January 2011 · Issue 12

EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

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Happy New Year

from all at EHDN

Enjoy reading this year's first edition. Don't forget to check the calendar on the back page for conferences in 2011!

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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 Townhill (Cardiff University, Cardiff, UK), Christiane Lohkamp (IHA, Stuttgart, Germany), Gabriele Stautner (Artifox Communication Design, Ulm, Germany).

REGISTRY 3.0 and behavioural-phenotype sub-studies

Olivia Handley, REGISTRY Project Manager,
London, United Kingdom

The protocol for behavioural assessment of Huntington's disease (HD) has been modified in REGISTRY version 3.0. The revised assessment protocol includes the interview-based Problem Behaviours Assessment (PBA, both short and full versions), and the self-report-based Hospital Anxiety and Depression Scale combined with the Snaith Irritability Scale (HADS-SIS). [Note that the PBA should only be administered by trained raters. Otherwise, the UHDRS-Behaviour should be used. Note also that the Hamilton Depression Rating Scale (clinician-based report) and the Becks Depression Inventory (self-report) will no longer be administered as part of REGISTRY]. The PBA and HADS-SIS are standard clinical assessments that capture neuropsychiatric features of HD and provide an overall impression of the frequency and severity of key neuropsychiatric problems over a period of 4 weeks prior to the interview. Whilst they are considered to be sufficient for identifying a clinical problem, there is a clear additional need to identify robust clinical outcome measures of specific psychiatric features that can both inform clinical practice and provide a reference point for future trials of new treatments as they are developed.

The Behavioural Phenotype Working Group has proposed a series of REGISTRY sub-studies aimed at testing the suitability of existing measures of specific behaviours in a large HD population. The three sub-studies are:

- **The APATHY sub-study.** None of the available apathy measures are validated in HD patients. The APATHY sub-study includes parallel companion-based and patient/clinician-based versions of the 18-item Apathy Evaluation Scale (Marin et al., 1991, Psychiatry Res. 38: 143-162). The companion version is based on direct observation of patient's behaviour in the home environment. The clinician version is based on clinical observations and the subject's self-report during interview.

- **The IRRITABILITY sub-study.** Irritability is a frequently reported neuropsychiatric symptom, but reduced awareness in HD patients may affect the reports of symptoms in more advanced stages of HD. The IRRITABILITY sub-study includes a companion-based Irritability Scale for HD (ISHD: a one-week diary-type assessment) and the 14-item Irritability Scale (Chatterjee et al., 2005, J Neuropsychiatry Clin. Neurosci. 17: 378-83; companion and self-report versions).

- **The Frontal System Behavioral Scale (FRSBE) sub-study.** The modified 24-item FrSBe (Grace et al., 1999, Assessment 6: 269-84) has shown sensitivity in premanifest HD populations (Duff et al, 2010, J Neuropsychiatry Clin. Neurosci. 22: 196-207). The FRSBE sub-study will examine rates of "frontal" behaviours (those thought to originate from deficits in frontal cortex function including apathy, executive dysfunction and disinhibition) across a range of HD disease stages. The FrSBe includes patient and companion versions.

These sub-studies share three common goals: First, to investigate differences between patient-based and companion-based assessment methods; second, to understand more clearly frontal behaviours in HD, and finally, to investigate the association between outcome measures, various demographic and clinical characteristics, and other neuropsychiatric scales (e.g. PBA-s, UHDRS behaviour, HADS-SIS).

Data will be collected at baseline and after one year. In the first instance, the sub-studies will be coordinated in English-, Dutch-, and German-speaking countries. Results will hopefully identify appropriate sub-scales that can be used in clinical interventions as well as inform power calculations for future clinical trials aimed at modifying HD symptom frequency and severity.

HD – Hidden no more

On 30th June 2010 an All Party Parliamentary Group (APPG) for Huntington's disease was established in the UK, to promote greater understanding and awareness of HD.

Charles Sabine, previous NBC war correspondent, who carries the HD mutation, inspired and led the group that worked together over the course of a year to establish the APPG.

