



MARCH 2010

News from Monika Benson, EDF President

Dear All,

The months of winter have been busy, with quite a lot of work for dystonia. I hope this Update will give you some idea of what the EDF Board and our advisors and Executive Director have been involved in over the past months.

EDF General Assembly 2010

It is a great pleasure for me to announce that the EDF GA 2010 will be held in Malmö, Sweden from Friday September 10 at 2 pm until Sunday September 12 at noon, at the hotel Savoy which is located very close to the central station. When you travel to Malmö you fly into Kastrup, the airport of Copenhagen, and from the airport there is a direct train to Malmö central station, taking less than 30 minutes. There will be more information about speakers and programme in the May newsletter. Please now make plans to come to Malmö, and I look very much forward to welcoming you all to Sweden and to my part of the country. It is my hope that it will be another EDF meeting filled with interesting information on dystonia and warm and useful exchanges among delegates and guests. Last year's event was voted one of the best ever, and we will try hard to create the same kind of meeting in 2010.

During the last week-end of January, the **EDF board** gathered in Brussels for the first meeting of 2010. Unfortunately, new Board member Alan Tamlyn, and advisors Lieve Van Gorp and Greet Ruelens were unable to attend. Fiona Ross, the chairwoman of TDS, was invited to advise the Board on strategy for the future.

Financial situation and funding

Our Treasurer, Herman de Craecker reported on the financial situation and Executive Director Alistair Newton gave an update on the funding plan for 2010 and the present funding position. The board also discussed prospects and new approaches for longer term funding of EDF activities. EDF is presently funded mainly by unrestricted grants from a small number of companies which provide drugs or medical devices to treat dystonia. The industry is in enormous difficulty worldwide and many large pharmaceutical companies are merging to make themselves more efficient and profitable. The general financial problems across the world have had an effect on all of us, not least EDF and its funding. Today companies give priority to supporting events like congresses or other projects that give them PR exposure, while funding for core costs is much less attractive. New ideas for funding were discussed such as:

- Increasing the EDF membership fee
- Approaching the companies which produce lesser-known drugs used in dystonia therapy
- Investigating the possibility of applying for funds from various international or private foundations

Medical Advisory Board

It was decided that the Medical Advisory Board needs to be restructured into a much larger group of dystonia specialists. This expert panel will give EDF a much better relationship with a wider span of physicians, surgeons and researchers across Europe. We ask you, our member groups for input and suggestions for members of the new MAB. You are invited to confirm names of specialists in your country who should be considered for these appointments. Please remember that it will not be possible to include all the names you might suggest, although we hope to make sure that most of our member countries have at least one specialist involved. The real need is to make sure that dystonia

patients across Europe are supported by the best specialists – not only that national interests are represented

Dystonia-Europe 2011 in Barcelona

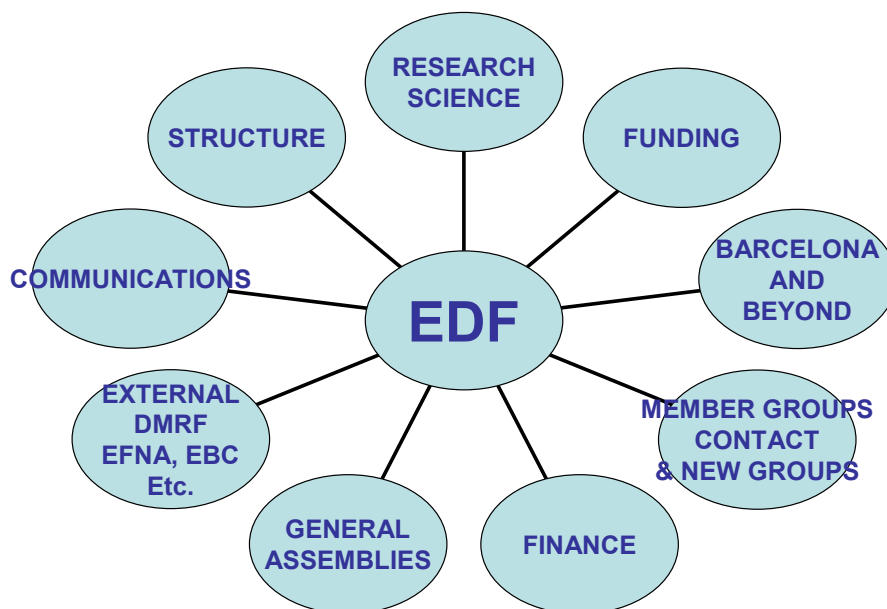
After receiving substantial and generous grants from a number of sponsors, including the pharmaceutical industry, the Dystonia Society and the Foundation for Dystonia Research (based in Belgium), enough funding has now been secured to start making firm arrangements for a medical conference to follow the 2008 Hamburg event. The EDF board is very happy to announce that the next **Dystonia-Europe medical conference** will take place in Barcelona during October 2011. The exact dates will be confirmed shortly and the EDF General Assembly will follow the congress, as happened in Hamburg in 2008.

