

# Autoimmune encephalitis following haematopoietic stem cell transplant: a new clinical entity or a previously unrecognised one?

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Central nervous system (CNS) autoimmunity, characterized by the presence of antibodies binding to brain receptors, ion channels, and related proteins (1) is increasingly recognized in children (2). Childhood-onset autoimmune encephalitis may be associated with tumours, particularly in post-pubertal girls with N-Methyl-D-aspartate receptor (NMDAR) antibody encephalitis (3), but the majority of these encephalitides are presumed to have a post infectious trigger (1,4). Recently, in a large single-centre study of 164 Australian children presenting with encephalitis, 10% were identified as having an autoimmune aetiology, a frequency which surpassed that of any single virus identified (5), mirroring cases reported in the California encephalitis project, where the frequency of NMDAR antibody encephalitis surpassed that of any of the identified viral encephalitides (6). This discovery, that several forms of encephalitis result from neuronal antibodies, and are immunotherapy-responsive, has led to a paradigm shift in the diagnostic approach with a focus on how to recognize, diagnose and treat these conditions early (2).

Haematopoietic stem cell transplant (HSCT) is used to treat a wide range of conditions in children. It involves intravenous infusion of haematopoietic stem cells that have been harvested from the patient (autologous transplant) or from a suitable donor (allogeneic transplant). Depending on the source of the stem cells, the procedure is referred to as bone marrow transplant (BMT), peripheral blood stem cell transplant (PBSCT) or cord blood transplant (CBT). Indications for HSCT include malignancy and other non-malignant conditions such as primary immunodeficiencies,

inborn errors of metabolism, haemoglobinopathies and autoimmune diseases.

Neurological complications during transplant and in the early and late post-transplant period are common. Case series report the incidence to be between 10% and 25% (7-9). Early in the course of transplant, before and during immune reconstitution, severe immunosuppression is associated with vulnerability to a wide range of bacterial, viral, fungal and protozoal CNS infections. Multiple drug exposure during the early phase of transplant has a high risk of drug related neurotoxicity. Posterior reversible encephalopathy syndrome (PRES), cerebrovascular events, recurrent or secondary malignancy and acute and chronic graft versus host disease are other possible causes of CNS disease during and following transplant (10,11). However, despite autoimmune complications of HSCT such as autoimmune cytopenias (idiopathic thrombocytopenic purpura/thrombocytopenia, autoimmune haemolytic anaemia, aplastic anaemia), autoimmune thyroid disease, insulin dependant diabetes mellitus, autoimmune hepatitis, myasthenia gravis, scleroderma, vitiligo, pemphigus and pemphigoid, being well recognised in both children and adults, autoimmunity affecting the CNS has been very rarely reported (12-14).

Interestingly, Rathore *et al.* (15) report a case of limbic encephalitis (LE) associated with voltage-gated potassium channel (VGKC)-complex, leucine-rich glioma inactivated 1 (LGI1) antibodies and thyroglobulin antibodies, 15 months following BMT for severe idiopathic aplastic anaemia. This report is intriguing as it is a rare report of LE

associated with VGKC-complex and LGI1 antibodies in a child. VGKC-complex antibody-associated CNS diseases, as measured by antibodies that immunoprecipitate 125I- $\alpha$ -dendrotoxin-labeled VGKC extracted from mammalian brain tissue, have been detected in patients with limbic LE, Morvan's syndrome, neuromyotonia, and cases of adult-onset epilepsy (16). Children with VGKC-complex antibody can present with LE (17,18), but this is infrequent compared to adults. The neurologic syndromes associated with VGKC-complex antibodies are broader in childhood, including a range of seizure syndromes (19), developmental delay (20), and acquired demyelination syndromes (21). The target antigens for some VGKC-complex antibodies are now known to be proteins tightly complexed with the channel, including the secreted synaptic protein LGI1, the transmembrane axonal protein contactin-associated protein 2 (CASPR2), and contactin 2 (22). However, in most pediatric cases these antibodies to the recognized VGKC-complex proteins are not found, but antibodies instead target intracellular epitopes on the VGKC subunits, or the intracellular interacting proteins (23). Given the heterogeneity of the clinical presentations in children with VGKC-complex antibodies, unless the target antigens are identified as reported in Rathore *et al.* (15), the exact significance of VGKC-complex antibodies in most children remains unclear. This is thus a report of convincing autoimmune encephalitis in a patient following HSCT.