The APPG was launched at the Houses of Parliament with a reception at which Members of Parliament were informed about the many issues relating to Huntington's disease.

The launch was a colourful affair, attended by over 500 family members with green T-shirts and balloons to declare that Huntington's disease is 'hidden no-more'.

The APPG aims to eradicate stigma, lobby for the best possible care and promote research into HD.

Young Adults Working Group

Ruth Sands (HDA Neurosupport Centre, Liverpool, UK) and Michael Orth (EHDN Central Coordination, Ulm, Germany)

Introduction

The prevalence of Huntington's disease (HD) is about 4-10 per 100,000 and approximately 4-5 times as many – about 150,000 people in Europe – are at risk of developing the disease. There is currently an increase in the number of clinical trials to test the efficacy of novel therapeutics for HD. This gives us much hope that the treatment of those with HD will improve in the foreseeable future. The Holy Grail, however, is a treatment that will prevent or delay the onset of HD in someone who carries the HD gene mutation. Inevitably, the development of such a therapy will require that clinical trials are performed in healthy HD mutation carriers. There is therefore an increasing interest and need to study this population of individuals. Novel tools that can be used to track clinically relevant changes for use in these future trials need to be developed. Yet young adults who have been tested and are known to carry the HD mutation, as well as those that are 'at-risk' and have a 50% chance of developing HD, are often overlooked in the services that are provided for people with HD. Few young adults are currently participating in ongoing clinical studies such as REGISTRY.

'At risk' also means that individuals grow up in a family with HD under the 'sword of Damocles' of having, or not having, inherited the HD mutation. This population needs genetic counselling, help and advice on making important life decisions as well as treatment for medical conditions. We know too little about their other needs. Improved knowledge in these areas may inform best clinical practice and provide a standard set of guidelines for establishing a clinic dedicated to these individuals. In addition, support networks for young adults are lacking in many countries. The Young Adults Working Group (YAWG) has been set up to address these issues.

Mission statements

We aim to

1. Identify the clinical needs of young people at risk for HD, both HD gene mutation carriers and non-mutation carriers in HD families
2. Facilitate their participation in ongoing clinical studies such as REGISTRY
3. Facilitate and initiate research with a literature review of the field
4. Increase the spread of information to this group
5. Facilitate the establishment of a support network for young people at risk of carrying the mutated HD gene

Projects

SURVEY – A survey to gain information about the needs of Young Adults across Europe.

LITERATURE REVIEW – A review of the literature in relation to pre-symptomatic gene carriers, with the aim of identifying potential assessment tools and areas for research.

WEBSITE – A website that will enable young adults to interact with research in an accessible and informative way.

REGISTRY BOOKLET – The group has produced a REGISTRY booklet for young adults that will be launched across Europe with the aim of increasing awareness and enabling more young adults to participate.

INFORMATION BOOKLET – A booklet available for electronic distribution to young adults that will cover key SUPPORT NETWORKS to make links between the young adults and their lay associations with the aim of creating support networks for young people across Europe.

Group membership

The YAWG has representation from 11 European countries, the USA and Canada. The group consists of family members, clinicians and representatives from lay organisations. For more information, please contact Ruth Sands (ruthunti@gotadsl.co.uk) or Michael Orth (michael.orth@uni-ulm.de).

Symptomatic Research and Therapy Working Group

Josef Priller (Charité, Berlin, Germany) and Daniel Ecker (Focus, Neuss, Germany)

Despite the myriad of available medicinal and other treatment options, symptomatic treatment of HD has made little progress over the past decades. Our Working Group would like to change this situation and contribute to improving the quality of life of HD patients.

Aims

The key objectives of this Working Group are to identify the most pressing medical needs of HD patients and to assess available treatment choices. Since much of the published evidence for treatment options is anecdotal or stems from poorly controlled and rather small-scale clinical trials, we aim to conduct randomised, controlled clinical trials (level I trials) to provide better evidence for therapeutic interventions in HD.

