Intractable myoclonus associated with anti-GluR3 antibodies after allogeneic bone marrow transplatation

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Neurological complications following allogeneic bone marrow transplantation (BMT) are most frequently caused by the immunosuppressive regimen, infections and cerebrovascular disorders.[1] Several papers have been reported the transmission of autoimmune diseases from the donor to the recipient after allogeneic bone marrow transplantation possibly due to the transfer of pathogenic cells or antibodies.[2-6] Antibodies to antigens of the central nervous system (CNS) have been reported to play a role in a number of neurological diseases including paraneoplastic syndromes,[7] Rasmussen's encephalitis (RE)[8] and epilepsy.[9,10] We describe the case of a 20 years old man who developed, after allogeneic BMT, a myoclonic encephalitis refractory to common anti-epileptic drugs whose serum and CSF harbored high levels of anti-GluR3 antibodies.

Case report:

A 20-year-old male underwent allogeneic BMT from his brother for aplastic anaemia. During the follow-up period, he received Cyclosporin A (CyA) 200 mg/die without infection, iatrogenic complication or GvHD. Two years later he suffered a severe head trauma with subsequent mild subdural haematoma and coma. Upon waking up from coma, he developed involuntary movements at the right arm and CyA was discontinued with no clinical improvement. On admission to the hospital, the patient presented with myoclonic jerks, dysarthria and dysphagia, which appeared mostly during voluntary movements. Routine laboratory tests were normal. In addition, the patient was found negative for antibodies against CMV, HIV, HSV 1,2,6 and 7, against neuronal antigens such as anti-Yo, -Hu, -Tr and -Ri, both in serum and CSF, as well as for antibodies against GAD, gangliosides and cardiolipin. Brain MRI and total body CT scan were normal. CSF analysis showed only mild pleiocytosis and the presence of a single clonal band. Despite the administration of conventional anti-convulsive drugs no improvement was obtained as sub-continuous myoclonic movements slowly spread to the left limbs. Based on the hypothesis of an immunomediated origin, monthly pulses (three months total) of combined non-specific immunotherapy regimen, consisting of steroids, plasma-exchange and cyclophosphamide (700 mg/m^2) were performed with a significant amelioration of myoclonus. At that time, therapy was discontinued due to the fact that the patient moved to another part of the country and was temporarily lost to follow-up. Two years later, the neurological condition was significantly deteriorated, sustained by a worsening of the myoclonus and the development of progressive left hemiparesis. A brain MRI showed mild cortical atrophy of the right hemisphere, Five years from BMT, the patient died due to acute respiratory failure caused by massive myoclonus involving respiratory muscles and pharynx. Anti-GluR3 antibodies were detected by ELISA using GluR3A and 3B peptides as previously described.[3] Recipient's serum and CSF and donor serum were strongly positive for anti-GluR3 antibodies[8] (see Table). The anti-GluR3 antibody index (12.94) was suggestive of an intrathecal synthesis of anti-GluR3 antibodies.

Table 1. Antibodies against GluR3A and GluR3B peptides in the serum of the epileptic patient and his brother.

	Anti-GluR3A antibodies		*Anti-GluR3B antibodies*	
Dilution	*1:10**	*1:200**	*1:10**	*1:200**
Control patients				
Mean of Serum, mean of n=111	1.467**	0.718**	1.380**	0.693**
Epileptic patient (BM recipient)				
Serum	2.208	0.857	2.345	1.430
IgGs	not tested	0.960	not tested	1.316
Patient's brother (BM donor)				
Serum	1.948	0.552	2.102	0.561

*Anti-GluR3 antibodies were measured by ELISA, using two different peptides (GluR3A and GluR3B) at two different sample dilutions (*), and expressed as absorbance at 450 nm. **Cut-off was defined by the mean OD value obtained from 111 healthy donors plus three standard deviations. OD values higher than cut-off were considered positive. Cut off level: GluR3A 1:10 OD 0.59 + 0.29*3, 1:200 OD 0.718+ 0.13*3. GluR3B 1:10 OD 0.56 + 0.27*3 ,1:200 OD 0.24 + 0.12*3*