Post-transplant acute limbic encephalitis (PALE) has been described as a complication of HSCT, occurring relatively early in the post-transplant period and frequently in association of human herpes virus 6 (HHV6) reactivation. In a proportion of cases of PALE, there is no evidence of HHV6 reactivation or other associated infection (24,25). Taken together with recent reports in adult and children demonstrating that up to 25% of unresolved cases of encephalitis in children were identified to have an autoimmune aetiology on retrospective testing for neuronal surface antibodies (5,26), similar findings may well be identified when evaluating previously unresolved cases of neurological complications following HSCT.

The reason(s) underpinning the increased risk of autoimmune complication following HSCT is likely to involve multiple mechanisms, and their respective interactions. Nevertheless, fundamental to all autoimmune disorders belies a break down in self-tolerance. At the time of HSCT, prior to infusion of stem cells, patients receive conditioning treatment to eliminate existing disease-causing cells, to create a niche into which the donor stem cells

can engraft and to minimise the chance of graft rejection. The intensity and type of pre-transplant conditioning, in some cases, appears to correlate with the risk of developing subsequent autoimmunity although the impact of this is not consistent across all patients and may vary according to the indication for BMT, suggesting other host genetic and environmental factors contribute to this risk of losing self-tolerance (12,13). Although it has also been postulated that a propensity for autoimmunity may be transferred from donor to recipient, the potential mechanisms for this are also unclear (12).

Crucially, induction of CNS autoimmunity additionally requires the disruption of the complex cellular and anatomical interactions between the immune and nervous systems across the blood brain barrier (27), one that may arise following prior neurological events such as infection. Recently, we, and others have reported that herpes simplex virus encephalitis trigger NMDAR antibodies (4,28,29) and potentially other brain autoimmunity (4). Interestingly, a refractory epilepsy syndrome in children following HHV6 associated PALE has been described in children most of whom developed generalised, anti-epileptic drug resistant seizures and developmental regression or arrest (30,31). Although an autoimmune aetiology was deemed unlikely in these case reports, as yet unidentified or untested autoantibodies may have been contributory.

Methodological advances in assays for detecting neuronal surface antibodies are currently facilitating the investigation of potential interaction between infection and autoimmunity (1,16). This will be further augmented by promising gains in deep sequencing techniques for detection of novel infectious triggers, likely to be more prevalent in the immunocompromised host. Such a technique has recently been utilised in the clinical setting to identify a novel astrovirus in a child with neurological deterioration post-HSCT (32). Non-infectious neurological events that potentially compromise the blood brain barrier during HSCT, such as PRES, may also contribute to an increased risk of developing CNS autoimmunity.

Overall, a careful systematic and serial evaluation of engraftment status, thymic function and detailed T and B cell immunophenotyping may further elucidate time windows when perturbations of self-tolerance occur. The importance of parallel sampling of humoral and cellular changes in the cerebrospinal fluid to investigate CNS autoimmunity is increasingly recognized, although this may be challenging to achieve in very young children.

The utility of active surveillance by measuring potentially

pathogenic tissue and organ specific antibodies in those at risk remains to be evaluated systematically, particularly in CNS autoimmunity. Patients may harbour antibodies long before becoming symptomatic (33) and antibodies may persist for many years following full recovery from disease (34). The major clinical implications for this case report of CNS autoimmunity, is the need for early recognition of such cases to ultimately optimise treatment. In the context of a child who has undergone HSCT, where empirical immunosuppressive or modulatory treatment may need to be instituted, atypical infections or atypical presentations of common infections need to be considered while taking care in balancing the risk of subsequent viral reactivation. Central to this management would be collaborative efforts between transplant physicians, immunologists, infectious diseases experts and neurologists.

