Quebec Cooperative Study of
Friedreich's Ataxia

Cooperative Study, Phase Two: Statement of the Problems

A. BARBEAU

SUMMARY: *A short summary of the state of our knowledge at the start of Phase Two of the Quebec Cooperative Study of Friedreich's ataxia is presented. The main questions raised by the discoveries made in the Phase One Survey are listed and the plan of our current investigations is outlined.*

RÉSUMÉ: *Nous présentons un court résumé de l'état de nos connaissances au moment du début de la Phase Deux de l'Etude Coopérative du Québec sur l'Ataxie de Friedreich. Nous faisons également une liste des questions et problèmes qu'il reste à préciser à la suite des travaux de l'enquête en Phase Un.*

From the Clinical Research Institute of Montreal.

Reprint requests for the complete supplement on Friedreich's ataxia (Phase Two, Part One) to: Dr. André Barbeau, Clinical Research Institute of Montreal, 110 Pine Avenue West, Montreal, Quebec, Canada H2W 1R7.

Friedreich's ataxia, described for the first time in 1861 (Friedreich, 1861) had remained more or less "Terra Incognita" until the last few years. Recent thorough reviews of the clinical aspects by Tyrer (1975) and of the biochemical aspects by Lubozynski and Roelofs (1975) failed to indicate real leads into the etiology of the disease. By 1974, when Claude St-Jean founded "L'Association Canadienne de l'Ataxie de Friedreich", the momentum for research into the ataxic disorders, which had been gained in France and Germany by the superb clinical and neuropathologic studies of the 1920's, had been lost. As has been stated (Barbeau, 1976a), there was a great need for a systematic, multicenter and multidisciplinary approach to this problem. Because Friedreich's ataxia is the most common spino-cerebellar degeneration, our initial attention was turned towards that disease.

The planning committee decided that our efforts would have to follow three phases. (Table 1). The first difficulty was the clinical definition of the disease. Here we faced the classic dilemma and philosophical conflict of the "lumpers" versus the "splitters". In a search for the primary biochemical defect of a disease, is it better to sample a large number of related clinical entities (all ataxias) and to define as Friedreich's all those who show biochemical change X or is it better to select subjects who respond to clear and constant clinical and genetic criteria and study only those for biochemical change X, thereby risking the exclusion of "clinical variants" who may have the same basic disease? As clinicians, most of the neurologists who composed the planning committee chose the second alternative, while the biochemists tended to favor the first. It was the statisticians who settled the argument when they demonstrated to us that the chances of missing a sub-group of patients with a subtle biochemical characteristic were many times greater when this sub-group was statistically pooled and submerged in a large heterogeneous collection of mostly unrelated diseases. However, our solution was the sort of compromise that would have pleased Salomon himself: we would study a well defined, restricted-criteria group of patients with typical Friedreich's ataxia and, if possible, always compare this with two control groups: age and sex matched normal individuals and an "ataxic" control group of atypical patients or related entities (for example, Charcot-Marie-Tooth; Olivo-ponto-cerebellar atrophy). This had the advantage of rapidly indicating if a given biochemical finding was characteristic or not. The decision whether it was specific would depend upon the further demonstration that the so-called typical cases were indeed a homogeneous group.

In 1975 and 1976 we conducted a thorough survey of 50 cases of Friedreich's ataxia. From this study a common clinical set of diagnostic criteria emerged and is therefore referred to as *typical Friedreich's ataxia* (Table 2). All our subsequent studies will use these genetic and clinical criteria to define the subgroup of ataxic patients. All other well known entities and all variants (such as Marie's spino-cerebellar de-

https://doi.org/10.1017/S0317167100024781 Published online by Cambridge University Press

generation) are excluded or used as neurological controls until we find a primary biochemical defect.

The survey served two purposes: first, it updated and confirmed or rejected a number of claims to biochemical defects that had been made. Except for the high prevalence of diabetes in Friedreich's ataxia, all other claims were eliminated from further consideration. The second purpose was the unearthing of biochemical leads to the possible etiology of the disease or to understanding the pathophysiology of some of its symptoms. In this respect our survey discovered a number of unsuspected biochemical abberrations (Table 3, and Barbeau, 1976b) which should serve as the basis for a systematic investigation.

The second phase of our study is directed towards clarifying the findings uncovered in the survey and towards answering the many questions raised by these results. The most prevailing question was "is this finding *primary* or *secondary* to the disease?" A number of studies were designed to answer the following specific questions:

1. What is the clinical and biochemical make-up of a variant form of ataxia discovered in the Charlevoix-Saguenay region? Is it Friedreich's ataxia or a form of spastic ataxia?
2. What are the electrophysiological correlations of the vestibular defects we suspect in many of our patients?
3. Can we locate the gene for all forms of olivoponto cerebellar atrophy (OPCA) on the sixth chromosome, as has recently been claimed (Jackson et al., 1977). If so, should we search for the same locus in Friedreich's ataxia?
4. How can we relate the changes in calcium found in the heart to the postulated taurine defect and to the cardiomyopathy?
5. Is there really an oxygen transport defect in Friedreich's ataxia, and does this contribute to the cardiomyopathy?
6. What is the significance of the hyperbilirubinemia? Is it specific for the disease? Is it present in all cases under the proper metabolic stress situations?
7. What is the defect in pyruvate oxidation? Is it generalized (and therefore possibly primary and genetic) or is it limited to certain tissues? Could it instead be the manifestation of a regulatory (secondary) defect?
8. How does the pyruvate dehydrogenase (PDH) complex function and how is it regulated in the brain?
9. What is the meaning of the urinary loss in taurine, β-alanine and aspartic acid? Is it a genetic transport defect? If so, is it a generalyzed defect? What is the role of taurine in the organism?
10. In view of changes reported in the literature (Rosenberg et al., 1970) regarding purine metabolism in some spino cerebellar degenerations, should we expect such modifications in Friedreich's ataxia?

