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Featured Article

Consensus classification of posterior cortical atrophy

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Abstract

Introduction: A classification framework for posterior cortical atrophy (PCA) is proposed to improve the uniformity of definition of the syndrome in a variety of research settings.

Methods: Consensus statements about PCA were developed through a detailed literature review, the formation of an international multidisciplinary working party which convened on four occasions, and a Web-based quantitative survey regarding symptom frequency and the conceptualization of PCA.

Results: A three-level classification framework for PCA is described comprising both syndrome- and disease-level descriptions. Classification level 1 (PCA) defines the core clinical, cognitive, and neuroimaging features and exclusion criteria of the clinico-radiological syndrome. Classification level 2 (PCA-pure, PCA-plus) establishes whether, in addition to the core PCA syndrome, the core features of any other neurodegenerative syndromes are present. Classification level 3 (PCA attributable to AD [PCA-AD], Lewy body disease [PCA-LBD], corticobasal degeneration [PCA-CBD], prion disease [PCA-prion]) provides a more formal determination of the underlying cause of the PCA syndrome, based on available pathophysiological biomarker evidence. The issue of additional syndrome-level descriptors is discussed in relation to the challenges of defining stages of syndrome severity and characterizing phenotypic heterogeneity within the PCA spectrum.

Discussion: There was strong agreement regarding the definition of the core clinico-radiological syndrome, meaning that the current consensus statement should be regarded as a refinement, development, and extension of previous single-center PCA criteria rather than any wholesale alteration or redescription of the syndrome. The framework and terminology may facilitate the interpretation of research data across studies, be applicable across a broad range of research scenarios (e.g., behavioral interventions, pharmacological trials), and provide a foundation for future collaborative work.

Keywords: Posterior cortical atrophy; Alzheimer's disease; Clinico-radiological syndrome; Pathophysiology; Biomarker

1. Introduction

The term posterior cortical atrophy (PCA) was coined by D. Frank Benson and colleagues to describe a series of patients with early visual dysfunction in the setting of neurodegeneration of posterior cortical regions [1] (Fig. 1). The PCA syndrome aligned with several other reports of patients with similar progressive loss of higher visual function (e.g., [2–12]). PCA typically presents in the mid-50s or early 60s with a variety of unusual visuoperceptual symptoms, such as diminished ability to interpret, locate, or reach for objects under visual guidance; deficits in numeracy, literacy, and praxis may also be apparent. Although episodic memory and insight are initially relatively preserved, progression of PCA ultimately leads to a more diffuse pattern of cognitive dysfunction.

Several single-center groups of researchers have proposed diagnostic criteria for the syndrome [13,14] or detailed inclusion criteria for individual studies (e.g., [15–17]). PCA has also been recognized and described in consensus criteria for typical and atypical Alzheimer's disease [18,19]. These existing criteria have reasonable consistency and have proved useful in many clinical and research contexts.

However, the extant detailed descriptions of PCA are based on clinical experience at single centers and have not been deliberated or validated more widely. Present-day PCA criteria were also formulated before the development of Alzheimer's disease (AD) pathophysiological biomarkers, and although recent AD criteria include PCA, the clinical phenotype is not described in detail and such criteria naturally do not encompass individuals with the PCA syndrome who are negative for AD pathophysiological biomarkers. Some inconsistencies exist among the core features described, with the Tang-Wai but not Mendez criteria excluding individuals with early Parkinsonism or hallucinations, while Mendez but not Tang-Wai stipulates the relative preservation of verbal fluency [13,14]. Such inconsistencies are mirrored explicitly or implicitly in the application of terminology, with the term PCA sometimes being used as a descriptive clinical (syndrome level) term and sometimes as a diagnostic (disease level) label. For example, some researchers consider PCA primarily or solely as an atypical form of AD (the "visual variant of AD," e.g., [20]), whereas others cite neuropathological evidence demonstrating that multiple pathologies can underlie the PCA syndrome (e.g., [15]). Inconsistency of terminology and usage likely reflects in part the interests or requirements of different investigators or research contexts. For example, syndromic classification is likely to be entirely appropriate for studies exploring behavioral interventions, whereas clinical trials of disease-specific pharmacological agents may additionally require consideration of the underlying molecular pathology. In the absence of criteria that clearly reflect this potential diversity of use, it remains unclear whether individuals with PCA should be included or excluded from conventional clinical trials for AD (e.g., owing to the potential unsuitability of the associated interventions, biomarkers, and/or outcome measures). Consequently, individuals Q5