital of the Ludwig-Maximilians-Universität München; German Center for Neurodegenerative Diseases (DZNE) (T.K.), Munich; Munich Cluster for Systems Neurology (SyNergy) (T.K.), Munich, Germany; Reference Unit of Hereditary Ataxias and Paraplegias (F.J.R.d.R.G.), Department of Neurology, IdiPAZ, Hospital Universitario La Paz, Madrid, Spain; Department of Neurodegenerative Diseases (L.S.), Hertie-Institute for Clinical Brain Research, University of Tübingen; Department of Neurology (I.G.), University Hospital of Bonn; German Center for Neurodegenerative Diseases (DZNE) (I.G.), Bonn; Department of Neurology (K.B.), Philipps University of Marburg, Germany; and Laboratory of Experimental Neurology (M.P.), Université Libre de Bruxelles, Brussels, Belgium.

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Glossary

CI = confidence interval; **CRF** = case report form; **EFACTS** = European Friedreich's Ataxia Consortium for Translational Studies; **FRDA** = Friedreich ataxia; **HbA_{1c}** = glycated hemoglobin A_{1c}; **ICD-10** = *International Classification of Diseases, Tenth Revision*; **INAS** = Inventory of Non-Ataxia Signs; **OR** = odds ratio; **SARA** = Scale for the Assessment and Rating of Ataxia; **SCAFI** = Spinocerebellar Ataxia Functional Index; **|Std.Res.|** = standardized residuals.

Friedreich ataxia (FRDA) is the most frequent early-onset autosomal recessive inherited ataxia. Pathologic GAA repeat expansions in FXN lead to decreased expression of the encoded gene product frataxin, a ubiquitous mitochondrial protein involved in the creation of iron-sulfur clusters.

The first symptoms, most often poor balance and impaired coordination, typically appear around puberty. Progression is characterized by worsening of ataxia, dysarthria, deep sensory loss, distal weakness, ocular fixation instability, and visual and hearing impairment. Nonneurologic features such as hypertrophic cardiomyopathy, diabetes mellitus, kyphoscoliosis, and foot deformities[1] are highly variable in frequency and severity. This is most evident in the case of cardiomyopathy, which in some patients may lead to early death.[2]

Studies on the prevalence of systemic features of FRDA, severity, and correlation with neurologic and genetic status have so far provided variable and sometimes contradictory results, often relying on retrospective analyses of case series with small sample sizes. More detailed knowledge about the various phenotypic features of FRDA is not only needed for clinical trials but also highly relevant for practicing clinicians.

We recently reported baseline[3] and 2-year follow-up data[4] about the neurologic and functional status of patients with FRDA from the prospective registry of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS, e-facts.eu). Here, we systematically investigate nonataxia symptoms in 650 patients with genetically confirmed FRDA from the EFACTS registry. In addition to estimating the prevalence of nonataxia features, we assessed correlations with genetics, age at onset, and neurologic status. These results considerably increase our knowledge about this rare neurologic and multisystem disease, providing guidance for the choice of outcome measures and study designs to test how different therapeutic strategies can target the various aspects of FRDA.

Methods

Study population

Within the EFACTS framework, patients with FRDA were enrolled into a prospective, longitudinal study at 11 European centers.[3] Baseline data included in this study were acquired between September 2010 and July 2015. Inclusion required a confirmed genetic diagnosis of FRDA. All centers applied identical structured interviews, questionnaires, clinical neurologic examinations, and rating scales to collect comprehensive data on demographics, medical symptoms, and conditions.[3,4]

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from all patients or their authorized surrogates at enrollment. This study was approved by the local ethics committee of each participating center and is registered with ClinicalTrials.gov, number NCT02069509.

Medical history documentation

To obtain a detailed medical history, we asked patients about symptoms and medical diagnoses, other than FRDA, they had received. Investigated symptoms included visual impairment that could or could not be corrected using glasses, partial or complete hearing loss, dyspnea, and associated limitations (none, slight, marked, unable to perform any physical activity), palpitations, chest pain, and syncope. Other medical diagnoses included diabetes mellitus (classified into type 1 and 2), metabolic/endocrine diseases, cardiovascular diseases, hypertension, pulmonary diseases, gastrointestinal diseases, hepatobiliary diseases, hemato/lymphatic diseases, allergy/immunologic diseases, renal diseases, gynecologic/urologic diseases, psychiatric disorders (including depression), other neurologic diseases, ENT (ear, nose and throat) diseases, ophthalmologic diseases, dermatologic diseases, musculoskeletal diseases, autoimmune diseases, and other diseases. We specifically asked for any history of cancer, including type, treatment, and outcome. These reports were complemented by disease-specific questionnaires and case report forms (CRFs), e.g., cardio-CRF and general examination CRF for scoliosis and foot deformities.

We measured vital signs, including body weight in kilograms and height in centimeters for the body mass index, blood pressure in millimeters of mercury (after sitting for 5 minutes), and pulse rate per minute. Patients were examined for the presence and severity (mild, moderate, or pronounced) of scoliosis and pes cavus, and any surgery for these conditions was recorded. Cardiologic assessment included a clinical examination, echocardiography (septum thickness in millimeters, intraventricular thickness in millimeters, and functional ejection fraction in percent), and ECG (presence of sinus rhythm, repolarization abnormalities, Q waves, arrhythmia, left ventricular hypertrophy, conduction abnormalities, and pacemaker).

To enable a quantitative analysis of medical history and diagnoses, the medical documentation data as described above were grouped according to ICD-10 (apps.who.int/classifications/icd10/browse/2016/en [May 24, 2017]). Diagnoses indicating acute injury, poisoning, or states influencing interaction with health services were stripped from the data. ICD-10 codes were shortened to a 3-character string (e.g., M41, E11, H52) to avoid fragmentation of data and issues caused by varying levels of detail in documentation. In cases in which more than one code could be applied to a group of diseases, one was chosen and consistently applied (e.g., F33 for depression). Cardiac hypertrophy (I51) and cardiomyopathy (I42) were combined for further analyses, as both refer to typical cardiac pathology in FRDA.

Clinical rating scales and genetic testing

We quantified severity of ataxia by using the Scale for the Assessment and Rating of Ataxia (SARA).[5] Nonataxia signs and symptoms, such as changes in reflexes and other motor, sensory, or ophthalmologic signs, were recorded using the count of the Inventory of Non-Ataxia Signs (INAS).[6] Self-reported symptoms of urinary dysfunction and related symptoms (N32, N39, R39) were combined with urinary dysfunction data from the INAS and merged into a single category. The same approach was chosen for data on visual system disorders: all data for abnormal eye movements from the INAS and medical history were combined into one category, based on the ICD-10 H55 code; all data on disorders of accommodation and refraction (ICD-10 H52) were supplemented with INAS data as well.

