

EUR - ATAXIA

EUROPEAN FEDERATION OF HEREDITARY ATAXIAS

EDITORIAL

This third issue of EURO-ATAXIA is for a major part dedicated to research into hereditary ataxias. The highlight in ataxia research in the past year has been the remarkable progress in Dominant Hereditary Ataxia (DHA). Neurology and Neurosurgery '92 was the title of the International Symposium on DHA held in Havana, Cuba between 7 - 11 December 1992. The conference attracted participants from research laboratories and universities throughout the world - as far away as Germany, Portugal, Norway and Japan. Dagmar Kroebel was there to represent EURO-ATAXIA. We print her speech overleaf.

The conference was opened on the afternoon of the 7th by Dr. Alberto Nodarse, the Symposium Convenor. He has also written a letter to EURO-ATAXIA, which we have pleasure in printing.

Furthermore we publish an extensive research report by Dr. Susan Chamberlain, which also focuses for a great deal on Dominant Ataxias.

EURO-ATAXIA's boardmeeting, held in Brussels on 13 March 1993, was almost entirely dedicated to the booklet we are producing on hereditary ataxias. Much progress has been made in the realisation of this project. There will be, amongst others, chapters on the history of ataxias, the clinician's point of view, genetics, cardiomyopathy, tests carried out in hospitals. The booklet will primarily be destined for patients and their families, but also has to be on a level to be used by a general practitioner.

LETTER FROM CUBA

One of the largest populations of patients with Dominant Hereditary Ataxia in the world is located in Holguin, an eastern province in Cuba. With more than one million inhabitants, the province has over one thousand patients with the disease and an undetermined number of genetically affected but still asymptomatic relatives.

Since 1983 efforts have been made to study every affected family and more than six hundred patients have been extensively studied in this way up to the present day. The research protocol includes preliminary epidemiological studies and clinical evaluation of patients and relatives to determine the hereditary pattern and the clinical features of the disease. Pathological and neurophysiological studies have also been carried out.

The clinical and pathological findings have made it possible to classify the hereditary ataxia from Holguin as a particular disease, different from other forms of hereditary ataxia and it has been definitely supported by recent molecular genetics findings that revealed that the transmission of the ataxia found in Holguin is linked to chromosome 12. The neurophysiological studies have shown functional disturbances at

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Editor

Michael Morgan
18 Stranmillis Road
Belfast BT9 5AA
Northern Ireland
Tel: +44 232 665671

Lay out & printing

Hans Doré
Mina Krüseman-erf 131
3315 GE Dordrecht
Netherlands
Tel: +31 78 212110

different levels of both Central and Peripheral Nervous Systems as well as subclinical alterations in unaffected individuals from the same families, contributing to the presymptomatic diagnosis of the disease. These studies have been carried out by Dr. Guillermo Orozco, neurologist at Lenin Hospital in Holguin, who has personally examined all patients and relatives of the Holguin families. Prof. Rafael Estrada (†) and Dr. Joaquín Galarraga from the Institute of Neurology and Neurosurgery, at Havana examined the autopsied material and Dr. Georg Auberger and Suzana Gispert, at the University of Düsseldorf, have carried out the molecular genetics studies and have discovered the location of Holguin's ataxia gene at chromosome 12. The clinical neurophysiology studies were carried out by myself.

Medical and welfare assistance has also been provided for ataxia patients in the province of Holguin. An official programme has been implemented to continuously survey patients needs and to assist them not only in health care but in psychological and social requirements.

On December 11th, an International Symposium on Dominant Hereditary Ataxia was held in Havana. Outstanding experts from Portugal, Japan, the US, Germany, Norway and England met together in Havana with the Cuban specialists in order to discuss the most recent findings on DHA. The Symposium travelled to Holguin, where the patients there were personally examined by each visiting expert. Extensive discussion was then held on every aspect of DHA. While it was felt that important knowledge on DHA has already been revealed, there still remains much more to be discovered. All Symposium participants re-affirmed their determination to continue and increase research into DHA, to contribute to the world-wide fight against ataxic diseases.

