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EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

The Huntington's Disease Youth Organization (HDYO)

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How can we get more people to participate in HD research?

Rhona MacLeod, co-lead facilitator, Genetic Testing and Counselling working group

Some of the barriers to participation in HD research need not exist. Two working groups recently put their heads together to identify them, a first step towards removing them.

Just before the EHDN plenary in Stockholm in September 2012, the Genetic Testing and Counselling working group (WG) met the Young Adults WG in a joint session to share ideas about improving participation in HD research.

The stimulus for the session was a set of proposals drawn up by the Young Adults WG, which in turn was motivated by a letter three of its members—Michelle O'Brien, Dirk Bakker and Katie Lingard—wrote to EHDN head Bernhard Landwehrmeyer. This happened prior to the launch of the Huntington's Disease Youth Organization (HDYO) in February 2012. In this letter, Michelle, Dirk and Katie expressed their appreciation of the commitment that professionals show to HD research, but they also raised concerns about the lack of feedback given to participants, and suggested that more could be done to improve participation.

During the 90-minute session, in which Michelle and Katie were joined by Tony Mims for their presentation on behalf of young adults, and Jennifer Thompson from Manchester gave the perspective of a neuropsychologist involved in research clinics, a number of issues were raised which are relevant, not just to young adults taking part in research, but also to the wider HD community. The following advice for researchers was highlighted:

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- Be clear with participants about the way your clinic is organised. Are they attending for a stand-alone research visit, or for a combined clinical/research appointment? If the appointment is for research purposes only, clarify whether a member of the clinical team will be in attendance.
- If no clinician is present at the research visit, research staff should be clear about whom they can refer participants to when clinical questions arise.
- Let participants know how long their appointment will last and whom they will see during their visit, and update them regularly on their progress through the appointment.
- Be clear as to whether feedback will be given from the assessments. Feedback should be given by an appropriately trained professional, usually a clinical geneticist or a neurologist. Individual scores from an assessment such as a cognitive test are not helpful. Questions about progress of the illness should be referred to a clinician.
- Consider the possibility of providing feedback in the form of a written summary afterwards. Remember to thank the individual for their contribution to the research.
- Be aware that online support exists for patients, such as HDBuzz and HDYO.

Clinicians used the joint session to find out more about young adults' experience of research. Among the questions they asked was how young people feel about participation in research being proposed to them again, soon after they had tested positive for the HD mutation. The young adults suggested that such an early invitation could actually help them, by giving them an opportunity to do something "positive" and take back control over their lives.

The clinicians were also interested in the optimal timing for a follow-up call after a person's research visit, and the young adults agreed that any time in the first three days was appropriate. They also made it clear that they did not mind being asked to participate in research, even after testing positive for the mutation, provided no pressure was applied and clinicians showed flexibility over the timing of their participation.

On the issue of flexibility in timing, there was a discussion of whether this could be increased further to make participation easier—by organising evening clinics, for example. The young adults challenged clinicians to make research clinics more appealing and positive in outlook, for example by including practical suggestions concerning excercise and diet, which help to increase feelings of control. Jennifer suggested appointing a research nurse or other individual to coordinate each clinic. This person would greet patients and ensure that they are seen promptly by different members of the team, as well as oversee sample- and note-taking, so as to eliminate needless waiting.

The young adults were clear that support needed to be included in research appointments. Contact with a genetic counsellor at the end of the research visit, or a phone call afterwards, was found to make a difference in this regard. Both the young adults and the clinicians said they would value more feedback on their assessments and on the running of their clinics, respectively, and more communication in general.

Overall, the joint session proved highly productive and demonstrated how collaboration between WGs can generate potential solutions to problems identified in HD care and research. Some of the ideas from the session will be included in the chapter "Genetic Counselling and Presymptomatic Testing", in the 4th edition of the reference book *Huntington's Disease* (Oxford University Press). The Young Adults WG has a network of contacts with young people and has offered to advise other WGs as and when the need arises.

Matt Ellison

HD-YO is one!

Matt Ellison, HDYO founder

The HD Youth Organization's founder reflects on its first year in existence.