As timed functional test, we used the performance-based Spinocerebellar Ataxia Functional Index (SCAFI),[7] consisting of walk (8-m walk at maximum speed), dexterity (9-hole peg test), and speech (number of repetitions of the syllables "PA-TA" within 10 seconds) components. Total composite SCAFI z scores were calculated as previously reported.[7] Quantitative assessment of the cerebellar signs in the upper limb with the Composite Cerebellar Functional Severity Score is reported elsewhere.[8] Functional disability stage was recorded according to the spinocerebellar degeneration functional score, which ranges from 1 (no functional handicap but signs at examination) to 7 (confined to bed).[9] Finally, GAA repeat lengths on both alleles of the *FXN* locus were determined at the Laboratoire de Neurologie Expérimentale of the Université Libre de Bruxelles in Brussels, Belgium.[10]

Statistical analysis

Data are reported as mean, SD, median, median absolute deviation, range, or frequency (relative to available data), as appropriate, for the total cohort and divided in typical-onset FRDA (age at onset ≤24 years) and late-onset FRDA (≥25 years) groups.[4] Differences between age-at-onset groups in frequency distribution of diagnoses or clinical characteristics were assessed using χ^2 tests, Welch t tests, or Wilcoxon rank sum tests, as appropriate. For contingency tables larger than 2 × 2, the absolute value of standardized residuals (|Std.Res.|) was computed to break down significant χ^2 tests.[11,12]

For the 8 most common diagnostic categories, we used logistic regression analyses to identify significant predictors for the presence of each diagnosis. Sex, GAA repeat length on the shorter *FXN* allele, presence of neonatal problems, age at onset of FRDA, disease duration of FRDA, and SARA scores were tested as predictors. For depression, we included whether a participant was wheelchair-bound as an additional predictor. For each logistic regression model, statistical significance was assessed using Wald tests, analyses of deviance were applied, and odds ratios were calculated from the model.

All statistical analyses were performed using R version 3.4.1[13] with a p value of 0.05 as threshold for statistical significance.

Data availability

Data supporting the findings of this study are included in this published article. Additional data are available from the corresponding author on reasonable request.

Results

FRDA cohort characteristics

Baseline data on 650 patients with genetically confirmed FRDA (aged 6–76 years, 53.1% female) were collected between September 15, 2010, and July 20, 2015 (table 1). Age at onset ranged from <1 to 65 years, and disease duration from <1 to 55 years. Five hundred forty patients (83.1%) were classified as typical-onset FRDA and 108 (16.6%) as late-onset; for 2 patients, no reliable data regarding age at onset were available. GAA repeat lengths were available for both alleles in 620 participants (95.4%) (allele 1: 588 ± 269.9 repetitions; allele 2: 899 ± 214.5). The majority of patients (97.4%) were homozygous for expanded GAA repeats in the *FXN* gene, with the shorter repeat (allele 1) containing at least 60 GAA triplets; the remaining patients (n = 16) were compound heterozygotes carrying an expanded GAA repeat on one allele and a *FXN* point mutation or deletion on the other. Patients with typical-onset FRDA had on average a longer disease duration ($t_{189.35} = -2.507$, $p = 0.013$), higher GAA repeat length on both *FXN* alleles (allele 1: $t_{196.36} = -19.088$, $p < 0.001$; allele 2: $t_{123.93} = -6.227$, $p < 0.001$), higher SARA ($t_{187.04} = -10.611$, $p < 0.001$) and INAS ($t_{180.22} = -6.500$, $p < 0.001$) scores, lower SCAFI ($t_{147.72} = 9.954$, $p < 0.001$), and higher disability stage ($W = 16{,}716$, $p < 0.001$) compared to patients with late-onset FRDA. There were no differences in age at onset, disease duration, SARA, INAS, and SCAFI scores, as well as disability stage when comparing patients with a *FXN* point mutation or deletion with homozygotes (data not shown).

Prevalence of nonataxia clinical features

Patients with FRDA reported an average of 5.1 ± 2.5 (range: 1–16) nonataxia features. Patients with typical-onset had more of these features than late-onset patients (typical FRDA:

Table 1 Basic characteristics of the EFACTS cohort

	Typical-onset FRDA (aged ≤24 y)	Late-onset FRDA (aged ≥25 y)	Total FRDA cohort
No. (%)	540 (83.1)	108 (16.6)	650 (100)
Age, y, n (%)	540 (83.1)	108 (16.6)	650 (100)
Median ± MAD [range]	29 ± 11.9 [6; 68]	50 ± 10.4 [32; 76]	31 ± 14.8 [6; 76]
Mean ± SD	30.0 ± 11.8	51.1 ± 9.8	33.5 ± 13.9
Sex, male/female, %	47.6/52.4	42.6/57.4	46.9/53.1
Age at onset, y, n (%)	537 (82.6)	108 (16.6)	645 (99.2)
Median ± MAD [range]	12 ± 4.4 [1; 24]	32.5 ± 7.4 [25; 65]	13 ± 7.4 [1; 65]
Mean ± SD	11.7 ± 5.0	35.1 ± 8.9	15.7 ± 10.5
Disease duration, y, n (%)	537 (82.6)	108 (16.6)	645 (99.2)
Median ± MAD [range]	17 ± 11.9 [1; 55]	14 ± 7.4 [2; 40]	16 ± 10.4 [1; 55]
Mean ± SD	18.4 ± 10.7	16.1 ± 8.1[a]	18.0 ± 10.4
Disability stage, n (%)	540 (83.1)	108 (16.6)	645 (99.2)
Median ± MAD [range]	6 ± 0 [1; 7]	4 ± 1.5 [1; 6][b]	5 ± 1.5 [1; 7]
Mean ± SD	4.9 ± 1.5	3.8 ± 1.3	4.7 ± 1.5
Genetics (GAA repeats), n (%)	512 (78.8)	106 (16.3)	620 (95.4)
Allele 1, median ± MAD [range]	685 ± 237.2 [6; 1,200]	237 ± 179.4 [43; 1,000]	645 ± 289.1 [6; 1,200]
Mean ± SD	652 ± 238.7	272.3 ± 174.2[b]	587.7 ± 269.9
Allele 2 median ± MAD [range]	920 ± 169.0 [270; 1,580]	810 ± 323.2 [150; 1,250]	912 ± 195.7 [150; 1,580]
Mean ± SD	930 ± 183.7	751.8 ± 283.0[b]	899.4 ± 214.5
SARA, n (%)	534 (82.2)	108 (16.6)	639 (98.3)
Median ± MAD [range]	24.5 ± 11.1 [2; 40]	13.0 ± 6.7 [1.5; 33]	22 ± 13.3 [1.5; 40]
Mean ± SD	23.0 ± 9.5	14.3 ± 7.4[b]	21.6 ± 9.7
INAS, n (%)	347 (53.1)	94 (14.4)	442 (68)
Median ± MAD [range]	5 ± 1.5 [1; 13]	4 ± 1.5 [1; 9]	5 ± 1.5 [1; 13]
Mean ± SD	5.4 ± 2.0	4.1 ± 1.6[b]	5.2 ± 2.0
SCAFI, n (%)	471 (72.5)	93 (14.3)	561 (86.3)
Median ± MAD [range]	−0.22 ± 0.85 [−1.5; 2.4]	0.64 ± 0.61 [−1.0; 2.0]	−0.08 ± 0.91 [−1.5; 2.4]
Mean ± SD	−0.13 ± 0.82	0.68 ± 0.69[a]	0.00 ± 0.85

Abbreviations: EFACTS = European Friedreich's Ataxia Consortium for Translational Studies; FRDA = Friedreich ataxia; INAS = Inventory of Non-Ataxia Signs; MAD = median absolute deviation; SARA = Scale for the Assessment and Rating of Ataxia; SCAFI = Spinocerebellar Ataxia Functional Index.
Differences were assessed using Welch *t* tests except for sex distribution for which a χ^2 test was used and disability stage for which the Wilcoxon rank sum test was applied.
Significant differences between typical-onset and late-onset groups as follows:
[a] $0.01 \geq p > 0.001$.
[b] $0.001 \geq p$.

