June 2010 · Issue 10

EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

The EHDN Plenary Meeting 2010 in Prague

The 6th Plenary Meeting of the European Huntington's Disease Network (EHDN) will be held in Prague (Czech Republic) from 3rd to the 5th September, in conjunction with the Bi-annual Meeting of the European Huntington Association (EHA). All sessions of the EHDN Meeting are open to clinicians, scientists, representatives of the EHA and members of families affected by Huntington's disease. Simultaneous translation of the sessions into Czech and Polish will be provided.

To attend the EHDN Meeting, you must register by July 31st 2010.

- **Registration costs € 85 and can be performed online at** www.euro-hd.net/html/ehdn2010/registration
- **The deadline for abstract submission is May 31st 2010. Please submit abstracts online at** www.euro-hd.net/html/ehdn2010/abstracts
- Please **book your accommodation** following the instructions at www.euro-hd.net/html/network/events/ehdn2010/location/accommodation
- For **more information** on the EHDN Meeting, please visit www.euro-hd.net/html/network/events/ehdn2010

CONTENT Click the Page

www.euro-hd.net

Subscribe here to the EHDN Newsletter:
Please go to the URL below and fill out the online form:
http://www.euro-hd.net/html/network/communication/newsletter
Please send us your comments, suggestions and overall feedback:
newsletter@euro-hd.net

Imprint: Editorial Board of the EHDN Newsletter: Prof. Gillian Bates (King's College London School of Medicine, London, UK), Prof. Jenny Morton (University of Cambridge, Cambridge, UK), Dr. Diana Raffelsbauer (PharmaWrite, Giebelstadt, Germany), Dr. Jenny Naji (Cardiff University, Cardiff, UK), Christiane Lohkamp (IHA, Stuttgart, Germany), Gabriele Stautner (Artifox Communication Design, Ulm, Germany).

FEATURE ARTICLE

Justo García de Yébenes, Ramón y Cajal Hospital, Madrid, Spain

Pridopidine shows beneficial effects in a Huntington's disease clinical trial

Background

For many years we have known that Huntington's disease (HD) is characterised by a mixture of clinical findings in the motor domain, including positive signs such as dyskinesias (mostly chorea and dystonia) and negative signs such as Parkinsonism, rigidity and akinesia. We also knew that the dyskinesias could be treated effectively by several drugs that impair dopamine neurotransmission, such as neuroleptics and dopamine depletors, but that these compounds worsen negative signs. In contrast, dopamine-stimulating agents improve negative signs, but there has always been the concern that they may aggravate dyskinesias.

Pridopidine (Huntexil®, ACR16) is a compound synthesised by Prof. Arvid Carlsson (Nobel laureate in Medicine, 2000) and his colleagues. It belongs to a new class of compounds named 'dopamine stabilisers'. These compounds do not change baseline activity at the dopamine receptor. Rather,

they stimulate the dopamine receptor when it is hypoactive and antagonise dopamine effects when there is excessive stimulation.

There are also some indications for a regulatory role of pridopidine in the extrasynaptic regulation of glutamate. Since the cortico-striatal glutamatergic pathway is so important for the function of the striatal projection neurones that are so heavily involved in HD, it is hoped that pridopidine may have disease-modifying effects on HD by regulating this function.

Justo García de Yébenes and Arvid Carlsson

The clinical trial

After promising results were obtained in small phase II clinical trials performed in Scandinavia, the EHDN endorsed a European pridopidine trial to be performed by Neurosearch (http://www.euro-hd.net/html/projects/acr16). This phase III, double-blind, placebo-controlled study in 8 European countries (MermaiHD) screened 499 potential participants of which 437 were randomised into one of three groups to receive either placebo, or 45 mg pridopidine once per day, or 45 mg pridopidine twice per day. The three treatment groups were comparable in terms of age, CAG repeat length, duration of disease and other baseline characteristics.

After randomisation, patients received treatment with placebo or 45 mg pridopidine once per day. They were evaluated for safety one week after dose-escalation, and after four weeks of treatment once per day, the patients in the high-dose group increased their medication to 45 mg pridopidine twice per day. They were evaluated for safety one week after escalation of the dose, and at that time de-escalation could take place if the patient complained of adverse events. Two more visits took place at weeks 8 and 12 and the final visit at week 26. After the double-blind phase of the study was completed, patients were given the option of taking pridopidine in the context of an open-phase study for an additional six months. There was no difference in adverse events or discontinuations of the trial between the three treatment groups.

The primary endpoint of the study was defined as a significant change in the modified UHDRS[1]-Motor (m-UHDRS-M) scale. In other words, the study would be considered a success if the difference in the m-UHDRS-M from baseline to week 26 was smaller in the groups of patients treated with pridopidine than in that treated with placebo. Secondary endpoints included other assessments such as a change in the total UHDRS-M scores, in eye movements, chorea and dystonia scores, as well as cognitive and behavioural parameters.

