European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Annual Meeting

Encouraging findings from clinical trials with new oral disease-modifying agents being developed to treat multiple sclerosis (MS), further evidence from epidemiological studies on the role of vitamin D status in the risk of developing MS and a greater emphasis on understanding MS in children were key themes emerging at this year’s European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) annual meeting.

Swedish study confirms MS link with low exposure to ultraviolet radiation

Low exposure to ultraviolet (UV) radiation is associated with increased risk of developing MS among both women and men, according to latest results from the ongoing Epidemiological Investigation of MS (EIMS). This is a population-based case-control including the general population aged 16-70 years in defined areas of Sweden.

Results based on 1231 incident cases of MS and 2682 controls showed that people with the lowest previous UV exposure had nearly twice the risk of developing MS compared to those reporting the highest exposure (odds ratio 2.9, 95% confidence interval 1.4-2.7). There was a statistically significant inverse trend – the lower UV exposure, the higher risk of MS. Vitamin D levels were significantly lower among cases than controls (p=0.04), with a significant inverse trend between levels of vitamin D and MS. The research group found no association between exposure to UV radiation and vitamin D levels and HLA-DRB1*15.

Reporting the findings, the group from the Karolinska Institute, Stockholm, said, “Low exposure to ultraviolet radiation is associated with an increased risk of developing MS among both women and men. Together with the observed association between vitamin D and MS, these findings support the hypothesis that vitamin D is causally related to risk of MS.

Canadian study in children with acute demyelination reveals MS risk factors

Vitamin D levels and the HLA-DRB1*15 allele are independent risk factors for MS in children, show new results from the Canadian Pediatric Demyelinating Disease Network. The study included 332 children (aged under 16 years) with acute demyelination recruited from 23 sites across Canada and monitored prospectively with serial clinical and MRI visits. During follow-up, MS was diagnosed in 63 children (19%).

Results revealed that children carrying at least one copy of the HLA-DRB1*15 allele had nearly three times the risk of developing MS than those without (hazard ratio 2.84). Children of European ancestry showed particularly high risk of developing MS if they carried the allele. In a preliminary subgroup of 83 children, in which 19 (23%) were diagnosed with MS, DRB1*15 carriers had more than a ten-fold risk (HR 10.57) compared to noncarriers. Increasing levels of serum 25-dehydroxy vitamin D were associated with reduced risk of MS, with a hazard ratio of 0.87 for each 10nmol/l increase. Mean 25-(OH) D levels within 40 days of the onset of symptoms were lower in children that went on to develop MS (mean 52 nmol/l) than in those that did not (66.2nmol/l) (p=0.004).

Heather Hanwell, from the University of Toronto, told the meeting, “Paediatric MS is not nearly as rare as we thought; three to ten per cent of MS cases begin to experience clinical signs and symptoms in childhood and adolescence.” She added, “The HLA-DRB1*15 allele and circulating 25-dehydroxy vitamin D levels are independently associated with MS diagnosis following acute demyelination in children. Further study is justified to determine whether improving vitamin D status from conception through childhood will reduce MS risk.”

Five year follow-up data show alemtuzumab achieves sustained reduction in relapses and disability in multiple sclerosis

Patients with multiple sclerosis (MS) treated with alemtuzumab show sustained reduction in relapses and disability after five years, according to results reported at ECTRIMS. The CAMMS223 study randomised 334 patients with early relapsing remitting MS to alemtuzumab (at doses of either 12mg/day or 24mg/day) for up to five days in two or three cycles, or to interferon beta-1a (44mcg, three times/week).

Results after five years of follow-up showed consistently lower annualised relapse rates in patients treated with alemtuzumab (0.11) compared with those randomised to interferon beta-1a (0.35). Only 13% of patients in the alemtuzumab group demonstrated sustained increase in disability compared with 36% of those taking interferon beta-1a.

“These long-term follow-up data suggest that alemtuzumab may have a significant disease modifying effect in patients with early active, relapsing-remitting MS,” said Dr Alasdair Coles, Senior Lecturer, University of Cambridge, UK, and lead investigator of the study. He added, “The efficacy after five years is as good as we saw after three years, despite patients being given no more treatment with alemtuzumab, so we are seeing a durable effect.”

Further results for patients with highly active relapsing remitting MS in the study (just over half of those taking part) showed the annualised relapse rate was reduced by 81% in those treated with alemtuzumab (0.09) compared to those treated with interferon beta-1a (0.47), after three years’ follow-up. 91% of alemtuzumab-treated patients were free of sustained accumulation of disability compared to 75% of those in the comparator group.