It is fair to say that since launching in February 2012, the Huntington's Disease Youth Organization (HDYO), has been an astounding success, providing young people affected by HD with information about the disease, and making a real difference to their lives through the support it offers them—wherever they may be in the world.

HDYO's website is split into six sections, serving kids, teens, young adults, parents, professionals and people diagnosed with juvenile HD (JHD) respectively. Containing a vast amount of HD-related information that is specifically geared to young people, the site has already been visited more than 200,000 times. As of November 2012, its educational sections had been shared more than 1,300 times.

The website provides more than just education, however. Support is also available, and can be accessed either by emailing HDYO directly, or by joining the HDYO forum and talking to other young people affected by HD, or via our "ask a question" section. Since our launch, we have received hundreds of emails, messages, questions and forum posts from young people all around the world eager for information, understanding and support. Their voice is beginning to be heard in the HD community, and they are beginning to receive the attention they deserve.

What makes HDYO even more impressive is its structure. It is run by young people for young people. The team consists of more than 75 individuals from around the world who volunteer their time and skills to help, whether it be in the day-to-day running of the organisation, or in translating content into different languages. The website is currently available in five languages—English, German, Spanish, Portuguese and Dutch—and other languages will be added in the coming months.

And the team is growing, as is HDYO itself. Its success has earned it huge backing, with more than 10 HD associations around the world now providing it with official support and financial contributions. These funds allow HDYO to look ahead to 2013 and beyond, and assess how to reach as many young people as possible in the future. We hope and expect that the organisation will go from strength to strength.

HDYO t-shirts and wristbands are available for purchase online here: https://en.hdyo.org/eve/store. Proceeds go towards the running of the organisation and the creation of new projects.

Olivia Handley

Update: Enroll-HD

Olivia Handley, Global Project Manager, Enroll-HD

Enroll-HD, the new global clinical observation study of HD, is poised to recruit its first South American participants.

Enroll-HD was launched in North America in July 2012 and currently has over 300 participants enrolled at 22 study sites in the US and Canada. During the next few months, it will start up in Argentina, Chile and Peru, as well as in Australia and New Zealand, and the number of active sites in North America will increase.

Enroll-HD will eventually combine the existing Registry and Cohort longitudinal clinical observation studies of HD into the first global study of the disease. Registry is a European study, while Cohort operates in North America and Australia. Enroll-HD will also include sites from the nascent Latin American network, Red Latinamericana de Huntington (RLAH), as well as sites in Singapore, South Africa and South Korea.

A major challenge for 2013 will be to initiate the transition of Registry sites into Enroll-HD, and preparation for this transition is already underway. Current activities include preparing for the successful migration of Registry data into the Enroll-HD database, translating new Enroll-HD study materials, and obtaining local regulatory and ethical approvals.

The Registry to Enroll-HD transition will be carried out in phases over an 18-month period. Countries have been assigned to specific phases, with the first wave of transition activities set to begin in the first quarter of 2013. For a site to be "transition ready", a number of milestones need to have been reached. These include complete close out of Registry (data monitored, closed and compensated), appropriate local regulatory and ethical approvals in place, and site contract fully executed. There will be a brief hold period at each site between the end of Registry and the first enrolment into Enroll-HD, so that all the Registry data can be prepared ahead of migration into the Enroll-HD study portal. Data will only be migrated for participants who explicitly consent to it. In the lead-up to these activities there will be regional investigator meetings across Europe, to review the transition process in detail.

All participants and sites taking part in Registry are encouraged to continue into the new unified Enroll-HD study. For further information, please contact EnrollHD@quintiles.com or visit www.enroll-hd.org

Jenny Townhill

Update: Registry substudies

Jenny Townhill, EHDN Central Coordination

Introducing four new substudies within Registry that have recently come online, and more that are planned.

An innovative feature of the Registry study is the inclusion of substudies within it. These are projects whose aim is to validate additional assessment tools for clinical or research purposes. They do so by collecting additional novel data that are linked to the Registry assessments and covered by the overall ethical approval for Registry. Four substudies have been launched to date: Physiotherapy Outcome Measures, Lifestyle Factors, Juvenile Huntington's Disease and Quality of Life.