Application of the high dose of Pridopidine (90 mg/day) resulted in an improvement of 1 point in the m-UHDRS-M score which represents nearly 10% of the baseline score. This change did not reach the prespecified level of statistical significance. The analysis of the data so far showed a statistically significant improvement, such as the scores for total UHDRS-M score, dystonia and eye movements. The scores for chorea were unchanged.

In summary, the results of the study showed that pridopidine has a unique effect on global motor function in HD patients without significant adverse effects and without associated worsening of other clinical deficits. The magnitude of change was not dramatic, but it was comparable with those of other medications used for the treatment of other neurodegenerative disorders.

The future

It is important to complete and analyse the results of the open-phase study that may provide additional clues as to the long-term effects of pridopidine. In addition, we are looking forward to the results of an ongoing study (HD ACR16 Randomized Trial, known as HART) performed with pridopidine in the USA. The HART study is not identical to the investigation performed in Europe (since it will only last for three months, uses daily doses of 22.5, 45 and 90 mg of pridopidine, and the number of patients included in each experimental branch is smaller). Nevertheless, if significant improvements are observed in the HART study, these will reinforce the results of the completed European trial.

Additional specific studies should include those aimed to investigate the effects of pridopidine on dystonia and ocular movements. Approval from the regulatory authorities to use pridopidine for the treatment of HD will be sought.

[1] Unified Huntington's Disease Rating Scale

Horizon Trial

A randomised, placebo-controlled, double-blind safety and efficacy trial of dimebon (latrepirdine) in patients with HD

Jenny Naji, EHDN Lanco Manager and Horizon Trial Liaison, Cardiff, UK

Horizon is a phase 3 clinical research trial aimed at testing whether or not latrepirdine (trade name dimebon) can safely improve cognition (thinking and reasoning) in patients with Huntington's disease (HD). The trial is being conducted as a collaborative study between the European Huntington's Disease Network (EHDN) and the Huntington Study Group (HSG) under the sponsorship of Medivation and Pfizer. We look forward to exploring similar partnerships in the future.

Background

Dimebon was originally developed in Russia during the 1970s as an antihistamine. Scientists discovered it had some interesting effects on brain cells around 20 years later. This eventually led to Medivation acquiring the drug in 2003, and initiating trials to investigate the therapeutic potential for dimebon in Alzheimer's disease and HD.

Dimebon has a novel mechanism of action compared to other drugs that have been assessed for the treatment of HD. In preclinical (animal) studies, it has been shown to protect brain cells from damage and enhance brain cell survival, potentially by stabilising and improving the function of mitochondria (the intracellular structures that provide cells with energy). Rats treated with dimebon showed improvements in learning and memory. A phase 2 trial of dimebon in HD, known as DIMOND, that involved 91 participants in the UK and the US, has been completed. It tested the safety and tolerability of dimebon, as well as the effect of dimebon on cognitive performance, motor function, and overall function in patients with HD. Dimebon was shown to improve significantly the scores obtained on a measure of general cognitive function. Based on the promising results of this study, the Horizon Trial was initiated.

The Horizon Trial

The trial will run for six months. The plan is to enroll around 350 individuals from approximately 50 research centres in North America, Europe and Australia. In Europe, the trial will run in approximately 22 EHDN study sites across 8 countries (Denmark, Sweden, Germany, Switzerland, UK, Italy, Poland and the Netherlands). The main objectives of the trial are to see if dimebon improves cognition, and if it has a beneficial impact on general functioning. Other outcomes such as motor function, behaviour and self-care will also be examined.

The trial is open to participants with manifest HD (over 30 years old) who suffer from some degree of cognitive impairment. They must also have a caregiver who can accompany them to the appointments, and who spends enough time with the participant that they can provide additional information to the study team about how the participant is getting on. Patients and their caregiver will visit their trial clinician's office about eight times and will receive trial-related medical care throughout the six month duration of the trial.

