The 2nd Meeting of the Italian Metabolomics Network

Firenze
Campus Novoli
15th – 16th December 2025

NMR BASED METABOLOMICS TO INVESTIGATE MOLECULAR MECHANISMS IN ADLD NEURODEGENERATIVE DISORDER

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Autosomal Dominant Leukodystrophy (ADLD) is an ultra-rare but underestimated leukodystrophy that occurs in adulthood [1]. This disorder is characterized by progressive degeneration of white matter due to duplication of the LMNB1 gene. Clinically, ADLD progresses slowly and presents with autonomic dysfunction early on, followed by pyramidal and cerebellar signs such as spasticity, tremor, and ataxia. Although affected individuals may survive for over twenty years post-onset, their quality of life is markedly compromised.

As this is an ultra-rare disease, research into reliable biomarkers and the underlying molecular mechanisms of ADLD remains limited. For the first time, we employed NMR-based metabolomics to analyze cerebrospinal fluid (CSF) and blood samples from two patients with confirmed LMNB1 duplication. Using the high-resolution magic angle spinning (HR-MAS) NMR spectroscopy, we present the first metabolic fingerprint of CSF. In this multi-fluid study, non-targeted NMR metabolomics revealed elevated levels of lactate in both CSF and plasma, indicating its potential as a key biomarker for ADLD. We observe, in comparison with CSF no ADLD samples, high level of lactate, together with low alanine levels. This suggests disturbances in energy and nitrogen metabolism within astrocytes. In particular, the absence of glutamate and gamma-aminobutyric acid (GABA), with only glutamine present, indicates possible disturbances in the glutamate/GABA-glutamine cycle, which is essential for the recycling of neurotransmitters by astrocytes. Furthermore, the absence of N-acetyl-L-aspartate (NAA) and low levels of myo-inositol suggest impaired myelin repair by oligodendrocytes. In conclusion, our metabolomic profiling of CSF offers promising non-invasive biomarkers that enhance understanding of the molecular pathology in ADLD. This approach underscores the potential of high-throughput metabolomics to inform diagnostic and therapeutic strategies for this rare disorder, which currently lacks effective treatment options.

References

1. Ratti, S. et al. (2021) "Cell signaling pathways in autosomal-dominant leukodystrophy (ADLD): the intriguing role of the astrocytes", Cell Mol Life Sci., 78(6), p.2781-2795. doi: 10.1007/s00018-020-03661-1.