Quebec Cooperative Study of
Friedreich's Ataxia

Clinical Description and Roentgenologic Evaluation of Patients with Friedreich's Ataxia

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SUMMARY: *The 50 patients in this survey were classified by a panel of neurologists into 4 clinical sub-groups: Group Ia ("typical" Friedreich's ataxia, complete picture), Group Ib ("typical" Friedreich's ataxia, incomplete picture), Group IIa ("atypical" Friedreich's ataxia, possible recessive Roussy-Levy syndrome), Group IIb (heterogeneous ataxias). The clinical symptoms and signs were analyzed for each of these groups. A constellation of signs constantly present in Friedreich's ataxia and obligatory for diagnosis was described. Other important symptoms, such as the Babinski sign, kyphoscoliosis and pes cavus were found to be progressive, but not essential for the diagnosis at any given time. Finally, a host of other symptoms can only be called accessory. The progression of scoliosis was found to be an important tool in the differential diagnosis of ataxias. Our study also indicates, in contrast to the opinion of some authors, that absent deep tendon reflexes in the lower limbs and early dysarthria are essential in "typical" Friedreich's ataxia.*

RÉSUMÉ: *Les 50 patients inclus dans cette revue furent classifiés par une équipe de neurologues en 4 sous-groupes distincts: Group Ia (ataxie de Friedreich "typique", tableau complet), Groupe Ib (ataxie de Friedreich "typique", tableau incomplet), Group IIa (ataxie de Friedreich "atypique — possibilité d'un Roussy-Levy récessif), Group IIb (hétérogène), Les symptômes et signes cliniques furent étudiés dans chacun des groupes de patients. Nous décrivons une constellation de signes et symptômes constamment présents dans l'ataxie de Friedreich et obligatoires pour le diagnostic. D'autres importants symptômes, tels le signe de Babinski, la cyphoscoliose et le pes cavus, s'avèrent être progressifs mais non essentiels pour le diagnostic à un moment précis. Finalement, il existe une grande variété de symptômes accessoires. La progression de la scoliose s'est avérée être un important outil dans le diagnostic différentiel des ataxies. Notre étude montre également, contrairement à l'opinion de certains auteurs, que l'absence des réflexes ostéo-tendineux aux membres inférieurs et une dysarthrie précoce sont deux nécessités dans l'ataxie de Friedreich "typique".*

One of the most difficult tasks for the clinician is to give a precise definition of the symptomatology obligatory for making a definite diagnosis. This is particularly so for the hereditary ataxias where intermediate and atypical forms seem to outnumber the classical presentation. Although the description of all the clinical aspects of Friedreich's ataxia has been given in detail by numerous authors, few have attempted to outline the minimal and essentials signs which must be present early to be considered pathognomonic of the disease. For example, Tyrer (1975) states "many neurologists would at least hesitate to diagnose Friedreich's ataxia clinically in the presence of exaggerated deep reflexes". while Greenfield (1954) contends that "their retention does not exclude the diagnosis, for loss of tendon reflexes might be gradual or they might be retained in some affected members of a family and lost in others". It is evident that the decision whether deep tendon reflexes must be abolished early in the disease has great significance in attempts to understand the pathophysiology of the illness. If these reflexes can be either abolished or exaggerated once the disease is full blown, it is difficult to imagine that we are dealing with a unique primary pathological mechanism. On the other hand, if absent deep tendon reflexes are an early development, before the appearance of most other symptoms, we would be justified in searching for early histological and chemical damage along the peripheral reflex arc.

Clear-cut clinical limits to de-

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lineate Friedreich's ataxia are needed to focus the biochemical search upon the patients most similar. There is both a difficulty and a paradox in this approach. Before the exact biochemical cause of a disease is known one is obliged to study as homogeneous a group of patients as possible, while once the enzymatic defect has been characterized, the clinical heterogeneity of the group has little importance. Unfortunately, at the start of this study we were totally ignorant of any possible biochemical defect in Friedreich's ataxia, while at the same time convinced that the label hid a collection of similar but etiologically different entities. Therefore, we had only two guidelines: the spectrum of signs observed within individual family units and the core symptoms seen in 100% of patients within a short time after the onset of the illness. In the present paper we will attempt to analyze our complete material (50 patients) in the light of these two guidelines, in order to permit later classification of the biochemical and physiological results.

