Anti NMDA receptor encephalitis associated with thymic hyperplasia: A case report

Sir,

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a rare disorder associated with antibodies against the NR1/NR2 heteromers of NMDAR and resulting in a characteristic neuropsychiatric syndrome.[1] Thymic hyperplasia is often detected in myasthenia gravis patients, but its association with autoimmune encephalitis is quite uncommon. To our knowledge, this is the first report of anti-NMDA receptor encephalitis presenting with thymic hyperplasia. NMDAR expression in the thymic tissue suggests that thymus might be involved in autoimmune encephalitis pathogenesis.

A 23-year-old woman was admitted with sleep onset seizures and behavioral changes. Neurological examination showed somnolence, disorientation, spontaneous eye movements with no side restriction. In the following days, she continued having multiple generalized tonic-clonic convulsions, as well as involuntary leg movements, oropharyngeal automatisms, confusion, aggression, dysarthria and stupor. Cranial magnetic resonance imaging (MRI) revealed gyral swelling, T2-FLAIR signal increase and diffusion restriction in the left parahippocampal and temporooccipital regions with no contrast enhancement [Figure 1]. The electroencephalogram (EEG) showed diffuse theta waves. Cerebrospinal fluid (CSF) examination was normal. Anti-NMDAR IgG and IgA antibodies were detected in serum and CSF by a commercial kit (Euroimmun, Luebeck, Germany), whereas antibodies to other well-characterized onconeural and ion-channel antigens were negative. Computed tomography (CT) scanning of the abdomen/pelvis and (18) F-FDG PET/CT were normal. The thorax MRI revealed thymic hyperplasia. Pathological examination of the thymus after thymectomy showed hyperplasia but no signs of teratoma or any other neoplasms. Immunofluorescence studies showed an intense expression of NR1 and NR2 subunits of NMDAR in hyperplastic thymus tissue. Double immunolabeling performed with anti-CD3 (1:1000, Santa Cruz, CA, USA) and anti-NR1 or anti-NR2 (both 1:500, Santa Cruz) antibodies and appropriate ALEXA-conjugated secondary antibodies (1:1000, Invitrogen, CA, USA)[1] showed a significant colocalization [Figure 2]. No appreciable NR1/NR2 expression was observed in non-CD3+ cells. Plasmapheresis significantly improved symptoms and reduced seizure frequency. No relapses were recorded in 2 years of follow-up and repeat imaging studies failed to show any tumors.

While it is conceivable that NMDARs expressed by tumor cells might trigger anti-neuronal autoimmunity, mechanisms by which anti-NMDAR encephalitis emerges in patients with no tumors are unclear. Expression and

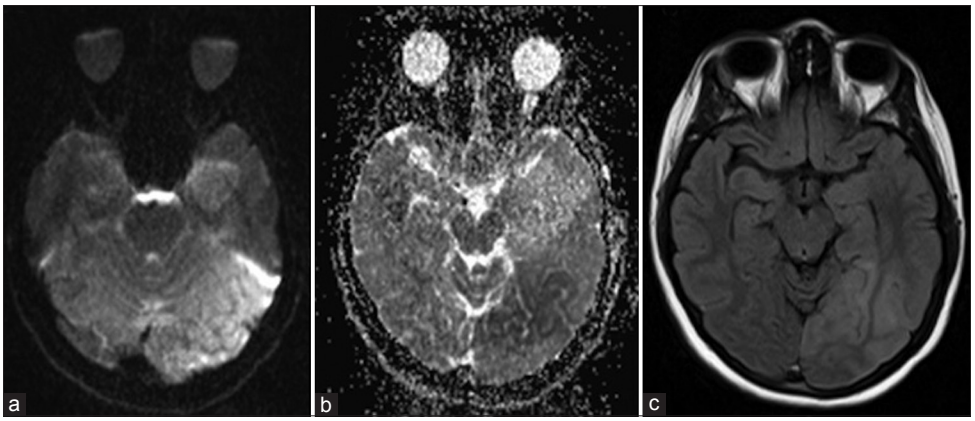

Figure 1: (a) Diffusion MRI (b) ADC Map (c) FLAIR sequence

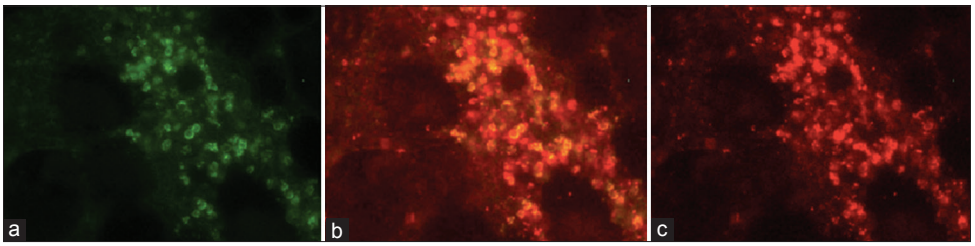

Figure 2: Thymus sections double immunolabeled with CD3 (Figure 2a; green) and NR1-antibody (Figure 2c; red). A significant colocalization of CD3 and NR1 expression was observed in Figure 2b (yellow) indicating that thymic T cells express NMDARs. Original magnificationx 100

functions of thymic and lymphocytic NMDAR have been scarcely investigated.[2] Thymic acetylcholine receptor expression has been proposed to breakdown tolerance and promote autoimmunity through mechanisms involving antigen sensitization and proinflammatory cytokine production.[3] NMDARs expressed by thymic cells might conceivably play a similar role in autoimmune encephalitis. Prompt amelioration of symptoms and absence of relapses in our case suggest that thymectomy might be considered in non-paraneoplastic cases particularly to prevent exacerbations commonly observed in autoimmune channelopathies.

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