The immunopathogenesis of ovarian teratoma-associated NMDAR-antibody encephalitis: mechanisms of B cell infiltration inform a rational approach to gynaecologic operative management

Adam Al-Diwani, Ruby Harrison, Josh Bull, Leticia Campo, Tasneem Hassan-Ali, Hubert Slawinski, Hanine Fourie, Helen Byrne, Georg Holländer, Belinda Lennox, Patrick Waters, Isabel Leite, Adam Handel and Sarosh R Irani

N-methyl-d-aspartate receptor-antibody encephalitis (NMDAR-Ab-E) is a life-threatening yet highly treatable Ab-mediated neuropsychiatric disease predominantly affecting younger adult women. There is an ovarian teratoma (OT) in about 25%, of which prompt recognition and resection is associated with faster neurologic disease resolution and reduced relapse risk. Endocrine and reproductive complications of oophorectomy are a crucial consideration in operative aspects of management. Furthermore, these patients usually lack mental capacity to consent, necessitating operative decisions to be made in the patient's best interests. A detailed mechanistic understanding of how OTs can drive NMDAR-Ab-E may inform operative decision making.

Here, we used IgA and IgM isotype-specific NMDAR-Ab serology, teratoma cell culture, multiplex histology and 10x single B cell RNAseq to investigate the immunopathogenesis of ovarian teratoma-associated NMDAR-Ab-E.

In 108 patients (284 sera) with definite anti-NMDAR encephalitis including 32 patients (79 sera) with OT we found a positive association between NMDAR-IgA (35/79, 44% vs. 42/206, 20%; ratio 2.17) and a negative association with NMDAR-IgM (24/79, 30% vs. 98/206, 48%; ratio 0.64). This was confirmed by multivariate analysis of samples from 0-100 days: NMDAR-IgA (β=0.29, P=0.0001) and NMDAR-IgM (β=-0.17, P=0.009). This implied OTs drive isotype-switching of the underlying NMDAR-Ab-secreting B cell population from IgM to IgA. Next, we cultured explants and dissociated cells from 3 resected teratomas in activation (IL1β, IL2, IL6, IL21, R848, TNFα, CD40L) or maintenance (IL6 only) cytokine conditions. Whereas the explants frequently produced specific antibodies in both conditions (55% vs 50%), the dissociated cells did this less often and only under activation conditions (20% vs 0%). The underlying cellular architecture was then directly visualised by multiplex B cell histology which revealed multiple B cell clusters with a high BCL6/AID core, consistent with a germinal centre structure. Finally, single B cell RNAseq revealed clusters of clonally-expanded IgA-specific affinity matured memory B cells.

Alongside the clinical efficacy of OT removal, this data is strongly suggestive of the causal primacy of OT in these patients. Unlike the majority of OTs, when associated with NMDAR-Ab-E the identification and removal of these lesions is highly time critical. Given the age and often excellent prognosis with adequate treatment the multidisciplinary team that looks after these patients should begin to discuss consensus guidelines on ensuring lesion removal whilst safeguarding future fertility. This may include novel operative approaches and/or ovarian cryopreservation.