

religious orientation and income. But the users of CAM were older ($p < 0.05$), had a longer duration of illness ($p < 0.05$) and a higher EDSS ($p < 0.001$) than non-users. CAM users reported more active coping behavior ($p < 0.01$) than non-users. In their personality users and non-users did not differ on the scale neuroticism ($p = 0.54$), but users scored higher on the scale openness to experience ($p < 0.01$). Regarding their locus of control users of CAM reported higher values on the scale internality than non-users ($p < 0.05$). **Conclusion:** Patients with MS are using CAM more often (81.1%) during their disease than former research has suggested. Besides age and aspects of illness (EDSS and duration of illness) the utilization of CAM is influenced by psychological factors like coping, locus of control and personality. Users report to a greater extent active coping and internal locus of control and they are more open to new experiences.

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Use of cannabinoids in MS: is it evidence based?

C. Vaney, Berner Klinik (Crans-Montana, CH)
Invited Speaker

Recent years have witnessed the rise of evidence-based medicine (EBM) as an approach towards rationalizing clinical practice in the face of a growing body of knowledge. While the goal of EBM is laudable, it is entirely based on the proposition that truth can be exclusively gleaned from statistical studies and that our clinical practice should essentially rely on clear, evidence based judgements. But how should we decide when we are faced - as often in science - with grey, rather than black and white results? Our dilemma is well illustrated by the results of a large recently published RCT study (CAMS) using an orally taken cannabis extract containing Delta⁹-THC and Cannabidiol (CBD), which failed to show a significant effect on the primary outcome measure, an objective reduction in muscle tone, as measured by the Ashworth score. Although these, and previous studies, have not been able to produce a convincing tone reduction, patient continue, despite its illegality, to obtain cannabis on the black market for self-medication, claiming that cannabis is the only substance that alleviates their muscle spasms. Do we have to accept that, in this case, a current practice is highly effective without being evidence - based? Or, phrased in other words, is the absence of evidence of effect not the same as the evidence of absence of effect? Critical voices suspect that MS patients just want to be put into high spirits to forget that they are severely disabled. Although the recreational qualities of THC cannot be denied, the large majority of patients dislike being stoned and prefer to take THC at night time just to have fewer spasms while falling a sleep. On the other hand, some authors, convinced of the efficacy of cannabis, have argued that the Ashworth scale was not sensitive enough to pick up clinically relevant changes in muscle tone. Since several - though not all - RCT testing conventional drugs (tizanidine, baclofen) showed a significant tone reduction and because in one of the THC extract study the combined effect of physiotherapy and THC reduced muscle tone clearly, it would be unfair just to blame the insensitivity of the measure to explain why the aforementioned studies did not show any measurable tone reduction. But maybe our studies are too narrow sighted and we have to take the focus from pure muscle tone reduction away, and ask ourselves if Cannabis hasn't any other, more relevant properties, our patients have already intuitively discovered, namely that the substance might influence favourably on the course of the disease, since there is increasing experimental evidence of a neuroprotective effect of cannabinoids? Here again clinical evidence is still lacking and further research is urgently needed using eventually other delivery methods for THC such as sublingual sprays or skin patches. Maybe the use of endocannabinoids that stimulate the receptors without inducing psychoactive effects will be future options for cannabinoid therapy.

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The Cannabinoids in MS study - final results form 12 months follow-up
J. Zajicek, P. Fox, H. Sanders, D. Wright, J. Vickery, A. Nunn, A. Thompson
on behalf of the UK MS Research Group

Background: The Cannabinoids in Multiple Sclerosis (CAMS) study was a multicentre randomised placebo-controlled study, which tested the