Particularly important was the speech of Dagmar Kroebel from EURO-ATAXIA who let us hear the collective voice of thousands of ataxic people, their claims and hopes. We know of your active contribution to the fight against ataxia and we hold your goals and aims to be an example to us all. I have translated Dagmar's speech into Spanish for the benefit of our own patients, doctors, social workers, welfare and public health officials - indeed everyone involved in fighting ataxia in Cuba. Her words are tremendously encouraging to all of us here.

As a Cuban doctor, I wish too thank EURO-ATAXIA for your support for the molecular genetics studies on the Holguin families that contributed to the obtained results. Cuban patients now have the possibility of a

prenatal diagnosis, something we wish could be achieved soon for all ataxic people all over the world. We wish our work here could also help in this.

Thank you for your courage, your determination to fight ataxia and to secure a place in society for all ataxic people everywhere. Cuban patients, neuroscientists and people support you.

Dr. Alberto Nodarse

Institute of Neurology and Neurosurgery

Havana

CUBA

(Ataxia Symposium Convenor)

Havana, December 20th, 1992

DAGMAR'S SPEECH: THE PATIENTS EFFORTS FOR ORGANISATION AND PROGRESS

In the period 1987/89 a few doctors and members of the German, Belgian, French, British and Irish ataxia groups came together to form the European Hereditary Ataxia Federation, or EURO-ATAXIA as it is more commonly known. Initially, three broad aims have been set down: first, to regroup patients in Europe and establish and maintain contact with the rest of the world; second, to disseminate information rapidly to and between all our members; and third, to encourage the formation of new ataxia self-help groups at all levels, local, national and international.

I would like to underline the fact that Hereditary Ataxias are generally considered to be rare diseases. This means that in countries where hospitals are decentralised, existing neurological centres may only see a very small number of ataxic patients, so that there might not be much professional and medical interest put into them. Consequently research is left uncoordinated or even non-existent. The opening up of Genetics as a research area has, however, led to renewed interest in all forms of Hereditary Ataxia.

But first, let us talk a little about statistics. It is estimated that one person out of twenty-five thousand will be affected by ataxia. So, in Belgium with its 10 million inhabitants, there should live about 400 ataxics; but only about 70 of whom are members of ataxia groups. In Germany, with its total population of 80 million, there should be 3200 ataxic people; however in the German Ataxia Group, Deutsche Heredo-Ataxie Gesellschaft, there are only 250 ataxic members. I don't think this overall tendency would be much different for Cuba either. The Cuban self-help association will face the same problems registering members. This also means that the official number of

affected persons in any one country is too small to attract government or private funding in ataxia research. For example, the European Commission recently withdrew subsidies to research because of the relatively small number of those affected, compared to Cancer, which is much more common and thus continues to receive a heavier research commitment from the European Commission as well as from individual government sources.

It may be estimated that there are about two hundred thousand people with ataxia world-wide. There are probably even more than that, and we can expect the official figures to rise with continually improving diagnosis methods.

One of the original ideas behind EURO-ATAXIA was to make politicians and the public aware of Hereditary Ataxia. We also wish to improve relations, both between doctors and other medical people, researchers, etc., and also between doctors and patients, because we think it essential to spread all new medical and scientific information as widely as possible. This meeting is a direct outcome of those ideas.

In 1989, representatives of all western European Ataxia groups came together for the first time in Antwerp, Belgium. They decided to work together and to share experiences, to spread scientific results and introduce patients to researchers. The 4th plenary assembly of EURO-ATAXIA was held near London, England on September 25-27, 1992.

Our most important publication is a Newsletter, EURO-ATAXIA, published twice a year (I have brought a few along; most of you had it sent by mail). This Newsletter is a sort of link between researchers and patients. We hope that it is interesting for both 'sides'. We, who are affected, want to know about the results and who is doing research on what.