SUBJECTS AND METHODS

Fifty patients with spinocerebellar degeneration were accepted into the study. The only criterion finally agreed to was that the diagnosis of Friedreich's ataxia had been made by two certified neurologists, one of which could be the investigator (prior to the start of this survey). Once accepted, the patients were hospitalized in one of the three services and submitted to the full list of examinations included in the detailed protocol. The complete neurological examination record sheet of the Mayo Clinic was used for grading. This was supplemented by a functional evaluation (studying general motor function, locomotor independence, equilibrium at rest and during walking, and coordination), an adaptation of the Norwestern Scale Evaluation for walking, dressing, hygiene, eating, elocution, writing and standing from a chair, and finally a complete evaluation of individual muscles which was conducted by the physiotherapy department. For each patient, a full genetic, genealogic and epidemiological survey was also carried out as well as cinematography following a standard protocol. In the course of hospitalization, a detailed ophthalmological examination was conducted by an ophthalmologist according to a set protocol and the patients were also seen by the psychologist for evaluation.

When all 50 patients had been completely investigated, but before compilation of the paraclinical and biochemical data, a panel of 15 neurologists (including the three main investigators) was convened. The full history and clinical presentations of each patient was reviewed with the help of the movie film. The members of this panel were asked to write their own list of criteria necessary for making the diagnosis of Friedreich's ataxia, based on their own experience, judgment and knowledge of the literature. All siblings of a single family group were presented consecutively. Each patient was then "diagnosed" individually, and confidentially, by each member according to his own criteria of Friedreich's ataxia, "typ-

TABLE 1

CHARACTERIZATION OF PATIENT GROUPS

(mean ± S.D.)

		GROUP Ia	GROUP Ib	GROUP IIa'	GROUP IIb
N		33	3	6	8
Sex	F	21	3	5	1
	M	12	0	1	7
Age at onset	F	7.05 ± 2.80	5.0 ± 0.0	10.20 ± 4.02	—
	M	10.33 ± 3.31	—	(15.0)	5.87 ± 3.18
	Both sexes	8.24 ± 3.35	5.0 ± 0.0	10.83 ± 4.09	5.62 ± 3.02
Duration of disease at time of study	F	13.67 ± 7.25	7.0 ± 6.0	15.6 ± 3.28	—
	M	9.5 ± 6.40	—	—	7.86 ± 4.63
	Both sexes	12.15 ± 7.13	7.0 ± 6.0	18.5 ± 7.68	9.0 ± 5.37
Mean age at time of exam	F	20.67 ± 8.57	12.0 ± 4.36	25.8 ± 4.15	—
	M	20.06 ± 5.34	—	—	13.71 ± 2.87
	Both sexes	20.42 ± 7.47	12.0 ± 43.6	29.5 ± 9.79	14.62 ± 3.70

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ical or atypical" or any other diagnosis which appeared more probable. When unanimity of diagnosis was not attained, open discussion took place and was followed by another concensus vote. In this way 4 groups of patients were delineated clinically from the original 50 subjects. These groups which will be retained for all further analysis were:

		No. cases
Group Ia:	"Typical" Friedreich's ataxia — Complete picture	33
Group Ib:	"Typical" Friedreich's ataxia — Incomplete picture	3
Group IIa:	Atypical Friedreich's ataxia — Possible autosomal recessive Roussy-Levy syndrome	6
Group IIb:	Not Friedreich's ataxia — Other diagnosis proposed	8

This classification, unanimously agreed to by the panel does not take into account, and will be confronted with, both paraclinical and biochemical findings. From the outset we realized that even the "typical cases with a complete picture" probably encompasses different pathogenic entities, but a clinical concensus was essential before attempting a biochemical classification.

