

RESEARCH IN ATAXIA, WHAT IT IS FOR

Hardly a few days ago, I had on the telephone a young woman pregnant for the first time who was worried about transmitting Friedreich's ataxia to her future baby.

The information which she gave me on her family confirmed the existence of a real risk which I evaluated empirically at 1 out of 32, which is almost 1000 times greater than the risk of the general population which is 1 out of 25,000 to 50,000.

Hardly three years ago, I would have been able to do nothing to ease her worries. It would not have been surprising that this couple would have preferred to interrupt the pregnancy rather than to take such a high risk of putting into the world a child afflicted with such a serious hereditary disease.

Friedreich's ataxia is a progressive disease characterized by a loss of coordination of the movements starting generally in adolescence and bringing about the loss of walking towards the beginning of the twenties. Language become difficult because of motor incoordination, but the intelligence remains untouched. Muscular weakness following neurological lesions provokes deformation of the feet, hollow foot, and of the spinal column, scoliosis. Friedreich's ataxia is no longer considered a simply neurological disease. Since its description by Nicolaus Friedreich 130 years ago, the disease which carries his name did not markedly hold the attention of clinical researchers, before a young Quebecois ataxic by the name of Claude St-Jean refused to be labelled by the name of a disease of which one knew neither the cause nor the mode of transmission and even less the cure. Under the impetus of this indefatigable fighter and thanks to the contribution of the organizer, Dr. André Barbeau, in 1973 the first cooperative Quebec study of the degeneration of the cerebellum and of the spinal chord took shape.

In the course of the decade which followed, more than 60 researchers and clinicians in Quebec and elsewhere worked in collaboration with the plan of identifying the nature and the evolution of Friedreich's ataxia and its variants, its mode of heredity and if possible, its cause. It is thanks to these studies in which around fifty ataxic Quebecois families took part that they succeeded in better defining the signs and symptoms of Friedreich's disease, its evolution and the most frequent complications. It became evident that they were confronting a disease which was not only neurological, but multi-systemic with, among other complications, cardiac problems, and in almost half of the cases, diabetes. It was not from their neuropathy which the person afflicted with Friedreich's ataxia would die but rather from heart failure.

The collaborating research also taught us that the heredity of Friedreich's ataxia is always recessive autosomic. To be at risk of developing the disease, a person must have been conceived starting from two parental germinal cells, each carrying a defective gene of which the combination provokes the eventual appearance of the characteristic signs and symptoms. How is it that the parents are not afflicted and that there is no positive family history, as far back as one can go?

The reply is simple. A person carrying one single gene of Friedreich's ataxia has a copy of the normal gene in all his cells, whereas the ataxic himself has only two defective copies.

In every preceding generation, one or the other of the parents had to be a carrier of one of these defective copies. We can thus go back very far in time and in space. The genealogical research carried out starting from a common ancestral couple, originally from Perche and presumed to have introduced a copy of the gene of Friedreich's ataxia to New France at the beginning of the 17th century. Jean Guyon, Mathurine Robin and 7 of their 8 children landed at Quebec in 1634. They baptized two other children there. The efforts of Dr. Barbeau and his Quebecois and foreign collaborators were unfortunately not rewarded by the discovery of the basic defect in Friedreich's ataxia. After having undergone a minute inventory of the scientific and medical literature, all the functions of the organism of ataxics turned out to have been altered by the disease, having been probed clinically and in the laboratory. Several dysfunctions in the use of sugars, in the formation of bile and in the transportation of amino acids were brought to light. Whether they affected only one group of ataxics and not all, whether they had the characteristics of a secondary effect rather than those of a cause, whether their corrections did not bring about improvement in the course of the disease, whatever, the greatest part of the anomalies reported could be eliminated as etiological factors.

In 1985, as much because of the disappointing results of the clinical research and the therapeutic trials as in the light of new possibilities which molecular genetics opened with finding the gene of Huntington's chorea, Dr. Barbeau and his scientific committee of the Canadian Association of Friedreich's Ataxia proposed as their new mandate "to find the chromosomal site of the genes of the different forms of recessive ataxias of French Canada: the diseases of Friedreich, Charlevoix-Saguenay and Acadian and to characterize the genes biochemically." Carried off by disease prematurely, he would not have the joy of learning of the finding of the gene of Friedreich's ataxia on chromosome 9, by Dr. Susan Chamberlain and her team at St. Mary's Hospital in London, in 1988. He would not know either of the founding of an international network of collaboration in genetic research which today consists of several teams of clinicians and fundamentalists with a common goal, the finding and the decoding of the genes responsible for the hereditary ataxias of the world.