5.3 ± 2.2, late FRDA: 3.9 ± 2.5; $t_{165.17} = -5.898$, $p < 0.001$, $d = 0.622$). The most common diagnoses, each reported in more than half of the cases, were abnormal eye movements (90.5%), scoliosis (73.7%), deformities of the feet—mainly pes cavus—(58.8%), urinary dysfunction (42.8%), and cardiomyopathy and cardiac hypertrophy (40.3%) (table 2, figure 1). Other relatively common conditions included disorders of accommodation and refraction (36.8%) and allergies other than hayfever and allergic rhinitis (9.7%). Less common diseases and health problems, each present in at least 20 patients, affected the respiratory (allergic rhinitis 7.2%, asthma 5.1%), auditory (hearing loss 10.9%), metabolic and endocrine (hypothyroidism 4%, type 1 diabetes mellitus 4%, type 2 diabetes mellitus 3.1%), and visual (vision loss of

Table 2 Clinical diagnoses and features of the sample

	Total cohort (n = 650)	Typical FRDA (540)	Late FRDA (108)
Musculoskeletal, n (%)			
Scoliosis (n = 649)			
Mild/mod/prncd	216/181/76 (33.3/27.9/11.7)	187/173/74 (34.6/32.0/13.7)	28[a]/7[a]/2 (25.9/6.5/1.9)
Surgery	75 (11.6)	75 (13.9)	0 (0.0)[d]
Foot deformities (n = 649)			
Mild/mod/prncd	73/166/135 (11.2/25.6/20.8)	64/149/133 (11.9/27.6/24.6)	8/16/2[a] (7.4/14.8/1.9)
Surgery	47 (7.2)	46 (8.5)	0 (0.0)
Osteoporosis	11 (1.7)	5 (0.9)	6 (5.6)[e]
Cardiovascular system			
Hypertrophy/cardiomyopathy, n (%)	262 (40.3)	249 (46.1)	12 (11.1)[f]
Echocardiogram (n = 426), M ± SD			
Septum thickness, mm	10.8 ± 2.43	11.0 ± 2.47	9.7 ± 1.90[e]
Intraventricular thickness, mm	10.5 ± 3.34	10.7 ± 3.49	9.6 ± 2.28[e]
Functional ejection fraction, %	63.2 ± 9.68	63.1 ± 10.11	63.6 ± 7.41
ECG (n = 437), n (%)			
Sinusal rhythm	421 (96.3)	363 (97.6)	58 (95.1)
Repolarization abnormalities	264 (60.4)	242 (65.7)	22 (36.1)[f]
Q waves	20 (4.6)	18 (5.2)	2 (3.2)
Arrhythmia	21 (4.8)	19 (5.1)	2 (3.2)
Left ventricular hypertrophy	80 (18.3)	74 (20.9)	6 (9.8)
Conduction abnormalities	26 (5.9)	23 (6.5)	3 (4.9)
Heart rate (n = 600)			
Beats/min, M ± SD	75.5 ± 12.18	76.3 ± 12.16	71.1 ± 11.45[e]
Bradycardia (<60 bpm)/tachycardia (>100 bpm), n (%)	34 (5.7)/18 (3.0)	24 (4.8)/16 (3.2)	10[a] (10.5)/2 (2.1)
Blood pressure (n = 600)			
s/d, mm Hg, M ± SD	119.6 ± 16.6/77.3 ± 12.3	117.5 ± 15.49/76.3 ± 12.2	130.9 ± 17.71/82.0 ± 11.5[f]
Atrial fibrillation/flutter, n (%)	18 (2.8)	18 (3.3)	0 (0.0)
Unspecified cardiac arrhythmia, n (%)	12 (1.8)	11 (2.0)	1 (0.9)
Sensory system, n (%)			
Abnormal eye movements[b]	588 (90.5)	490 (90.7)	96 (88.9)
Accomm./refrac. disorders[b]	239 (36.8)	201 (37.2)	37 (34.3)
Blindness and low vision	20 (3.1)	17 (3.1)	3 (2.8)
Uns. optic nerve, vis. path	10 (1.6)	10 (1.9)	0 (0.0)
Hearing loss	71 (10.9)	67 (12.4)	4 (3.7)[d]
Endocrine system and metabolism			
Diabetes type 1/2, n (%)	26/20 (4.0/3.1)	26/16 (4.8/3.0)	0/4 (0.0/3.7)[d]
Glucose non-/diabetic (n = 263)			
M ± SD, mmol/L	9.7 ± 3.8/4.9 ± 0.7	9.8 ± 4.0/4.9 ± 0.6	8.3 ± 1.9/5.1 ± 0.8

Continued

Table 2 Clinical diagnoses and features of the sample *(continued)*

	Total cohort (n = 650)	Typical FRDA (540)	Late FRDA (108)
HbA_{1c} non-/diabetic (n = 291)			
M ± SD, mmol/mol	59.8 ± 13.6/34.2 ± 4.3	59.0 ± 13.4/33.7 ± 4.2	70.0 ± 17.8/36.1 ± 4.2
Hypothyroidism, n (%)	26 (4.0)	18 (3.3)	8 (7.4)
Lipoprotein metabolism disorder, n (%)	19 (2.9)	14 (2.6)	5 (4.6)
Body mass index (n = 599), M ± SD	22.8 ± 4.23	22.4 ± 4.18	24.8 ± 3.92[f]
Digestive system and dysphagia, n (%)			
Gastroesophageal reflux	18 (2.8)	15 (2.8)	2 (1.9)
Uns. functional intestinal disorder	17 (2.6)	16 (3.0)	1 (0.9)
Mal. upper alimentary tract	15 (2.3)	12 (2.2)	3 (2.8)
Dysphagia (n = 645)			
Mild/mod/severe	282/150/11 (43.7/23.3/1.7)	234/128/10 (43.7/23.9/1.9)	48/20/1 (44.4/18.5/0.9)
Neurologic, n (%)			
Migraine	19 (2.9)	16 (3.0)	3 (2.8)
Sleep disorders	12 (1.8)	9 (1.7)	3 (2.8)
Epilepsy and recurrent seizures	11 (1.7)	11 (2.0)	0 (0.0)
Sen. symp. feet (n = 627)			
Mild/mod/prncd	152/208/211 (24.2/33.2/33.7)	118/164/190 (22.7/31.6/36.6)	34[a]/44[a]|20[a] (32.1/41.5/18.9)
Paresis	385 (59.2)	356 (65.9)	28 (25.9)[f]
Face/tongue (n = 643)			
Mild/mod/prncd	69/9/1 (10.7/1.4/0.2)	67/9/1 (12.6/1.7/0.2)	2[a]/0/0 (1.9/0.0/0.0)
Upper limbs (n = 646)			
Prox mild/mod/prncd	101/28/8 (15.6/4.3/1.2)	97/28/8 (18.1/5.2/1.5)	3[a]/0/0 (2.8/0.0/0.0)
Distal mild/mod/prncd	136/98/30 (21.1/15.2/4.6)	121/97/30 (22.6/18.1/5.6)	15[a]/1/0 (13.9/0.9/0.0)
Lower limbs (n = 644)			
Prox mild/mod/prncd	132/125/70 (20.5/19.4/10.9)	119/123/69 (22.3/23.0/12.9 s)	13[a]/2[a]/0[a] (12.1/1.9/0.0)
Distal mild/mod/prncd	94/105/163 (14.6/16.3/25.3)	76/98/162 (14.2/18.3/30.3)	18/7[a]/0[a] (16.8/6.5/0.0)
Reflexes (n = 643)			
Hyperreflexia/mixed/areflexia	17/81/512 (2.6/12.6/79.6)	6/43/477 (1.1/8.1/89.4)	11[a]/38[a]/42[a] (10.2/35.1/38.9)
Other, n (%)			
Unspecified allergy[c]	63 (9.7)	51 (9.4)	12 (11.1)
Depression	92 (14.1)	75 (13.9)	17 (15.8)
Anxiety	20 (3.1)	18 (3.3)	2 (1.9)
Urinary system disorders[b]	278 (42.8)	236 (43.7)	42 (38.9)
Allergic rhinitis	47 (7.2)	38 (7.0)	8 (7.4)