RESULTS AND DISCUSSION

Using the above classification, we analyzed the patterns of clinical symptoms and signs to see if minimal absolute criteria necessary for diagnosis could be delineated and to compare our findings with the literature (Tyrer, 1975).

a) *Sex distribution*

The distribution of male and female cases was quite uneven (Table 1). In Groups Ia and Ib, females outnumber males 2:1. This is also true for Group IIa, while the reverse situation obtains in Group IIb. Our findings are similar to those of Friedreich (1876), 7 of whose 9 patients were female. However, Bell and Carmichael (1939) found an equal distribution between males and females amongst 472 published cases (not personally verified). Tyrer and Sutherland (1961) in 13 cases had 8 females. Finally, Hewer (1968) amongst the 82 autopsies of Friedreich's ataxia he reviewed, found 38 females and 44 males. Unless there are specific modifying factors, or heterogeneity of the group, one would not expect any sex differences in a recessively inherited disease.

b) *Age of onset*

The exact age of onset is always difficult to establish. This is especially so when the patients are first seen at an older age. From Friedreich's paper (1876), onset about the time of puberty has been suggested. Most authors (Bell and Carmichael, 1939; Mollaret, 1929; Sjögren, 1943; Wilson, 1954; Greenfield, 1954; Tyrer and Sutherland, 1961; Brown, 1962; Dyck and Lambert, 1968; Brain and Walton, 1969) agree that the age of onset is before 20 or at the latest 25, although most cases start between 7 and 15 years of age. In our study (Table 1) the mean age of onset for group Ia is 8.24 ± 3.35. It is slightly later (10.83 ± 4.09) in group IIa, while group IIb cases start younger (5.62 ± 3.02). In no instance did the onset occur after age 16. An unexplained finding is the significantly lower age of onset in females in Group Ia. This is reflected in the longer duration of the disease at time of examination since the mean age of both sexes at that time is identical. Such variations may partially explain the apparently greater severity of the illness in female patients in our study as judged by motor performance tests and clinical examination. In conclusion, we think that true Friedreich's ataxia must always be clinically manifest before the end of puberty (i.e., at the vest latest before age 20).

c) *Frequency of neurological signs and symptoms*

Table II lists the percentage occurrence of the most common signs and symptoms in the clinical subgroups. It is seen that some symptoms are constant (i.e., present in 100% of cases) in typical Friedreich's ataxia. Such symptoms occur within the first year of the disease. These signs and symptoms are:

1) *Ataxia of gait:* This is the earliest finding in all reported series. Clumsiness in running, frequent stumbles and awkwardness in walking can be seen at 4 and 5 years of age. Since cerebellar ataxia requires a certain level of maturation of the nervous system for its full expression, it is not surprising that it is not recognized much before age 3. However, the first hints of truncal ataxia may be suspected soon after the infant begins to sit without support at 7-9 months and attempts standing at 8-10 months. Thus, in agreement with Heck (1964), we find that ataxia is the sine qua non of Friedreich's disease. Furthermore, progression of the ataxia to all extremities without a remission was the rule in all our typical cases of Friedreich's. Never was ataxia in the four limbs absent after 2 years of development of the disease.

2) *Areflexia* (absent deep tendon reflexes) in the lower limbs (knee jerk and Achilles tendon) was found in all our typical cases, and in all the 50 patients studied. Investigations of other forms of ataxia, for example the dominant form of spinocerebellar degeneration, revealed normal or exaggerated deep tendon reflexes and this was almost constant in familial spastic paralysis (Strümpell's disease). We differ from the findings of Bell and Carmichael (1939), corroborated in part by Greenfield (1954), who both accepted the presence of exaggerated reflexes in this disease. The confusion probably derives from the fact that these previous studies are of the retrospective type, and most likely include a variety of entities. Moreover, we refer here to areflexia of the lower limbs, but in these patients it is possible to have normal, or only slightly decreased deep tendon reflexes in the upper limbs. In conclusion, we would not accept the diagnosis of typical Friedreich's ataxia in a patient who, after 2 years of disease, still has deep tendon reflexes in the lower limbs.

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TABLE 2

NEUROLOGICAL SIGNS AND SYMPTOMS IN PATIENT GROUPS

(% OF TOTAL NUMBER)

