NEUROINFLAMMATION AND NEUROAXONAL INJURY IN PREDICTING ADVERSE DISEASE PROGRESSION IN PARKINSON'S DISEASE

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Abstract. Parkinson's disease (PD) shows variable progression, and clinical assessment alone may not fully predict future functional decline. This narrative review summarizes recent evidence on neurofilament light chain (NfL), caspase-1, interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) as potential prognostic biomarkers. Current data suggest that NfL has the strongest association with neuroaxonal injury and adverse clinical outcomes, while caspase-1, IL-6, and MMP-9 may provide complementary information on neuroinflammation. Further prospective studies are required to confirm their independent and combined prognostic value.

Keywords: Parkinson's disease; neurofilament light chain; caspase-1; interleukin-6; MMP-9; neuroinflammation; prognosis; functional decompensation.

Background. Parkinson's disease (PD) has heterogeneous progression, and motor severity alone does not fully capture future falls, dysphagia, cognitive decline, or loss of independence. Neuroaxonal injury and immune responses are plausible complementary processes for risk assessment. Neurofilament light chain (NfL) reflects axonal damage, whereas caspase-1, interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) represent distinct aspects of inflammatory or proteolytic activity. Their clinical usefulness must be evaluated beyond established clinical predictors.

Objective. To summarize published evidence concerning NfL, caspase-1, IL-6, and MMP-9 in PD and assess the rationale and limitations of combining them to predict clinically meaningful functional deterioration.

Materials and methods. A focused narrative synthesis of peer-reviewed clinical

studies and a systematic review published in 2022–2025 was undertaken. Evidence was organized by biomarker, clinical association, and remaining validation needs. This abstract does not report original measurements, pooled estimates, or results from the proposed PARK-PROTECT study.

Evidence synthesis. In a 2025 systematic review and network meta-analysis encompassing 78 studies and 13,120 participants, blood and cerebrospinal fluid NfL concentrations were higher in several atypical parkinsonian syndromes than in PD, supporting NfL as a marker of neuroaxonal injury rather than a disease-specific test [1]. A separate PD cohort associated elevated baseline plasma NfL with subsequent milestones, including repeated falls, dysphagia, wheelchair use, and need for nursing care; these observational associations require external confirmation [2]. In a small proof-of-principle plasma study (32 patients with PD; 13–16 controls, depending on assay), caspase-1 and other inflammasome-related proteins were elevated, but diagnostic comparisons with atypical parkinsonism and prospective prediction of disability were not established [3]. An early-PD longitudinal study linked a composite inflammatory component driven mainly by IL-2 and IL-6not IL-6 aloneto faster progression of certain non-motor symptoms, particularly mood-related symptoms [4]. A clinical study reported associations between circulating MMP-9 and PD features, indicating potential relevance to inflammatory and extracellular-matrix processes without establishing independent prognostic utility [5]. Importantly, a human genetic investigation did not support a causal role for the NLRP3 inflammasome in PD risk or progression; biomarker associations should therefore not be interpreted as proof of causal mediation or a validated therapeutic target [6].

Conclusions. NfL currently provides a stronger clinical prognostic rationale than the other markers considered. Caspase-1, IL-6, and MMP-9 may add complementary information, but their incremental value for predicting functional decompensation remains unproven. A prospective, appropriately validated model

should test whether these measures improve prediction of prespecified eventssuch as recurrent falls, dysphagia, or new dependenceover clinical assessment alone. Assay standardization and adjustment for age, intercurrent infection, and comorbidity are essential.

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