

4. Rasmussen A, Matsuura T, Ruano L, et al. Clinical and genetic analysis of four Mexican families with spinocerebellar ataxia type 10. *Ann Neurol* 2001;50:234–239.
5. Teive HAG, Roa BB, Raskin S, et al. Clinical phenotype of Brazilian families with spinocerebellar ataxia type 10. *Neurology* 2004;63:1509–1512.
6. Matsuura T, Ranum LP, Volpini V, et al. Spinocerebellar ataxia type 10 is rare in populations other than Mexicans. *Neurology* 2002;58:983–984.
7. Matsuura T, Ashizawa T. Polymerase chain reaction amplification of expanded ATTCT repeat in spinocerebellar ataxia type 10. *Ann Neurol* 2002;51:271–272.

H. Verhelst, MD
 R. Van Coster, MD,
 PhD
 N. Bockaert, MD
 G. Laureys, MD, PhD
 S. Latour, PhD
 A. Fischer, MD, PhD
 F. Haerynck, MD

LIMBIC ENCEPHALITIS AS PRESENTATION OF A SAP DEFICIENCY

X-linked lymphoproliferative disease (XLP) is a rare immune cell disorder caused by mutations in the Src homology 2 domain-containing gene 1A (SH2D1A). This gene, located on the X-chromosome, encodes a small cytoplasmic adaptor known as signaling lymphocytic activation molecule (SLAM) associated protein (SAP). SAP is expressed in natural killer cells (NK) and T-cells. It interacts with SLAM and plays a critical role in regulating signaling.¹ Clinical manifestations of patients with XLP vary. Most patients die following exposure to Epstein Barr virus (EBV). Boys who survive an EBV infection may develop dysgammaglobulinemia, lymphoma (usually B-cell type), or, less frequently, aplastic anemia, lymphoid granulomatosis, or vasculitis.²⁻⁴ Survival into adulthood is rare, although patients treated successfully by bone marrow transplantation (BMT) are recorded.⁵

Limbic encephalitis is characterized by profound memory impairment, dementia, seizures, usually complex partial, and psychiatric disturbances. On MRI, signal changes are detected on the medial sides of the temporal lobes or in the hippocampi.^{6,7}

We report a patient with limbic encephalitis caused by SAP deficiency.

Case report. The medical history of the proband was noteworthy. At age 9 he was diagnosed with cervical B-cell non-Hodgkin lymphoma (monoclonal kappa, EBV negative) for which he received chemotherapy according to the LMB-84 protocol. After stopping treatment no specific problems occurred; weight and length evolution was just below percentiles 3. At age 15, he was hospitalized for 5 days for pneumonia with *Streptococcus pneumoniae*. He had no antibody response to pneumococcal polysaccharide antigen. Blood results revealed for the first time a hypogammaglobulinemia. The family history was unremarkable.

At age 16 he presented with clinical characteristics of limbic encephalitis. He was admitted to the hospital because of a generalized tonic clonic seizure. Several months prior to this seizure he had had episodes of decreased alertness and short-term memory deficit. Clinical neurologic examination revealed mild facialis paresis and paresis of the right

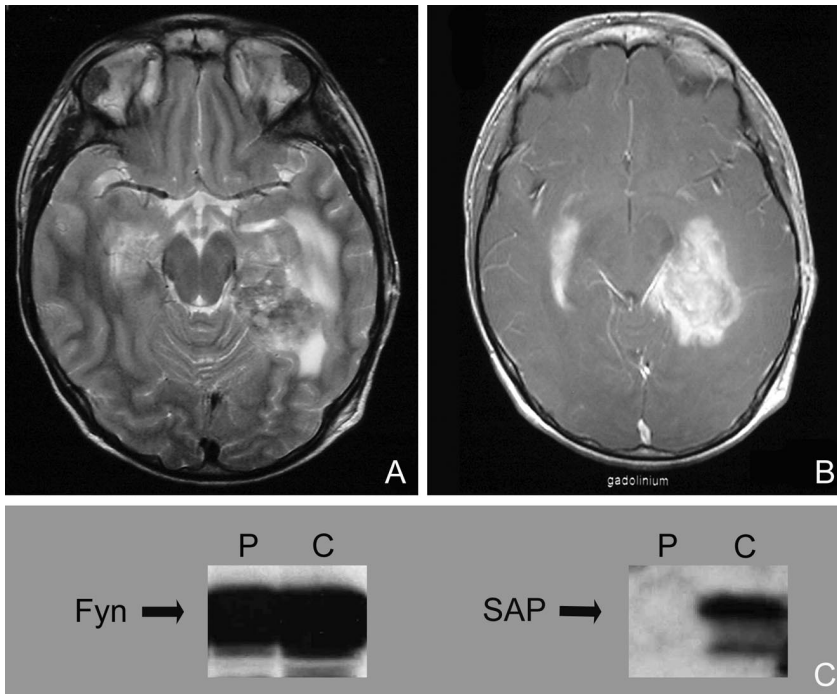
arm and leg. In the left mesial temporal lobe a large mass with irregular contours was seen on CT. MRI showed bilaterally abnormal signals in the mesial temporal areas, on the left more than on the right (figure, A and B). Cerebral stereotactic biopsy revealed signs of vasculitis with infiltration of T lymphocytes, mainly CD 8+ cells, granulomata, and absence of plasma cells. In situ hybridization for EBV and herpes simplex virus (HSV) was negative. In CSF, viral culture and PCR for EBV, cytomegalovirus, HSV, human herpesvirus 6, and enterovirus were negative. In plasma, hypogammaglobulinemia was present (immunoglobulin G <1.3 g/L, immunoglobulin M <0.2 g/L, immunoglobulin A 0.3 g/L). No evidence was found for a tumor outside the CNS.