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### References

- Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. *Ann N Y Acad Sci* 2015;1338:94-114.
- Lim M, Hacoheh Y, Vincent A. Autoimmune encephalopathies. *Pediatr Clin North Am* 2015;62:667-85.
- Florange NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009;66:11-8.
- Armangue T, Leypoldt F, Málaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol* 2014;75:317-23.
- Pillai SC, Hacoheh Y, Tantsis E, et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. *Pediatrics* 2015;135:e974-84.
- Gable MS, Sheriff H, Dalmau J, et al. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clin Infect Dis* 2012;54:899-904.
- Azik F, Yazal Erdem A, Tavit B, et al. Neurological complications after allogeneic hematopoietic stem cell transplantation in children, a single center experience. *Pediatr Transplant* 2014;18:405-11.
- Uckan D, Cetin M, Yigitkanli I, et al. Life-threatening neurological complications after bone marrow transplantation in children. *Bone Marrow Transplant* 2005;35:71-6.
- Weber C, Schaper J, Tibussek D, et al. Diagnostic and therapeutic implications of neurological complications following paediatric haematopoietic stem cell transplantation. *Bone Marrow Transplant* 2008;41:253-9.
- Yoshida S, Hayakawa K, Yamamoto A, et al. The central nervous system complications of bone marrow transplantation in children. *Eur Radiol* 2008;18:2048-59.
- Pruitt AA, Graus F, Rosenfeld MR. Neurological complications of transplantation: part I: hematopoietic cell transplantation. *Neurohospitalist* 2013;3:24-38.
- Holbro A, Abinun M, Daikeler T. Management of autoimmune diseases after haematopoietic stem cell transplantation. *Br J Haematol* 2012;157:281-90.
- Khalil A, Zaidman I, Bergman R, et al. Autoimmune complications after hematopoietic stem cell transplantation in children with nonmalignant disorders. *ScientificWorldJournal* 2014;2014:581657.
- Sherer Y, Shoenfeld Y. Autoimmune diseases and autoimmunity post-bone marrow transplantation. *Bone Marrow Transplant* 1998;22:873-81.
- Rathore GS, Leung KS, Muscal E. Autoimmune Encephalitis Following Bone Marrow Transplantation. *Pediatr Neurol* 2015;53:253-6.
- Vincent A, Bien CG, Irani SR, et al. Autoantibodies associated with diseases of the CNS: new developments and future challenges. *Lancet Neurol* 2011;10:759-72.
- Haberlandt E, Bast T, Ebner A, et al. Limbic encephalitis in children and adolescents. *Arch Dis Child* 2011;96:186-91.
- Hacoheh Y, Wright S, Waters P, et al. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *J Neurol Neurosurg Psychiatry* 2013;84:748-55.
- Suleiman J, Dale RC. The recognition and treatment of

- autoimmune epilepsy in children. *Dev Med Child Neurol* 2015;57:431-40.
20. Dhamija R, Renaud DL, Pittock SJ, et al. Neuronal voltage-gated potassium channel complex autoimmunity in children. *Pediatr Neurol* 2011;44:275-81.
  21. Hacoheh Y, Absoud M, Woodhall M, et al. Autoantibody biomarkers in childhood-acquired demyelinating syndromes: results from a national surveillance cohort. *J Neurol Neurosurg Psychiatry* 2014;85:456-61.
  22. Irani SR, Gelfand JM, Al-Diwani A, et al. Cell-surface central nervous system autoantibodies: clinical relevance and emerging paradigms. *Ann Neurol* 2014;76:168-84.
  23. Hacoheh Y, Singh R, Rossi M, et al. Clinical relevance of voltage-gated potassium channel-complex antibodies in children. *Neurology* 2015. [Epub ahead of print].
  24. Chamberlain MC, Chowdhary S. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. *Neurology* 2008;70:491-2; author reply 492-3.
  25. Ogata M, Fukuda T, Teshima T. Human herpesvirus-6 encephalitis after allogeneic hematopoietic cell transplantation: what we do and do not know. *Bone Marrow Transplant* 2015;50:1030-6.
  26. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010;10:835-44.
  27. Ransohoff RM, Engelhardt B. The anatomical and cellular basis of immune surveillance in the central nervous system. *Nat Rev Immunol* 2012;12:623-35.
  28. Bamford A, Crowe BH, Hacoheh Y, et al. Pediatric Herpes Simplex Virus Encephalitis Complicated by N-Methyl-D-aspartate Receptor Antibody Encephalitis. *J Pediatric Infect Dis Soc* 2015;4:e17-21.
  29. Hacoheh Y, Deiva K, Pettingill P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. *Mov Disord* 2014;29:90-6.
  30. Howell KB, Tiedemann K, Haeusler G, et al. Symptomatic generalized epilepsy after HHV6 posttransplant acute limbic encephalitis in children. *Epilepsia* 2012;53:e122-6.
  31. Raspall-Chaure M, Armangué T, Elorza I, et al. Epileptic encephalopathy after HHV6 post-transplant acute limbic encephalitis in children: confirmation of a new epilepsy syndrome. *Epilepsy Res* 2013;105:419-22.
  32. Brown JR, Morfopoulou S, Hubb J, et al. Astrovirus VA1/HMO-C: an increasingly recognized neurotropic pathogen in immunocompromised patients. *Clin Infect Dis* 2015;60:881-8.
  33. Leite MI, Coutinho E, Lana-Peixoto M, et al. Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. *Neurology* 2012;78:1601-7.
  34. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014;13:167-77.

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