Continued

Table 2 Clinical diagnoses and features of the sample *(continued)*

	Total cohort (n = 650)	Typical FRDA (540)	Late FRDA (108)
Asthma	33 (5.1)	28 (5.2)	5 (4.6)
Unspecified dermatitis	17 (2.6)	17 (3.1)	0 (0.0)
Psoriasis	10 (1.6)	5 (1.0)	4 (3.7)

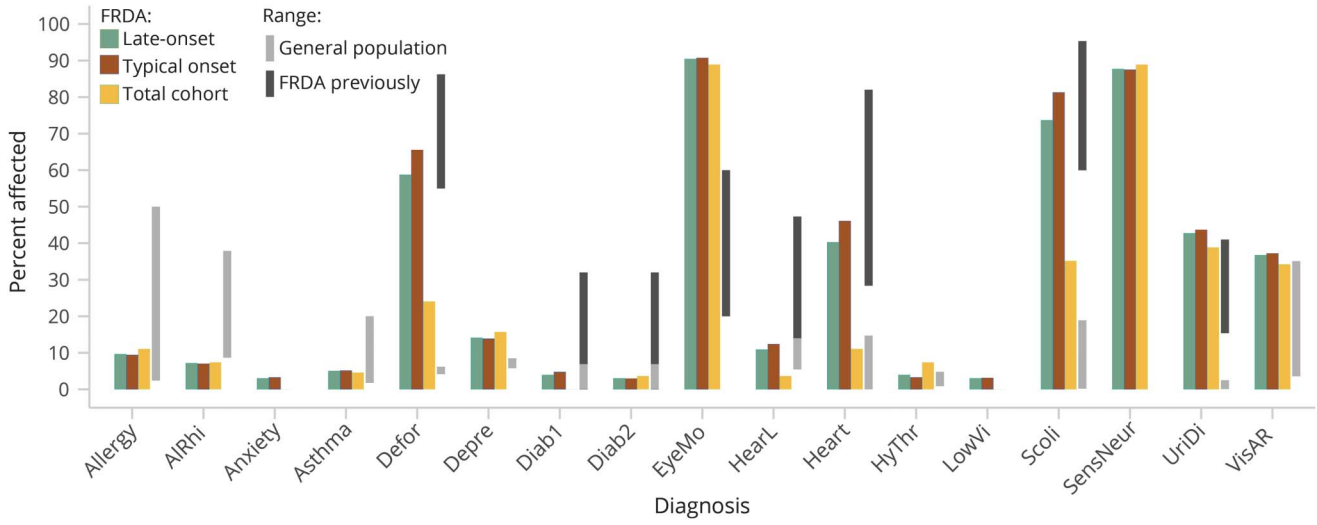
Abbreviations: accomm./refrac. = accommodation/refraction; bpm = beats per minute; FRDA = Friedreich ataxia; HbA_{1c} = glycated hemoglobin A_{1c}; M = mean; mal. = malformation; mod = moderate; prncd = pronounced; prox = proximal; s/d = systolic/diastolic; sen. symp. = sensory symptoms; uns. = unspecified (disorder of); vis. = visual.
Diagnoses are listed only if they were present in at least 10 patients of the entire sample.
[a] Standardized residuals of χ^2 test with >|2|.
[b] Marks features that combine self-report information with data from the Inventory of Non-Ataxia Signs.
[c] Without hayfever and allergic rhinitis.
Significant differences in frequency distributions (χ^2 test/Fisher exact test) or means (Welch *t* tests) between typical-onset and late-onset groups as follows:
[d] $p \leq 0.05$.
[e] $p \leq 0.01$.
[f] $p \leq 0.001$.

various severities 3.1%) systems. The most common psychiatric disturbance was depression (14.2%), while anxiety disorder affected only 3.1% of patients.

Deformities of the feet ($\chi^2_1 = 7.322$, $p = 0.007$), cardiomyopathy and cardiac hypertrophy ($\chi^2_1 = 44.389$, $p < 0.001$), scoliosis ($\chi^2_1 = 96.153$, $p < 0.001$), hearing loss ($\chi^2_1 = 6.125$, $p = 0.013$), and diabetes type 1 ($\chi^2_1 = 4.239$, $p = 0.039$) were more common in the typical-onset than in the late-onset group (table 2, figure 1). Regarding severity distribution, we observed a difference between typical- and late-onset groups for scoliosis ($\chi^2_2 = 14.71$, $p < 0.001$), with more mildly and moderately affected typical-onset than late-onset FRDA patients (mild |Std.Res.| = 3.820, moderate |Std.Res.| = 2.517) but no difference for severe scoliosis (i.e., pronounced or surgery). Pronounced feet deformities were more frequent in typical-onset cases (right |Std.Res.| = 3.082, left |Std.Res.| = 3.092).

