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Pathophysiology and clinical features of dementia

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Background. Dementia is a complex clinical syndrome resulting from dysfunction of multiple brain systems caused by heterogeneous mechanisms, ranging from the toxic effect of drugs to infection, ischemia, hormonal unbalances, systemic pathologies and specific brain diseases, characterized by peculiar pathologic changes, for instance the abnormal deposition of hyperphosphorilated tau protein or α-synuclein. The main clinical categories are: i) cognitive impairment; ii) behavioral and psychological symptoms (BPSDs); iii) physical and motor symptoms. In turn, all of them affect both quality of life (QoL) and activities of daily living.

Cognitive symptoms. Memory deficit (1) is the most obvious presentation of dementia. In Alzheimer's disease (AD), early involvement of hippocampus and entorhinal cortex (that storage mnesic material) already in the pre-dementia stage (Mild Cognitive Impairment) leads to a deficit of episodic memory, while the involvement of left inferolateral temporal cortex is the basis of deficit in semantic memory. According to the current theory of AD, derived from the Braak & Braak model, dysfunction of associative neocortex results first from its disconnection from the mesial temporal lobe. Disconnection of dorsolateral prefrontal cortex (DLFC; a key station both in encoding -mainly left side- and retrieval -mainly right side- of information) leads to deficit of both episodic and working memory. The latter is defined as the temporary storage and manipulation of information that is assumed to be necessary for a wide range of complex cognitive activities and has a phonological (connections of DLFC with language areas in the dominant hemisphere) and a spatial (connections with parietal-occipital cortex and subcortical structures) aspect. Due to these widespread networks, working memory can be affected in several primary dementias, including AD, Lewy-Body (LBD), and Parkinson's (PDD) dementia. In posterior areas of the brain, temporal-parietal disconnection has been associated with other cognitive disturbances, such as apraxia and agnosia. Disruption of language networks in the left temporal lobe, inferior parietal lobule and posterior-inferior frontal lobe is the main pathophysiological basis of language impairment in AD but especially in Progressive Primary Aphasias (PPA) (2), which cause mainly non-fluent or fluent ("semantic dementia") aphasia, often accompanied by dyscalculia. The involvement of temporal structures of the non-dominant hemisphere is instead the basis of impaired recognition of faces, another features of Fronto-temporal dementia (FTD) with prevalent involvement of the right hemisphere. The "pure" frontal dementia (Frontal Lobe Degeneration: FLD) is responsible of impairment in executive functions, cognitive flexibility, problem solving and abstract reasoning. Diffuse or multiple damage of white matter affects intra- and inter-hemispheric cortical connection and is the main mechanism leading to cognitive deficit of those vascular dementia (VaD) not due to single or few large infarctions. Executive functions, cognitive flexibility and attention-concentration disturbances are particularly frequent in VaD, whereas memory function is relatively less affected than in AD.

Behavioral and psychological symptoms (BPSDs) (3). Apathy and depression are early found in AD and are thought to derive from dysfunction of the frontal lobes and anterior limbic system, mainly anterior cingulate and amygdala. As AD progresses, other BPSDs, such as hallucinations, delusions, agitation, aggressive behavior and abnormal motor behavior are reported with increasing frequency. The pathophysiology of these symptoms remains to be elucidated, but the spreading of lesions and atrophy to the neocortex and the burden of white matter lesions has been suggested to play a role in AD as well as in VaD. In FLD, various combinations of apathy, dishinibition, abnormal eating behavior and withdrawal from social situations are usually the earliest and most typical presentation due to impairment of anterior and mesial aspects of frontal lobes. In LBD, hallucinations (especially visual) are one of the major diagnostic criteria and have been reported to be associated with damage of occipital cortex.

Physical (4) and motor symptoms (5). Tremor, axial rigidity and bradikinesia can complicate AD in the advanced stage due to spreading of pathological changes to cortical and deep motor structures. On the contrary, they are found early in LBD, in which Lewy bodies deposition can diffusely involve the

basal ganglia and the mesencephalic nuclei of motor system, and obviously in PDD. In these conditions, unexpected falls have been related to axial rigidity and inability to maintain the center of gravity. Parkinsonism or signs of motor neuron impairment has been described in FLD. Incontinence ensues early in FLD but usually late in AD and is related to involvement of frontal lobes, the cortical station of micturition control. The involvement of the hippocampus-hypotalamus-hypophysis axis in AD may cause relative hypercortisolism and a hypercatabolic state which together with eating inadequacy may lead to malnutrition.

References

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