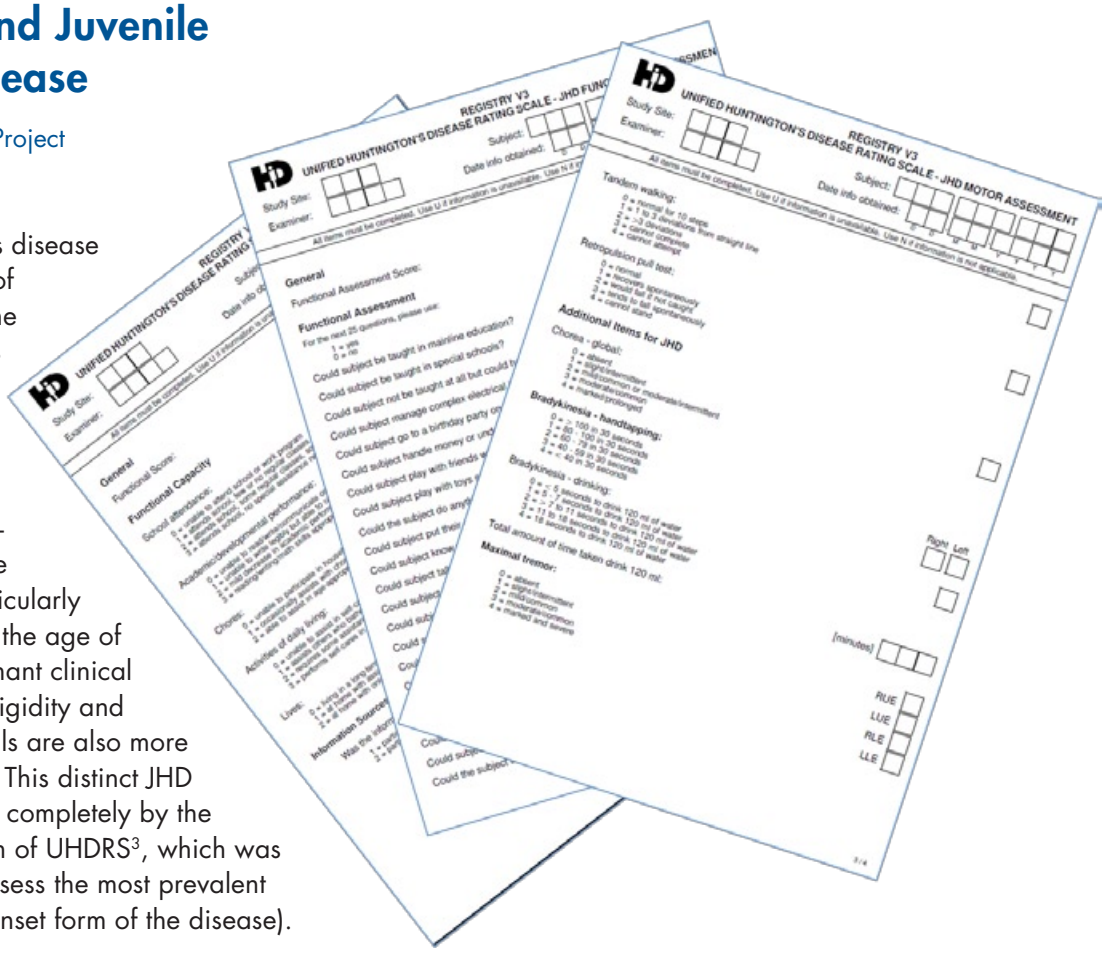
Recruitment is now well underway. For more information about Horizon, including the trial inclusion/exclusion criteria, and a list of participating sites, visit http://www.horizontrial.com/ or contact Jenny Naji (NAJIJJ@cf.ac.uk).

Elections for the EHDN Executive Committee and the EHDN Scientific and Bioethical Advisory Committee

In 2010, one member of the EHDN Executive Committee (EC), Arvid Heiberg (Norway), will rotate out of office. Stephen Dunnett (UK) is standing for re-election to the EC. Three members of the EHDN Scientific and Bioethical Advisory Committee (SBAC) will also rotate out of office. All regular EHDN members can nominate candidates for election to the EC and SBAC committees. To nominate please visit http://www.euro-hd.net/html/network/project/voting before May 31st.

REGISTRY 3.0 and Juvenile Huntington's disease

Olivia Handley, REGISTRY Project Manager, London, UK



Juvenile-onset Huntington's disease (JHD), in which the onset of symptoms occurs before the age of 20 years, accounts for approximately 5% of the HD population. The clinical presentation of JHD can be strikingly different from that of adult-onset HD. In young people affected by JHD, and particularly in those with onset before the age of ten years, there is a dominant clinical picture of bradykinesia[1], rigidity and dystonia[2]. These individuals are also more likely to develop epilepsy. This distinct JHD phenotype is not captured completely by the items of the current version of UHDRS[3], which was originally developed to assess the most prevalent HD phenotype (the adult-onset form of the disease).

In REGISTRY version 3.0, the JHD sub-study has been developed and coordinated by the EHDN JHD Working Group. It will pilot a modified assessment scale in an attempt to characterise this rare phenotype better and to track its course. The JHD assessment, which is accompanied by a training video, takes approximately 30 minutes to complete. It includes a modified motor section of the UHDRS with additional items to assess bradykinesia (hand-tapping, drinking), maximal tremor and global chorea, while still retaining the complete original motor assessment. The UHDRS Functional component (Functional Assessment Scale, Independence Scale, and Total Functional Capacity) has been adapted to measure functional abilities more relevant to young persons with JHD by including questions about schooling, play and epileptic seizures. For instance, the JHD TFC scale replaces 'occupation' with 'school attendance', and 'finances' with 'academic/developmental performance'. In addition, parents/guardians of those affected by JHD will be invited to record symptoms, as well as details of any symptomatic treatments being used, in a diary. This additional information will allow a more in-depth monitoring of the progression of symptoms in JHD and hopefully enable a better understanding of the usefulness of different treatments in managing these symptoms in young HD patients.