Cardiologic assessment allowed for better characterization of heart disease in FRDA. Heart rate was within the normal range in the overall cohort (75.5 ± 12.18), but it was faster in the typical-onset compared to the late-onset group ($t_{137.09} = -4.016$, $p < 0.001$). Mean blood pressure was also in the normal range in the overall cohort (119.6/77.3 ± 16.6/12.3), with higher systolic ($t_{124.28} = -6.916$, $p < 0.001$) and diastolic ($t_{139} = 4.383$, $p < 0.001$) values in the late-onset group. On echocardiography, average septum and left ventricular wall

Figure 1 Frequencies of clinical diagnoses for the total cohort and by onset groups



Percentage of the sample affected by the respective diagnosis, for the entire sample and split by typical- and late-onset FRDA. Dark gray lines show prevalence range from other studies on FRDA (because of missing separation between types in the literature, data for diabetes refer to both types), and light gray lines show prevalence ranges in the general population. Allergy is without allergic asthma, hayfever, and allergic rhinitis. AlRhi = allergic rhinitis; Defor = deformities of the feet; Depre = depression; Diab1 = diabetes type 1; Diab2 = diabetes type 2; EyeMo = irregular/abnormal eye movements; FRDA = Friedreich ataxia; HearL = hearing loss; Heart = heart disease, mainly cardiomyopathy and cardiac hypertrophy; HyThr = hypothyroidism; LowVi = blindness and low vision; Scoli = scoliosis; SensNeur = sensory neuropathy; UriDi = diseases of the urinary system; VisAR = disorders of visual accommodation and refraction.

thicknesses were slightly above normal at 10.8 ± 2.4 mm and 10.5 ± 3.3 mm (normal range 6–10 mm[14]). Mean ejection fraction was in the normal range at 63.2% ± 9.68% (normal range 55%–75%). ECG showed a sinus rhythm in 64.8% of patients, repolarization abnormalities were in 40.6%, and left ventricular hypertrophy in 12.3%.

Analysis of nonataxia neurologic signs and symptoms revealed a very high prevalence of sensory neuropathy, as indicated by impaired perception of vibration in 91.4% and 89.5% of patients (left and right side at the external malleolus or at the metatarsophalangeal joint I, respectively). The typical-onset group was more severely affected (L: $\chi^2_3 = 13.14$, $p = 0.004$; R: $\chi^2_3 = 12.84$, $p = 0.005$). Motor weakness/paresis was also highly prevalent and more common in the typical-onset group, with 65.9% of the sample being affected vs only 25.9% in the late-onset group ($\chi^2_1 = 60.4$, $p < 0.001$). For each of the assessed regions (face/tongue, upper limbs proximal and distal, lower limbs proximal and distal), standardized residuals for each distribution test suggest that paresis was generally more severe in the typical-onset group. Weakness was more pronounced distally and in the lower limbs.

Measures of glucose metabolism indicated a mean fasting blood glucose level of 5.32 mmol/L (SD = 1.90) and a mean HbA_{1c} level of 36.73 mmol/mol (SD = 9.68). Glucose levels were different between FRDA patients with and without diabetes ($F_{2, 260} = 143.1$, $p < 0.001$, $\eta^2 = 0.52$), as well as HbA_{1c} levels ($F_{2, 288} = 245.5$, $p < 0.001$, $\eta^2 = 0.63$).

Finally, 8.9% of all patients reported problems at birth, including premature birth, cesarean section, forceps deliveries, and perinatal hypoxia. These were more common in the typical-onset group (10%) than in late-onset FRDA (2.8%; $\chi^2_1 = 5.024$, $p = 0.025$).

A full overview of clinical features (with diagnoses present in at least 5 patients of the cohort) and differences between groups can be found in table 2.

Predictors of clinical characteristics

Logistic regression models identified significant predictors for all 8 most common diagnoses (table 3). Presence of abnormal eye movements was predicted only by SARA score (odds ratio [OR] = 1.090, 95% confidence interval [CI]: 1.037–1.148). Scoliosis was predicted by earlier age at onset (OR = 0.934, CI: 0.910–0.957) and higher SARA scores (OR = 1.086, CI: 1.049–1.124). Foot deformities were also predicted by age at onset (OR = 0.952, CI: 0.928–0.975) and SARA score (OR = 1.056, CI: 1.026–1.088), as well as by GAA repeat length on the shorter *FXN* allele (GAA1) (OR = 1.001, CI: 1.000–1.002) and disease duration (OR = 1.028, CI: 1.001–1.057). Urinary dysfunction was predicted by age at onset (OR = 1.025, CI: 1.004–1.048), disease duration (OR = 1.030, CI: 1.006–1.055), and SARA score (OR = 1.078, CI: 1.048–1.110). The presence of cardiovascular disease was predicted by sex (male OR = 1.688, CI: 1.280–2.423), age at onset of FRDA (OR = 0.930, CI: 0.902–0.957), and GAA1 (OR = 1.001, CI: 1.000–1.002). Disorders of accommodation and refraction were less common in male patients (OR = 0.593, CI: 0.415–0.844) and were further predicted by the occurrence of perinatal problems (OR = 3.735, CI: 2.027–7.049), disease duration (OR = 1.024, CI: 1.000–1.048), and SARA scores (OR = 1.038, CI: 1.010–1.067). Higher SARA scores (OR = 1.073, CI: 1.021–1.128) and perinatal problems (OR = 2.990, CI: 1.423–6.063) predicted presence of depression. Finally, higher SARA scores were the only predictor for the presence of any type of diabetes (OR = 1.097, CI: 1.036–1.168).

Pairwise morbidities

To assess the frequency of certain combinations, we calculated pairwise frequencies of diagnoses affecting at least 3% of the sample (figure 2). The most common co-occurrences were observed for nystagmus and irregular eye movements, which co-occurred with no less than 75% of any clinical feature, mostly above 90% and even in 100% of diabetes type 2 cases. The second most common co-occurring feature was scoliosis, which was present in 69% to 96% of cases with other features, except for only 55% of cases with anxiety. Deformities of the feet were also commonly combined with other features, ranging from 42% to 88% of the cases with any given feature. Finally, 60% of patients with anxiety also had disorders of visual refraction and accommodation.

First symptoms at FRDA onset

Instability was the most common first symptom in both the typical- and late-onset groups (77.2%). Scoliosis (23.1%) was the second most common first symptom of FRDA, and falls (19.8%) were the third (figure 3). Diabetes (0.6%) and cardiomyopathy (4.6%) were reported much less frequently. Unspecified other symptoms at onset were reported by 22.3% of patients. Differences in frequency distribution of first symptoms between typical- and late-onset groups failed to reach statistical significance ($\chi^2_5 = 10.369$, $p = 0.065$); however, standardized residuals indicated that cardiomyopathy was more common in the typical-onset group (|Std.Res.| = 2.119), and other unspecified first symptoms more common in the late-onset group (|Std.Res.| = 2.266). Other unspecified first symptoms mainly include motor difficulties and foot deformities.

Discussion

With this work, we provide an exhaustive and accurate description of the clinical phenotype of FRDA. Our study is based on a large European cohort of 650 patients, which was collected through a multicentric study supported by the EFACTS project. On the strength of the considerable sample size and the prospective study design, we could overcome the major limitations that prevent clinical studies in rare diseases from providing robust results. Our data confirm that the most common nonneurologic features of FRDA are abnormal eye movements, skeletal abnormalities, i.e., scoliosis and foot deformity, and hypertrophic cardiomyopathy. It is of interest