Discussion

Despite a number of studies suggesting a role for autoantibodies in the pathogenesis of CNS disorders herein we provide data supporting a role for antibodies against GluR3 in the pathogenesis of myoclonus. In this case, the possibility of an immune reaction against a cerebral antigen was postulated by the presence of an IgG clonal band in the CSF of the epileptic patient and by the clinical response to immunosuppression. In addition, the detection of anti-GluR3 antibodies in the CSF and serum of the affected individual, suggests the possibility of an ongoing autoimmune response directed against a CNS antigen, namely GluR3, recognized by the specific antibodies whose CSF concentrations are consistent with an intrathecal production. Anti-GluR3 antibodies were also detected in the serum of the bone marrow donor. Despite the lack of information on the prevalence of anti-GluR3 antibodies in healthy individuals, we reported such antibodies in less than 1% of 111 healthy subjects.[8] In this case, no serum and CSF samples of the patient were available from the pre-BMT period. Thus it remains an enigma whether anti-GluR3 antibodies present in the donor were transferred together with the graft or were generated in the host immune following the immune reconstitution. Whatever is the case, these results suggest that the presence of anti-GluR3 antibodies in the peripheral blood is not, per se, necessarily pathogenic, as they can be found also in healthy individuals, such as the bone marrow donor. Interestingly, in line with this suggestion, Levite et al11 have recently detected significantly elevated levels of anti-GluR3 antibodies in the serum of both monozygotic twins discordant for RE (as well as in the CSF of the ill twin) suggesting a possible common exposure to an immunogenic insult in the framework of a predisposing genetic background. Based on all our findings, the proposed scenario is that the leakage of the BBB due to the head trauma may have been the critical prerequisite event permitting the pathogenic autoimmune attack of specific glutamate receptors in the CNS (i.e. neuronal and glial ionotropic GluR3) by specific antibodies, thereby contributing to the outburst of epilepsy. In addition, these findings raise the possibility that pathogenetic CNS specific antibodies can be adoptively transferred from the donor to the recipient of bone marrow.

Claudio Solaro,[1] Renato Mantegazza,[2] Andrea Bacigalupo,[3] Antonio Uccelli[4]

[1]Dept. of Neurology ASL3 genovese Genoa, [2]Myopathology and Immunology Unit, National Neurological Institute Carlo Besta, Milan, [3]II Division of Haematology, S. Martino Hospital, Genoa, [4]Centre of Excellence for Biomedical Research, University of Genoa, Italy

Correspondince: Claudio Solaro MD
Department of Neurology ASL3 genovese Genoa
Via Oliva 22 16154– Genoa, Italy.
Tel: +39 010 6449944 Fax: +39 010 6449977,
E-mail:csolaro@libero.it

References

1. Padovan CS, Yousry TA, Schleuning M, Holler E, Kolb HJ, Straube A. Neurological and neuroradiological findings in long-term survivors of allogeneic bone marrow transplantation. Ann Neurol. 1998 May;43(5):627-33.
2. Daikeler T, Gunaydin I, Einsele H, Kanz L, Kotter I. Transmission of psoriatic arthritis by allogeneic bone marrow transplantation for chronic myelogenous leukaemia from an HLA-identical donor. Rheumatology (Oxford). 1999 Jan;38(1):89-90.
3. Alajlan A, Alfadley A, Pedersen KT. Transfer of vitiligo after allogeneic bone marrow transplantation. J Am Acad Dermatol. 2002 Apr;46(4):606-10
4. Kishimoto Y, Yamamoto Y, Ito T, Matsumoto N, Ichiyoshi H, Katsurada T, Date M, Ohga S, Kitajima H, Ikehara S, Fukuhara S. Transfer of autoimmune thyroiditis and resolution of palmoplantar pustular psoriasis following allogeneic bone marrow transplantation. Bone Marrow Transplant. 1997 May;19(10):1041-3. 42.
5. Hallstrand TS, Sprenger JD, Agosti JM, Longton GM, Witherspoon RP, Henderson WR Jr. Long-term acquisition of allergen-specific IgE and asthma following allogeneic bone marrow transplantation from allergic donors. Blood. 2004 Nov 15;104(10):3086-90.
6. Sonwalkar SA, James RM, Ahmad T, Zhang L, Verbeke CS, Barnard DL, Jewell DP, Hull Ma Fulminant Crohn's colitis after allogeneic stem cell transplantation. Gut 2003;52 (10):1518-21
7. Giometto B, Taraloto B, Graus F. Autoimmunity in paraneoplastic neurological syndromes. Brain Pathol 1999; 9(2):261-273.
8. Rogers SW, Andrews PI, Gahring LC, Whisenand T, Cauley K, Crain B et al. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. Science 1994; 265(5172):648-651.
9. Mantegazza R, Bernasconi P, Baggi F, Spreafico R, Ragona F, Antozzi C et al. Antibodies against GluR3 peptides are not specific for Rasmussen's encephalitis but are also present in epilepsy patients with severe, early onset disease and intractable seizures. J Neuroimmunol 2002; 131(1-2):179-185.
10. Levite M. Autoimmune epilepsy. Nat Immunol 2002; 3(6):500.
11. Ganor Y, Freilinger M, Dulac O, Levite M. Monozygotic twins discordant for epilepsy differ in the levels of potentially pathogenic autoantibodies and cytokines. Autoimmunity. 2005 Mar;38(2):139-50.