2nd European CMT Specialists Conference
Antwerp, 23-25 October 2025

Presentation PL4-01

Acetylated α-Tubulin as a clinical plasma biomarker of disease severity in CMT1A

CJ. Maltby (1); C. Laurini (2,3,4), J. Pinto (1), B. Sorrenti (2,3,4), M. Patelli (4), K. Ootake (5), SC. Previtali (2,3,4), M. Bianchi (1)

(1) Ulysses Neuroscience Ltd, Pioneer Life Sciences, Building 10 Cherrywood Business Park, Loughlinstown, Co. Dublin, Republic of Ireland
(2) Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
(3) Neuromuscular Repair Unit, Institute of Experimental Neurology (INSPE) and Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy
(4) Vita-Salute San Raffaele University, Milan, Italy
(5) Neuroscience Drug Discovery Unit, Takeda Pharmaceutical Company Limited, 26-1, Muraoka-Higashi 2-chome, Fujisawa 251-8555, Japan

Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common inherited peripheral neuropathy and is caused by a 1.5Mb duplication on chromosome 17p11.2 encompassing the PMP22 gene. This results in PMP22 overexpression, progressive demyelination, and peripheral nerve dysfunction. Clinically, CMT1A presents with distal muscle weakness, sensory deficits, foot deformities, and gait disturbances, typically beginning in childhood. Although several clinical and electrophysiological scales exist to monitor disease progression, they are limited by subjectivity and insensitivity to slow progression. Neurofilament light chain (Nf-L), a biomarker of axonal injury, has shown limited correlation with CMT1A severity or progression, restricting its utility in clinical trials.

To address this, we evaluated acetylated α-tubulin (Acet-Tub)—a microtubule-stabilising post-translational modification—as a candidate blood-based biomarker in the plasma of 45 genetically confirmed CMT1A patients and age- and sex-matched healthy controls. Acetylation at lysine 40 (K40) of α-tubulin, catalyzed by αTAT1 and removed by HDAC6, supports microtubule stability and axonal transport, key for neuronal health. Dysregulated α-tubulin acetylation is implicated in neurodegeneration, suggesting that reduced acetylation may reflect axonal dysfunction in CMT1A.

We confirmed that plasma Nf-L is elevated in CMT1A but does not correlate with clinical severity. In contrast, Acet-Tub levels were significantly reduced in CMT1A patients and showed a strong inverse correlation with the Overall Neuropathy Limitations Scale (ONLS) and the Charcot-Marie-Tooth Examination Score (CMTES).

These findings indicate that impaired axonal integrity is coupled with a decrease in microtubule stability. Acetylated α-tubulin is a downstream target of HDAC6 currently under investigation for the treatment of CMT, and thus serves as a novel and disease-relevant biomarker reflecting molecular pathology and clinical severity in CMT1A.