Table 3 Logistic regression

Predictor	Odds ratio	95% CI, lower	95% CI, upper	*z*	*p*
Disorders of accommodation and refraction, $\chi^2_6 = 59.574$, $p < 0.001$					
Sex, male[c]	0.593	0.415	0.844	−2.891	0.004
Allele 1	1.000	0.999	1.001	0.224	0.823
Neonatal problems[d]	3.735	2.027	7.049	4.163	<0.001
Age at onset	1.015	0.994	1.038	1.393	0.164
Disease duration[b]	1.024	1.000	1.048	1.992	0.046
SARA[c]	1.038	1.010	1.067	2.654	0.008
Abnormal eye movements, $\chi^2_6 = 46.843$, $p < 0.001$					
Sex, male	0.984	0.533	1.830	−0.050	0.961
Allele 1	1.001	0.999	1.002	0.688	0.491
Neonatal problems	1.089	0.387	3.922	0.148	0.882
Age at onset	1.026	0.992	1.064	1.446	0.148
Disease duration[a]	1.050	0.998	1.110	1.791	0.073
SARA[d]	1.090	1.037	1.148	3.230	<0.001
Scoliosis, $\chi^2_6 = 167.763$, $p < 0.001$					
Sex, male	0.805	0.522	1.238	−0.989	0.323
Allele 1	1.001	1.000	1.002	1.609	0.108
Neonatal problems	0.540	0.253	1.205	−1.558	0.119
Age at onset[d]	0.934	0.910	0.957	−5.246	<0.001
Disease duration	0.990	0.960	1.021	−0.671	0.502
SARA[d]	1.086	1.049	1.124	4.671	<0.001
Urinary dysfunction, $\chi^2_6 = 100.013$, $p < 0.001$					
Sex, male	0.765	0.537	1.087	−1.491	0.139
Allele 1	0.999	0.999	1.000	−1.131	0.258
Neonatal problems	0.902	0.473	1.694	−0.317	0.751
Age at onset[b]	1.025	1.004	1.048	2.277	0.023
Disease duration[b]	1.030	1.006	1.055	2.463	0.014
SARA[d]	1.078	1.048	1.110	5.177	<0.001
Heart disease, $\chi^2_6 = 113.675$, $p < 0.001$					
Sex, male[c]	1.688	1.180	2.423	2.857	0.004
Allele 1[b]	1.001	1.000	1.002	2.388	0.017
Neonatal problems	1.662	0.902	3.118	1.613	0.107
Age at onset[d]	0.930	0.902	0.957	−4.833	<0.001
Disease duration	0.986	0.963	1.010	−1.114	0.265
SARA	1.022	0.995	1.051	1.567	0.117
Deformities of the feet, $\chi^2_6 = 162.185$, $p < 0.001$					
Sex, male	0.856	0.587	1.246	−0.812	0.417
Allele 1[c]	1.001	1.000	1.002	2.621	0.009

Continued

Table 3 Logistic regression *(continued)*

Predictor	Odds ratio	95% CI, lower	95% CI, upper	*z*	*p*
Neonatal problems	1.420	0.702	3.016	0.949	0.343
Age at onset[d]	0.952	0.928	0.975	−3.906	<0.001
Disease duration[b]	1.028	1.001	1.057	2.034	0.042
SARA[d]	1.056	1.026	1.088	3.706	<0.001
Depression, $\chi^2_7 = 46.199$, $p < 0.001$					
Sex, male[a]	0.663	0.404	1.076	−1.648	0.099
Allele 1	0.999	0.998	1.001	−0.970	0.332
Neonatal problems[c]	2.990	1.423	6.063	2.980	0.003
Age at onset[a]	1.026	0.996	1.057	1.730	0.084
Disease duration[a]	1.027	0.997	1.058	1.780	0.075
SARA[c]	1.073	1.021	1.128	2.764	0.006
Wheelchair-bound	0.804	0.352	1.850	−0.581	0.604
Diabetes (both types), $\chi^2_6 = 39.467$, $p < 0.001$					
Sex, male	0.792	0.402	1.532	−0.686	0.493
Allele 1	1.001	0.999	1.003	1.051	0.293
Neonatal problems	2.099	0.775	5.113	1.562	0.118
Age at onset	1.028	0.977	1.079	1.115	0.265
Disease duration	1.029	0.991	1.069	1.496	0.135
SARA[c]	1.097	1.036	1.168	3.033	0.002

Abbreviations: CI = confidence interval; SARA = Scale for the Assessment and Rating of Ataxia.
For each of the logistic regression models, statistical values are given, namely, the odds ratios for each included predictor, the upper and lower bounds of the 95% CI, as well as the results of the Wald test. Significant predictors as follows:
[a] $0.1 \geq p > 0.05$.
[b] $0.05 \geq p > 0.01$.
[c] $0.01 \geq p > 0.001$.
[d] $0.001 \geq p$.

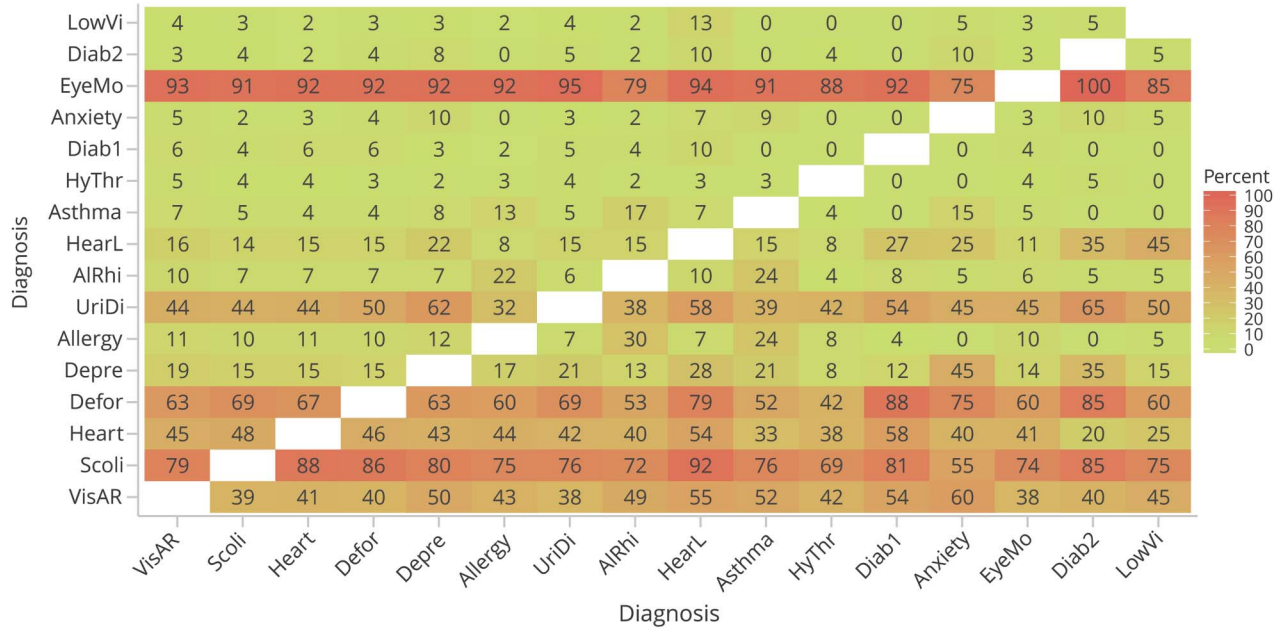
that the prevalence of many other commonly reported morbidities in FRDA, such as depression and diabetes, were only slightly increased or within the same range as in the general population. Major predictors for the presence of nonataxia features were earlier age at onset, more severe ataxia, and longer GAA1 repeats.