The Physiotherapy Outcome Measures study, led by Monica Busse and Lori Quinn, successfully completed recruitment in 2012. It took a number of different scales designed to assess patients' mobility, balance and general movement ability, and tested these on a total of 75 HD participants in Registry. The measures showed high test-retest reliability, and overall the results suggested that three particular scales (Berg Balance Scale, Physical Performance Test and Timed Up and Go) may be useful as clinical trial outcome measures.

The Lifestyle Factors substudy, led by Kaye Trembath and Martin Delatycki, is designed to replicate previous research conducted in Australia and New Zealand, that demonstrated a link between lifestyle and age at onset of HD. Specifically, this research indicated that an active lifestyle may delay the onset of symptoms of HD. Supporting that observation, studies in HD mouse models have shown that rearing mice in an enriched environment also delays the onset of symptoms. If these findings are corroborated, at-risk and premanifest individuals could potentially be given lifestyle strategies which, if employed from an early age, could delay the onset of their disease. The aim of the substudy is to collect data on 200 participants using a single questionnaire-based interview. The target for recruitment is expected to be reached in spring 2013, and the results should be available before the end of the year.

The open-ended Juvenile Huntington's Disease (JHD) substudy, led by Oliver Quarrell, was launched in November 2011. Its aim is to validate a modified version of the Unified Huntington's Disease Rating Scale (UHDRS) for use in patients suffering from the rare form of HD that begins before the age of 18, and has a different pattern of symptoms from the adult form of the disease. The modified motor scale within the UHDRS assesses symptoms specific to JHD, such as tremor, while the modified functional scale assesses aspects that are more appropriate for younger people, such as progress in school and playing with friends. Data have already been collected on more than 60 participants, and preliminary results are expected early in 2013.

The Quality of Life substudy was launched in July 2012 and aims to recruit up to 550 participants from each language area in the EHDN. HD patients and their carers or companions are asked to complete questionnaires about the impact of HD on their quality of life, and on their ability to undertake daily activities. Data collection will continue for five years, and a series of interim analyses will be performed.

Looking forward, new substudies are planned for Enroll-HD, and all EHDN researchers and clinicians are encouraged to propose new substudies for inclusion in this global study. Any queries about the substudies should be addressed to Jenny Townhill: townhilljj@cf.ac.uk

Ralf Reilmann, Principal Investigator of Siena Biotech's Phase II study of selisistat

Update: Selisistat

Goran Westerberg, Clinical Development, Siena Biotech SpA and Tim McLean, Clinical Operations Manager, EHDN

Results are expected this spring of a phase II randomised, placebo-controlled study of the selective SirT1 inhibitor selisistat.

Selistat is being developed by Siena Biotech SpA as a disease-modifying therapy for HD. SirT1 is a protein deacetylase capable of modulating the acetylation status of mutant huntingtin, and selisistat has been found to be efficacious in a range of disease-relevant *in vitro* and *in vivo* models. Siena Biotech has compelling mechanistic data to support the therapeutic application of SirT1 inhibitors to HD.

Following the successful completion of a Phase I study in healthy volunteers in 2010, a further exploratory pharmacodynamic Phase Ib study was conducted, the results of which indicated that selisistat lowers circulating soluble huntingtin and modulates SirT1 gene targets.

The Phase II study was endorsed by the EHDN and conducted across 12 of the network's study sites in Germany, the UK and Italy. A total of 144 subjects in early stage disease were recruited between November 2011 and May 2012, and the study was completed two months ahead of schedule, demonstrating the significant potential within the EHDN to promote the rapid recruitment of HD patients into drug trials. More information about Siena Biotech can be found here: www.sienabiotech.com

Paul and Dina De Sousa

HD inside and out

Paul De Sousa, University of Edinburgh

A scientist recounts how he and his wife found their place in the HD community.

In March 2008 my wife Dina was tested and confirmed to be a carrier of the mutant *htt* gene. Her decision to be tested came after her father, Antonio Ferreira, was also found to be a carrier. Antonio passed away in January of this year. For 10 years prior to his diagnosis, he was misdiagnosed with psychiatric, cognitive and motor deficits that, in hindsight, appear to have been obvious manifestations of HD. As is commonly the case, it was only after Dina's father's diagnosis that the family's history of the disease emerged—a history of which they had seldom spoken.