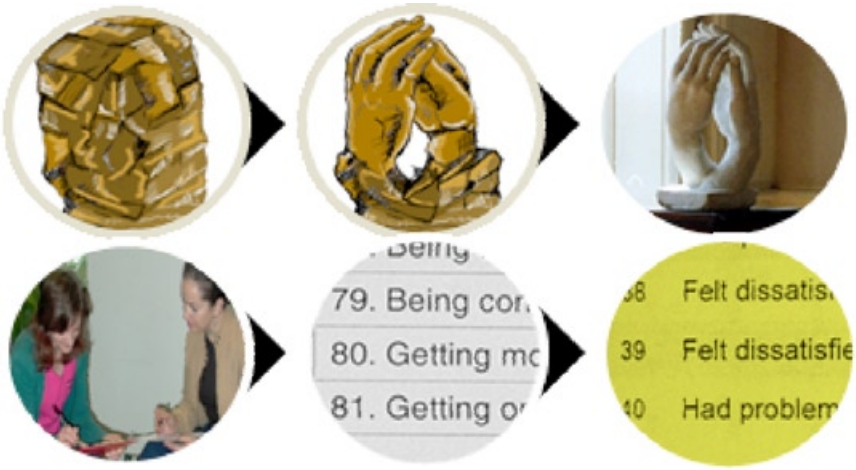
Historically, scale development and evaluation have involved large samples of individuals. This approach is costly, time consuming and, in the case of JHD, where incidence is very rare, not easy. Instead, for this study, a statistical approach known as Rasch analysis will be used, which lends itself to studies restricted by small sample sizes. In the first instance, data will be collected from 30 JHD REGISTRY participants* and subjected to statistical analysis. The outcome of these analyses will provide evidence of which specific items are the most useful for assessing signs and symptoms in JHD and will therefore generate a crucial first step towards developing this scale for wider clinical use.

**In an attempt to maximise the inclusion of all JHD REGISTRY participants, the JHD Assessment Scale has been translated into all languages used in REGISTRY.*

[1] slowing of voluntary movements
[2] sustained muscle contractions that cause abnormal postures and torsions
[3] Unified Huntington's Disease Rating Scale

Quality of Life Working Group

Christiane Lohkamp (DHH, Stuttgart, Germany) and
Aileen Ho (Reading, UK)



Raw Material *Sculpting Process* *Refined Product*

What is quality of life?

Health-related Quality of Life (QoL) encompasses all aspects of well-being, from physical status to social functioning. In recent years, health-related QoL instruments have gained a wide application in assessing the efficacy of treatments targeted at specific patient populations. In Huntington's disease (HD) trials, they are a valuable complement to more objective clinical outcome measures, and reflect the perspective of people living with HD.

Rationale and Aim

A key objective of the EHDN's QoL Working Group is the creation of an HD-specific QoL questionnaire. We believe that this work is fundamentally important because robust patient- and carer-reported outcome measures will be invaluable in future drug trials and non-drug interventions. They will assist in the evaluation of whether or not, from the patients' and carers' points of view, meaningful improvements have been achieved.

Update on activities

The group has developed a questionnaire that will capture health-related QoL in patients with HD. The scientific process of developing a robust and finely-tuned disease-specific questionnaire can be likened to that of creating a finely-chiselled sculpture. It involves the step-by-step transformation of an abstract concept into a solid and tangible object.

We started out with a series of interviews in the U.K., visiting people living with HD and their partners. We listened to their first-hand experience, in order to understand the many and sometimes subtle ways in which HD affected their everyday lives. Like the master sculptor starting out with a roughly hewn chunk of marble, we used these hours of recorded conversations about people's personal experience as the basic matter from which we could develop a questionnaire.

We then distilled this interview material into a list of questions that we could take back to people living with HD, to see if the questions were relevant and adequately represented their everyday experience. We then put this long list of questions to the international community, to get feedback from a large number of other people living with HD across Europe, and beyond. The responses and feedback obtained from this long list prompted a further reduction and rephrasing of the questions in order to arrive (without losing important information) at a better, shorter and easier-to-complete questionnaire. We have now reached a critical and exciting stage where we have a short prototype of the patient questionnaire that we are in the process of validating.

The group is also in the midst of developing a suitable instrument for gauging QoL of carers and is at the stage in this process where pilot data from the revised carer questionnaire is being analysed in order to inform subsequent modifications.

Group membership and meetings

The QoL Working Group has continued to grow steadily with representation from across Europe and beyond. Our next general working group meeting is planned for the EHDN Plenary Meeting in Prague. Core members will also participate in a meeting in the summer. For more information, please contact Christiane Lohkamp (chris.lohkamp@dhh-ev.de) or Aileen Ho (a.k.ho@reading.ac.uk).

Advanced HD Working Group

Nicholas Stoy and Sophie Duport
(The Royal Hospital for Neuro-disability, London, UK)

Why advanced HD?

