Primary Demyelinating Diseases of the CNS

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Primary demyelinating diseases are defined by a common physiopathology targeting the oligodendrocyte and its membrane, the myelin sheath, surrounding the axons. Origins of these diseases are various, most frequently resulting from immune disorders, but also due to infection or metabolic disorders. In demyelinating diseases from immune origin, myelin proteins are targeted by inflammatory cells leading to damages associated in a various extend with neuron destruction (Barnett and Prineas, 2004; Kutzelnigg et al, 2005).

Only one viral agent, JC virus produces an infectious disease affecting the oligodendrocyte leading to progressive multifocal leukoencephalopathy (PML) that most frequently evolves fatally. Acute metabolic disorders may also result in oligodendrocytes death in the so called osmotic demyelination affecting the myelin of the pons (central pontine myelinolysis) or the corpus callosum (Marchiafava-Bignami disease).

The presentation will focus on immune disorders affecting the myelin.

Multiple Sclerosis

MS is the most common autoimmune inflammatory demyelinating disease of the CNS characterized by phagocytic attacks of myelin. CNS inflammation is characterized by resident microglial cell activation and circulating leukocytes penetration due to endothelial cell adhesion associated with various degrees of blood brain barrier (BBB) permeability (Barnett and Prineas, 2004; Frohman et al, 2006). Besides BBB permeability, phagocytic activity of activated microglia and infiltrated hematogeneous macrophages plays a major role in MS lesion development (Lucchinetti et al, 2001). These cells are involved in the direct attack of myelin and in the removal of myelin debris.

Multiple sclerosis which usually spasms chronically over a long period results in neurologic deficits. Several clinical phenotypes are now well established, some patients being affected by acute relapses followed by remissions (relapsing remitting MS, RRMS), other showing progressive deficits either after several relapses (secondary progressive MS, SPMS) or from the onset (primary progressive MS, PPMS) (Thompson et al, 2000).

Diagnosis of MS is supported by clinical, laboratory and imaging data (Polman et al; 2005). MRI has a significant impact upon both the diagnosis of brain and spinal cord lesions and the evaluation of MS therapies (Miller et al, 1998; Filippi et al, 2002). Lesions can be detected on T2-weighted images based on their water content. Given intravenously, gadolinium chelates have been used classically to reveal BBB permeability in inflammatory MS lesions. Gadolinium molecules cross passively the open BBB and diffuse into the intercellular space. MS lesions with gadolinium enhancement are considered today as acute inflammatory lesions, although some chronic lesions may also show gadolinium enhancement. Some observations demonstrated also the absence of gadolinium enhancement in the early onset of acute MS lesions. Gadolinium enhancement in MRI is not a good predictor of impairment or disability.

Ninety percent of patients first present with isolated syndromes that are clinically suggestive of multiple sclerosis, such as optic neuritis or brain-stem or spinal cord syndromes (O’Riordan et al, 1998). MS can develop months or many years later (Brex et al; 2002). The presence of cerebral white-matter lesions that meet the Barkhof/Tintore diagnostic criteria (Korteweg et al, 2006) is associated with an increased risk of multiple sclerosis. Abnormalities on MRI have therefore been used to select patients with isolated syndromes for trials of disease-modifying therapies aimed at delaying the onset of multiple sclerosis. However, one should keep in mind that number of patients with MS do not meet the diagnostic criteria. The McDonald criteria are widely used to diagnose MS and classify patients as having probable or definite MS (Polman et al; 2005). These criteria take into account the temporal evolution of the disease either clinically (a second clinical attack considered as significant to establish diagnosis) or by MRI (new lesions seen on MRI performed three months or later after the first attack). Modified McDonald criteria are currently under investigation: in 2006, new criteria were proposed in which dissemination in space requires at least one T2 lesion in at least two of four locations (juxtacortical, periventricular, infratentorial, and spinal-cord) and dissemination in time requires a new T2 lesion on a follow-up scan (Swanton et al, 2007).

MRI techniques may help in showing inflammation (T2, Gadolinium, USPIO, diffusion imaging, spectroscopy, …), change in perfusion (perfusion imaging), tissue destruction (T1 black holes, Magnetization Transfer, fractional anisotropy) or functional impairment (fMRI) (Narayana et al, 1998; Rocca et al, 2000; Wuerfel et al, 2004). Iron oxide particles (USPIO) which are captured by macrophages are being currently used to visualize macrophage activity in MS lesions (Dousset et al, 1999; Dousset et al 2006). Discrepancies with gadolinium are
of interest to take into account the heterogeneity of the disease (Dousset et al, 2006). USPIO may also help to monitor disease activity during therapeutic trials since most of new immunomodulatory drugs target the kinetic of inflammatory cells (Petry et al, 2007).

Neuromyelitis Optica (NMO)
Otherwise known as Devic’s disease, it is an idiopathic, severe, inflammatory disorder that preferentially affects the optic nerves and spinal cord. Although NMO shares several common features with MS, they are clinical, laboratory and immunopathological evidence that it is a distinct disease. On MRI, spinal cord lesions usually extend contiguously over three or more vertebral segments (unusual in MS spinal cord lesions) in combination with a normal cranial MRI or with abnormalities that do not reach criteria for MS. A serum antibody marker, NMO-IgG appears specific for NMO, suggesting that the disease may include cases of longitudinally extensive transverse myelitis and Japanese opticospinal MS (Wingerchuk et al, 2007).

Acute Demyelinating Encephalomyelitis
Traditionally, acute demyelinating encephalomyelitis (ADEM) is characterized by a severe inflammatory attack, frequently secondary to infectious events or vaccinations. Although the pathophysiologic mechanism of ADEM remains unknown, an autoimmune response to myelin basic protein triggered by infection or immunization is considered to be a possible etiologic factor. In most cases ADEM is monophasic, but in some patients it may be recurrent and relapses may occur immediately after the onset of the disease. In approximately 30% of cases, a first episode of ADEM subsequently evolves to typical MS, with a clear dissemination in time and space. The ability to determine which patients with ADEM will subsequently develop MS after a single clinical episode has prognostic and therapeutic implications because early treatment of MS may be advantageous. ADEM patients present clinically with associated symptoms, MS patients present more often with isolated symptoms. With regard to MRI data, the most important finding for the differentiation between ADEM and MS is likely the gray matter involvement in patients with ADEM (De Seze et al, 2007). In MS proteins of the CSF show more frequently an abnormal distribution with oligoclonal bands which are rare in ADEM (De Seze et al, 2007).