Until 1988 most European research concentrated on Friedreich's Ataxia and Dominant Hereditary Ataxias were treated as a secondary matter. These forms of cerebellar atrophies were considered to be extremely rare. Genetics research on Cuban families brought forward the importance of Dominant Hereditary Ataxias

In 1990, Dr. Georg Auburger went to Düsseldorf to found a neurological research laboratory. He was especially interested in the Cuban ataxia. At the same time he supported clinical research among German patients. In Summer 1990 EURO-ATAXIA had the opportunity to invite the Cuban biologist, Dr. Suzana Gispert, to Düsseldorf to help build up the laboratory. In September the Cuban neurologist, Dr. Orozco, was invited to lecture on the Cuban Dominant Hereditary Ataxia at the 2nd EURO-ATAXIA

plenary assembly in Zeist, Holland. The work in Düsseldorf was very successful and this Spring Cuban ataxia could be localised on Chromosome 12. Deutsche Heredo-Ataxie Gesellschaft supported this team financially. The sums collected from donations weren't high but it wasn't just meant to bridge financial bottle-necks. Above all, it gave ataxic people the opportunity to 'participate' actively in research, to give them hope that something is done.

Our third aim is to activate so-called 'self help' groups. We, who are confronted with these diseases on a daily basis must learn to live with their consequences.

Next to the immediate physical problems come communication difficulties, such as dysarthria. All of us have a funny way to talk and some of us can't speak at all anymore. Without speech, however, most consider us to be mentally handicapped.

In self-help groups we meet other affected people and have the opportunity to share experiences. They give a certain security because we consider each others handicaps as 'normal'. It gives a lot of people the possibility to strengthen their self-confidence. Healthy people don't seem to care and leave sick people alone with their problems. Nobody really understands the ataxic person. The neurologist may know the medical side of things, but has only a small amount of time to spend with his patients. That is why we need the company of other affected.

I ask the scientists here in the meeting to tell me their wishes and proposals they have for our group; also to communicate to me their addresses if they want to get the Newsletter.

I would like to talk now about another problem: prenatal diagnosis. Some people, especially in the media, would have us believe that it is something like a free ticket to abortion. Cuban families have the possibilities for this diagnosis now. Today most people know about the genetics of heredity, and this means that if one parent has the disease, both can decide not to have any children and avoid passing the disease on. But if prenatal diagnosis can predict that there is no danger for the child to have ataxia the parents can choose to found a family.

Who would deny anyone this freedom?

Dagmar Kroebel

GERMAN REPORT

DHAG stands for Deutsche Heredo-Ataxie Gesellschaft, which, translated, means simply, German Hereditary Ataxia Association. The name, DHAG, is designed to be all-embracing, covering all

the main ataxias - Friedreich's (FA), Cerebellar (CA), and even the more exotic sounding ones such as Ataxia Telangiectasia or even Olivo-Ponto-Cerebellar Atrophy (OPCA). Some of the older groups in Europe - FAG in the UK, FASI in Ireland - only mention Friedreich's ataxia in their name, and now face repeated (and sometimes heated) debates over changing their names to include all ataxias. DHAG has avoided this problem. The first steps in setting up the organisation were made in 1983 by Günther Oesterle, a sufferer, living in Stuttgart. As is all too familiar a story, it was the sheer isolation of ataxics in Germany, together with a desire to exchange information and stimulate research, that motivated him to get a group started. He was sponsored by the Genetic Information Centre at the University of Freiburg, and formally launched DHAG in April 1983. Günther has remained President since that time. I nearly met him in 1989 when I travelled to Wiesbaden, near Frankfurt, for DHAG's annual conference. Unfortunately Günther was hospitalised in Stuttgart at this time, and so couldn't attend the conference.

DHAG has now over 500 members - the 500th member was welcomed and honoured at the 1991 conference - and of these about two-thirds are disabled members, the rest being able-bodied family members and friends who have taken an active role in the organisation. Moreover, these 500 people are from what used to be West-Germany. Now that Germany is re-united it would be interesting to find out how many ataxic people there are in the eastern part of the country. This, in fact, opens a line of questioning that EURO-ATAXIA will need to address themselves to: what is the situation regarding the ataxias in all the countries of Eastern Europe, including Russia itself.

The funding of DHAG is by annual subscription: DM 60.- for individuals, DM 90.- for families. DHAG doesn't fund medical research projects directly though it brings together individuals, families and medical and scientific personnel, and so keeps up the pressure for research.