	GROUP Ia	GROUP Ib	GROUP IIa	GROUP IIb
N	(33)	(3)	(6)	(8)
1) Ataxia of gait	100	100	100	100
2) Progression of ataxia in last 2 years	100	100	16.7	66.7
3) Areflexia in lower limbs (deep tendon)	100	100	100	100
4) Dysarthria	100	100	100	37.5
5) Post. column signs in lower limbs	100	100	100	62.5
6) Muscle weakness	100	100	83.3	75.0
7) Extensor plantar signs	96.9	66.7	100	100
8) Pes Cavus	96.9	0.0	100	75.0
9) Scoliosis > 10^{o} (minimum 11^{o}) (0-10^{o} is "normal")	90.9	100	33.3	0.0
10) Nystagmus	42.4	33.3	33.3	0.0
11) ↓ visual acuity (optic atrophy)	45.4	100	66.7	0.0
12) Paresthesias	30.3	0.0	50.0	25.0
13) Essential type tremor	24.2	0.0	66.7	12.5
14) Deafness (partial)	24.2	0.0	16.7	21.5
15) Vertigo	21.2	0.0	50.0	12.5
16) Spasticity	15.1	0.0	0.0	0.0
17) Pain	6.1	0.0	16.7	12.5
18) Cardiopathy	96.9	100	100	37.5

3) *Dysarthria* was mentionned as an early and essential symptom by Friedreich (1863) in all of his 9 patients. It was equally constant in the patients surveyed by Bell and Carmichael (1939), but was not a major feature of those reported by Tyrer and Sutherland (1961) nor in those of Dyck and Lambert (1968). We found it present within the first two years of evolution in all our patients from Groups Ia, Ib and IIa. Only in Group IIb was it generally not a feature. It is probable that the damage in the latter group is mainly spinal or peripheral, while in the former groups the cerebellum is also partially involved. An extremely useful analysis of ataxic dysarthria has been given by Brown and collaborators (1970).

4) *Posterior column signs in the lower limbs* are also constantly present (Table 2). Proprioception and/or vibratory senses were diminished or abolished in all our cases early in the disease. In this, we concur with Saunders (1913), Wilson (1954), Heck (1964) and most other authors.

5) *Muscle weakness* with or without hypotonia is equally frequent as the disease advances. It is constant (100%) in Group I, but not in Group II.

Less constant than the above-listed primary signs and symptoms are a group of findings present in over 90% of patients, and clearly progressive in nature. These secondary signs are not obligatory for the diagnosis, but eventually they will appear in each of the cases:

1) *Extensor plantar responses* (Babinski sign) will probably always appear within the first five years of the disease. The only two patients without bilateral Babinski signs are the two youngest in our series, a girl 7 and a girl 8, both examined within the first year of their disease, one each in Groups Ia and Ib.

2) *Pes Cavus*, a dystonic posture of the foot secondary to the weakness and hypotonia, was found in all but one patient, a 13 year old girl in Group Ia, It was also absent in a few cases in Group IIb. Interestingly, 3 sisters (Group Ib) who otherwise have all the signs and symptoms of typical Friedreich's ataxia have no evidence of pes cavus. Rather, flat feet are seen even in the oldest girl, 15, after 13 years of progressive ataxia. In all other cases retrospective analysis clearly indicates that the pes cavus is evolving into a progressively more severe form. This sign can be found alone in otherwise unaffected members of the family.

3) *Kyphoscoliosis:* The most evident progressive symptom is scoliosis or kyphoscoliosis. It was noted by Friedreich (1863) and in various proportions (56% to 88%) by subsequent authors (Greenfield, 1954; Heck, 1964). The angle of scoliosis was measured according to the methods of Cobb (1948) or Ferguson (1945) and expressed in degrees. This was based on a study of an anterior - posterior (AP) view of the spine with the patient erect when possible. Otherwise, an AP view of the spine with the patient supine was done.

Some kyphoscoliosis, usually of the mid-thoracic region was found in all 36 patients with typical Friedreich's ataxia. No congenital malformation or acquired lesion of the spine was noted. The average degree of scoliosis was 37.8°. The 14 patients with atypical recessive ataxia showed a mild deformity averaging 8° (Table 3). As is common in other types of idiopathic or neuromuscular scoliosis, most of the patients with Friedreich's ataxia had a right-sided convexity to their scoliosis. These results are compatible with previous reports: Boyer (1962), Hartman (1960), Schilero (1952), Thoren (1964), Tyrer (1975).