The FRDA neurologic phenotype, in addition to gait and limb ataxia, which we measured by SARA, includes as major nonataxia signs progressive, predominantly distal weakness, and distal sensory neuropathy leading to loss of tendon reflexes and perception of vibration. The mixed sensory and cerebellar ataxia is caused by alterations of the proprioceptive pathways in the peripheral nervous system, spinal cord, and nuclei of the cerebellum; the muscle weakness is also related to changes of the pyramidal tracts.

The most frequent nonataxia feature in the studied cohort of patients with FRDA was nystagmus and irregular eye movements, affecting almost the collective sample as it is well known that the entirety of the visual system is involved in FRDA. Several studies reported that 20% to 60% of patients showed gaze-evoked nystagmus, mainly on lateral gaze[15]; however, the most common oculomotor abnormality in FRDA, as also confirmed by the present study, is fixation instability interrupted by voluntary saccades or square wave jerks.[16,17] It is possible that square wave jerks on lateral gaze have been interpreted as gaze-evoked nystagmus, artificially increasing estimates of its prevalence. For the general population, the prevalence of abnormal eye movement, in particular nystagmus, has been estimated to be approximately 0.2%,[18] which is far exceeded by patients with FRDA. Our analysis reveals that its presence seems to be independent of factors such as type of onset, sex, and disease duration. However, logistic regression modeling pointed toward abnormal eye movements being predicted by higher SARA scores.

Scoliosis was the second most frequent nonneurologic feature in FRDA and the second most common first symptom of

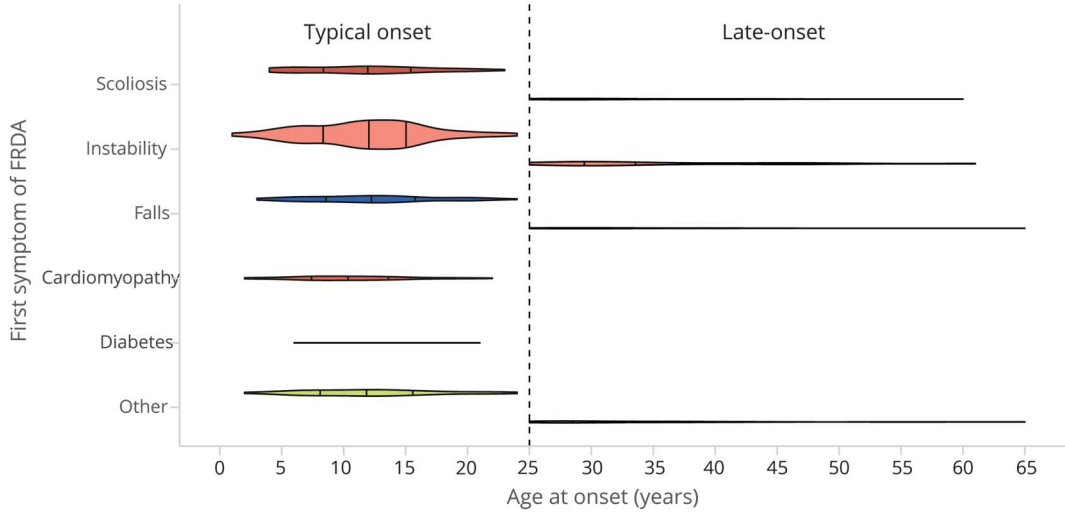
Figure 2 Pairwise co-occurrence of clinical characteristics



For each diagnosis on the x-axis, the number indicates the percentage of patients also having the diagnosis given on the y-axis. Allergy is without allergic asthma, hayfever, and allergic rhinitis. AlRhi = allergic rhinitis; Defor = deformities of the feet; Depre = depression; Diab1 = diabetes type 1; Diab2 = diabetes type 2; EyeMo = irregular/abnormal eye movements; HearL = hearing loss; Heart = heart disease, mainly cardiomyopathy and cardiac hypertrophy; HyThr = hypothyroidism; LowVi = blindness and low vision; Scoli = scoliosis; UriDi = diseases of the urinary system; VisAR = disorders of visual accommodation and refraction.

FRDA, following gait instability. Although scoliosis has always been considered a typical feature of FRDA, its prevalence had been variably estimated to be from 33% to 100%.[1,19–23] The 74% prevalence figure in our cohort is close to the average of the older studies, confirming that scoliosis is highly increased in FRDA compared to the normal population, where its prevalence in infantile and juvenile populations is between 0.19% and 18.7%,[24,25] and up to 13.4% in adults.[26] Foot deformities, mainly bilateral pes cavus, made the second most common nonneurologic feature in FRDA, occurring in 59% of cases. This is close to the lower estimates in older studies, which ranged from 55% to 90%.[1,15,19–22,27] For comparison,

Figure 3 First symptoms of FRDA by age at onset



Distribution of first symptoms at initial presentation of FRDA for typical- and late onset-groups: the thicker the shape at a given point, the more patients presented this symptom at the respective age at onset; vertical lines within each shape represent quartiles. FRDA = Friedreich ataxia.

foot deformities are found in 5.2% of the normal elderly population.[28] Both scoliosis and foot deformities were more common and more severe in the typical- compared to the late-onset group, and were predicted by earlier age at onset and higher SARA scores. In regression analyses, foot deformities were also predicted by longer GAA1 repeats and longer disease duration. Scoliosis and foot deformities were also frequently co-occurring with other clinical abnormalities, such as cardiac impairment, hearing loss, or diabetes. Although the pathogenesis of neuromuscular deformities is complex and less addressed, this highlights the clinical relevance of musculoskeletal symptoms in FRDA, so clinicians should be aware and screen for such associations.

Clinical features affecting the urinary system, including urinary incontinence, hesitance, and retention, were found in about 42% of patients with FRDA in the EFACTS cohort. It is assumed that the underlying mechanisms for urinary disturbances are multifactorial, as the disease involves central and peripheral pathways of the nervous system. This clinical finding was not different between typical- and late-onset patients and is in line with the previous reports.[20,21] Their presence was predicted by both higher age at FRDA onset and longer disease duration, implying that they become more common with higher age, which is generally consistent with the FRDA literature,[29] and higher than in the normal population. In addition to age at onset and disease duration, the presence of clinical features affecting the urinary system was predicted by SARA scores, showing that this feature is more likely the more severely a person is affected by disease.

Heart disease in FRDA is of critical clinical relevance. Hypertrophic cardiomyopathy is a recognized cause of premature death in FRDA, by arrhythmia or cardiac failure, reducing life expectancy to 29 to 38 years.[2,19,30,31] The pathogenesis of cardiomyopathy in FRDA involves a severe reduction of cardiac frataxin levels, iron accumulation, and inflammatory mechanisms.[32] Again, previous prevalence data for hypertrophic cardiomyopathy or left ventricular hypertrophy are quite heterogeneous, ranging from 28% to 100%.[1,15,19,21,22,27] In the EFACTS cohort, about 40% of patients with FRDA presented cardiac involvement, mainly left ventricular hypertrophy. The prevalence of hypertrophic cardiomyopathy in a general population of young adults is approximately 0.17%.[33] Cardiac-related symptoms (cardiomyopathy and cardiac hypertrophy) were more frequent in the typical-onset group and associated with earlier age at onset, strongly supporting the notion that cardiac symptoms may develop early in the course of the disease. However, some cardiac-related symptoms, such as increased blood pressure in the late-onset group, were highly likely the consequence of aging and not directly FRDA-related. In addition, a higher number of GAA repeats and male sex were predictors for the presence of heart disease, while ataxia severity measured by SARA was not, confirming the notion that cardiomyopathy and neurologic diseases evolve independently, as previously reported.[34] In the clinic, our results underline the importance of regular cardiologic follow-ups of patients with FRDA.

