LETTER TO THE EDITOR

UNLOCKING POTENTIAL: HOW SERUM L1EV A-SYNUCLEIN MAY REVOLUTIONIZE PARKINSON'S DIAGNOSTICS

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Parkinson's Disease (PD) poses many challenges and the urgent need for early diagnosis, emphasizing the limitations of motor symptoms in providing timely detection is imperative. The MDS research criteria, including motor changes, non-motor symptoms, and dopaminergic functional imaging findings, are crucial markers for prodromal PD diagnosis. Shijun Yan *et al.* recent study introduces serum L1EV α-synuclein levels as a potential biomarker, detecting early pathogenesis shifts, serving as a cost-effective and accessible tool for screening high-risk individuals. The benefits of this multi-marker approach benefits in evaluating disease prognosis and progression. Serum L1EV α-synuclein's role in uncovering non-motor features, such as depression and anxiety, in prodromal PD underscores its significance for improving patient quality of life. The potential for early intervention using this biomarker offers hope for halting neurodegeneration and delaying clinical PD development. The global applicability of this promising biomarker needs to be looked into, while the need for more diverse racial and ethnic studies regarding it are required. Ultimately, the letter argues that identifying high-risk individuals through L1EV α-synuclein enables timely neuroprotective interventions, providing patients with valuable insights into disease progression and reducing uncertainty and fear.

Keywords: Parkinson's Disease; Serum L1EV α-synuclein levels; Prodromal Diagnosis; Biomarker; Neurodegeneration

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To the editor,

Parkinson's Disease (PD) generates a worldwide burden of an estimated 7-10 million patients, constituted by an array of motor and non-motor symptoms.[1] These motor symptoms only aid in diagnosis once widespread neurodegeneration has already occurred. This signifies an urgent need to diagnose PD prior to such a stage, or identify prodromal PD associated with an increased risk of PD development. The MDS research criteria includes subtle motor changes, a list of varying non-motor symptoms, and pathological findings on dopaminergic functional imaging, as markers for diagnosis of prodromal PD.[2]

A recent study published by Shijun Yan *et al*. highlighted the use of serum L1EV α-synuclein levels to identify individuals at a high risk of developing PD, by detecting the homeostatic shift in α-synuclein that is characteristic of early pathogenesis.[3] The authors discuss the utility of this blood-based serology in addition to markers such as hyposmia and cognitive deterioration, rapid eye movement sleep behavior disorder (RBD), and GBA1 gene status in the sub-stratification of those at-risk individuals which have the greatest probability of PD and related Lewy body disease development. The study showed higher serum L1EV α-synuclein levels in participants with a positive CSF SAA, thus suggesting its potential as a proxy biomarker for neuronal α-synucleinopathy. In addition, L1EV α-synuclein measurement happens to be a cost-effective, and easily accessible method to screen high-risk individuals, as opposed to an abnormal DaT SPECT or other labor-intensive clinical assessments that were previously used to measure additive risk. Thus, the study ultimately discusses the diagnosis of prodromal PD using serum L1EV α-synuclein concentration, allowing clinicians to detect the pathology in its early stages.

Therefore, this biomarker can be used as part of a multi-marker approach to evaluate prognosis and progression of disease in individuals, which will have many benefits. For instance, an idea about the expected time for conversion of prodromal PD to clinical PD will not only form a basis for disease-modifying clinical trials, but also be of great value to patients of probable prodromal PD.[2] Depression and anxiety are common non-motor symptoms of PD, which may manifest in prodromal PD. The early diagnosis followed by

suitable treatment can greatly improve quality of life in patients and reduce caregiver burden.[4] Thus, serum L1EV α-synuclein levels can prove highly beneficial in this regard by acting to alert clinicians toward otherwise overlooked non-motor features of PD. In coming times, the use of such a multi marker approach in the diagnosis of prodromal PD will permit early intervention, which could potentially halt the process of neurodegeneration, ultimately delaying, or even preventing the development of clinical PD.[5] Conclusively, using L1EV α-synuclein as a biomarker to identify high risk individuals will not only allow neuroprotective interventions to be initiated earlier, but will also enable patients to be counseled effectively regarding the expected progression and outcome of their disease, helping to decrease the inevitable uncertainty and fear. Since the study conducted by Shijun Yan *et al*. included mostly White participants, similar studies need to be conducted across a wide array of racial and ethnic groups, so that the generalization of their results and the widespread employment of this highly promising biomarker can be assessed worldwide.

Abbreviations:

- Parkinson's Disease; PD
- rapid eye movement sleep behavior disorder; RBD
- L1CAM-positive extracellular vesicle; L1EV

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