Genetic data and natural history of Friedreich’s disease: a study of 80 Italian patients

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Summary. The clinical and genetic features of 80 patients with Friedreich’s disease from 64 families are described. Diagnostic criteria were: no evidence of dominant inheritance, onset by the age of 20 years, progressive unremitting ataxia of limbs and gait, and absence of knee and ankle jerks. Furthermore, at least one of the following accessory signs was present: dysarthria, extensor plantar response and echocardiographic evidence of hypertrophic cardiomyopathy. Two peaks of onset age were evident at 6–9 and 12–15 years. Analysis of intrafamily variation of onset age and absence of clustering of cardiomyopathy and diabetes did not suggest genetic heterogeneity. Peripheral nerve impairment was an early finding and showed slight further progression, whereas involvement of the cerebellar and corticospinal pathways appeared later and mainly accounted for the progressive worsening of the disease.

Key words: Spinocerebellar degeneration – Friedreich’s disease – Diagnostic criteria – Genetics – Natural history

Introduction

Nicolaus Friedreich [17] described a familial disorder characterized by early-onset ataxia and dysarthria, and late sensory loss and muscle wasting. Varying degrees of weakness were present, and nystagmus was an occasional feature. Moreover, he noted the presence of scoliosis, foot deformity and cardiac symptoms. After Erb’s paper on tendon reflexes [15], Friedreich [18] reported areflexia in his patients. For this entity Brousse [3] proposed the term Friedreich’s ataxia. However, Barbeau [2] suggested the title Friedreich’s disease (FD), since ataxia is not even a principal feature.

FD is the commonest form of hereditary ataxia, comprising about 50% of cases in large series [22, 34]. Birth incidence has been estimated to be from 2.1 to 5.4 x 10⁻⁵ in the United Kingdom [36] and from 3.6 to 4.0 x 10⁻⁵ in southern Italy [31]. In the past the term FD has sometimes been used inappropriately, even to include patients with increased tendon reflexes. Geoffroy et al. [19] and Harding [21] defined the diagnostic criteria for FD in 36 and 115 patients, respectively. Both authors considered as obligatory criteria recessive inheritance, progressive ataxia of limbs and gait and lower limb areflexia. They considered as frequently occurring, but not essential, extensor plantar response, skeletal deformities and cardiomyopathy. According to Geoffroy et al. [19] the onset never occurs after the age of 20 years, and always before 25 according to Harding [21]. Dysarthria, decreased lower limb deep sensation and weakness are obligatory signs for Geoffroy et al. [19], whereas for Harding [21] these are not essential for an early diagnosis, although they eventually develop in all cases.

Data of intrafamily variation of onset age and age of becoming wheelchair-bound suggest that FD may be genetically heterogeneous, even when strict diagnostic criteria are applied [36]. Chamberlain et al. [9] recently concluded from a study of 22 families that the mutation causing FD maps to human chromosome 9p22-CEN, and found no evidence of genetic heterogeneity. This finding also appeared in the milder Acadian form [10].

Disease progression is another question open to debate. Ouvrier et al. [28] suggested that axon loss in the peripheral nerve may increase with age. In contrast, Caruso et al. [7] suggested that disturbances due to peripheral nerve degeneration appear first and do not progress during the disease and that further clinical worsening may result from progressive impairment of the cerebellar and corticospinal pathways.

In this paper we describe the clinical and genetic features of 80 patients from 64 families. A genetic analysis was performed to investigate the possibility of genetic heterogeneity. The clinical data of the patients were compared with those reported by Geoffroy et al. [19] and by Harding [21]. We also studied the progression of signs and symptoms during the disease.
Patients and methods

Eighty patients affected by FD, examined since 1973 at the Department of Neurology of the Second School Medicine, University of Naples, were included in this study. FD represented 44% of all index cases of inherited ataxias and 67% of the early-onset forms.

A detailed history was taken in each case. Each patient was examined by at least one of the authors. The diagnosis of FD was made according to the following criteria: no evidence of dominant inheritance, onset by 20 years of age, progressive unmitting ataxia of limbs and gait, and absence of knee and ankle jerks. Furthermore, at least one of the following signs was present: dysarthria, extensor plantar response and echocardiographic evidence of hypertrophic cardiomyopathy. We also included in this series 1 patient with an apparently later onset (23 years), whose sister’s onset was at 18, and 2 brothers with normal speech, plantar response and echocardiogram, whose elder brother had the fully developed disease.