TABLE 1

Quebec Cooperative Study of Friedreich's Ataxia — Plan of Study

PHASE ONE: A Prospective Survey of a sufficient number of cases

PHASE TWO: Etiological Investigations

- Part One: Clinical and Biochemical studies
- Part Two: Pathophysiology
- Part Three: Experimental therapeutic approaches

PHASE THREE: Genetic screening and therapeutic trials. Prevention if possible.

TABLE 2

Genetic, Clinical and Paraclinical Criteria for "Typical" Friedreich's Ataxia

A. Genetic
   1. Always inherited in autosomal recessive fashion.

B. Clinical
   1. Age of onset before end of puberty.
   2. Ataxia, first of lower limbs, then of all four limbs, progressing relentlessly without remission and usually accompanied by muscle weakness.
   3. Presence of dysarthria very early in the disease.
   4. Absence or marked decrease in vibratory and/or position sense in the lower limbs.
   5. Absence of deep tendon reflexes in the lower limbs.
   6. Progressive development, within two years after onset, of pes cavus and kyphoscoliosis.

C. Paraclinical
   1. Presence of a progressive cardiomyopathy, generally of the hypertrophic type, which is best detected by a combination of vectocardiography and echocardiography.
   2. Absence of sensory nerve conduction (evoked potentials) in the lower limbs with a considerable slowing in the upper limbs.
   3. Essentially normal (or lower limits of normal) motor conductions, with normal E.M.G.

https://doi.org/10.1017/S0317167100024781 Published online by Cambridge University Press

11. Finally, is there any significance to the occasional indications of a defect in cholesterol transport?

Answering so many fundamental questions is a major challenge which has again been taken up with great enthusiasm by members of our cooperative team. Many of the questions have been answered, many new ones have been raised, but we have made important steps towards our ultimate goal: understanding and eventually conquering Friedreich's ataxia.

ACKNOWLEDGMENTS

The multidisciplinary studies carried out in the various centers involved in this investigation were supported almost entirely by public funds raised expressly for this by the Association Canadienne de l'Ataxie de Friedreich. Certain more specific studies in individual centers also received financial help from a variety of sources: the Medical Research Council of Canada, the Jeanne Mance Foundation of the Hôtel-Dieu Hospital, the W. Garfield Weston Foundation. The Ministries of Health (Federal and Provincial) gave considerable indirect support to this research by underwriting the extremely expensive item of the patients hospitalization in metabolic units.

REFERENCES

BARBEAU, A. (1976a). Quebec Cooperative Study of Friedreich's ataxia: Design of the Investigation. Can. J. Neurol. Sci., 3, 271-274.

BARBEAU, A. (1976b). Friedreich's ataxia 1976 — An Overview. Can. J. Neurol. Sci., 3, 389-397.

FRIEDREICH, N. (1861). Lieber degenerative atrophie der spinalen hinterstränge. Congress sitzungskericht der Deutchen Aerzte und Naturforscher, Speier.

JACKSON, J. F., CURRIER, R. D., TERASAKI, P. E. and MORTON, N. E. (1977). Spino-cerebellar ataxia and HLA linkage. New. Engl. J. Med., 296, 1138-1141.

LUBOZYNSKI, M. F. and ROELOFS, R. I. (1975). Friedreich's ataxia. A review of recent literature. South, Med. J., 68, 757-763.

ROSENBERG, A. L., BERGSTROM, L. and TROOST, B. T. (1970). Hyperuricemia and neurologic deficits. A family study. New Engl. J. Med., 282, 992-997.

TYRER, J. H. (1975). Friedreich's ataxia. Handbook of Clinical Neurology, edited by P. J. Vinken and G. W. Bruyn, North Holland, Amsterdam, Vol. 21, pp. 319-364.

TABLE 3

Biochemical Leads in Friedreich's Ataxia Uncovered By the Prospective Survey

1. CARBOHYDRATE METABOLISM
   a. increased incidence of clinical or chemical diabetes in Friedreich's ataxia
   b. decreased oxidation of pyruvate in vivo with a possible defect in pyruvate dehydrogenase (PDH), particularly its third component, lipoamide dehydrogenase (LAD)
2. OXYGEN METABOLISM
   a. possible decreased oxygen transport because of a diffusely hypertrophic and hypokinetic left ventricular myocardium, and because of the progressive kyphoscoliosis with subsequent impairment of lung function
3. IONIC METABOLISM
   a. increased accumulation of calcium in heart tissues
4. BILIRUBIN METABOLISM
   a. increased incidence of unconjugated hyperbilirubinaemia in some patients
5. AMINO ACID METABOLISM
   a. increased renal clearance rates of taurine, β-alanine and aspartic acid
6. LIPID METABOLISM
   a. low concentrations of cholesterol and/or triglycerides in some patients