Strategy: The future of EDF

The basis for the discussion on this topic at the January Board meeting was a presentation by Fiona Ross, Chairwoman of The Dystonia Society. It is very clear to the Board that the main thing which stops EDF from developing is the lack of resources: financial and human. Although the workload is constantly increasing, the EDF Executive Director is the only paid employee and is employed for only 3 days per week. His responsibilities are to control and organise almost all EDF matters and deal with the administrative tasks, secure funding for all activities, raise sponsorship for congresses and represent EDF generally, with specific representation in leadership roles in a number of pan-European neurological organizations.

In order to relieve the Executive Director from some of the day-to-day work it would be useful to have some administrative help. But funding for such assistance is not available, and his work-load needs to be reduced, so it was decided that each of the EDF Board members must take responsibility for specific tasks, although the ED will continue to be involved in almost every area to some extent.. These were divided as follows:

EDF – MAIN AREAS OF BOARD RESPONSIBILITY



New areas of Responsibility

Funding, Barcelona, GA, communications, external relations - Monika Benson

Structure and possible revision of statutes: Alan Tamlyn

Finances and GA: Herman De Craecker

Website: Sölvi Engeland

Research and science: Ginger Butler, Göran Bylund, Greet Ruelens, Lieve Van Gorp

Member group contact: Ginger Butler and Göran Bylund

In order to increase and improve the ongoing contact between EDF and our member groups Göran Bylund and Ginger Butler have been appointed to take on this task. They are responsible for 8 countries each:

Ginger: UK, Ireland, France, Belgium, Spain, Portugal, Netherlands, Croatia

Göran: Sweden, Finland, Norway, Denmark, Italy, Germany, Austria, Switzerland

Research

Ginger Butler informed the board about the latest developments of the epidemiology project in the North East of England, which includes a new method for sampling material for genetic analysis. Instead of collecting blood samples from dystonia patients they now sample saliva on swabs, a method which makes the collection of samples much easier from large numbers of patients.

A new device which seems to be very useful for patients with blepharospasm was mentioned by Fiona Ross. This is a mechanical device incorporated in a pair of spectacles, which presses lightly on the skin close to the eyes and significantly reduces contractions in the affected muscles.

David Marsden Award 2011

After advice from our research advisers, the Board decided that the amount of the David Marsden Award will be increased to 5000 Euros from 2011.

2009 GA Presentations

In this newsletter you will also find the summaries of presentations at the GA in Brussels last autumn by Dr. Laura Cif and Dr Marina Koenig-Tijssen. The other GA presentations were published in our December 2009 Update.

EDF visit to the 2010 DMRF annual meetings

The Executive Director and I were invited to attend the recent annual meeting of DMRF (Dystonia Medical Research Foundation), in Scottsdale, Arizona, where we had the opportunity to listen to the DMRF medical advisors when they discussed and argued over 30 applications for 12 research grants that were available. A total sum of \$750,000 was agreed to be provided over the next two years. Some of the research areas are:-

- The basic mechanisms of the basal ganglia
- Understanding the mechanisms of exciting new treatment techniques such as Deep Brain Stimulation. Why it works on some patients and not on others.
- The fundamental aspects of TorsinA function
- Understanding the role of the cerebellum in dystonia
- Neuroplasticity
- Genetics, and the genome analysis of dystonia
- And many more!..