DHAG is not a single entity - there are 15 regional groups throughout (West) Germany, each organising various social activities in the course of the year: from coffee-mornings and day trips, to weekend-seminars, full-scale holidays and of course, trips to the annual national conference. An interesting innovation run by DHAG is a telephone hot-line (operated by Gudrun Brunner on +49 9725 9150 if you can speak German and can afford international phone calls), which provides a ready point of contact, offers advice and just generally gives members the opportunity to

express their fears and share their worries about life. It's an aspect of ataxia that rarely seems to get much attention: the scale of emotional anxiety and the fact that many people just want to talk things over with somebody. This, surely, is something that should be considered by all ataxia groups in Europe.

A quarterly journal, HERAX-FUNDUS, keeps members up to date on DHAG activities. DHAG's representative in EURO-ATAXIA is Monika Müller, from Munich.

Contact:

Deutsche Heredo-Ataxie Gesellschaft

Bundesverband e.v.

Haussmannstr. 6

D-7000 Stuttgart 1

GERMANY

HEREDO-ATAXIE PRIZE 1994

Deutsche Heredo-Ataxie Gesellschaft is once again awarding a prize - of DM 5000 - for a piece of original work on Hereditary Ataxia. Papers dealing with either medical, psychological or sociological aspects are invited, but must be in the German language. The closing date for receipt of finished articles (4 copies please) is December 1993. The prize itself will be awarded at next year's Deutsche Heredo-Ataxie Gesellschaft AGM, on 26 March 1994. For further details please

contact:

Dr. Herbert Pongratz

Friedrich Bauerstr. 4b

D-8520 Erlangen

GERMANY

MEDICAL SOCIOLOGY

Medical Sociology is fast developing as an important sub-discipline, one which may be of possible benefit to ataxia research and management. The European Society of Medical Sociology (ESMS) recently held a major conference on 'Health in Europe' at the University of Edinburgh, in September 1992. The area of interest covered by Medical Sociology is very wide, ranging from quantitative studies on the incidence and epidemiology of diseases within whole populations to qualitative studies on the psycho-social aspects of coping with a progressive disability.

An example of the former was a paper entitled, *Genes in the Netherlands: The impact of Genetic Diseases,*

presented by Marian Edens and Johan Groothoff. This is an ongoing project, concentrating on the impact of seven specific genetic diseases in Holland (among them diabetes, Cystic Fibrosis, Down's syndrome Spina Bifida etc.) The project was carried out on behalf of the Dutch Ministry of Welfare, Health and Culture. It found that a general registration of the impact of these diseases is missing. Available registrations do not aim at a longitudinal study of patients and so impact cannot be measured. Because of this missing information, policy-making and scientific evaluation is made more difficult. The lack of Data on incidence and impact should therefore be addressed through a more comprehensive approach, based on Continuous monitoring. Although ataxia's were not included in the original project, they too, surely, would benefit from a similar approach based on Continuous monitoring.

On the other hand there were small-scale qualitative studies of the life-histories of people with disabilities. A particularly good example was a study of people with Parkinson's disease, concentrating on how they come to be labelled 'deviant' through public perception of problematic behaviour, how they internalise this as 'shameful deviance', and how they strive to avoid the resultant stigmatisation. Again, whilst this study was not specifically about the ataxia's as such, it nevertheless addresses the important, yet sadly neglected, psycho-social aspect of disability. It both provides a model and points a way forward for ataxia researchers. But will this challenge be met?

Contact:

Prof Per-Gunnar Svensson

ESMS

Centre for Public Health Research

S-651 82 Karlstad

SWEDEN

Tel: +46 54 19 40 95

Fax: +46 54 10 15 65

HUMAN GENOME ANALYSIS PROGRAMME

The Human Genome Analysis Programme is stimulating the mapping of the human genome in Europe. It aims to improve the understanding, prevention, diagnosis, relief - and in the long run also therapy - of genetic diseases. This challenging task requires co-ordination on a massive scale. To save time, work and money, it is essential to improve communications between research teams and to speed up the exchange of data, materials and technology.

Resource Centres have therefore been set up, supported by the Human Genome Analysis Programme. There are currently (October 1992) eight such centres.