These patients all had highly active disease; with at least two relapses in the year before treatment in the trial, and at least one gadolinium enhancing brain lesions identified by magnetic resonance imaging.

Two phase 3 trials are currently further evaluating alemtuzumab in the treatment of MS, with results expected in 2011.

Global study confirms increase in MS in women

The ratio of women developing MS compared to men has increased over the last 60 years, revealed results from the MSBase Registry. Researchers identified cases of definite MS with birth years ranging from 1930 to 1989 through the international registry and calculated the female to male sex ratios. Figures were adjusted to take account of any differences in the birth rates for each country using national birth registers.

Results for the whole population of 11,028 patients showed a progressive increase in the adjusted female/male sex ratio from the first to the last decade, from 1.78 to 2.96 (p=0.05 for the trend). This increase was more pronounced in northern countries, where the sex ratio increased from 1.93 to 4.55 (p=0.0001 for the trend).

“The results confirm a worldwide increase of the female/male sex ratio among MS patients, and demonstrate a greater increase in northern countries. These data seem to suggest a general increase of MS incidence with a significant influence of gender-related and environmental factors,” said G. Graziano, from the MSBase Registry Research Group.

Teriflunomide significantly reduces relapse rate and disease progression in relapsing MS

Further encouraging news with oral disease-modifying agents were reported in results from the phase III TEMSO study showing that teriflunomide significantly reduced relapse rate and disease progression in patients with relapsing MS.
Teriflunomide blocks de novo pyrimidine synthesis, which inhibits the replication and function of activated, but not resting, lymphocytes. The study randomised 1,088 patients with relapsing MS to teriflunomide (7mg or 14mg) or placebo, once daily for 108 weeks.

Results showed that both doses of teriflunomide reduced the primary endpoint of annualised relapse rate (ARR) by 31.2%, from 0.539 with placebo to 0.37 with the 7mg dose and to 0.369 with the 14mg dose. There was also a significant increase in the time to first relapse of 29.8% with the higher dose of teriflunomide, and a 30% reduction in disability progression. In addition, MRI shows significant reduction in disease activity with active treatment.

“This is somewhat happy news,” said Paul O’Connor, from the University of Toronto, Canada, as he reported the findings. He noted that teriflunomide was well tolerated with a similar number of patients reporting adverse events as with placebo. Nausea, diarrhoea and minor hair thinning were more common with active therapy. Altogether, these observations indicate that teriflunomide is a safe and effective new oral monotherapy for relapsing MS,” he concluded.

Study confirms anti-JCV antibodies in natalizumab-treated patients developing PML

Around half of MS patients treated with natalizumab have antibodies to JC virus (JCV), according to results from the largest cohort yet to look at this issue. JCV infection is one of the key factors necessary for the development of PML, so detection of anti-JCV antibodies in blood may be a useful tool to identify previous or ongoing JCV infection in order to stratify PML risk in MS patients treated with natalizumab.

A novel two-step enzyme-linked immunosorbent assay (ELISA) was used to detect anti-JCV antibodies in blood from natalizumab-treated patients enrolled in TYSABRI safety studies. A chi-square test was used to assess associations between factors and prevalence of anti-JCV antibodies.

Results showed a seropositivity rate of 48.0%. There was an increasing prevalence of anti-JCV antibodies in men compared to women. There was also an increasing prevalence with age, regardless of gender. Treatment with natalizumab and prior treatment with immunosuppressants did not appear to affect the prevalence of anti-JCV antibodies.

Reporting the findings, Meena Subramanyam, from Biogen Idec, said, “Together, these data represent one of the largest cohorts of MS patients evaluated for the presence of anti-JCV antibodies, demonstrating an overall prevalence of anti-JCV antibodies of approximately 50 to 60% and delineating the prevalence by factors such as age and gender.”

He noted that large, prospective clinical studies are underway to expand on previous observations that antibodies to JCV were detected in all 17 of 17 MS patients prior to being diagnosed with progressive multifocal leukoencephalopathy (PML), to determine the potential utility of the ELISA test to stratify PML risk in natalizumab-treated patients.

Survey suggests healthcare professionals may underestimate mobility loss in MS patients

Healthcare professionals may underestimate the extent of mobility impairment in patients with MS, according to a new survey. The survey, commissioned by Biogen Idec, of 180 healthcare professionals from Canada, France, Germany, Spain, Sweden and the UK showed that 56% considered that their MS patients experience some loss of mobility, which is lower than published data which suggest up to 85% of people with MS suffer impaired mobility.