For Dina, the desire to be tested was as unambiguous as our decision to acknowledge the disease in our lives, and to be pro-active in our response to it. We are both scientists: Dina is a research assistant in an academic developmental biology lab, and I am a principal investigator of academic and applied labs engaged in research and banking of stem cells for regenerative medicine. This gives us an advantage in terms of our understanding of the disease, but understanding isn't everything. We also felt the need to engage with others who were affected by the disease, as well as with people who were involved in providing care for them, or in developing treatments to manage and ultimately cure HD. And there, EHDN offered us an unparalleled and uplifting experience.

I first participated in an EHDN plenary meeting in Lisbon in 2008, and together Dina and I attended the subsequent plenaries in Prague and Stockholm. These experiences have been tremendously illuminating and empowering for us both. Since Dina received her diagnosis, we have become involved in disease-tracking studies (Predict and Track-On) and two EHDN working groups, Standards of Care and Biomarkers. In collaboration with others who are established in the field, I am exploring ways in which I might contribute scientifically. Grant applications have been submitted to develop a cell-based therapy for HD, using clinical-grade human embryonic stem cells generated in my lab, and to use these kinds of cells or comparable cells derived from HD-affected donors to model the disease and test the effectiveness of novel antisense oligonucleotide-based therapies.

Coming to grips with the knowledge that our family is affected by HD, and the implications of that knowledge, has taken time, but we have taken courage from the positive and supportive reception we have received at all levels of the HD community. We know we are not alone and feel there is good reason to be optimistic, if not for a cure, then for improvements in the capacity to manage disease progression and the quality of our lives. Initially, we were afraid that the disease would define our lives. Now, we know that it is how we respond to it that defines us.

Saying the unsayable

Beatrice De Schepper

The President of the European Huntington Association reviews a no-holds-barred account of life in a family affected by the disease.

Beatrice De Schepper

Marjon Mol's fictional account of living with HD, *Do I want to know?*, tells the story of Brandon and his family. Brandon has HD, and through the voices of his relatives, we learn about their different perspectives on the disease and the impact it has on the family, past, present and future.

As a member of a family affected by HD myself, I was eager to read this book and found the story easy to relate to. I recognised the taboo against discussing the disease, which exists not only in older generations, but in younger ones too—the generation represented by Brandon's niece, Flora, as well as the one represented by his aunt, Janice, who was young in the 1950s.

Marjon Mol describes very well the doubts and fears experienced by a person in the early stages of the disease, and his determination to try and carry on as before. Gradually, through the eyes of those closest to him, we see how Brandon loses control over his movements and moods, and the shame he feels for not being the man he once was; his anger and frustration at this erosion of his strength and power, and the desperation he feels at his growing inability to protect those he loves.

The advent of diagnostic and predictive genetic testing brought relief from the terrible uncertainty that those at risk of HD have to live with, but themselves created new tensions within families, and this book explores these with great sensitivity and realism. Even within the nuclear family, people often feel the need to keep their having done the test secret. And when they receive the results, they have to deal with all the difficulties that come with revealing those results to other family members—individuals who, themselves, may have declined to take the test, or taken it and discovered that they are gene carriers.

Marjon Mol expertly captures the thoughts and feelings of those closest to the patient, as they try to cope in their different ways. Reading her book, I realised how big an impact HD has had on my family, and how the disease has influenced me in the past, and continues to do so. She unflinchingly lays bare family life, when the family is afflicted by a dominant hereditary disease, but she does so with her heart and soul. I recommend this book to anyone who has any contact with an HD gene carrier.

Do I want to know? can be ordered from the author by sending an email to marjon@marjonmol.eu

Dates for your diary

Save the dates for the 2013 World Congress on Huntington's Disease in Rio de Janeiro, Brazil, 15-18 September 2013, www.wchd2013.com
and for EHDN2014 in Barcelona, Spain, September 2014