There are two resource centres dealing specifically with the Human Gene Mapping Project (EUROGEM), with a wider network of 24 separate laboratories. The aim of EUROGEM is to produce a high-density genetic linkage map with a resolution of 5-10 centiMorgans (cM), an essential step towards mapping genetic diseases.

The *DNA Probe bank*, based in UK, collects existing probes, isolates new markers, makes computer records of all probes (and ensures quality control of all new markers), before distributing them to participating laboratories and analysing resulting feedback.

The *Membrane Resource Centre* is based in Paris and supplies DNA from 40 large families (517 individuals) in the form of Southern blots. Human genomic placental DNA is also provided. EUROGEM members are committed to map 40 probes on all 40 families and to send back their genotypic data to the Human Polymorphism Study Centre (CEPH) in Paris, which, in turn, makes genotypic data available to the international scientific community via a public database.

Other Resource Centres supported by the Human Genome Analysis Programme include:

- *Cosmid libraries for a Consortium on Ordered Clone Libraries*, based in London.
- *DNA libraries*, based in Middlesex, UK.
- *Resource Centre for the distribution of YAC clones*, based in Paris.
- *European Data Resource for Human Genome Research*, in Heidelberg, Germany.
- *Danish Family Bank (RClint)*, based at the University of Copenhagen.
- *Single Chromosome Workshops*, from HUGO in London.

RESEARCH REPORT FROM LONDON

Friedreich's Ataxia

At the time of writing last year, we believed that we had bracketed the gene between two 'signposts' or markers on the DNA molecule. These markers lie extremely close to each other and from the distance between them, we predicted that the interval contained probably no more than two or three genes. Our strategy at that stage was, therefore, to concentrate on the isolation and characterisation of

these genes and the subsequent search for the alteration or 'mutation' which would confirm that we had, at last, cloned the Friedreich's ataxia gene.

The characterisation of any new gene may represent the efforts of several researchers over a 6-12 month period. Consequently, the development of new markers in the region which facilitate the reduction in size of the interval and hence, the number of genes to be studied, remains a primary objective for all of the research groups.

In addition, the analysis of new markers increases the level of information derived from any single family participating in the study. Consequently, families which on previous analysis had contributed little information as to the position of the Friedreich's ataxia locus, subsequently provide new information which in some cases, can influence future strategy.

As a result of the analysis of new markers developed by the Strasbourg group, three such families were identified. The data generated from these three families indicated that the Friedreich's ataxia gene was not located within the interval of interest.

Following the elimination of laboratory error by re-sampling of the families in question, the possibility of misdiagnosis was examined. In this respect, the research groups are totally dependent on the clinicians to ensure that only families in which a diagnosis of the Friedreich's ataxia has been confirmed are included in the study. Over the past few years, diagnosis of the hereditary ataxias has improved dramatically. However, it is now becoming evident that an increasing number of patients with onset below the age of 20 (when a diagnosis of Friedreich's ataxia would have been given based on age of onset alone) are now being diagnosed as having other forms of cerebellar ataxia and vice versa.

We have been fortunate to have the most experienced clinicians in the field evaluating the families and to the best of their knowledge, the diagnoses in these families are accurate. The question therefore arises as to whether a very small proportion of families (less than 1%) may have a disorder which is clinically indistinguishable from Friedreich's ataxia, but is caused by a mutation within another gene, possibly located on another chromosome. The precedent clearly exists for a number of other genetic disorders, including the dominantly inherited cerebellar ataxias, and only the molecular analysis of the disease locus will finally resolve this issue. However, until the gene is finally isolated the argument becomes circuitous.

In the meantime, we have to continue to work towards our goal and devise a strategy which will allow us to take account of all these permutations. Should we ignore the data from the three families

which exclude the gene from the original region of interest even though their disease may be caused by mutation in a different gene OR should we place our full trust in these results and concentrate our efforts completely outside of the interval flanked by our two original markers?

In reality, we are trying to cover both options continuing with the characterisation of the genes which we have already isolated from within the interval and at the same time developing new markers and isolating new genes from the flanking regions. In doing so, we divide our efforts considerably and hence, progress more slowly.