We also heard the news that the US National Institutes of Health (NIH) had granted \$6,500,000 to set up and run a Dystonia Research Coalition, which will co-ordinate this work at a number of centres in North America and Europe. Such a large collaboration has huge potential to produce faster and better results to help dystonia patients and we will keep you informed on progress when it becomes available.

In addition to the Scientific Advisory Board meeting, we also attended the DMRF annual Board meeting, where Art Kessler took over the Presidency from Claire Centrella, who has now retired after leading DMRF to great success over the past few years. The opportunity was also taken to hold discussions with DMRF Executive Director Janet Hieshetter and Scientific Officer Jan Teller, on possible future joint activity between our two organisations.

The 3-day meeting gave me new hope for all dystonia patients. There are so many bright and dedicated doctors and scientists across the world, working for us, trying to find a cure. And I am sure one day it will happen! I am also very impressed by the way DMRF is run and operated, and by the generosity of the American members and Board of directors, who raise enough money every year to support their tremendous activity, including an office of 10 staff and a large number of research projects not only in the US but also in Europe. It is my hope that EDF can develop in such a successful way and follow in the footsteps of DMRF for our distinct European infrastructure and culture.

EDF website

Sölvi Engeland is working on designing a new EDF website, and this will be launched at the 2010 GA.

European Dystonia Awareness week/day

Once again I would like to confirm that from 2009 no EDF grants have been available for the Dystonia Awareness day/week. The large insurance company, which was the funding source for these grants, has not supported EDF for several years and the money provided to member groups during that time has come from core resources, further weakening EDF's financial position. This cannot be sustained and member groups are urged to make arrangements for funding and to decide on their own dates for this event. It has become clear that too many EDF members now have established dates for their awareness events each year and it is better to allow national groups to decide their own agenda completely for dystonia awareness.

Next Board Meeting

The next EDF board meeting will be held on the week-end of April 24 and 25 at the Fondation Universitaire in Brussels.

And, finally.....

.... I would like to ask you all if you have had any special dystonia event in your country/member group? And if so, I would very much appreciate if you could write a summary and forward it to me at monika.benson@telia.com. I think it is extremely important that we share as much information as possible between our groups.

I hope you all enjoy this wonderful time of the year when sun finally returns to our part of the globe and when nature slowly but surely awakens again.

My warmest wishes to you all, for a nice and relaxing Easter Holiday.

Monika Benson
President, EDF

ANNUAL GENERAL ASSEMBLY 2010

JOIN US IN MALMÖ!

As mentioned in the President's Update, this year's General Assembly will be held in **Malmö, Sweden on Friday to Sunday 10-12 September**. More details will be sent you in due course. In the meantime, please make your plans to join your colleagues and friends in Malmö! As in previous years, EDF will cover the cost of hotel accommodation and meals for one delegate from each member group. Costs for additional delegates/observers are expected to be at a similar level to 2009, and will be sent to you soon.

EUROPEAN DYSTONIA FEDERATION

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Presentations at the 2009 General Assembly

In the last issue of Update, we were unable to publish the presentations made by Dr Marina de Koning-Tijssen and Dr Laura Cif at our 2009 GA in Brussels. These papers are now presented in this publication

Dystonia plus syndromes: What is it and why is it important?

Introduction

Dystonia syndromes can be divided in primary and secondary dystonias. In patients with secondary dystonia an identifiable exogenous cause or inherited or degenerative disease is the cause of the dystonia. Usually other neurological abnormalities are detected at examination.

In primary (idiopathic) dystonia, dystonia is the only clinical sign, occasionally accompanied by tremor. Primary dystonia, sporadic or familial, are thought to be of genetic origin in most cases. Among the primary dystonia there is a group of primary-plus (or dystonia-plus) syndromes, characterized by dystonia in combination with other movement disorders such as myoclonus or Parkinsonism. The dystonia-plus syndromes all have a genetic origin.

Three dystonia-plus syndromes forms are discussed in the presentation: the dopa-responsive dystonia, the myoclonus dystonia and the rapid onset Parkinson dystonia.