A second survey of 436 MS patients illustrated the impact of impaired mobility. Almost three-quarters (72%) said their mobility problems had had significant impact on their working lives and nearly two-thirds (64%) had lost earnings due to MS-related mobility issues.

Professor Shibeshih Belachew, from the University of Liege, Belgium, said, “Loss of mobility can have a huge impact on all aspects of life for patients living with MS. It has physical and psychological effects that can drastically reduce patients’ ability to work.” He suggested that the survey findings indicate the need for greater dialogue about mobility issues between patients and healthcare professionals. Mobility impairment can start early in MS, with the survey showing that 45% of patients reported mobility issues within the first month after being diagnosed.

Early identification and management of mobility issues, including exercise and physical therapy, can help to improve quality of life for people with MS, Professor Belachew concluded.
World Parkinson Congress

Conference details: 28 September-1 October, 2010; Glasgow, UK. Reviewed by: Patrick Lewis, UCL Institute of Neurology.

The second World Parkinson Congress took place at the Scottish Exhibition and Conference Centre in Glasgow from the 28 September to 1 October, in a venue made famous by the likeness of its main hall to a metal armadillo. The World Parkinson Congress brings together several thousand researchers, clinicians, care givers and patients, providing a distinct forum where all the people studying and impacted by Parkinson’s can exchange experiences, ideas and the latest research. This is by no means an easy task, as the different constituencies have very different expectations of a conference such as this but, having attended both of the Congresses held to date (the last one was in Washington DC in 2006), I have been impressed by how well the WPC achieves this.

The Congress, co-chaired by Andrew Lees (UCL Institute of Neurology, London UK) and Stanley Fahn (Columbia University, New York USA), opened on the Tuesday, with a plenary session that emphasised the range of participants at the meeting. This included an introduction by Gavin Hastings, former captain of the Scottish and British Lions rugby teams, during which he gave a touching description of his wife developing and living with Parkinson’s.

On to the conference itself and, as is clear following a cursory glance at the academic literature over the last 12 months, we live in exciting times with regard to research into the genetic and cellular basis of Parkinson’s, with major advances occurring, most notably in the genetic definition of this disorder. This was underlined by a presentation from Haydée Payami (Wadsworth Center, New York USA) following on from her recent Nature Genetics paper (Hamza et alia) describing a genome wide association study for idiopathic Parkinson’s disease. Her team are interrogating the data generated for this study and claim to have discovered a possible gene locus for the protective impact of caffeine in some Parkinson’s patients. Although this was very much a preliminary report, it is one that is of increasing interest to cell biologists researching PD, and this will only encourage them to redouble their efforts.

Another hot topic that was the subject of several talks in Glasgow was the possibility that alpha synuclein pathology in Parkinson’s may be spreading via a prion-like mechanism. Research into this exploded following the description of Lewy body pathology spreading into fetal grafts implanted into the brains of patients (see the review by Brundin et alia for details), with a number of researchers using cell and animal models to try to dissect the mechanism of propagation. Again, this is an aspect of Parkinson’s that we are only just beginning to understand, but it is encouraging to see some really outstanding work in progress.

Stem cells, and their potential to be used as replacement therapy for human disease, are an emotive subject for patients, for clinicians, for researchers and for society. There were several very impressive reports, on the clinical use of foetal transplants, the future use of stem cells in Parkinson’s and on the basic biology of stem cells. Patrick Brundin from the University of Lund, Sweden, gave a comprehensive report on where transplants stand as a clinical treatment whether or not to try and identify what is causing the disease in their family.

Continuing the genetics theme, there were some fascinating talks on altered rates of cancer in patients with mutations in LRRK2, the most common genetic cause of Parkinson’s disease. Susan Bressman at the Beth Israel Medical Center in New York and Rivka Inzelberg of the Meir Hospital in Haifa both presented data showing that the common G2019S mutation of LRRK2 is linked to an increased rate in cancer (the New York study, by Saunders-Pullman and co-workers, has just been published). The balancing act between cell death, manifesting as neurodegeneration, and cell proliferation, manifesting as cancer, and their links to monogenic forms of disease is one that is of increasing interest to cell biologists researching PD, and this will only encourage them to redouble their efforts.