In conclusion, I would like to stress two points. On the question of clinical diagnosis, the problems raised by our studies should not cause concern to the vast majority of our members who will have received an accurate diagnosis, particularly if this has been given within the past ten years. Secondly, concerning the use of the linked markers for genetic counselling purposes and specifically for pre-natal diagnosis. Whether the gene is located within or immediately outside the interval defined by the original linked markers, the distances involved are still so infinitesimally small, that the markers can continue to be used with absolute confidence; the error rate remaining at 2%. Families who have received counselling advice based on the analysis of these markers can therefore be assured that the advice given is accurate.

Dominantly Inherited Cerebellar Ataxia

In contrast, research into dominantly inherited forms of cerebellar ataxia has received a major boost within the last few months. Whilst Friedreich's ataxia is caused by defects in a single gene, previous studies have demonstrated that dominantly inherited forms of cerebellar ataxia result from mutation in at least two and probably several different genes. One such gene has previously been located on chromosome 6 and several groups are currently engaged on working towards its characterisation. Consequently, genetic studies similar to those carried out for Friedreich's ataxia are more complicated, not least because the clinical expression of dominantly inherited cerebellar ataxia can be so variable. From our own studies, we know that defects in two different disease genes can give rise to symptoms which are clinically indistinguishable. Conversely, age of onset, rate of progression of the ataxia and severity can vary even between affected members of a single family, who obviously share a common mutation. Genetic analysis may provide the only means by which the

classification and hence, the identification of the underlying defects, can be achieved.

To carry out a strategy parallel to that adopted for Friedreich's ataxia - mapping the gene to a particular chromosome and then moving in on its location to isolate or 'clone' the defect itself - it is absolutely essential that the analysis is carried out on families which can be assumed to have mutations within the same gene. Large pedigrees arising from the introduction of the disease into a population by a single common ancestor (a founder population) provide an invaluable resource for mapping studies. This explains why we seem to be concentrating on families from Thailand or Cuba rather than our own U.K. families in the first instance, as in general, European families are often too small to be included in the initial analyses. The extended pedigrees with more than 50 affected family members provide what we refer to as 'a genetic model' for the disorder.

Once the chromosomal assignment of the disease gene has been determined in these families, new markers can be developed for genetic counselling of both the specific population and the smaller European families in which linkage to the same locus can later be confirmed. More importantly, mapping the disease gene allows us to move towards cloning the genetic defect itself and once this is achieved, to determining the mechanism by which the premature degeneration of the specific nerve cells occurs. This could in turn provide insight into the mechanisms giving rise to the other forms of hereditary ataxia.

Within the last few months, the research group at St. Mary's (and in particular Rebecca Twells) working in collaboration with Dr. Jim Weber from Marshfield, USA, has determined the chromosomal assignment of the gene locus for dominant ataxia in the large Cuban patient population under study in our Department for the past four years. This achievement was made following the exclusion of the disease locus from approximately 40% of the chromosomes. The research has been supported by both Action Research and the Friedreich's Ataxia Group. Further details concerning this data will appear in a future edition of FAX. The location of this gene has been confirmed independently by a team in Düsseldorf.

Already, markers which flank the disease locus have been identified, thus defining the region for further analysis. At the moment, however, these markers are probably too far apart to be reliably used for genetic counselling, even in the Cuban patient population. Our immediate task therefore must be to generate new more tightly linked markers from the interval.

One of the initial questions we need to answer is whether mutation in this new gene locus is specific to

the Cuban patients or responsible for the disease in other populations as well. Preliminary studies indicate that this disease gene is also mutated in European populations and over the next period, we will be working in collaboration with clinicians and research teams throughout the world, to establish the true incidence of the new locus.

Susan Chamberlain

St. Mary's Hospital Medical School, September 1992.

NOTE: The St. Mary's Research Group would be pleased to hear from families with dominantly inherited cerebellar ataxia and at least two surviving affected family members, willing to participate in our research project by the donation of blood samples. Please contact either FAG Headquarters or Dr. Susan Chamberlain at the above address (+44 71 7231252 ext. 5488).

