

ALLERGY Net

ALLERGY 2011 DOI: 10.1111/j.1398-9995.2011.02718.x

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Cytotoxic T lymphocytes mediate neuronal injury in patients with X-linked agammaglobulinemia and progressive neurodegenerative disease

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Keywords: cytotoxic T cells; progressive neurodegenerative disease; X-linked agammaglobulinemia.

Patients with X-linked agammaglobulinemia (XLA) may develop progressive neurodegenerative disease (PND) during treatment with intravenous immunoglobulin (IVIG). PND was first reported in 14 patients receiving IVIG for various primary immunodeficiency diseases (1), but no infectious agents were identified as a possible cause of the disease. Recently, Quan et al. (2) reported that encephalitis in a patient with XLA might be associated with astrovirus. However, it remains unclear whether PND in other patients may have developed because of astrovirus infection or other currently unknown infectious agent. We report here two new children with XLA who presented with PND during IVIG replacement therapy.

Patient 1 was born of nonconsanguineous Hungarian parents. He suffered

from recurrent pneumonia, otitis media and sinusitis since the second half of infancy. At 3 years of age, he developed chronic arthritis and received nonsteroid anti-inflammatory agents. Diagnosis of XLA was made at age 3 with immuno-

logical tests revealing low number of CD19⁺ B cells (<0.3% of blood lymphocytes) and low concentrations of serum immunoglobulins (IgM, 0.03 g/l; IgG, 0.05 g/l; IgA, 0.04 g/l). Mutational analysis of the Bruton's tyrosine kinase

Brain tissue histology revealed a robust influx of CD8⁺ T lymphocytes into cerebral and leptomeningeal tissues.