Update on activities

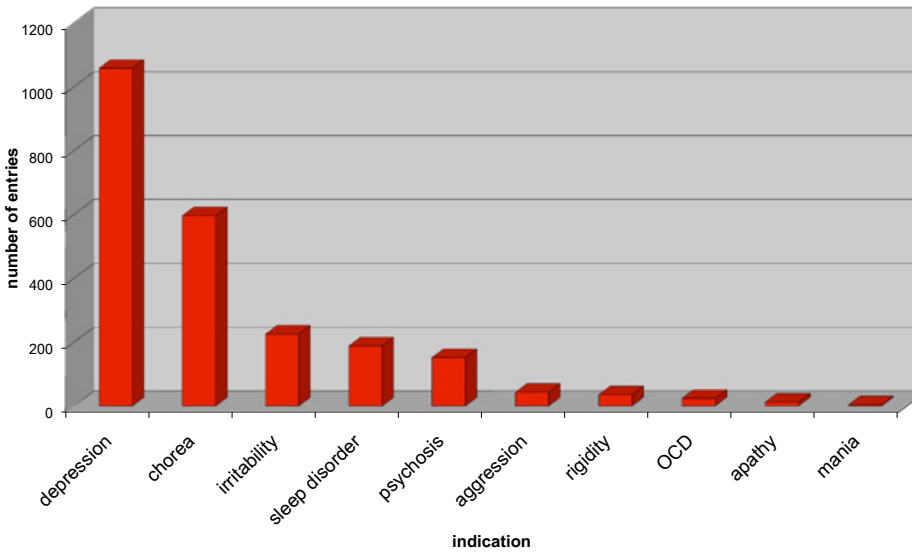
At the first meeting of the Working Group, the following symptoms were identified as key targets for the symptomatic treatment of HD: apathy, anxiety, bradykinesia, cognitive impairment, depression, dysphagia, dystonia, irritability/aggression, pain, perseveration, psychosis, side effects of antipsychotic therapy, sleep disorder and weight loss. Treatment of juvenile HD was also discussed.

Next, we performed a systematic evaluation of prescription practices in HD centres across Europe to assess whether the above clinical needs are met. Based on more than 7,000 concomitant medication reports from the REGISTRY database between 2004 and 2007 (see figure) and a specifically designed drug use survey for all EHDN members (available at http://www.euro-hd.net/html/projects/surveys/dus/), we found that many of the prevalent clinical symptoms of HD are not medicated. Moreover, medication choices were often influenced by cultural background, rather than resting upon evidence-based criteria.

We have decided to evaluate and establish efficient symptomatic therapies for HD based on studies that fulfil the criteria of evidence-based medicine. Treatments being evaluated in this manner include tiapride and tetrabenazine for the treatment of chorea, and propranolol for the treatment of irritability. An international, multicenter, randomised and placebo-controlled phase II clinical trial to assess the use of bupropion for the treatment of apathy in HD will be sponsored by the Charité Hospital (Berlin) with funding from the Huntington Society of Canada/Huntington Study Group and EHDN. We expect that these trials will improve our diagnostic tools and provide level I evidence for symptomatic therapies of HD.

Membership

The Group currently consists of 38 members, and we meet once a year. If you are interested in joining, please contact Josef Priller (josef.priller@charite.de) or Daniel Ecker (daniel.ecker@focus-cdd.de).



Summary by Diana Raffelsbauer, Freelance Medical Writer, PharmaWrite, Germany
January 2011 · Issue 12

Comprehensive behavioral testing in the R6/2 mouse model of Huntington's disease shows no benefit from CoQ_{10} or minocycline

Liliana B. Menalled et al., PLoS ONE (2010), 5: e9793

Coenzyme Q_{10} and minocycline failed to improve motor function and general health in R6/2 mice.