In summary, I found the Congress both enlightening and satisfyingly different from the majority of conferences on Parkinson’s. From the point of view of basic researcher, the interaction between the patients, the clinicians and researchers is both a valuable and humbling experience, bringing into clear focus the human faces of the disease you are researching and I am looking forward to the next Congress, to be held in Quebec, Canada, in 2013.ddie

Acknowledgements

The author would like to thank Julia Fitzgerald for critical comments.

Dr Lewis is a Parkinson’s UK research fellow, and is funded by Parkinson’s UK, the Michael J Fox Foundation and the Brain Research Trust.

References


Image – Clyde Auditorium, freely available image from Wikipedia.
20th Congress of the European Neurological Society

Conference details: 19-23 June, 2010; Berlin, Germany.

It was towards the end of June, when summer finally arrived in Central Europe too and the European Neurological Society gathered for their 20th anniversary meeting in Berlin, Germany. More than 3000 participants attended the meeting which again not only offered lectures held by the best experts in their respective fields of neurology during official symposia, but also high-quality education in the form of teaching courses, workshops and practical sessions. From the nearly 900 abstracts submitted, 125 were selected for an oral presentation. As in the past, the posters exhibited were highlighted by the popular poster walks, with an expert leading the discussion.

The topics treated during the meeting encompassed all fields in the neurological science and ranged from scientific research to clinical treatments. How rich the presented content was, is shown by the following summary.

Pathogenesis

Micro(mi)RNAs involved in the differentiation and regulation of CD4+ cells have been shown to play a role in relapsing remitting multiple sclerosis (RRMS); this might contribute to finding new therapeutic targets. On the contrary, the search for genetic risk factors involved in the susceptibility to progressive course of MS remains inconclusive. Nevertheless, novel targets have been identified, such as the HLA class II region, and represent potential candidates for further studies.

Calcitonin gene-related peptide (CGRP), which is a key molecule in the pathogenesis of migraine, has been shown to trigger migraine-like attacks in migraine patients with and without aura.

Gelatinase matrix metalloproteinases (MMP)-2 and 9 provide a link between neuronal degeneration and skin alteration in patients with amyotrophic lateral sclerosis (ALS). Another study showed a mitochondrial impairment in skin fibroblasts of patients with ALS, which is likely related to oxidative stress. These findings suggest that the skin abnormalities may be a biomarker for monitoring ALS in the context of neuroprotective treatment trials.

Clinical findings

In myoclonus-dystonia, the clinical spectrum of DYT11 mutations includes patients with a non classical phenotype (i.e., lower limb onset, generalized distribution, and absence of family history).

The clinical characteristics of 1241 ALS patients included in an Italian prospective epidemiological register have been presented. Pyramidal and flail arm phenotypes had the better prognosis, while bulbar and respiratory phenotypes had the worst one. A smaller study showed that a more rapid progression was associated with a later onset of symptoms in patients with primary lateral sclerosis (PLS).

Compared with patients with Alzheimer’s disease (AD), patients with frontotemporal lobar degeneration (FTLD) are characterised by a faster cognitive decline, which is independently associated with the language subtype and an early memory impairment.

In FTLD patients carrying exon 8 delCACT mutation of Progranulin (GRN) gene, cerebrospinal fluid (CSF) levels of total tau protein, phosphorylated-tau, and β-amyloid 1-42 were normal. This suggests that normal CSF biomarker may be consistent with a diagnosis of FTLD caused by GRN mutations.

Neuroimaging

The assessment of the regional distribution of damage to the normal-appearing white matter (NAWM) and gray matter (GM), using quantitative magnetic resonance (MR) techniques, may contribute to a phenotypic characterization of different neurological diseases, including MS, migraine, Leber’s hereditary optic neuropathy (LHON), Parkinson’s disease and atypical parkinsonisms, Alzheimer’s disease (AD) and other dementias. Furthermore, it may improve the understanding of specific disease-related symptoms, such as fatigue in MS. The study of WM damage in AD patients also contributed to the understanding of atypical forms of early onset AD, such as posterior cortical atrophy and logopenic/phonological progressive aphasia.

MR imaging studies have identified objective markers of long-term clinical worsening in patients with different neurological conditions, such as thalamic damage in patients with MS and corticospinal tract damage in those with ALS.