The dopa-responsive dystonia (Segawa syndrome)

What is it? Segawa syndrome or DRD is characterized by diurnal fluctuation of dystonic symptoms in 75% of cases, Parkinsonism and a dramatic therapeutic response to L-dopa. Age of onset varies widely, but is mainly in childhood. Juvenile Parkinsonism is an important differential diagnosis. Prevalence was reported as 0.5 cases per million and females are more frequently affected than males (2.5:1)

DRD is inherited in an autosomal dominant trait with reduced penetrance (30%), penetrance is higher in females compared to males. The disease locus, *DYT5a*, was assigned to the long arm of chromosome 14, encoding the *GCHI* gene for GTP-cyclohydrolase I. Other more rare genes can also give the DRD phenotype.

It is important to recognize DRD as it is a treatable disorder. Treatment with low doses (20–300mg) of L-dopa results in complete remission of symptoms in most cases of DRD.

Why is it important? 1.) DRD is a treatable disorder than should be recognized. 2.) In adult patients it should be differentiated from **Parkinson's** disease. 3) Genetic counselling

Myoclonus dystonia

What is it? Myoclonus-Dystonia (M-D) is a clinically characterized by myoclonic jerks and dystonic postures or movements of the upper body, often combined with psychiatric symptoms such as depressed mood or anxiety. M-D usually becomes clinically manifest within the first two decades and is often responsive to alcohol. Dystonia 11 is very rare. Prevalence data do not exist. M-D is autosomal dominantly inherited and is caused by mutations in the epsilon-sarcoglycan gene (*SGCE*) on chromosome 7q21 (*DYT11*). Penetrance of M-D is highly dependent on the parental origin of the disease allele, resulting from maternal imprinting. In many patients with the M-D phenotype *DYT11* mutations are lacking, suggesting the involvement of other genes or environmental factors. Treatment options are limited. In severe M-D deep brain stimulation of the globus pallidus internus (GPI) can be effective.

Why is it important? 1.) Recognition in children to prevent excessive diagnostics. 2.) Treatment options such as DBS in severe patients. 3.) Genetic counselling

Rapid-onset dystonia–parkinsonism

What is it? Rapid-onset dystonia–parkinsonism (ROPD) is characterized by abrupt onset of dystonia and Parkinsonism, which develop within minutes to days of onset. Dystonia typically affects limbs and face with characteristic rostrocaudal gradient. The phenotype is mainly dystonia, but parkinsonian features can occur such as bradykinesia and loss of postural reflexes. Signs and symptoms can be initiated or worsened by stress. Age of onset varies from childhood up to the sixth decade, but ROPD usually starts in late adolescence.

Second period of rapid deterioration occurs in about 50% of the patients. ROPD is a very rare disorder.

ROPD is inherited in an autosomal dominant trait with reduced penetrance. The gene *ATP1A3* gene is located on chromosome 19q12. It encodes for the Na⁺/K⁺-ATPase subunit $\alpha 3$ (ATP1A3). Treatment options are limited.

Why is it important? 1.) Recognition in patients to prevent excessive diagnostics. 2.)

Prognosis, as 50% of the patients remains stable during life and 50% have another episode with rapid deterioration and remain stable after the second period. 3.) Genetic counselling.

Further reading:

Müller U. The monogenic primary dystonias. *Brain*. 2009 Aug;132(Pt 8):2005-25. Review.

Kinugawa K, Vidailhet M, Clot F, Apartis E, Grabli D, Roze E. Myoclonus-dystonia: an update. *Mov Disord*. 2009 Mar 15;24(4):479-89. Review.

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Brashear A, Dobyns WB, de Carvalho Aguiar P, Borg M, Frijns CJ, Gollamudi S, Green A, Guimaraes J, Haake BC, Klein C, Linazasoro G, Münchau A, Raymond D, Riley D, Saunders-Pullman R, Tijssen MA, Webb D, Zaremba J, Bressman SB, Ozelius LJ. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the *ATP1A3* gene. *Brain*. 2007 Mar;130(Pt 3):828-35.

DEEP BRAIN STIMULATION SURGERY: CURRENT STAGE OF DEVELOPMENT IN DYSTONIA AND INDICATIONS

LAURA CIF

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Dystonia is a neurological disorder characterized by abnormalities in the control of movement, with involuntary muscle contractions causing twisting movements and abnormal postures. Dystonia represents the third most common movement disorder in humans and comprises a large number of clinical syndromes. Several classifications are available for dystonia and provide a basis for the establishment of guidelines for pharmacological and surgical treatment. According to the spread of the symptoms to different body parts, dystonia is first classified as focal, segmental, multifocal, generalized or hemidystonia. According to its cause and the existence of associated symptoms, dystonia is then classified into the following categories: primary, dystonia-plus, secondary and hereditary degenerative groups. According to the age of onset, early (before age 26) and late onset (after age 26) dystonia groups are further defined.