While the EHDN is making strenuous efforts towards finding disease-modifying or symptomatic treatments for Huntington's disease (HD), the harsh reality for people affected by the disease is the inevitable progression through the different stages. The Advanced HD Working Group (WG), from its inception, is resolutely pragmatic. The advanced stage of the illness is not "like the previous ones, just worse". There are ways to improve not only practice and care but also quality of life for people with advanced HD. There is much support, advice and guidance that can be offered to families, carers and professionals.

Striving towards quality of life in advanced HD

What is advanced HD?

This is an important topic for discussion, not least because it is the name of our new group! More substantively, a working definition of advanced HD was required for validation of the novel late-stage UHDRS[1], first presented at the inaugural meeting of our group by Anne-Catherine Bachoud-Lévi and Katia Youssov. The question of defining advanced HD also sparked a lively e-mail discussion amongst group members. Patients with the most severe disabilities are readily identified, but it was the transition between the 'middle' and 'later' stages that proved most difficult to define. There are three established descriptive scales of disease progression: The total functional capacity (TFC) developed by Shoulson *et al.*, and the more loosely-defined Three Clinical Stage Scale and the Five Clinical Stage Scale. The final consensus was that a TFC score of 5 or below should be used to define 'advanced' HD. In a practical sense, this usually means that the person is significantly dependent on somebody else for his or her personal care.

Aims

The Advanced HD WG aims to map the provision of care for advanced HD patients. This embraces healthcare settings, standards of care, therapies and support provided for those affected by HD (family, carers and professionals). It will support and enable participation of people with advanced HD in REGISTRY, as well as other research projects of the network.

Current projects

1. To design questionnaires for clinicians/organisations to gather information about the provision of care for people with advanced HD, distribute the questionnaires to the network, collect the data and produce a report on the findings.
2. To provide training in the novel 'Late Stage UHDRS' in its current version, and facilitate its implementation.
3. To support the REGISTRY v.3 advanced HD sub-study.

Group membership and meetings

The inaugural meeting of the WG was organised in June 2009 at the Royal Hospital for Neuro-disability, London, UK. The programme included a tour of facilities, with demonstrations (gardening, computer access, music therapy). This was found to be a practical way of sharing good practice and innovative approaches. Future meetings will include, where possible, a tour of the local facilities/installations and demonstrations. The group aims to meet twice a year.

The membership reflects the multidisciplinary approach necessary to care for those with advanced HD. It spans Europe (UK, France, Netherlands, Germany, Italy and Spain are represented at present), and has links to associated members of the Network (USA). The WG is actively seeking scientists and clinicians from all European countries (and worldwide) who share an interest in the advanced stages of HD to join us.

The WG has converging aims and is developing links with other WGs such as Standard of Care, Physiotherapy, Quality of Life and Cognitive Phenotype, amongst others. The 2010 spring meeting of the group takes place in Leiden, Netherlands.

For more information, please contact Nicholas Stoy (nicholasstoy@yahoo.co.uk) or Sophie Duport (sduport@rhn.org.uk).

[1] Unified Huntington's Disease Rating Scale

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt, Germany
June 2010 · Issue 10

Irritability in pre-clinical Huntington's disease

Stefan Klöppel et al., Neuropsychologia (2010), 48: 549-557

Neuronal circuits involved in processing irritation are impaired in pre-symptomatic Huntington's disease.

Background

Irritability, one of the main psychiatric features of Huntington's disease (HD), is related to impulsivity and aggression and involves both the amygdala and the medial orbitofrontal cortex (OFC). The OFC has an inhibitory effect on the amygdala. Put simply, the stronger the activation in the OFC, the weaker the activation in the amygdala, and consequently, the better the control of impulsive aggression and irritability.

Study design

Aiming to study the neuronal circuitry associated with irritability in pre-symptomatic HD, Klöppel el al. developed a task to induce irritation in subjects while measuring their brain activity by functional magnetic resonance imaging (fMRI). They enrolled 16 pre-symptomatic HD mutation carriers (pre-HD) and their companions (controls) into the study.

Two squares on a screen were shown to participants and they were asked to identify the larger one (see figure). They were told that their computer was connected to their partner's computer and that both players had to answer correctly to win the round. Although they had given a correct answer, they were sometimes told that they or their partner had given the wrong answer in order to induce irritation. After the task, participants were examined with different questionnaires to assess irritability, anger, tension and impulsivity.

Results

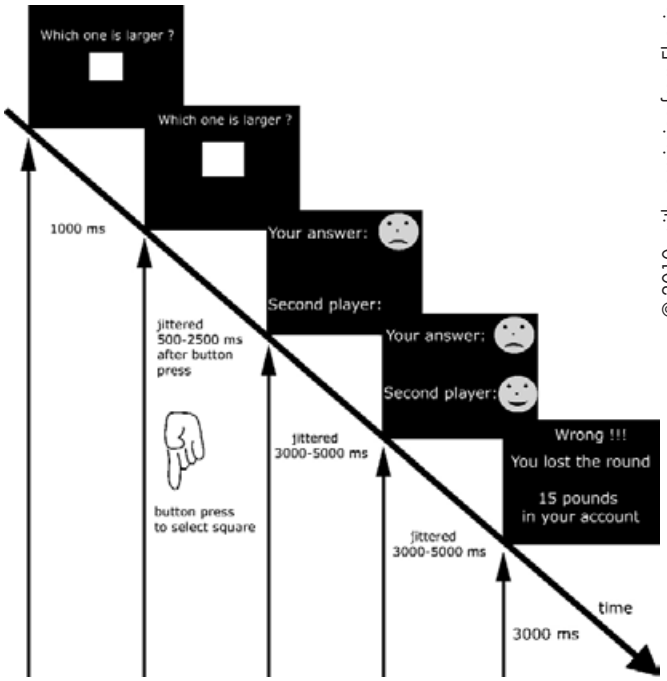
In summary, the study revealed the following findings:

Behavioural data

Both groups performed the task equally well and average scores were in the normal range. No significant differences between the groups were found in any of the questionnaires, including those testing irritability and impulsivity.

Imaging data

In controls, the OFC and amygdala were negatively coupled to each other, i.e. the stronger the activation in the OFC, the weaker the activation in the amygdala.



Overview of the task: Subjects had to identify the larger of two squares shown sequentially and received feedback on the correctness of the answer of the first and second player. A separate screen indicated if the round was won (when both players answered correctly) or lost.

Surprisingly, in the pre-HD group this correlation was positive, i.e. both OFC and amygdala were activated. The difference between the two correlations was statistically significant ($p = 0.05$).

Correlational analysis

In controls, stronger negative emotions caused by negative feedback resulted in greater neuronal activations of the amygdala, a pattern not observed in the pre-HD group ($p = 0.05$ for the interaction). Controls with lower levels of irritation showed higher activations in the OFC. No correlations between the level of irritation and OFC activity were found in pre-HD.

In all three analyses, outcome measures for the pre-HD group did not correlate with estimated years to clinical onset.

Conclusions

Despite similar baseline levels of irritability and task-induced irritation, fMRI analysis detected altered neuronal processing of irritation in pre-HD individuals. Only the control group showed the expected inverse correlation between activation in the amygdala and OFC. These data suggest that the mechanism of controlling impulsive aggression is disrupted in HD mutation carriers and could make them more prone to psychiatric symptoms such as irritability.

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt, Germany
June 2010 · Issue 10

An ovine transgenic Huntington's disease model

Jessie C. Jacobsen et al., Human Molecular Genetics (2010), 19: 1873-1882

This work describes the development of the first transgenic ovine (sheep) model of Huntington's disease.

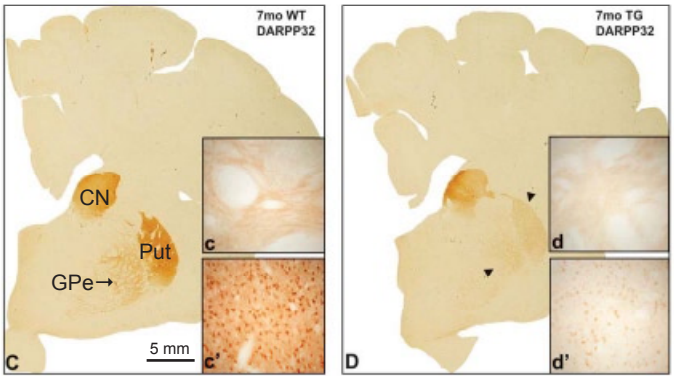
Background

Several mouse models have been developed to study Huntington's disease (HD) and to test candidate drugs before they can advance to clinical trials in humans. However, for some applications, rodent models of HD have disadvantages, such as a short life span (< 3 years) and anatomical differences in the rodent brain compared to the human brain. Such differences inevitably set experimental and therapeutic barriers, and hence, researchers have been looking for other animals that could be used for modelling HD. Sheep are a good alternative because they can live for more than 10 years and their brain anatomy is comparable to that seen in the human brain. Sheep also have large brains that will allow surgical interventions such as cell replacement and gene therapies to be tested.

Methods and Results

Jacobsen et al. created HD transgenic sheep that carry the full-length human *HTT* gene encoding the huntingtin protein with an expanded polyglutamine tract of 73 residues. The transgene DNA was microinjected into pronuclei of single-cell zygotes, and the resulting embryos were transferred into recipient ewes. Of the 150 live births, six lambs were transgenic (designated as animals G_0/1-6). Fluorescent *in situ* hybridisation and Southern blot analysis revealed that in five of the six animals, the transgene had integrated at a unique site, and in those animals there were between 2 and 14 copies of the transgene at each site. The animals with the lowest copy numbers (G_0/5 and G_0/6) were shown to have the highest levels of transgene expression. These two ewes were initially selected for breeding via *in vitro* fertilisation, resulting in the birth of 14 lambs.