If we define as abnormal anything at or above 11°, all but three patients in Groups Ia and Ib have abnormal scoliosis, whereas fewer than 33% of patients are affected in Groups IIa and IIb. This difference may be one of the most important differential signs. Of the three patients with probable Friedreich's ataxia and less than 10° of scoliosis (Groups Ia, Ib), two had been operated on for correction of this defect. The other, with a scoliosis of 5°, was in his second year of the disease. When the deformity was classified into three grades of severity for the typical Friedreich's ataxia cases we found the following distribution (Table 4): slight (0-20°): 12 patients; moderate (20-40°): 7 patients; and severe (> 40°): 17 patients. In general, patients with early onset and long evolution of the disease showed the most severe deformities (Table 4 and Figure 1). We concluded that a progressive scoliosis is an essential feature of Friedreich's ataxia. Such progression, with years of disease, is illustrated in Figure 2. It can also be seen here that lack of progression is characteristic of the atypical Friedreich's syndrome or the other types of spinocerebellar degeneration.

Finally, there is a group of signs and symptoms which appeared in only a few instances. Because they are not common, these symptoms can only be called accessory. Amongst these are: a decrease in visual acuity (which we found to be almost always due to partial optic atrophy), nystagmus, paresthesias, partial deafness, a tremor of the essential type, vertigo, spasticity and occasional pains in the lower limbs. Mention should be made here of the relatively high incidence of optic atrophy, essential tremor and paresthesias in Group IIa, thought at present to be a recessive variant of Roussy-Levy disease.

Equally well known as part of the syndrome of Friedreich is a progressive cardiomyopathy (see infra). The evaluation of heart size is difficult on plain films of the chest, especially when scoliosis is present. Previous studies showed an incidence of cardiomegaly on plain films varying between 10% and 50% (Boyer, 1962; Gach, 1971; Nadas, 1951; Schilero, 1952; Soulie, 1965 and Thoren, 1964). Our study shows cardiomegaly, of a slight to moderate degree, in 12 of the 36 patients with "typical" Friedreich's ataxia, but cardiac size always within normal limits in the atypical group of patients (Figure 3).

Mention should be made of the brief study of intelligence testing.

TABLE 3

RADIOLOGICAL FINDINGS IN FRIEDREICH'S ATAXIA

	Mean Age (in years)	Mean Duration of illness	Number of Scoliosis	Convexity		Average Degree of Scoliosis	Slight to Moderate Cardiomegaly
				Right	Left		
"Typical" Friedreich's ataxia Groups Ia, Ib.	19.83	12.0	36/36 (100.0%)	27	9	37.8°	12/36 (33.3%)
Atypical Friedreich's ataxia Groups IIa, IIb	21.0	13.1	9/14 (64.3%)	7	2	8°	0/12

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TABLE 4

SEVERITY OF SCOLIOSIS IN FRIEDREICH'S ATAXIA

Grade	Degree	Number of patients	Mean	
			Age at onset (in years)	Duration of illness (in years)
Slight	0-20°	12	7.7	8.5
Moderate	20-40°	7	10.3	7.0
Severe	> 40°	17	6.2	15.1

TABLE 5

VERBAL I.Q. SCORES IN FRIEDREICH'S ATAXIA

	GROUP I		GROUP IIa		GROUP IIb	
	N	I.Q. Score	N	I.Q. Score	N	I.Q. Score
A) RESULTS						
Male	7	104.0 ±	—	—	3	78.6 ±
Female	13	83.0 ±	5	86.6 ±	—	—
Both sexes	20	90.35±	—	—	—	—
B) NO. CASES < 90						
Male	0		—		2	
Female	7		2		—	
Both sexes	7		2		2	

Unfortunately, such an analysis could only be carried out in 28 of our 50 patients, and in an incomplete way. As reviewed by Tyrer (1975), Bell and Carmichael (1939) found that while the mental faculties might be unimpaired and even above average, a considerable proportion of the patients showed signs of mental deterioration which were part of the disease in particular families and not merely co-existent with the disease. On the other hand, Davies (1949a, b) studied 20 cases of Friedreich's ataxia and 17 control chronic invalids and found no difference in the intelligence of the 2 groups. Similarly, Wilson (1954) reported that Friedreich's patients commonly exhibited a fair average level of intelligence.

For our own patients, the Ottawa-Wechsler intelligence battery was administered, but in view of the severe physical handicap it is difficult to draw conclusions from the non-verbal tests. The pattern of verbal results is shown in Table 5. It is seen that in Group I the overall verbal intelligence is barely at the lower limits of normal (90.35 ± 14.07). However, there is a significant difference between male and female subjects, with the latter showing lower scores. Only amongst females, are scores below 90 found (35% of cases). In Group II, 50% of the patients tested, irrespective of sex, have scores below 90.