For the group of dystonia patients who do not respond to pharmacological therapies, or where the effect of botulinum toxin injections is incomplete, the possibility of surgical treatment is considered. Following the development of ablative surgeries in the treatment of movement disorders and the advent of deep brain stimulation (DBS) for treating Parkinson's disease and essential tremor, it has been known since 1999 that DBS is an effective symptomatic treatment for primary dystonia. Quadripolar electrodes are implanted under general anaesthesia, bilaterally in the posteroventral part of the internal globus pallidus (GPi), recognized as the most effective DBS target for treating dystonia. The targets are chosen by direct visualization on MRI, and confirmed immediately afterwards by postoperative stereotactic MRI whilst the patient still under general anaesthesia. The electrodes are connected to the neurostimulators usually located in the abdominal area within 5 days of electrode implantation.

Patients receive high frequency continuous stimulation (>100Hz) via the stimulators, in monopolar or bipolar mode with the following parameters: variable pulse width (90-450 μ sec); amplitude between 0.3 and 2.1 V, according to the clinical response and the mode of stimulation.

Initially, DBS was used only for primary generalized dystonia. Over time, new indications have emerged and now patients with severe generalized primary and secondary dystonia but also with pharmaco-resistant segmental and focal (torticollis) forms can benefit from DBS therapy.

With long term follow-up (more than 5 years), several types of outcome can be observed: very good initial response (improvement greater than 80% as assessed with the available motor scales) with the efficacy maintained over time; incomplete initial responses; worsening of the symptoms with DBS in some patients; occurrence of new symptoms. Clinical improvement and maintenance of the efficacy over time do not seem to be linked to the severity of symptoms before surgery, but to disease duration before surgery. Therapeutic effect can be obtained in severe and permanent dystonic conditions (dystonic storm refractory to medical treatment), in hyperkinetic forms but also in more fixed dystonias.

After several years of follow-up with DBS, when DBS is discontinued, very different patterns of response can be observed: immediate recurrence of symptoms, after several hours/days or no recurrence even after several weeks with stimulators switched-off. Additional electrodes could be required to complete an incomplete initial therapeutic effect or because of disease progression after initial complete clinical response.

The most challenging issues remain the definition of the indications for DBS, ensuring the best and most secure surgical procedure and identifying the most efficient electrical settings. Single lead implantation, multiple electrodes simultaneously implanted or the application of staged DBS techniques could be all therapeutic options for treating dystonia. It is necessary to provide DBS devices with longer life span for the internal pulse generators to avoid frequent surgery. Design of new electrodes could be required in order to provide a more homogeneous electric field in the brain structures to be stimulated. Three-D stereotactic models of the target and of the electric field have been developed and should allow less empirical adjustments of the electrical settings, adapted to the anatomical space of the patient. Increasing the level of stimulation, or the addition of new activated contacts do not always allow further clinical improvement or compensate for disease progression, DBS being a procedure which is only partially adaptable.

The best candidates for DBS seem to be patients with primary generalized, segmental or focal dystonia (torticollis unresponsive to botulinum toxin injections can be substantially improved by DBS). From the group of dystonia-plus syndromes, myoclonus-dystonia (DYT11) can be treated efficiently by DBS.

From the group of secondary forms, tardive dystonia due to use of antipsychotic drugs represents a very good indication for DBS therapy. Selected cases of anoxic cerebral palsy can be suitable for DBS.

For the group of hereditary degenerative dystonias, PKAN (pantothenate kinase associated neurodegeneration) represents a medical condition where severe dystonia is a hallmark of the syndrome and often is responsive to DBS.

After more than 10 years of experience with DBS for dystonia in adults and children, GPi DBS remains the best available therapy for selected patients in whom pharmacological treatment failed to improve clinical symptoms. No significant difference in results between children and adults is recorded.