notion that cannabinoids may be effective in treating the symptoms of multiple sclerosis (MS). We now report results from up to 12 months follow-up. **Methods:** 657 patients with stable MS and muscle spasticity were randomised across 33 UK centres to receive oral cannabis extract, Δ⁹ tetrahydrocannabinol (Δ⁹-THC) or placebo. The study was based on the Ashworth scale of muscle spasticity, but data on other measures of symptoms and disability were also collected. After the main 15-week study period, patients were given the option of resuming their medication, in a double blind fashion, for up to 12 months. We sought to monitor all patients over this period using a range of measures, whether or not they continued medication. **Findings:** There was evidence of a treatment effect on muscle spasticity as measured by change in Ashworth score from baseline to 12-months follow-up in an intention to treat analysis, $p = 0.04$ unadjusted for ambulatory status and centre, $p = 0.01$ adjusted. In the group taking Δ⁹-THC, the Ashworth score was reduced by an average of 1.82 ($n = 154$, 95%CI = 0.53,3.12) compared to either cannabis extract ($n = 172$, mean 0.1, 95% CI = -0.99,1.19) or placebo ($n = 176$, mean -0.23, 95% CI = -1.41,0.94). Additionally, in the follow-up period there was suggestive evidence for treatment effects on disability of Δ⁹-THC compared to placebo, particularly in the Rivermead Mobility Index. There were no major safety concerns. Overall, patients felt that these drugs were helpful in the treatment of their disease. **Interpretation:** These results require cautious interpretation since the study was designed as a short-term study of MS-related symptoms. However, they provide preliminary evidence for a role for cannabinoids in long-term disease management, which supports the hypothesis that cannabinoids may have a neuroprotective action. Further studies are urgently needed.

Plenary Session 2

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Pathophysiology of spasticity

G. Sheean, University of California (San Diego, USA)

Damage to the upper motor neurons (UMN) and pathways, from whatever cause, may result in several types of motor overactivity, including spasticity. Some of these motor overactivities arise from disinhibition of spinal reflexes, which are normally controlled by a balance of inhibitory and excitatory upper motor neuron inputs. Spasticity is a form of hypertonia arising from hyperexcitability of the spinal tonic (sustained) stretch reflex. This reflex is both length and velocity dependent. It is arguable whether the tonic stretch reflex is a native reflex that is disinhibited by damage to the UMN tracts or a completely new one, because it does not exist in normal people. If due to release of a suppressed reflex it is also not entirely clear whether it emerges through lowered threshold or increased gain. Hyperexcitable phasic (brief) stretch reflexes cause deep tendon hyperreflexia and clonus. Both phasic and tonic stretch reflexes are mediated by Ia muscle spindle afferents. Overactive flexor withdrawal reflexes produce flexor spasms and are mediated by flexor reflex afferents. In some cases, extensor reflexes are increased, causing extensor spasms in the lower limbs. Another contribution to increased muscle tone is spastic dystonia, in which there is continuous muscle contraction in the absence of voluntary effort (at rest) or reflex activity. Like spasticity, spastic dystonia is sensitive to stretch. Biomechanical changes in muscles and associated tissues also lead to increased tone (reduced compliance or increased stiffness) and reduced range movement from contractures (reduced length). Voluntary movement requires coordinated action of agonist and antagonist muscles and depends upon reciprocal inhibition in the spinal cord. In the UMN syndrome, reciprocal inhibition fails, leading to pathological co-contraction and impaired movement. In some cases, this causes movement opposite to that intended, for example, finger flexion when attempting finger extension. In other cases, action-induced dystonic posturing interferes with movement. For example, muscle tone may be normal at rest but attempting to stand or walk induces strong extension of the leg and ankle plantarflexion. The basic mechanisms underlying these motor overactivities are unknown. The delay in their emergence after UMN damage suggests that it is not a

simple matter of imbalance between descending inhibitory and excitatory inputs but one of neuronal plasticity.

Closing Session

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Overview of ongoing clinical trials

J. Noseworthy, Mayo Clinic Rochester Dept. of Neurology (Rochester/Minnesota, USA)
Invited Speaker

The purpose of this lecture is to review the current status of clinical trials of experimental therapeutics in multiple sclerosis (MS). The first segment of the lecture will include a summary of what has been learned from work completed to this point. What progress has been made? How has this changed how we view MS in the short- and long-term? How certain are we that these observations will be sustained and form the basis for future work? How much have our immune-modulating agents impacted the course of the disease? We will apply the principles of evidence-based medicine to examine the magnitude of the results of published results on disease course. What are the limitations of the trial designs used to date? Are there alternative designs that might be exploited in the future? We will next explore the studies currently in progress. We will highlight the expectations that accompany this activity, the possible outcomes of these studies and the time lines for these trials. What might these studies tell us and how might we use these possible outcomes to plan the next generation of trials? We will look at how sponsors have partnered with investigators to perform complex combination trials. We will revisit how well the partnerships between academia and industry are working and consider what more might be done to align industry and academia in the search for more effective therapies. In the final segment of the lecture we will explore what may be ahead in the next few years. What advances can we expect in validating the concept of pathogenic heterogeneity and what is ahead in the search for non-invasive biomarkers of these putative disease subtypes? How would advances in this work change future trial design? How will the sweeping advances in the neurosciences expand the opportunities for meaningful advances in the therapeutics of MS? What might we expect from the fields of immunology, transplantation, blood-brain barrier research, ion channels, neuropathology, neuro-protection, axonal repair, and remyelination?

