ECNP Targeted Expert Meetings (TEMs)
27-28 August 2010, Amsterdam, The Netherlands

Report on the TEM Neurological Disorders

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On behalf of
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Multiple sclerosis (MS) is the most common neurological disease of young adults in the Western world. It is a chronic inflammatory disease, which primarily leads to focal demyelinating lesions in the brain and spinal cord. Thus, MS is a neurological disease and patients are in general seen and treated by neurologists. However, patients also suffer from cognitive impairment and a large spectrum of psychiatric syndromes. These aspects of the disease are frequently neglected in patient care and only a little research has been performed to define these conditions, to determine their pathogenetic mechanisms and to develop and validate their treatment. The aim of this TEM 2010 was to discuss the state of the art of our knowledge and to identify areas of future research in this area.

Cognitive impairment in MS

Cognitive impairment is a very frequent clinical problem in MS patients. In contrast to classical dementia, cognitive disturbances in MS patients mainly affect the speed of information processing, executive functions, perceptional processing and memory acquisition. Its differentiation from fatigue is difficult and requires extensive neuropsychological testing. Particularly severe cognitive impairment is seen in a subset of patients with childhood onset of MS.

Several studies have addressed the structural correlates of cognitive impairment seen by MRI or pathology. These studies identified multiple potential structural substrates. They include focal white matter lesions, in particular in the frontal white matter, the thalamus and hippocampus, diffuse injury in the global white matter as well as cortical demyelination or atrophy. Correlations between single MRI parameters and clinical severity are weak, but can be improved by the use of composite parameters. The situation is further complicated by compensatory changes, seen in functional MRI especially during early phases of the disease. In addition, pre-existing cognitive reserve diminishes clinical severity of cognitive disturbances. An unresolved question deals with cognitive dysfunction in patients at the very early stages of the disease. In such patients cognition is impaired even in the absence of structural lesions seen by MRI or pathology. It is, thus, likely that the inflammatory process in the nervous system itself may lead to functional disturbance of cognition. Potential candidates for such effects are pro-inflammatory cytokines, which are able to induce sickness behaviour in experimental animals.

Even less is known regarding the therapy of cognitive impairment in MS. Current anti-inflammatory or immunomodulatory therapies show some effects, which seem to be related to the anti-inflammatory action. Pharmacotherapy with cholinesterase inhibitors has been tested in few studies with inconsistent results. Cognitive rehabilitation revealed positive effects, but only few studies met sufficient quality standards.

Neuropsychiatric syndromes in MS

Neuropsychiatric syndromes in MS patients include depression, bipolar disorder, euphoria, pseudobulbar affect and in rare instances psychosis.
Depression is most frequent and depressive episodes occur in 25 to 50% of the patients. One problem in the diagnosis of depression in MS patients is the overlap of somatic

symptoms due to depression with somatic symptoms caused by focal MS lesions in the brain. These include fatigue, change in appetite, weight loss or weight gain, altered sleep and mentation. The importance of neuropsychiatric syndromes in MS is highlighted by the fact that about 15% of MS patients are first seen by a psychiatrist before the disease is diagnosed and that MS patients have a seven times higher suicide rate compared to the normal population. The pathogenetic basis of depression in MS is largely unknown. MRI shows some correlations with focal lesion load (prefrontal and supra-insular), brain atrophy (hippocampus; CA2/3, dentate gyrus) and white matter lesions, which may disturb the connection between amygdala and pre-frontal cortex. As with cognitive disturbances, pro-inflammatory cytokines and dysfunction of the hypothalamic-adrenal axis were also discussed, but these concepts largely reside on a speculative basis.

Regarding therapy the situation is rather unsatisfactory. It is generally suggested that established treatments for psychiatric diseases should be applied in MS patients, when necessary. Controlled clinical studies, which prove their efficacy in MS patients, are nearly non-existing. Furthermore, it is unclear whether these treatments may interfere with the disease process of MS itself.

Conclusions:
This TEM clearly identified major future needs in MS research in the areas of cognitive impairment and neuropsychiatric syndromes. The importance of these topics for the patients is undisputed, but current knowledge on the underlying mechanisms and treatment is sparse. Much more intense interdisciplinary interaction between neurologists, psychiatrists and basic scientists is mandatory to advance this field in the future.