Background

Coenzyme Q_{10} (CoQ_{10}) is a component of the electron transport chain in mitochondria, the organelles that generate energy for cells. Besides improving energy supply, CoQ_{10} also acts as an antioxidant and, therefore, has been used as a dietary supplement. Minocycline is an antibiotic of the tetracycline group. In both cell and animal models of Huntington's disease (HD), minocycline has been reported to have beneficial effects on various processes implicated in HD pathogenesis.

Although both drugs have been used off-label in HD patients, previous efficacy studies in transgenic HD mice have yielded conflicting results. Using recently published best practices for both husbandry and the preclinical assessment of compounds in HD mouse models, the present study aimed to re-evaluate the therapeutic effects of CoQ_{10} and minocycline in R6/2 mice.

Materials and Methods

Wild type and R6/2 transgenic mice (expressing a mutant version of the N-terminus of human huntingtin) were assigned to one of the following treatments:

- diet supplemented with 400 mg/kg CoQ_{10} or 1200 mg/kg CoQ_{10} per day
- food supplemented with 200 mg/kg minocycline or 750 mg/kg minocycline per day
- intraperitoneal injections of 5 mg/kg minocycline or saline (as control) per day.

Control groups received unsupplemented food. Researchers were blind regarding the treatment administered.

Body weight was monitored and the following behavioural assays were performed: rotarod, open field, rearing-climbing and forelimb grip strength. Effects on survival were determined. CoQ_{10} and minocycline levels in plasma and brain samples were also measured.

Results

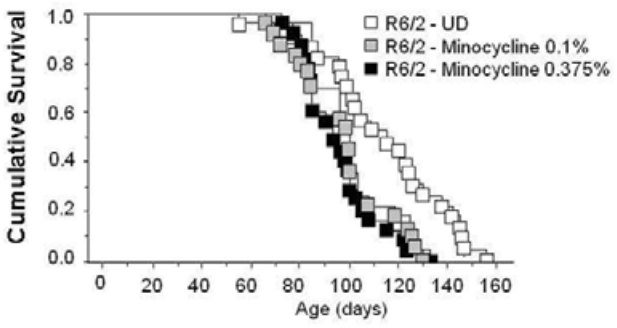
Neither dose of CoQ_{10} showed beneficial effects on survival, body weight, latency to fall from the rotarod, locomotor activity and rearing in the open field, climbing in the rearing-climbing test and grip strength performance, except for small or transient changes. A similar lack of improvement was obtained with minocycline delivered by injection. The low oral dose of minocycline transiently increased body weight and rearing, whereas the high dose decreased these measures. In the other tests, the effects were either slightly and transiently beneficial, negative or not detectable. More importantly, both oral doses of minocycline had a negative effect on survival (see figure).

Conclusions

Neither CoQ_{10} nor minocycline had significant beneficial effects on measures of behaviour, motor function, body weight and survival in the R6/2 mouse model. High doses of minocycline, on the contrary, reduced survival.

Implications for human trials

DOMINO, a phase II clinical trial of minocycline in HD patients conducted by the Huntington Study Group (USA) concluded in 2009 that "minocycline is not associated with a meaningful slowing of the rate of functional decline and that further study of minocycline administered at 200 mg/day in HD is not warranted". Two clinical trials are ongoing to study the efficacy and safety of CoQ_{10} in manifest and premanifest HD subjects, respectively: the 2CARE and PREQUEL studies. Results of the PREQUEL trial are expected in February 2011 and of the 2CARE study in 2014.



Treatment with 200 mg/kg (0.1%) minocycline and 750 mg/kg (0.375%) minocycline reduced survival of R6/2 mice in comparison to mice fed with unsupplemented diet (UD).

Summary by Diana Raffelsbauer, Freelance Medical Writer, PharmaWrite, Germany
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A randomized, placebo-controlled trial of latrepirdine in Huntington's disease

Karl Kieburtz et al., Archives of Neurology (2010), 67: 154-160

Latrepirdine is well tolerated and safe. Is it also efficacious? A silver lining on the horizon of HD.