Peripheral motor and sensory conduction velocity investigations, performed in all but 11 patients, showed a markedly reduced amplitude of sensory response and a moderate slowing of conduction velocities, indicating a loss of the largest nerve fibres. Fourteen of the patients underwent sural nerve biopsy, which revealed a severe loss of the large-diameter fibres and a predominance of fibres with uniformly short internodes [7, 8].

Nine additional patients fulfilled the above criteria with the sole exception of an onset age later than 20. These patients have been described previously [12] and were not included in this study.

Severity of disease was scored according to the Inherited Ataxia Progression Scale (IAPS) [4]: stage I, asymptomatic affected sibling; stage II, symptoms present but mild; stage III, patient needs constant care and cannot work; stage IV, patient confined to wheelchair. In addition, signs were scored according to the Inherited Ataxia Clinical Rating Scale (IACRS) [4], the maximum score on which is 38 (see Table 1). Disability was scored according to the Northwestern University Disability Scale (NUDS) [6].

Statistics

The segregation ratio was calculated assuming multiple incomplete ascertainment (Weinberg’s “proband” method) according to Emery [14]. Genetic heterogeneity was tested using the Kruskal-Wallis test and Spearman correlation coefficient of onset age between sibs and by examining the concordance of some accessory signs within sibships by chi-square corrected according to Yates. Different occurrence of findings in the stages of the disease was evaluated by chi-square. Departure from normality of the frequency distribution of onset age was tested by chi-square [35].

Results

General features

Of the 80 patients, 48 were male and 32 female. Sex distribution was not significantly different from that expected for an autosomal recessive disease (Yates’ chi-square = 2.81). Patients were from 64 families, 59 of them from southern Italy. An additional 11 sibs were reported in records to be affected, but they were unavailable for the study and were not considered.

Mean age (SD) at the time of the last examination was 25.0 (10.1) years (range 8–55). Two patients died at the age of 10 and 17 respectively; both were cardiopathic and one was also diabetic. The mean onset age was 11.6 (4.5) years (range 2–23). The mean follow-up period was 3.7 (3.5) years, the longest being 14 years.

Table 1. Inherited ataxia clinical rating scale (IACRS) [4] (modified version for Friedreich’s disease)

For all items the score 0 = normal or absent

1. Speech: 1 = mild dysarthria at test sentences
   2 = slowed and/or irregular, understandable
   3 = staccato and/or explosive, difficult to understand
   4 = not understandable

2. Coordination test
   a. Finger-to-nose test:
      1 = slight dysmetria, but well centred
      2 = marked dysmetria (the patient does not centre the target)
   b. Heel-to-knee test:
      1 = slight dysmetria
      2 = marked dysmetria, or test impossible

3. Gait ataxia:
   1 = gait possible without support, but with disbalance
   2 = gait possible but sometimes needing support
   3 = gait possible only with constant support
   4 = gait impossible

4. Stance ataxia:
   0 = no swaying with eyes closed and head in extension
   1 = no swaying only with eyes open and head straight
   2 = swaying with eyes open and head straight
   3 = standing possible with broad base and swaying
   4 = impossible

5. Nystagmus:
   1 = evoked
   2 = spontaneous

6. Hypotonia:
   a. Arm-pulling response:
      1 = present (the fist does not hit the thorax)
      2 = marked (the fist hits the thorax)
   b. Hypotonia:
      1 = in lower limbs only
      2 = in upper and lower limbs

7. Muscle strength
   a. At upper limbs:
      1 = weakness against resistance
      2 = weakness against gravity
   b. At lower limbs:
      1 = weakness against resistance
      2 = weakness against gravity

8. Tendon reflex
   a. In upper limbs:
      1 = reduced
      2 = absent
   b. In lower limbs:
      (score as for upper limbs)

9. Babinski sign:
   1 = no response from the big toe
   2 = Babinski
   3 = flexion reflex
   4 = spontaneous Babinski

10. Vibratory sense (at styloid apophysis of radius bone and external malleolus)
   a. At upper limbs:
      1 = decreased (sensation time under 11s, with 128 Hz tuning fork)
      2 = absent
   b. At lower limbs:
      (score as for upper limbs)

The score in bilateral tests is the average of right and left sides.