A chicken-or-egg dilemma resolved: autoantibodies initiate neurodegeneration

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IgLON5-antibody disease occupies a unique position at the interface between autoimmunity and neurodegeneration[1]. By typically presenting with multiple, slowly progressive neurological features including a complex sleep disorder, movement disorder and bulbar dysfunction, clinical observations are consistent with a neurodegenerative syndrome. Indeed, brainstem-predominant tau pathology was reported as a universal and striking neuropathological feature.[1] Yet, ~75% of patients have a robust class II HLA allele association, mild CSF pleoytosis has been reported when sampled early and the IgLON5-antibodies bind an extracelluar epitope – suggesting their direct pathogenic potential.[1-3]

Hence, since its original description, debate has centred on a fundamental question: does a primary tauopathy provoke a secondary immune response, or do pathogenic autoantibodies initiate a cascade that culminates in neurodegeneration? In this issue of *Brain*, Reinecke and colleagues provide compelling neuropathological and *in vitro* evidence suggesting that the IgLON5-autoantibodies come first and tau follows,[4] a concept which represents an inflection point with implications extending beyond this rare disorder (Figure 1).

Early clinical findings in IgLON5-antibody *associated* disease reported very limited clinical responses to immunotherapies, supporting the concept of an atypical neurodegenerative tauopathy with autoantibodies as an epiphenomenon. This view was strengthened by seminal autopsy work demonstrating a distinctive mixed three-repeat and four-repeat tauopathy, reinforcing parallels with primary tauopathies[5].

However, compelling exceptions soon emerged. Some patients' brains showed minimal or absent tau despite pronounced clinical disease,[6] prompting a neuropathological staging reclassification to illustrate a spectrum, from early cases with minimal tau to advanced disease with fully developed brainstem tauopathy.[7] In parallel, studies narrowed the responsible HLA Class II association to the HLA-DQB1*05 allele, revealed patient T cells could be activated by IgLON5 peptides and early investigations also reported that passive transfer of patient IgG to mice induced motor impairments with phosphorylated tau midbrain accumulation.[2,8] Together, these observations have swung the pendulum to support a model of time-dependent tau deposition *secondary* to the presence of IgLON5-autoantibodies.

The data from Reinecke and colleagues convincingly supports this concept and simulates a longitudinal timeline of how pathology unfolds in IgLON5-antibody disease (Figure 1).[4] They report early-stage disease is characterised by nuclear tau phosphorylation, not mature cytoplasmic

tau inclusions, most notably at serine 422 (pTau S422). This is accompanied by disruption of the nuclear membrane in neurons that also show surface IgG4 deposition, consistent with the dominant known subclass of IgLON5-antibodies. These data elegantly indicate a direct link between the antibodies and the subtle, early pathological hallmarks of IgLON5-antibodies.

Equally striking was the emergence of nuclear injury. Lamin B1 immunostaining revealed marked nuclear invaginations and crenellations at the earliest disease stages. The directionality of this observation was reinforced by *in vitro* data showing that purified IgLON5-antibodies reproduce remarkably similar nuclear membrane deformities when applied to rat hippocampal neurons, directly linking initial antibody binding to secondary nuclear injury. These findings align closely with prior evidence that IgLON5-antibodies irreversibly reduce membrane IgLON5 clusters and destabilise the neuronal cytoskeleton,[9] and with broader insights from tau biology, in which nuclear lamina disruption and failure of nucleocytoplasmic transport are increasingly recognised as early drivers of neurodegeneration. In autopsy specimens obtained from later time points, the authors observed cytoplasmic tau inclusions appeared with the familiar ordered sequence of tau post-translational modifications, firmly positioning tau pathology downstream in the immunopathological cascade, further supporting an “autoantibody-first, tau-second” model of disease pathogenesis.

Therefore, IgLON5-antibody *mediated* disease emerges as an autoantibody-induced secondary tauopathy. With these autoantibodies initiating the often fatal natural disease cascade, treatment timing assumes decisive importance: the therapeutic window appears early, and once downstream tau pathology is established, immunotherapies appear far less effective.[3] Consistent with this, the largest international cohort to date shows that immunotherapy administration within the first year was the only modifiable factor associated with lower long-term disability and improved survival.[3]

Although primarily relevant to post-mortem assessments, these observations reshape diagnostic neuropathology. Reliance on conventional tau markers alone risks missing early disease, whereas inclusion of IgG4, Lamin B1 and pTauS422 can reveal autoantibody-mediated neuronal stress prior to overt tauopathy, thereby refining recognition and staging of IgLON5-antibody disease. More broadly, IgLON5-antibody disease now offers a rare vantage point at the interface of immunity and neurodegeneration. Alongside nuclear lamina disruption and cytoskeletal derangement, a substantial proportion of cases also develop classical tau inclusions and, in roughly one-third, TDP-43 pathology,[7] echoing signatures observed in primary neurodegenerative disorders. Uniquely, however, in IgLON5-antibody disease, the initiating trigger is identifiable and potentially

modifiable, offering an unparalleled opportunity to interrogate how immunity modifies downstream protein aggregation.

These collective observations prompt future research questions aimed at maximally exploiting this exciting disease model. The sequence from autoantibody binding to nuclear stress and subsequent tauopathy is now better defined, but what dictates the striking heterogeneity of clinical disease trajectories remains uncertain. Older patients often follow a faster and more aggressive course, whereas younger individuals may exhibit a slowly smouldering evolution, suggesting that age-related loss of neural resilience, cumulative co-pathologies and region-specific vulnerability critically shape how autoantibody-mediated injury is translated into sustained degeneration.[7] Equally unresolved is the precise mechanism of the autoantibodies, IgG4 antibodies are broadly considered to block protein-protein interactions: knowledge of this precise molecular interaction(s) may offer more directed therapies to prevent commoner forms of neurodegeneration. Beyond IgG4 binding itself, coexisting IgG subclasses, T-cell infiltrates in early disease, and microglial activation with up-regulation of MHC-II expression point to active immune modulation rather than purely passive receptor blockade.[7,10]

At a broader level, this work illustrates how sustained autoimmune injury can act as an initiating event in neurodegenerative cascades. In contrast to other forms of autoimmune encephalitis, in which antibodies predominantly cause reversible synaptic dysfunction or phagocyte-mediated synaptic pathology, autoantibodies here may induce persistent cellular stress that disrupts cytoskeletal integrity and nuclear homeostasis and promotes downstream tau post-translational modification. This work establishes immune-mediated disease as a potential upstream driver of neurodegeneration and underscores a critical therapeutic window to prevent otherwise irreversible degenerative change.

While the philosophical chicken-egg dilemma will remain a challenge to resolve, in the case of IgLON5-antibody disease it now appears convincingly cracked, without ruffling feathers.

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Competing interests

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Figure 1. The evolution of IgLON5-anitbody mediated disease. Proposed stages of IgLON5-antibody disease progress from prominent membrane associated IgG4 autoantibody binding and early nuclear pathology with tau phosphorylation at pS422 (Stage 1) to further phosphorylations and accumulation of 4R tau, alongside reduced IgG4 (Stage 2), through to 3R tau modifications including acetylation. This highlights the transition from primary antibody-mediated neuronal dysfunction to a florid distinctive tauopathy, linking early immune-mediated injury to downstream neurodegenerative pathology.