Mild Cognitive Impairment (MCI)

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**General concepts.** The concept of MCI expresses the need to early identify patients with a brain disease potentially evolving to dementia but still autonomous in the complex/instrumental Activities of Daily Living (ADL). As such, it is an intermediate state between normal aging and dementia (1). The syndrome can be divided into two broad subtypes: amnestic MCI (aMCI) characterized by reduced memory, mainly episodic memory, and and non-amnestic MCI (naMCI) in which other cognitive functions are impaired. MCI can involve one cognitive domain, either memory or others (single-domain MCI), or more than one cognitive domain (multi-domain MCI). aMCI often represents an early stage of AD, while outcome of the naMCI subtypes appears more heterogeneous –including, vascular dementia, frontotemporal dementia or dementia with Lewy bodies. However, MCI has multiple sources of heterogeneity, including clinical presentation, aetiology (systemic co-morbidity, psychiatric pathologies, iatrogenic), and prognosis. Moreover, the definition of healthy aging lies on educational and socio-economic factors and has a crucial step in the choice of sound neuropsychological tools. On the other hand, the phenomenic label of dementia requires failure of complex/instrumental ADL, but is largely dependent on both informants and clinical judgement (2). The diagnostic and prognostic role of behavioral symptoms and motor dysfunctions should be better defined. A multidisciplinary diagnostic approach including biological and neuroimaging techniques represents the best option to predict the conversion from MCI to dementia.

**Neuroimaging.** Structural (MRI) and functional (fMRI, SPECT, PET) neuroimaging are two of the three accepted ‘biomarkers’ to diagnose AD and other neurodegenerative disease in their MCI state (3). In aMCI, functional failure if focussed around the posterior cingulate and the precuneus, with extension to superior and inferior parietal lobule. aMCI ‘converters’ to AD may also show impairment in lateral temporal and frontal associative cortex. Medial Temporal Lobe (MTL) dysfunction has been highlighted by accurate segmentation methods, but it is often missed by voxel-based or VROI-based analysis (4). Few data are available in naMCI, which seems characterized more by temporal and frontal cortex dysfunction (5). A relevant improvement comes in the diagnosis of LBD-MCI where Dopamine Transporter (DAT) and DOPA imaging promise to be a powerful method (6), although data in patients is still poor. Similarly, the early sensitivity of FDG-PET in the MCI stage of fronto-temporal dementias waits for confirmation. Data in MCI of Parkinson’s disease (PD) suggests the involvement of posterior parietal (precuneus, inferior parietal lobule, supramarginal gyrus) and associative occipital cortex in aMCI of PD (7), whereas multi-domain MCI could show also an impairment of lateral frontal cortex (8). An emerging field is the imaging of amyloid burden by PET, including both $^{11}$C and $^{18}$F radiopharmaceuticals. MCI is confirmed to be a very heterogeneous pool, as either increased or normal amyloid burden has been shown. Amyloid burden may be increased in other frequent conditions of the elderly population, such as cerebral amyloid angiopathy, which should be correctly identified. Acetylcholine receptor imaging and glia-activation imaging are other fields of active research in MCI.

**Conclusion.** MCI is mainly a ‘working formulation’ rather than a distinct nosological entity. The pathophysiological substrate must be elucidated by means of a multidisciplinary approach, since a large variety of neurological, psychiatric, and systemic conditions can be involved. In this context, multi-modal functional neuroimaging and morpho-functional imaging are needed. While data in aMCI preceding AD is already robust enough, data in other MCI subtypes is still incomplete and requires further validation in follow-up studies.

**References**