Health Science Reports

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LETTER TO THE EDITOR OPEN ACCESS

Workup of Parkinson's Disease, Parkinson Plus, Lewy Body, and Alzheimer's Dementia Should Include SPECT, PET and Genetics

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Received: 9 April 2024 | **Revised:** 18 September 2024 | **Accepted:** 14 October 2024

Funding: The author received no specific funding for this work.

To the Editor,
We read with interest the narrative review article by Prajjwal et al. on the association between Parkinson's disease (PD), PD-plus (progressive supranuclear palsy [PSP], multisystem atrophy [MSA], corticobasal degeneration [CBD], vascular PD [VPD]), Lewy body dementia (LBD), and Alzheimer's disease (AD) [1]. It was concluded that PD, PD plus, LBD, and AD are interconnected in terms of pathophysiology, including impaired mitochondrial function, protein clumping, increased oxidative stress, and inflammatory brain processes, which are amenable to specific treatment [1]. The study is impressive, but some points require further discussion.

A first point is that SPECT and PET studies have not been discussed as a means of distinguishing between PD, PD-plus LBD, and AD. The dopamine transporter (DaT) scan using the tracer ioflupan is useful for the diagnosis of PD, which shows unilateral or bilateral reduced uptake of the tracer in the striatum [2]. In LBD, perfusion SPECT typically shows severe bilateral parietotemporal and occipital hypoperfusion and DaT scan shows mildly reduced presynaptic dopamine transmission in the putamen and caudate nucleus [3]. In CBD, perfusion SPECT typically shows diffuse hypoperfusion affecting the frontal, parietal, and temporal cortex, basal ganglia and thalamus, in association with reduced striatal dopamine transmission predominantly in the putamen [3]. In AD, both perfusion SPECT and FDG PET show typical hypoperfusion and hypometabolism in the bilateral parietal cortex [3] and amyloid PET shows cortical amyloid deposits [3]. Another imaging modality that should have been discussed is ^{123}I-MIBG sympathetic imaging. ^{123}I-MIBG imaging is particularly valuable in distinguishing Lewy body diseases (including PD, LBD, and pure autonomic failure) from other PD-plus syndromes such as PSP, MSA, CBD and from AD. This imaging technique is also recognized in the 'Diagnosis and Management of Dementia with Lewy Bodies' guidelines: Fourth Consensus Report of the DLB Consortium' [4]. There is also a lack of discussion on the Seed Amplification Assay (SAA), which is a powerful tool for detecting the presence of pathogenic synuclein seeds.

The second point is that mitochondrial disorders (MIDs) have not been discussed as differential diagnoses of PD, PD-plus, LBD, and AD. Several syndromic and non-syndromic MIDs can mimic PD, PD plus, LBD, and AD [5]. Therefore, it is important that MIDs are thoroughly ruled out before diagnosing PD, PD-plus, LBD, and AD. Exclusion of MIDs is crucial because diagnostic and therapeutic management and outcomes can vary significantly between MIDs and the other disorders.

A third point is that genetic causes of PD were not discussed in the review. Nowadays, mutations in several genes such as *GBA, PRKN, SNCA, PINK1, DJ1, DNAjC6, RIC3, ATP13A2, LRRK2, MAPT, LRP10, NUS1, ARSA, TMEM230*, or *VPS35* are known to be associated with PD [6]. Particularly in patients with a positive family history of PD and early onset of the disease, hereditary PD should be suspected and genetic testing initiated. It is critically important to know whether PD is genetic or degenerative in nature, as therapy and outcome can vary significantly between these causes.

The fourth point is that there is a discrepancy between the sentence in the abstract that PD plus is characterized by unique

clinical features, imaging, and response to L-DOPA, and the sentence that these unique features make it difficult to distinguish PD from PD-plus [1]. Either PD plus manifestations are truly unique and therefore different from PD, or they are not. This discrepancy should be resolved.

One form of neurodegeneration not included in the review is frontotemporal dementia. What was the reason?

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Removing these limitations could strengthen the conclusions and reinforce the study's message. All unresolved questions must be clarified before readers can uncritically accept the review's message. The distinction between PD, PD plus, LBD, and AD requires the use of clinical and MRI criteria as well as SPECT and PET examinations, biomarker assays, and genetic examinations.

Author Contributions

Josef Finsterer: investigation; conceptualization; validation; data curation; writing–review & editing.

Acknowledgements

The author has nothing to report.

Ethics Statement

The author has nothing to report.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

All data are available from the corresponding author.

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