NO EFFECT OF L-5-HYDROXY-TRYPTOPHAN ON ATAXIA

Some attempts have been made to treat patients suffering from ataxia with 5-Hydroxy-Tryptophan (5-HTP). Some of these clinical studies resulted in partly positive effects of 5-HTP on ataxia, others did not. Therefore we wanted to test the effect of 5-HTP on ataxia with a double-blind cross-over study in 40 patients with degenerative cerebellar diseases (20 with Friedreich's ataxia, 13 with Cerebellar atrophy and a further 7 with olivo-ponto-cerebellar atrophy). The mean duration of treatment with 5-HTP was 6.2 months and the dose prescribed was 1000 mg per person per day. Ataxia was documented and quantified using a clinical score: posturography (ataxia of stance); a registration of finger forces and a registration of speech abilities. Apart from minor gastrointestinal side effects in 8 patients, which did not cause real problems in the treatment, no relevant side effects were noted with long-term administration of 5-HTP in a dose of 1000 mg per day. In particular, none of our patients developed signs of an eosinophilia-myalgia syndrome. In summary therefore, we did not find any significant effect of 5-HTP on ataxia, so that a treatment with 5-HTP no longer seems to be recommended for patients with ataxia.

Priv.-Doz. Dr. K. Wessel

Member DHAG

*Department of Neurology, Med. University of Lübeck
GERMANY*

EURO-ATAXIA: MEMBERS & CONTACTS**EURO-ATAXIA BOARD**

Dr. Manfred Van den Kerchove, President
Lambrechtschoekenlaan 209-A11
B-2170 Antwerpen
BELGIUM

Michael Morgan, Vice-President
18 Stranmillis Road
Belfast BT9 5AA
NORTHERN IRELAND

Dagmar Kroebel, Secretary-General
Haagwindelaan 19
B-3090 Overijse
BELGIUM

Theo Schimmel, Treasurer
Roggeveld 41
NL-3764 ZC Soest
NETHERLANDS

Monika Müller
Lindwurmstrasse 80
D-8000 München 2
GERMANY

Evelina Raveggi
Via P. della Dalle 12/1
I-50127 Firenze
ITALY

José Cuadrado
Santiago Rusiñol, 10-9º-3ª
E-28040 Madrid
SPAIN

EURO-ATAXIA MEMBERS

Association Belge de l'Ataxie de Friedreich
Rue Longue 68
B-6260 Bouffloulx
BELGIUM

V.Z.W. Liga voor Ataxie van Friedreich
Kleine Kuipersstraat 27
B-8000 Brugge
BELGIUM

Deutsche Heredo-Ataxie Gesellschaft
Bundesverband e.v.
Hausmannstr. 6
D-7000 Stuttgart 1
GERMANY

Associazione Italiana per la lotta alle Sindromi
Atassiche
Via Cattaneo 22
I-20013 Magenta (MI)
ITALY

Friedreich's Ataxia Group
Copse Edge
Thursley Road
Elstead
Godalming
Surrey GU8 6DJ
UNITED KINGDOM

Friedreich's Ataxia Society of Ireland
San Martino
11 Mart Lane
Foxrock
Dublin 18
REPUBLIC OF IRELAND

Northern Ireland Friedreich's Ataxia Group
18 Stranmillis Road
Belfast BT9 5AA
NORTHERN IRELAND

Asociacion Española de Ataxias Hereditarias
C/. Poeta Alberola, 25, bajo, dcha.
E-46018 Valencia
SPAIN

VSN – Werkgroep Ataxie van Friedreich
Mina Krüseman-erf 131
NL-3315 GE Dordrecht
NETHERLANDS

EURO-ATAXIA CONTACTS OUTSIDE EUROPE

National Ataxia Foundation
750 Twelve Oaks Center
15500 Wayzata Boulevard
Wayzata, MN 55391
USA

Association Canadienne de L'Ataxie de Friedreich
3800, Rue Radisson, Suite 11
Montréal, Québec H1M 1X6
CANADA

EURO-ATAXIA is registered as a Charity in Belgium: VZW 9240/92

Secretary-General: Dagmar Kroebel, Haagwindelaan 19, B-3090 Overijse, Belgium, Tel: +32 2 6571510

Bank account in Belgium: 068-2063656-08.