With a prevalence of 37%, visual problems (abnormal eye movements) were a further most common nonataxia feature in the EFACTS cohort. The entire visual system may be affected in FRDA. Decreased visual acuity had been previously reported in approximately 20% of patients.[1,19,35] Disorders of accommodation and refraction may just be comorbidities rather than FRDA-related features, considering that the frequency of occurrence of these features reported herein is close to that previously reported for the general population.[36] According to logistic regression analysis, the presence of these features was associated with female sex, history of perinatal problems, and higher SARA scores.

Depression was diagnosed in 14% of all patients with FRDA. This number is only slightly higher than the general population prevalence rate of about 8.5% in Europe, with women being more frequently affected than men.[37] It may be surprising that depression is not more prevalent in such a severe and chronic disease affecting young individuals. Rates reported in previous studies are extremely variable, ranging from high estimates of 92% of patients with FRDA showing an affective disorder with mild mood disturbances, or even 36.3% with major depression,[38] down to 8%.[39] Methodology is likely to be an important issue in assessing depression. Whereas in this study we only considered cases with an established clinical diagnosis of depression, some previous studies used questionnaires for the assessment of depressive symptoms, but their results are also quite divergent, reporting either no difference or increased scores in patients with FRDA compared to controls.[40–42] Despite some controversial findings, overall data suggest that depression and affective disturbances are not a common feature in individuals with FRDA, in strong contrast to other neurodegenerative diseases.

The prevalence of diabetes in the normal population depends on age. Among children and adolescents, prevalence rate estimates are 0.3% for type 1 and 0.06% for type 2,[43] while type 2 affects 6.4% of adults.[44] In our FRDA cohort with a mean age of 34 years, type 1 diabetes was reported in 4%, exclusively in typical-onset FRDA, and diabetes type 2 in about 3% in both onset groups. Overall, this is at the lower end of what had previously been reported for diabetes in FRDA, ranging from 6% to 19% of the cases,[1,15,20–22,45] increasing to 32% when cases of impaired glucose tolerance are added.[19] However, this is mainly in line with a recent published work about the relevance of diabetes in FRDA in an American cohort presenting 9% of adults and 3% of children with diabetes.[46] Of note, the only predictor for the presence of diabetes in patients with FRDA was higher SARA scores. Thus, we failed to confirm previous work showing associations between diabetes and the size of GAA trinucleotide expansion in the *FRDA* gene,[21,47] longer disease duration, and a younger age at onset.[21] We have no explanation for the lower prevalence of diabetes in our cohort, which may explain

the other discrepancies. Underdiagnoses is not very likely, but not excluded, mandating continuing follow-up of glycemic parameters. However, the mechanism of the association between FRDA and diabetes is still not clear but may relate to a combination of insulin resistance of peripheral tissues, decreased insulin secretion resulting from pancreatic beta cell dysfunction, and mitochondrial dysfunction.[48]

Hearing loss due to auditory neuropathy affected about 11% of the EFACTS cohort, which is in approximate agreement with the lower estimates from earlier studies, reporting a range between 8% and 39%.[1,19,20,27] Bladder dysfunction had a prevalence of about 8.2% in our series, mainly involving urinary urgency and incontinence, making it less frequent than reported in previous work.[19–21] However, 42.9% of the total cohort reported abnormalities in the INAS regarding urinary dysfunction. This demonstrates the importance of these measures to also investigate first abnormalities and that, again, underdiagnoses cannot be excluded, as data from the present study came from medical history rather than direct assessment. A recent study with a specific questionnaire to FRDA patients showed that up to 80% of patients reported lower urinary tract disorders, 64% bowel symptoms, and 83% sexual symptoms; here urinary dysfunctions were more frequent in late-onset FRDA patients and on those with longer disease duration (Lad et al., 2017).[49] We did not find other pathologies to be overrepresented in our FRDA cohort compared to estimates in the general population. Of note, in a similar American cohort of 641 patients with FRDA, 10 patients (1.6%) had inflammatory bowel disease, a 3.5 times higher prevalence than in the general population,[50] but we could not confirm this finding. Methodologic issues, though not immediately apparent, may be involved here as well. In any case, further investigations of possible comorbidities of FRDA are needed, which may shed light on unexpected shared pathogenic mechanisms.

Although the key strength of our study is the detailed characterization of such a large cohort of patients with FRDA, our study has some limitations. Identification of most clinical features relied on self-report of symptoms and previous medical diagnoses by patients, resulting in an inconsistent level of detail in the available data. We tried to overcome this issue by standardization of diagnoses according to ICD-10, but this procedure might have caused additional blurring of data. We identified predictors for the most common nonataxia features of FRDA, but with the present data, we cannot determine when and to what extent these symptoms typically evolve over the course of the disease. A more detailed analysis of the clinical onset of FRDA, including the occurrence of more subtle signs and symptoms, would be highly desirable, particularly with the perspective of therapeutic trials targeting the very early stages of the disease. Finally, here we reported cross-sectional baseline data, which do not allow conclusions on the progression of clinical features over time.

This large European FRDA cohort study represents a further step toward a deeper understanding of this rare devastating disease. It provides a comprehensive characterization of the FRDA phenotype, with distinct differences between typical-onset and late-onset patients, and identifies predictors for highly relevant clinical symptoms. This knowledge is critical for clinical practice as well as for trial design, where the multisystem nature of FRDA challenges the use of merely one-dimensional outcome measures.

Author contributions

All authors gave final approval of the version to be published and take responsibility for the conduct of the research. Kathrin Reetz: acquisition of data, study concept and design, analysis and interpretation of data, drafting the manuscript, reviewed and revised the manuscript. Imis Dogan: study concept and design, analysis and interpretation of data, drafting the manuscript, reviewed and revised the manuscript. Christian Hohenfeld: study concept and design, analysis and interpretation of data, supervision, reviewed and revised the manuscript. Claire Didszun: acquisition of data, supervision, reviewed and revised the manuscript. Paola Giunti: principal investigator (PI) of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Caterina Mariotti: PI of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Alexandra Durr: PI of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Sylvia Boesch: PI of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Thomas Klopstock: PI of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Francisco Javier Rodríguez de Rivera Garrido: PI of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Ludger Schöls: PI of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Ilaria Giordano: acquisition of data, supervision, reviewed and revised the manuscript. Katrin Bürk: PI of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Massimo Pandolfo: PI of EFACTS, acquisition of data, supervision, reviewed and revised the manuscript. Jörg B. Schulz: PI of EFACTS, study concept and design, acquisition of data, supervision, reviewed and revised the manuscript. EFACTS Study Group: acquisition of data, supervision, reviewed and revised the manuscript.

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