

## Annual General Assembly of November 17, 2002

### **Talk given by Dr. Bernard Brais**

#### Introduction:

I am at the same time a neurologist, geneticist and historian. I am also responsible for the ataxias clinic with Dr. Luc Marchand (Hôtel-Dieu of Montreal) since the departure of Dr. Massimo Pandolfo and before that Dr. Botez. I am a neurologist and geneticist at the neuromuscular clinic at the Lucie-Bruneau Centre (in Montreal) for more than a year and I am in charge of the young children with Dr. Michel Vanasse at the clinic of Marie-Enfant Hospital (Montreal).

In the coming months, I will start to meet the ataxic people in Jonquière where I have a clinic with Dr. Jean Mathieu and Michel Vanasse. We will go towards the Saguenay where I work a lot on the difficult cases of Jean Mathieu but particularly the ataxic persons who do not have common forms. This will be the theme of my presentation and particularly of the project which you subsidize and which has progressed very much thanks to Dr. Duquette.

I will speak about a problem which is very particular to Quebec, for there are forms more frequent than others, there are large groups i.e. dominant ataxias (a father or a mother afflicted who transmits the gene to half of their children). These forms are rare and do not explain the ataxias in Quebec as a whole.

What are very present in Quebec are recessive ataxias: both parents have nothing, but unfortunately one child out of four (4) will inherit the mutation.

The key example is Friedreich's ataxia. It is not the only one known, there is also that of the Saguenay, vitamin-dependant (vitamin E), telangiectasia and also a series of which the mutations, the genes, are known, and for some there are treatments which are a little bit preventive like telangiectasia which is very rare in Quebec. For the majority of the people whom we follow at the Hôtel-Dieu, we know that they have ataxia, we know that they have a degeneration, an atrophy of the cerebellum and we tell them: "This is what your disease is." So what!... For the ataxia of Charlevoix-Saguenay, it is very clear. A simple diagnosis is sufficient.

There are spino-cerebellar ataxias which present other manifestations, other systems which are not affected, but it remains that they do not have the same classic expressions as Friedreich's ataxia. Some have been transmitted from a parent to their children, others not at all. For the recessive ataxia of Charlevoix-Saguenay, we have made a lot of progress on the level of understanding during these last years, but there again it is in the order of 10% of the people who come to the clinic. There are others among them also who have no labels. They are considered as ataxia, but we cannot ascribe other things to them.

When we gave our first assessment coming from the first individuals tested until July 2002, that is to say 153 persons, we noticed that of the 55 persons who were diagnosed ataxic, 33 were proved, from a diagnostic point of view. The majority were Friedreich's.

In fact, 35% had been tested and 60% of them had obtained a diagnosis (i.e. the form of the ataxia). Therefore we were able to give a diagnosis on less than a third of the people.

It is unfortunate, but the lack of knowledge, learning, does not permit us to say more about it. We do what we can in order to have a firm diagnosis. On the other hand, genetics will allow us to clarify a little better.

In fact, 21% of our clientele have a proved diagnosis. What is very clear is that a great number of ataxics are recessive; therefore people got it from two parents who are not afflicted.

Charlevoix-Saguenay ataxia is not present only in this region but also in Montreal and elsewhere. We say that there are ataxias of a regional character. The people of this region have been afflicted, not because they were cousins, but because they presented the same genetic patrimony (because all Quebecois are cousins). The probability that they have a common ancestor is more than 96%. As a person from the Saguenay, it is even greater, and they no longer marry among cousins, no, the opposite. This is what interests me as a neurogeneticist: this reality to better understand what is going wrong at home.

Quebec is a genetic mosaic. This genetic reality of the regional mosaic makes some regional mutations responsible for ataxia more frequent in certain regions. The classic example is the ataxia of Charlevoix-Saguenay, but there are others. Jean-Pierre Bouchard identified an ataxia in Beauce. All the south shore of Beauce, de La Chaudière to Rimouski, where many people suffer from this ataxia which is relatively less severe compared to Friedreich's. It is a late ataxia arriving in the forties which can be associated with problems of coordination in examination and that is about all. They identified about 36 persons in one year. This tells us that certain regions have more chance than two individuals who decide to marry and share their genetic material, even if they are not cousins. The sharing of common recessive mutations is therefore increased as well as their chances of having children with an ataxia.