ALS patients with mild disability have been shown to experience a dysfunction of resting state (RS) connectivity of the sensorimotor network. RS fMRI revealed also abnormalities of the visual network in LHON patients, which were correlated with structural damage along the visual pathways and disease duration.
Treatment
A substantial proportion of relapsing/remitting multiple sclerosis (RRMS) patients treated with cladribine were free from clinical and radiological disease activity over a short-course treatment (96 weeks). Fingolimod significantly reduced the annualized relapse rate compared with placebo regardless of prior disease-modifying therapies. In these patients, interferon β-1b affected the development of permanent black holes, which is a marker of permanent tissue destruction, at year 2 from active lesions at year 1, to a similar or better extent than glatiramer acetate. Data from the ‘TYSABRI observational program’ showed that MS patients under natalizumab exhibit a very low level of disease activity and the safety profile is consistent with that from the preregistration trials.

In patients with atrial fibrillation who have already suffered from a stroke or TIA, dabigatran 110 mg was as effective as warfarin, while dabigatran 150 mg bid was superior to warfarin. Both dosages of dabigatran also resulted in a relatively low rate of cerebral haemorrhages. Bevacizumab in combination with fotemustine is a promising treatment for recurrent high grade gliomas with acceptable toxicity.

Apart from this excellent opportunity for education in cutting-edge neurological science and exchange of knowledge and experiences, the meeting’s various social events also offered the possibility for more personal conversations and for meeting colleagues in a relaxed atmosphere. The dinosaurs in the Museum of Natural History watched as leading neurologists from all over the world mingled with residents and students at the occasion of the Welcome Reception. The banquet in the famous TIPI Tent offered the right ambience for the last evening of this meeting, which ended the next day again with high-quality workshops, teaching courses and two highlight symposia treating hot topics in neurology.

Prof Massimo Filippi, Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute and University, Milan, Italy

7th FENS Forum of European Neuroscience

On Saturday July 3rd, neuroscientists from all over Europe, as well as colleagues from more distant continents, gathered in the RAI Congress Centre in Amsterdam to participate in the openings ceremony of the FENS Forum 2010, the 7th biannual conference of the Federation of European Neuroscience Societies. Attendees thus started to familiarise both with each other and the conference venue. The latter was characterised by a spacy atmosphere, not in the least due to an excellent ordering of poster boards surrounding the exhibition area with a large central meeting point. Weather was fine and rented bikes were widely used, next to public transportation. The oral forum presentations comprised 9 plenary sessions, 10 special lectures and 7 blocks of 8 parallel 90 min symposia with 4 speakers each. Seven workshops were given before the opening. Themes reflected the wide scope of topics at molecular, cellular, neuronal network and behavioural levels, aimed at understanding both normal brain function and brains affected by disease. In this respect, the symposium was of interest for basic neuroscientists as well as neurological and psychiatric disciplines.

In particular the synergy of the four presentations in the symposia provided an excellent forum for enhancing synergy and generating novel points of view. As a symposium organiser, I personally experienced such positive interaction between contributing speakers in the symposium ‘Prefrontal and parietal-premotor contributions to free choice selection’. Our symposium illustrated research on a fundamental level, providing a balanced perspective on a hierarchy in action selection, reaching from response freedom of single neurons at early sensorimotor processing stages to action selection experienced as the result of free will. Sensing a free will is closely related to the feeling of ownership of one’s body. In the symposium of Henrik Ehrsson on this topic, the illusion of feeling an observed rubber hand provided a starting point for future perspectives on practical applications to enhance the sense of prosthetic limbs as being a ‘real’ part of one’s own body.

The fMRI work of Maurizio Corbetta in stroke patients can also be placed at the interfaces of basic neuroscience, clinical neurology and rehabilitation. Identifying sites of interaction between separate resting state networks involved in attention and controlling arm movement, respectively, distant from the lesion location, helped to predict recovery and functional outcome. Such new brain scan technology may thus offer new approaches in treatment and targeted strategies for rehabilitation. With regard to molecular aspects of stroke treatment, Denis Vivien presented results from animal experiments demonstrating that immunotherapy with antibodies might prevent secondary brain damage following stroke, including side-effects of acute thrombolysis.

Advances at molecular level of neuronal functioning were addressed in plenary lectures concerning, for example, the role of adhesion molecules in synaptic plasticity and regeneration (Melita Schachner), and tau pathology in neurodegenerative disorders (Maria Spillantini). In a symposium on microRNAs, new data on their role in fine-tuning synaptic development and the consequence of deregulation for the emergence of neurodegeneration in Alzheimer’s and Parkinson’s disease were addressed. Clearly, given the quality of presented research, an increasing number of neuroscientists from outside Europe can also be expected to attend future FENS conferences. It is expected to attend future FENS conferences. http://forum.fens.org/2010.