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Perspective of future MS research

D.A.S. Compston, University of Cambridge (Cambridge, UK)
Invited Speaker

In the 1990s, multiple sclerosis was considered a typical complex autoimmune trait in which strategies for elucidating the aetiology and providing treatments would rapidly fall into place. In the event, progress has been relatively slow. Using linkage and association, several genes show some reproducibility for an effect on susceptibility and the clinical course or phenotype. For the future, six main categories can be predicted: autoimmune genes determining susceptibility to inflammation across a range of disorders; ubiquitous genes which determine specificity for the development of multiple sclerosis; domestic genes relevant for the pathogenesis in isolated populations; pleiotropic genes that determine particular phenotypes; modifying genes orchestrating variations in the clinical course; and epistatic genes clustering to provide heterogenous contributions to the pathogenesis. The inflammatory concept of tissue injury in multiple sclerosis has recently been challenged: areas remote from macroscopic inflammation are abnormal; lesions sampled ultra-early in the course show loss of oligodendrocytes in the absence of inflammatory injury; and there is pathological heterogeneity with some cases showing oligodendrocyte apoptosis. Together, these data suggest a primary disease

process independent from inflammation. But a preferred formulation is that the inflammatory and degenerative components are inter-related, and not as competing events. The phases of symptom onset, recovery, persistence and progression in multiple sclerosis can be considered as functional impairment with intact structure due to direct effects of inflammatory mediators; demyelination and axonal injury with recovery through plasticity and remyelination; and chronic axonal loss due to failure of enduring remyelination from loss of trophic support for axons. Cell death may occur in response to a state of injury from which protection would be anticipated under favorable neurobiological conditions. Conversely, an optimal growth factor environment may save cells from otherwise lethal events. This analysis leaves a clear agenda for future research: aggressive suppression of the immune response early in the course combined with neuroprotection and strategies for enhanced remyelination, as the basis for limiting and repairing the damage.

POSTERS

Neuropsychology

Scales and scores

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Normative data of neuropsychological screening battery in a healthy Latin-American population

S. Vanotti, F. Cáceres on behalf of the RECONEM Working Group, Argentina

Background: Cognitive dysfunction (CD) is common in patients with Multiple Sclerosis (MS), 40% to 60% of the patients show impairment on tests of attention, memory and executive function. Through the Reconem survey, performed in Argentina in the year 2002, a prevalence of 46% of CD in MS patients has been confirmed. To study cognitive impairment in the Argentine MS population the Neuropsychological Screening Battery for MS (NSB-MS) (Rao, 1991) has been administered. It is a valid instrument to detect cognitive impairment in MS since it has 87.5% of sensitivity and a 96.8% of specificity. There is not normal values of the NSB-MS in a Spanish Latin-American language population. **Objectives:** To normative the NSB-MS in a healthy Latin-American population, obtaining a reference control population. To examine the influence of demographic factors: gender, age, educational level. **Methods:** This is a multicentric descriptive cross-sectional study. 28 MS centers from 8 different areas from Argentina participated. Each center recruited 10 healthy controls. The NSB-MS was administered in an specially adapted Spanish version. MMSE and Beck Depression Inventory were other outcome measures. Statistical analyses were performed using computer version for SPSS. Data were stored in a double fashion entry. All score variables were adjusted by age (years), gender and instruction level (years) using Stepwise Multiple Regression. Only adjusted mean values were used for statistical comparisons and Logistic Regression Analyses. **Results:** 292 healthy controls from Argentina in Spanish language, aged 20 to 60 have been evaluated. Education was categorized by years of schooling as: 0-7, 7-12 and >13 years. The age factor has been divided in four groups which represents different decades. Subjects with history of neuropsychiatric or neurological disease have been excluded. Female 82.9 % and male 17.1%, the mean age (years) is 40.8 % (SD 11.2) and the mean Instruction level (years) is 13.8 % (SD 3.1). **Conclusions:** The scoring on the NSB-MS was associated with age and educational level but not with sex and dominance. We have obtained values in an extend population in regard to age and level of instruction in Spanish language. Results are of great clinical utility since it allows comparing the performance between a patient in regard to a local reference group. It also compliments clinical studies in the evaluation of MS in Latin-American population.

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