I am going to speak to you about one of these forms. The question of territory will be my way to proceed in carrying out my project. The first thing that I ask a patient is: "What region do you come from?" For if you tell me that you come, for example, from Portneuf, I immediately think of another patient who comes from this region, for it can be the same disease, not withstanding the degree of evolution. It can allow me to see how the disease evolves. It is this type of regional filter which I use and it is a method that works.

I am going to speak to you about an ataxia which is frequent in Quebec. A year ago, I saw some ataxics who had this particularity: they all had a significant font of the muscles of the hand. They all had small hands. One thinks immediately of a disease of the nerves which is associated with this. In Friedreich's ataxia, one also finds this font.

In 1980, Jean-Pierre Bouchard had described two families from New Brunswick of whom the mother was originally from Quebec and the father, of Acadian origin, from New Brunswick, and he had observed an amyotrophy of the muscles. This is a very particular combination.

Of the eleven families, six have the same mode of transmission. The parents are not afflicted, a quarter of the children are afflicted; they show a weakness in the hands, some are going to develop deformities in the bones of the hands, the feet. We do not yet know if there is a loss of hearing which can be associated with it. But it is a family from Lanaudière, not Charlevoix.

In Quebec, we divide the genetic patrimony into two (2) large groups: that of the north-east which we associate with the Charlevoix-Saguenay ataxia (the genetics of the callous body)

and of other diseases closer to the region of the Saguenay which is a more homogenous ET patrimony, a patrimony of the south which has more interbreeding because it is a region which was colonized much later and with a great number of settlers from the second French regime, therefore much more diversity, and in fact there was a founding influence, except that we have not found it. The contribution of the Acadians is very significant.

We are in the process of studying the construction of the genetic patrimony. There are four founding peoples: the French Acadians from the lower river, the Anglophones, the Loyalists who came from the United States and a large Anglo-Norman contingent who came from Jersey to work in the Baie des Chaleurs. There are, besides, several families by birth who are still there. They have their own genetic diseases. Friedreich's, for example, is present with the Anglo-Normans and we are attempting to know if this is an Acadian contribution.

That which is certain at this time is that the characteristics as we perceive them are produced at around 16-17 years of age, which is rather late. There are this amyotrophy and this significant font of the muscles. All the people do not have reflexes (disease of the peripheral nerve which controls the perception of touch), a particular movement of the eyes difficult to control and no cardiac diseases. Life expectancy is good and on the level of the scan, the cerebellum is affected. We have been able to observe that there was a rise in an embryonic protein. Now with all these observations we can very easily say: "You have this disease."

With biochemical tests it was possible to see that this ataxia resembled another form of ataxia which has been defined since 1998. Even if the clinical descriptions do not completely correspond, they are associated with the rise in this same protein.

Recently, Dr. Duquette looked at several cases who gave blood for a diagnosis in the context of the study, and we realized that for the region identified as the carrier of the gene responsible for recessive ataxia, nearly everyone shares this region. Well then, when I told you that it was a family affair.

This ataxia has already been identified in a list of names of 20 persons. All these people seem to share the same descendance. It was an Acadian who came to New Brunswick who gave this mutation. In fact we have arrived at trying to find a gene which we have identified in a very small region which can really explain the disease well. We will subsequently try to explain the mutation of the gene in question.

I told you at the beginning of my talk that it was impossible to give a clear diagnosis to all the persons who came to the clinic. The reason is that we do not possess all the tests in order to prove it. In a few months, some of you will know that you have this disease. This is going to affect many children who are being born and who will be born with the disease. This represents an enormous problem. We must contact the people (for diagnosis) of Quebec and of Acadia.

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