The human huntingtin protein could be detected in two of the G_0/5 offspring at one and seven months of age respectively in both central nervous system (CNS) and non-CNS tissues arising from the three primary germ layers. The basal ganglia of wild-type sheep were confirmed to be anatomically and biochemically similar to the human basal ganglia as judged by immunolabelling with calbindin-D28k, substance P and enkephalin antibodies. A first immunohistochemical study of two G_0/5 offspring using the antibodies listed above did not reveal any cell loss or macro/microscopic changes in the basal ganglia of one- and seven-month old animals. However, further analysis of structures known to be vulnerable in HD showed some changes in the CB1 receptor[1] (a presynaptic receptor which mediates reduction in GABA[2] release) and DARPP-32[3] (a marker of medium spiny neurones). The density of CB1 labelling in neurones of the caudate nucleus and globus pallidus was significantly decreased, indicating a reduced or dysfunctional expression of CB1 receptors in these regions. The most striking neuropathological change observed was a significant reduction of DARPP-32 immunoreactivity in the globus pallidus and putamen of the seven-month old G_1/5 transgenic sheep (see figure), which was not observed in a transgenic sheep sacrificed at one month of age. This finding is consistent with the pre-symptomatic striatal D_1 dopamine receptor loss observed in humans.



CN = caudate nucleus; Put = putamen; GPe = external globus pallidus

DARPP-32 immunolabelling in the control (WT) and transgenic (TG) animals at 7 months of age showing the loss of immunoreactivity in the transgenic sheep (arrow heads). Photomicrographs of the globus pallidus (d and c) and putamen (d' and c') demonstrate loss of immunoreactivity in the absence of significant cell loss in the transgenic animal (D) compared to the control (C).

Conclusions

The HD transgenic sheep described here represent a promising animal model for testing candidate drugs and surgical approaches aimed at preventing or delaying the onset and progression of HD.

[1] cannabinoid receptor type 1
[2] gamma-aminobutyric acid (an inhibitory neurotransmitter)
[3] dopamine- and cyclic AMP-regulated phosphoprotein

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt, Germany
June 2010 · Issue 10

Serines 13 and 16 are critical determinants of full-length human mutant huntingtin induced disease pathogenesis in HD mice

Xiaofeng Gu et al., Neuron (2009), 64: 828-840

Changing only two amino acids in the N terminus of huntingtin can significantly reduce the pathogenic potential of the mutant protein *in vivo*.

Background

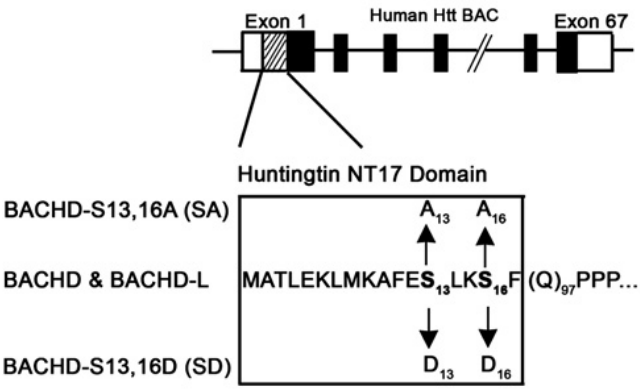
Huntington's disease (HD) is caused by a mutant form of the protein huntingtin (HTT) that carries an expanded polyglutamine tract that begins at amino acid 18. There is evidence to suggest that domains of HTT other than the polyglutamine tract may modulate its toxicity and therefore HD pathogenesis. Posttranslational modifications, i.e. biochemical changes that occur after the protein has been made, have been also implicated in the disease process.

Aims

This study aimed to test whether or not mutation of two amino acids in the N terminus of HTT could influence the toxicity of the expanded protein in BAC[1] transgenic mice expressing full-length human mutant huntingtin with 97 glutamines. The N-terminal 17-amino acid domain of HTT can be phosphorylated on two serines located at positions 13 and 16. These amino acids were mutated to either aspartate (SD), which has a similar structure to a phosphorylated serine, or alanine (SA), which cannot be phosphorylated (see figure). Both mutations were tested in various *in vitro* and *in vivo* assays.

Results

Both the SD and SA mutant proteins retained the function of wild-type HTT, as they were able to rescue *Htt* knockout mice during development and in adult cortical neurones. BACHD transgenic mice with 97 polyglutamines exhibit motor deficits and behavioural impairments in comparison to wild type (WT) mice, and a similar phenotype was observed in mice carrying the SA mutant protein. In contrast, mice with the SD protein did not show any motor deficits in rotarod performance at 2, 6 and 12 months of age. This means that the mutation serine to aspartate abolished the motor phenotype in the BACHD mouse model. A comparable pattern was observed in tests of anxiety and depression, with



Representation of the mutations serine to alanine (S13,16A) and serine to aspartate (S13,16D) within the N terminus of the BACHD construct.

BACHD and SA mice showing an enhanced anxiety-like behaviour, and SD mice behaving like WT mice.