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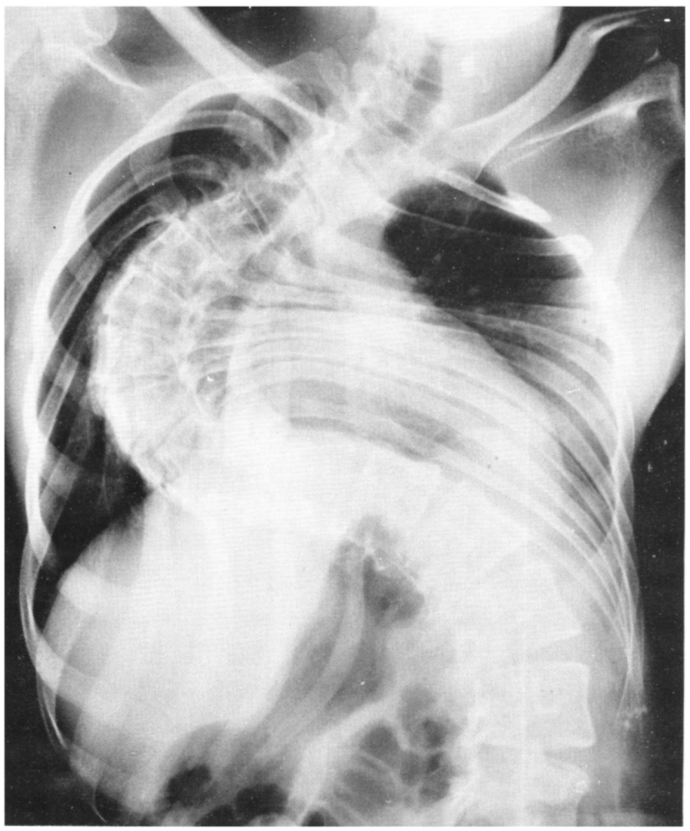

Figure 1—Patient SBL-7; severe 120° thoracic scoliosis. Heart probably of normal size.

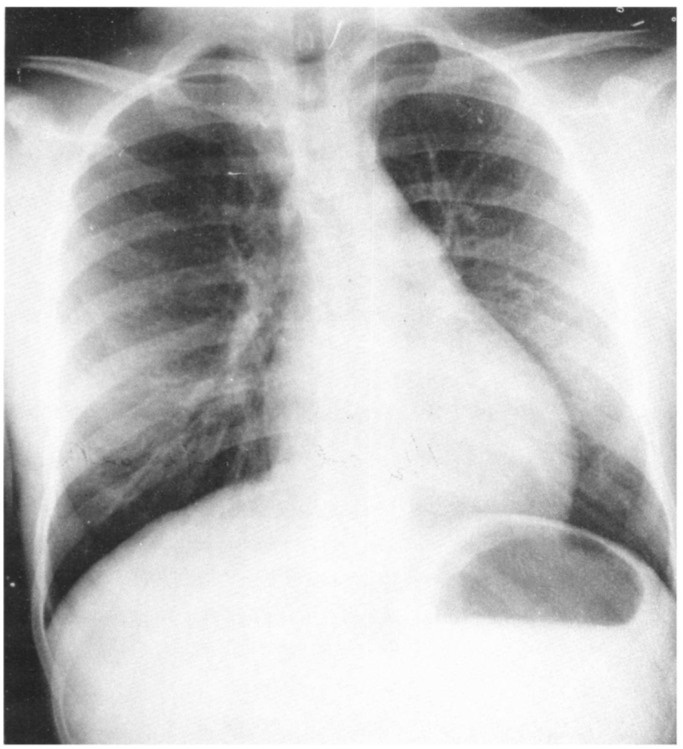

Figure 3—Patient SBL-2; slight cardiomegaly and minimal scoliosis.