Background

Latrepirdine (Dimebon) is an antihistaminic drug that was introduced to treat allergies 27 years ago. Recently, latrepirdine has been shown to enhance neuronal survival and improve learning and memory in preclinical studies of Alzheimer's disease (AD) and Huntington's disease (HD). The drug acts by stabilising the membranes of mitochondria. This activity may prevent programmed cell death and improve neuronal function.

A placebo-controlled trial in AD patients had shown significant improvements in cognition, behaviour and functional capacity at 6 and 12 months. An open-label, dose-escalation study in HD patients found that doses up to 20 mg 3 times a day are well tolerated. The aim of the present study was to test the tolerability and safety of this dosage, and to explore its effects on the clinical symptoms of HD. The trial was sponsored by Medivation Inc. and managed by the Huntington Study Group (HSG).

Subjects and Methods

Ninety-one participants with mild to moderate HD (UHDRS-TFC[1] ≥ 5) were assigned to receive either 20 mg of latrepirdine or placebo 3 times daily for 90 days. Group assignment was 1:1, randomised and double-blind. Safety and tolerability were assessed by standard laboratory and clinical examinations, such as physical examinations, vital sign measurements, ECG[2], urine analysis and blood tests. The primary outcome measure was the ability of participants to complete the study on the assigned dose. Adverse events were monitored. Efficacy was rated using the UHDRS (motor, behavioural, cognitive and functional subscales), MMSE[3] and the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog).

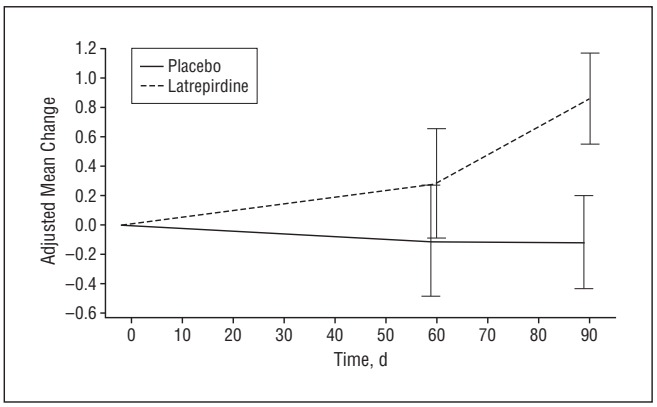
Results

Latrepirdine was well tolerated, with 87% of participants completing the study on the 60 mg/day dose (vs. 82% in the placebo group). Overall, 70% of subjects on latrepirdine reported an adverse event (vs. 80% on placebo). The only adverse events reported more frequently in the latrepirdine group were headache (15%) and sleepiness (7%), but this difference was not statistically significant compared to placebo. No clinically relevant differences in the laboratory and clinical tests were detected between the two groups.

Latrepirdine improved cognitive performance on the MMSE (treatment effect = 0.97 point, p = 0.03) compared to a stable performance in the placebo group (see figure). In a subgroup of patients, who were more cognitively impaired at baseline, the treatment effect was 1.63 points (p = 0.008). However, no effects were seen on the UHDRS cognitive tests or the ADAS-cog scale, or the UHDRS motor and functional assessments. The UHDRS behavioural scores improved on latrepirdine, but the group difference was not significant.

Conclusions

Administration of 20 mg latrepirdine 3 times daily was well tolerated and safe during the 90-day treatment period and may improve cognition. The effects of latrepirdine on the clinical symptoms of HD are being further studied in the ongoing clinical trial HORIZON (a collaborative project of EHDN and HSG sponsored by Medivation and Pfizer; for further details, see EHDN *News* of June 2010).



Mean changes in MMSE scores over a period of 90 days. There was an improvement in the group treated with latrepirdine but not in those treated with placebo.