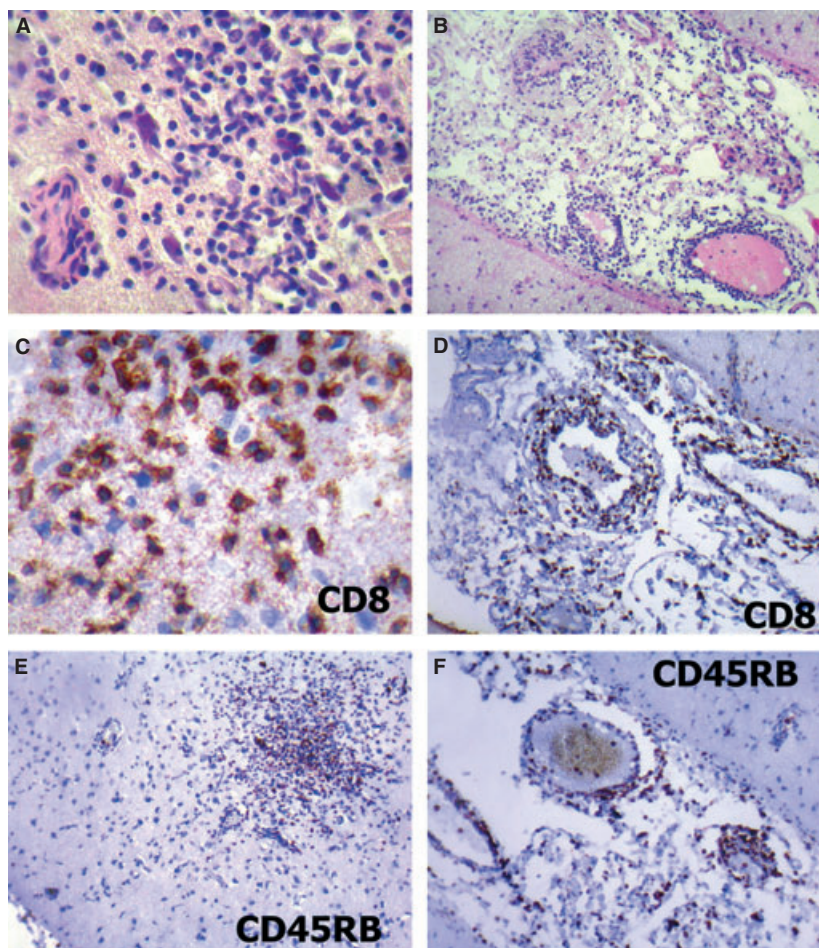


Figure 1 Brain histopathology shows multifocal perivascular infiltrations of lymphoplasmacytic cells in the cerebral cortex (A) and leptomeninges (B). The majority of the cells are CD8⁺ lymphocytes (C and D), with a smaller component of CD45RB (E and F) and CD3⁺ cells (not shown). On the H&E images (A and B), there are many cortical neurons that are surrounded by lymphocytes and show features of acute neuronal injury.

gene (*BTK*) (3) unveiled missense mutation (c.1855C > T; p.P619S), and heterozygous mutation was detected in his mother. Treatment with monthly IVIG was started with 400 mg/kg Humaglobin® for 7 months and 400 mg/kg Intraglobin CP® thereafter. At age 6, he started to act oddly and showed the first signs of mental breakdown. He had difficulty to coordinate standing and walking and complained of weakness and difficulty swallowing. He could hardly keep his head straight. Three months later, his mental and motor capabilities started to fade, and his ability to use objects and his skills worsened rapidly. Four months after the onset of the neurological signs and symptoms, brain MRI was performed. Axial T2w and coronal FLAIR images showed that the supratentorial ventricular system was widened and the sulci were also wider owing to diffuse atrophy. He rapidly lost motor function, mental and psychosocial capabilities, and ability to move and died at 8 years of age.

Patient 2 was born of nonconsanguineous Russian parents. From 6 months of age he developed recurrent bacterial and viral infections of the respiratory tract and skin. The diagnosis of XLA was made at age three and a half, and he was put on monthly replacement therapy with 400 mg/kg IVIG (Humaglobin®) for 6 months, and Octagam® thereafter. We detected hemizygous deletion mutation of *BTK* (c.1580_1583delGTTT or c.1581_1584delTTTG; p.C527fsX528). At age 4, he started to lose motor skills and there were violations of gait, stumbling and falling. Neurological symptoms continued to progress, especially deterioration of speech and

pronunciation, and a lack of understanding of speech. His mental ability deteriorated rapidly, and his ability to walk without assistance was gradually lost. MRI was performed at five and a half years of age. Axial T2w and coronal FLAIR images showed diffuse cerebral atrophy, some focal lesions with high signal intensity on T2w and FLAIR in the periventricular and subcortical regions. Brain tissue histology at age 6 showed massive perivascular CD8⁺ lymphocyte infiltration in the cerebral cortex and leptomeninges (Fig. 1). Cortical neurons were surrounded by lymphocytes but not neutrophils and showed the features of both neuronal injury and areas of astrogliosis. The majority of infiltrating lymphocytes expressed granzyme B, which may have mediated T-cell-dependent brain injury. The patient has become cachectic, immobile and unable to drink and eat and died at age 7.

PCR-based assays (serum and cerebrospinal fluid) failed to unveil potential causal agents for the disease. Unbiased pyrosequencing (4) used in Patient 2 failed to define virus-specific genetic markers in brain biopsy material. These findings provide further evidence that cytotoxic T cells play a critical role in the pathogenesis of PNG in patients with XLA (5). Viral sequences could not be identified in brain biopsy by metagenomic analysis, suggesting that causative agents other than astrovirus are to be defined. We propose that prospective, multicenter analysis by using standard high-throughput assays is needed to define the role of astroviruses or other potential agents that may cause this formidable neurological complication of patients with XLA.

Conflict of interest

The authors declare that they have no conflict of interest.

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Accepted for publication 25 August 2011

Allergy 2011

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DOI: 10.1111/j.1398-9995.2011.02718.x

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