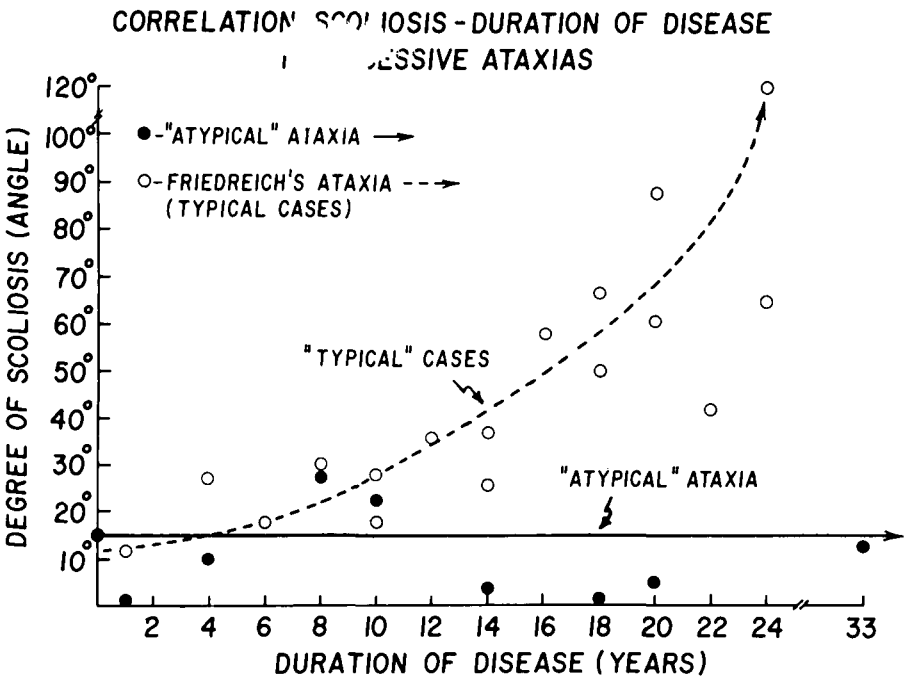

Figure 2—Progressive nature of the scoliosis with years of evolution of Friedreich's ataxia.

CONCLUSION

An analysis of our material confirms many points in the literature, but there are a few significant differences and some new observations. Typical Friedreich's ataxia (Groups Ia and Ib) can be characterized by a number of primary and constant symptoms which are obligatory for diagnosis (Table 6), some secondary signs which are almost always present (over 90% of cases) and which are clearly progressive, and finally by a large number of accessory symptoms and signs which cannot be used for a diagnosis.

Patients in Group Ib are identical to Group Ia, but lack any evidence of pes cavus. Whether this one family suffers from a distinct disease or is only a variant of Friedreich's ataxia, still has to be decided.

Group IIa differs from typical Friedreich's ataxia mainly through lack of progression of the ataxia and a very mild degree of scoliosis. In these patients, the rate of deterioration appears to be slow. Finally,

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TABLE 6

SIGNS AND SYMPTOMS OF FRIEDREICH'S ATAXIA

PRIMARY SYMPTOMS AND SIGNS: (100% constant: obligatory for diagnosis)

1) Onset before end of puberty and never after age 20
2) Ataxia of gait
3) Progression of ataxia within last 2 years preceeding examination to all extremities, without remission
4) Dysarthria
5) Decrease in position and/or vibratory sense in lower limbs
6) Muscle weakness
7) Deep tendon areflexia in lower limbs

SECONDARY (PROGRESSIVE) SYMPTOMS AND SIGNS: (present in more than 90% cases, eventually 100%; not obligatory for diagnosis)

1) Babinski sign (extensor plantar response)
2) Pes cavus 3) Scoliosis 4) Cardiomyopathy

ACCESSORY SYMPTOMS AND SIGNS: (less than 50% of cases)

1) Decrease in visual acuity (usually optic atrophy)
2) Nystagmus
3) Paresthesias
4) Partial deafness
5) Essential type tremor
6) Vertigo
7) Spasticity
8) Pain
9) Decrease in I.Q.

Group IIb is heterogeneous, varying from one family to the next. Specifically dysarthria, posterior column signs and muscle weakness are lacking.

Our analysis of the distribution of signs and symptoms in each of the sub-groups unanimously delineated by our panel of 15 neurologists, indicates that there are good reasons to separate the total sample into at least 4 clinical constellations. In later papers, we will see whether such groupings correspond to paraclinical and biochemical findings.

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