1 Unified Huntington's Disease Rating Scale – Total Functional Capacity
2 electrocardiography
3 Mini-Mental State Examination, a test to screen for cognitive impairment

Summary by Diana Raffelsbauer, Freelance Medical Writer, PharmaWrite, Germany
January 2011 · Issue 12

Cell loss in the motor and cingulate cortex correlates with symptomatology in Huntington's disease

Doris C. V. Thu et al., Brain (2010), 133: 1094-1110

The extent of cell loss in two different regions of the cerebral cortex varies greatly between HD patients depending on whether the main symptoms they present are in the motor domain, behavioural domain, or both.

Background

The symptoms of Huntington's disease (HD) vary markedly between individuals. Some patients show pronounced motor symptoms but only mild behavioural and/or cognitive disturbances. Others present severe mood problems and cognitive impairments but minimal movement abnormalities, while others are affected in all three domains to a similar extent. The cause of this variation is unknown.

Tippett et al. (Brain 2007, 130: 206-21) have shown previously that mood dysfunction correlates with gamma-aminobutyric acid (GABA) receptor and cell loss in the striatum. However, in recent years, a number of studies have shown that atrophy of the whole brain and thinning of the cerebral cortex occur in premanifest and manifest HD, demonstrating that HD pathology extends beyond the striatum. The present study aimed to examine whether or not the symptom variability in HD can be related to different patterns of neurodegeneration in the cerebral cortex.

Methods

The study was double-blinded and used unbiased stereological cell counting methods to quantify cell loss in the primary motor cortex and anterior cingulate cortex in the *post mortem* brains of 12 HD patients and 15 control subjects. The primary motor cortex is involved in the control of movements, whilst the anterior cingulate cortex plays a role in the regulation of emotions and mood.

Detailed information of motor and behavioural symptoms was collected retrospectively from family members and from mining clinical records. HD patients were classified into three groups depending on whether their dominant symptoms were in the motor domain, behavioural domain, or both domains.

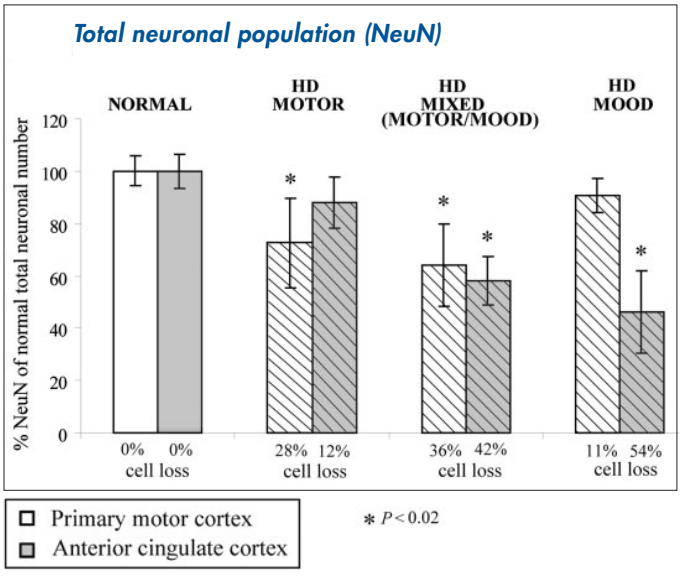
Results

The total average number of neurones in both primary motor cortex and anterior cingulate cortex was significantly reduced in HD patients compared to control subjects. Surprisingly, the extent of cell loss varied greatly between individuals, ranging from 0 to 51% in the motor cortex and from 0 to 65% in the cingulate cortex. Some brains that showed major cell loss in the motor cortex had minimal cell loss in the cingulate cortex, whereas other brains showed the opposite trend.

The pattern of cell loss clearly correlated with the symptom phenotype (see figure). Brains from individuals with predominantly motor symptoms showed major cell loss in the motor cortex with no significant cell loss in the cingulate cortex. By contrast, brains from patients in whom mood was primarily affected showed extensive cell loss in the cingulate cortex, with no significant cell loss in the motor cortex. Brains from individuals with mixed motor and mood symptoms showed considerable cell loss in both the motor and cingulate cortices. In each of the affected regions, the neurones that remained showed marked pathological changes in morphology. There was no correlation between CAG repeat number and cell loss from either region.

