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Neurological manifestations in Inborn Errors of Immunity (IEI)

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Background: Inborn Errors of Immunity (IEI) comprise a rapidly expanding group of monogenic and phenocopy disorders. The latest IUIS classification (2024/2025) enumerates >500 gene-defined IEI alongside phenocopies caused by somatic variants or disease-driving inflammatory disorders, underscoring the diversity of immunological pathways with potential neurotropism.

Objective: In my lecture, I will discuss current evidence on neurological involvement across IEI and outline implications for diagnosis and management, using the IUIS-2024/25-nomenclature as framework. Clinical examples from our cohort at the Pediatric Immunology Unit, Medical University of Vienna, will serve for outlining diagnostic guidelines.

Summary: Neurological disease in IEI arises via four overlapping mechanisms: (1) **Infectious susceptibility of the CNS** (e.g., enteroviral meningoencephalitis in agammaglobulinaemia; herpes simplex encephalitis in TLR3-pathway defects), (2) **Sterile neuroinflammation/autoimmunity** (e.g., interferonopathies causing leukodystrophies such as Aicardi–Goutières syndrome; CTLA4/LRBA and STAT1/STAT3 GOF with CNS demyelination or encephalitis), (3) **Neurovascular/vasculitic injury** (e.g., DADA2-associated strokes), and (4) **Neurodevelopmental/degenerative trajectories** inherent to DNA repair and proteostasis defects (e.g., ataxia-telangiectasia, PSMB8-associated syndromes). Recent reviews highlight that **neurological phenotypes** may be **sentinel presentations**—even in individuals **without recurrent infections**—widening the clinical index of suspicion for IEI in neurology clinics. Notably, the IUIS 2024/25 reports emphasise variant-specific mechanisms (loss or gain of function vs neomorphic) within the same gene (e.g., STAT1/STAT3, IRF4, OTULIN), which can pivot neurological risk and treatment response.

Implications for practice: When IEI is suspected in unexplained CNS infection, encephalitis, vasculitis, or leukodystrophy. Apparent movement disorder, or neurodevelopmental delay, clinicians should: integrate the **current IUIS classification** for targeted phenotyping; combine **early genetic testing** (including TRIO Exome sequencing, mosaicism/low-VAF detection) with immune profiling of blood/CSF; and pursue **treatable targets**, including immunoglobulin replacement, pathogen-directed therapy, pathway-specific immunomodulation (e.g., JAK/IL-1 blockade in defined autoinflammatory IEI), and **HSCT/gene therapy** where indicated to allow modern and **precision medical treatment**. Moreover, structured neurological surveillance should be embedded in longitudinal IEI care pathways.

Conclusion. Neurological disease is common, mechanistically diverse, and increasingly **actionable** across IEI. Anchoring evaluation and nomenclature to the IUIS 2024 update improves diagnostic yield, informs precision therapy, and should be standard in neuro-immunology practice.