In Quebec alone, research in genetics led to close to 65 multiplex families, that is to say having more than one afflicted child, for Friedreich's disease and 19 families for Charlevoix-Saguenay ataxia. This latter disease, which is called ARSACS in medical jargon, comes from the region of Charlevoix and of Saguenay-Lac-St-Jean. ARSACS manifests itself earlier than Friedreich's disease, walking being difficult even in childhood. The ill present a spastic walk and will have a prominent muscular font especially on the level of the extremities. ARSACS does not affect the intelligence, does not provoke cardiomyopathy, nor diabetes. It is a disease which, like Friedreich's disease destroys little by little the ill person's ability to interact with his environment, making it impossible for him to realize vital, familial and social goals which all normal adolescents desire. The psychological and emotional impact of these irremediably progressive diseases is enormous as much for the individual and his family as for the society in general, which sees itself deprived of some of its most valuable human elements, for ataxics are for the most part in the image of Claude St-Jean, gifted with an intelligence and a force of character out of the ordinary. The gene responsible for ARSACS is not the same one as that for Friedreich's disease. The research carried out in Quebec, principally in the laboratory which the Canadian Association for Friedreich's Ataxia maintains in St. Justine's Hospital in Montreal, allowed us to exclude the ARSACS gene on chromosome 9 and several other chromosomal sites where the genes responsible for chronic, the dominant familial ataxia, etc., are located. It is of primary importance that this research work continues, with the goal of finding this gene and of knowing its structure and function, for besides permitting

for the time being the detection of healthy carriers and the prevention of recidivism in at-risk families, the acquired knowledge regarding a form of ataxia benefits other diseases of the same nature. There exists, for example, an "Acadian" variant of Friedreich's ataxia found in some families living in the Acadian peninsula of New Brunswick and as far away as Louisiana, with the "Cajuns". The Acadian Friedreich's ataxia is a less severe and more slowly progressive form than the classical form. Nevertheless, recent studies carried out by the researchers at St. Justine's Hospital confirm that it pertains to a disease of which the responsible gene is narrowly linked to the region of chromosome 9 where the gene of classical Friedreich's disease is located. Up until now, 10 Acadian families have been listed and studied by Quebec researchers. A surprising fact, one finds with Acadian ataxics, as with classical Friedreich ataxics of Quebec, genetic particularities suggesting that there has been a simultaneous or successive introduction of several genes responsible for Friedreich's disease in these two populations. Genealogical studies have not yet allowed bringing the families of Acadian Friedreich's ataxia back to their common ancestors, but this step may be soon realized with the support of the Acadian community of New Brunswick and the financial help of ACAF.

To come back to our pregnant young woman, recent achievements in molecular genetics allow us to answer her question without delay. We have listed the members of the paternal and maternal families the most susceptible of helping us to establish the molecular characteristics of chromosome 9 involved in the transmission of Friedreich's ataxia to two members of the paternal family. With the relatives' and their doctors' collaboration, blood samples were taken starting the next day in order to extract DNA from the required white cells at St. Justine's, carried out genetic markings, with the help of probes specifically for the chromosomal area of interest. Each of the two chromosomes 9 carrying the genes responsible for Friedreich's ataxia in this family was characterized. If either one or both spouses were proved to be non-carriers of these two genes, the chance of having an afflicted child would be, properly speaking, nonexistent. If the two spouses were proved, on the other hand, to both be carriers, the initial risk of 1 out of 32 would go to 1 out of 4. We then will offer them the possibility of a prenatal diagnosis by amniocentesis, this now common technique which allows us to obtain liquid and amniotic cells with the help of the taking of a transabdominal sample of the pregnant woman at the beginning of the second three months. In the case which we are talking about, certainly the prenatal diagnosis will allow us to determine the molecular characteristics of both the paternal and the maternal chromosomes transmitted to the foetus at conception and accordingly the presence of the absence of the chance of eventually developing the disease. This indirect advantage of medical research is not the prevention which interests them, but rather the treatment. What is the use of doing research if the only persons which can benefit from it are those who are not sick? It is a very difficult question, which challenges the reason not only for research in hereditary ataxia, but medical research in general. At the start it appears to be more beneficial to concentrate the greatest part of human energy and financial resources in a direction in which we know for a fact to be guaranteed success in the short or long term, than to take the chance of wasting energy and resources in probing several courses of research at the same time especially when we do not have an indicator as to the cause of the disease in which we are interested. This is the approach which Dr. André Barbeau favoured by founding the Quebecois cooperative group in 1973. It is again this philosophy which underlies the present and future approaches to molecular genetics. The principle is simple. When we don't know what to do, we have to count on the cooperation of the ill.

In Quebec and in Acadia, cooperation is no problem. The problem is if we can go ahead with the research with two technicians as quickly as we would with four or six. The slowness of medical research on hereditary ataxias comes more from a lack of financial resources than from the lack of imagination of the researchers or a technological delay. People often ask us, "Can one catch this like AIDS?", or "Is this transmitted by the blood, or a microbe, or a germ perhaps?" Now you know the answer, no? Hereditary ataxias are as their name says, familial diseases which are genetically transmitted. To each new child who is conceived, the two parental cells contribute respectively between 50,000 to 80,000 genes, their exact number is not yet made clear, but what we know is that among these genes, two are defective, one of paternal origin and the other of maternal origin, and this is sufficient to change an individual's course of life, his family's and that of the society in which he lives. In supporting research in ataxia, an individual who is not afflicted and who has no familial history of ataxia, contributes in a way an insurance policy for his own children and the generations to follow. If it happened to them, you would indeed be very glad to know that every day we are getting a little closer to the desired solution.

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