Conclusions

The heterogeneous pattern of cell loss in the motor and cingulate cortices correlates with the variability of motor and mood symptoms presented in each case. The authors concluded that the HD mutation produces variable topographical patterns of cortical neurodegeneration that contribute to specific symptoms.



Total number of neurones (expressed as a percentage of the control) in the primary motor cortex and anterior cingulate cortex of the three different HD groups (motor, mixed and mood).

Upcoming Meetings 2011

Jan 28-30	4th European Neurological Conference on Clinical Practices, Lisbon, Portugal www.paragon-conventions.net/enccp2011/
Feb 7-10	6th Annual CHDI Conference on HD Therapeutics, Palm Springs, CA, USA https://www.regonline.com/builder/site/Default.aspx?EventID=909676
Feb 21-22	7th Annual Update Symposium on Clinical Neurology & Neurophysiology, Tel Aviv, Israel www.isas.co.il/neurophysiology2011/
Mar 9-13	10th International Conference on Alzheimer's & Parkinson's Diseases, Barcelona, Spain www2.kenes.com/adpd/Pages/Home.aspx
Mar 12-15	19th EPA European Congress of Psychiatry, Vienna, Austria www2.kenes.com/epa/Pages/home.aspx
Mar 26-29	26th International Conference of Alzheimer's Disease, Toronto, Canada www.adi2011.org/default.aspx?PageID=Home
April 9-16	63rd Annual Meeting of the American Academy of Neurology, Honolulu, HI, USA www.aan.com/go/am11
April 17-20	British Neuroscience Association Bienniale Meeting, Harrogate, UK www.bna.org.uk/events/view.php?permalink=2UBKYZP4BY
Apr 22-24	XIII International Meeting of the Polish HDA Members and HD Conference, Warsaw, Poland www.huntington.pl/
May 28-31	21st Meeting of the European Neurological Society, Lisbon, Portugal www.congrex.ch/ens2011
May 28-31	European Human Genetics Conference 2011, Amsterdam, The Netherlands https://www.eshg.org/eshg2011.0.html
June 5-9	15th International Congress of Parkinson's Disease and Movement Disorders, Toronto, Canada www.movementdisorders.org/congress/congress11/
June 5-10	The Gordon Research Conference on CAG Triplet Repeat Expansion Disorders, Il Ciocco, Italy www.grc.org/programs.aspx?year=2011&program=cag
June 24-26	26th Annual National Convention of the Huntington's Disease Society of America, Minneapolis, MN, USA www.hdsa.org/national-convention/convention.html
Sept 11-14	5th World Congress on Huntington's Disease, Melbourne, Australia www.worldcongress-hd2011.org/
Sept 29-Oct 1	Asia Pacific Stroke Conference, Colombo, Sri Lanka www.apsc2011.com/
Oct 9-14	14th European Congress of Neurosurgery, Rome, Italy www2.kenes.com/eans/Pages/home.aspx
Oct 11-15	12th International Congress of Human Genetics, Montreal, Canada www.ichg2011.org/
Oct 13-15	21st Alzheimer Europe Conference, Warsaw, Poland www.alzheimer-europe.org/EN/Conferences/Warsaw-2011
Oct 13-16	5th World Congress on Controversies in Neurology, Beijing, China comtecmed.com/cony/2011/
Oct 20-22	1st European Neurorehabilitation Congress, Merano, Italy www.enrc2011.eu/
Oct 20-23	7th International Congress on Vascular Dementia, Riga, Latvia www2.kenes.com/vascular2011/Pages/home.aspx
Nov 12-16	Neuroscience 2011: Annual Meeting of the Society for Neuroscience, Washington, DC, USA www.sfn.org/am2011/
Nov 12-17	20th World Congress of Neurology, Marrakesh, Morocco www2.kenes.com/wcn/Pages/Home.aspx
Dec 11-14	XIX World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders, Shanghai, China www2.kenes.com/parkinson/Pages/Home.aspx