Striatal and cortical volumes at 12 months of age were reduced in SA mice (as in BACHD mice), but not in SD or WT mice. This means that the SD protein does not cause degeneration of the brain, i.e. it is not pathogenic *in vivo*. Protein aggregates were detected in the cortex and striatum of both BACHD and SA mice, but not in SD or WT mice. In an assay to test protein aggregation *in vitro*, an SA containing fragment of mutant HTT was shown to aggregate more rapidly, whereas the SD containing fragment aggregated more slowly. Mutation at both serines 13 and 16 altered protein aggregation in a cumulative manner by either slowing down the process or by redirecting it to a different pathway (reduced fibril formation).

Conclusions

SD but not SA mutations in the context of full-length mutant HTT can prevent motor and behavioural deficits, selective neurodegeneration and the accumulation of protein aggregates in BACHD transgenic mice. The authors concluded that the two serines may act as a molecular switch to regulate disease pathogenesis and that targeting this pathogenic mechanism may have a dramatic therapeutic impact.

[1] bacterial artificial chromosome

Upcoming Meetings 2010

June 8-13	19th Annual Meeting of the International Behavioral Neuroscience Society, Sardinia, Italy http://www.ibnshomepage.org/annualmtg10.htm
June 10-11	EHDN Cognitive Phenotype Working Group Meeting, Manchester, UK http://www.euro-hd.net/edit/network/news
June 13-17	14th International Congress of Parkinson's Disease and Movement Disorders, Buenos Aires, Argentina http://www.movementdisorders.org/congress/congress10/
June 19-23	20th Meeting of the European Neurological Society, Berlin, Germany http://www.congrex.ch/ens2010/
June 24	EHDN Biomarkers Working Group Meeting, Lund, Sweden https://www.euro-hd.net/html/network/news
June 25-27	25th National Convention of the Huntington's Disease Society of America, Raleigh, NC, USA http://www.hdsa.org/events/index.html?month=6&year=2010
July 3-7	7th Forum of the Federation of European Neuroscience Societies, Amsterdam, The Netherlands http://fens2010.neurosciences.asso.fr/
July 8	EHDN UK Investigator's Meeting, Birmingham, UK http://www.euro-hd.net/edit/network/news
July 8	Meeting of the UK and Ireland Huntington's Alliance (HDA, SHA, HDAI and HDANI), Dublin, Ireland http://www.hda.org.uk/hda/events.php
July 10-15	International Conference on Alzheimer's Disease 2010, Honolulu, HI, USA http://www.alz.org/icad/
Aug 4	EHDN Biological Modifiers Working Group Meeting, Boston, MA, USA https://www.euro-hd.net/html/network/news
Aug 4-7	HD2010: "The Milton Wexler Celebration of Life", Cambridge, MA, USA http://www.regonline.com/HD2010
Aug 28-Sept 1	23rd Congress of the European College of Neuropsychopharmacology, Amsterdam, The Netherlands http://www.ecnp.eu/emc.asp?pageId=1516
Sept 3-5	6th Bi-Annual Plenary Meeting of the European Huntington's Disease Network, Prague, Czech Republic https://www.euro-hd.net/html/ehdn2010

EHDN 2010 Additional Meetings, Prague, Czech Republic
https://www.euro-hd.net/html/ehdn2010/meetings

Meetings of EHDN Working Groups:

Sept 1	Motor Phenotype
Sept 2	Quality of Life
	Young Adults
	Genetic Testing and Counselling
	Symptomatic Research and Therapy
	Cognitive Phenotype
	Neuroprotective Therapy
	Advanced HD
Sept 3	Environmental Modifiers
Sept 4	Physiotherapy
Sept 5-6	Behavioural Phenotype
Sept 7	Genetic Modifiers

Sept 5-6	13th Bi-Annual Meeting of the European Huntington Association, Prague, Czech Republic
Sept 25-28	14th Congress of the European Federation of Neurological Societies, Geneva, Switzerland http://efns2010.efns.org/
Sept 30	Annual General Meeting and Carer's Meeting of the Huntington's Disease Association Northern Ireland, Newtownards, Northern Ireland http://www.hdani.org.uk/
Oct 1-3	Family Conference of the UK Huntington's Disease Association, Telford, UK http://www.hda.org.uk/hda/events.php
Oct 16	4th Annual Huntington Disease Clinical Research Symposium, La Jolla, CA, USA http://www.huntington-study-group.org/NewsEvents/EventsUpcomingMeetings/HuntingtonDiseaseClinicalResearchSymposium/tabid/62/Default.aspx
Oct 23-24	Convention of the German Huntington Help, 40th Anniversary of the German Huntington Self-Support Group, Duderstadt, Germany http://www.huntington-hilfe.de/index.php/deutsch/Start/Termine
Oct 28-31	4th World Congress on Controversies in Neurology, Barcelona, Spain http://comtecmed.com/cony/2010/
Oct 30-31	Meeting of the Danish Huntington Association, Fredericia, Jutland, Denmark http://www.lhc.dk/
Nov 12-13	1st National Congress on Huntington's Disease, Madrid, Spain
Nov 13-17	40th Annual Meeting of the Society for Neuroscience, San Diego, CA, USA http://www.sfn.org/am2010/