Despite IV treatment with antiepileptic drugs and high-dose corticosteroids, immunoglobulins, and antibiotics, his neurologic condition worsened. His short and long-term memory further deteriorated. He started having difficulty walking and experienced impaired coordination of his right arm, finally becoming wheelchair dependent. Control cerebral MRI showed no improvement. As treatment for his vasculitis he received high dose corticosteroids and anti-CD20 IV, and methotrexate and hydrocortisone intrathecally.

BMT was considered as therapeutic option. Nevertheless, his clinical condition further deteriorated so that search for a matched unrelated donor was cancelled. He died 10 months after the first signs of limbic encephalitis.

Discussion. We present a patient with clinical signs suggestive of limbic encephalitis in whom a brain biopsy revealed limbic vasculitis characterized mainly by CD8 T-cell infiltration representing a lymphoproliferative disorder. The history of B-cell lymphoma, hypogammaglobulinemia, and signs of cerebral vasculitis in this boy was suggestive of XLP.²⁻⁴ Absence of SAP in his lymphocytes as seen on immunoblotting (figure, C) confirmed the hypothesis of a lymphoproliferative syndrome of the CNS. A mutation in the SH2D1A gene on Xq25 could not be detected. The rate of SH2D1A mutation detection varies depending upon family history. In most familial XLP patients with pedigree typical

Figure MRI at the time of admission and expression of signaling lymphocytic activation molecule (SLAM) associated protein (SAP) in lymphocytes



(A, B) MRI at the time of admission. (A) T2-weighted image, axial scan, (B) T1-weighted image, with gadolinium, axial scan. Inhomogeneous signal alterations with necrotic and hemorrhagic component are seen in the left mesial temporal area extending to the left thalamus, the left capsula interna, and the left nucleus lentiformis. Surrounding edema. Inhomogeneous gadolinium enhancement. Similar but smaller lesion at the right mesial temporal area. (C) Expression of SAP in lymphocytes from the patient. Cell lysates from phytohemagglutinin (PHA) blasts of the patient (P) and a healthy control (C) were analyzed by Western blotting with anti-SAP antibodies (panel at the right). Immunoblot with anti-Fyn antibodies (panel at the left) is shown as control of loading.

for X-linked inheritance, a mutation can be identified but in isolated patients, such as the proband, *SH2D1A* mutations are extremely rare.¹

Limbic encephalitis can occur as a paraneoplastic phenomenon, by direct invasion of a virus, or as post-infectious autoimmune process.^{6,7} Here, we report a patient with limbic encephalitis caused by SAP deficiency.

Where SAP protein is found absent in lymphocytes, BMT can be considered as a therapeutic option. This, however, should be done at an early stage of the disease. To our knowledge, all reported patients older than 15 years and treated by BMT did not survive.⁵ In the proband, at the time of the diagnosis, the disease was in an advanced stage so that treatment by BMT was no longer possible.

From the Departments of Child Neurology (H.V., R.V.C., N.B.), Pediatric Hematology and Oncology (G.L.), and Child Immunology (F.H.), Ghent University Hospital, Belgium; and Unité 768 INSERM (S.L.) and Department of Child Immunohematology (A.F.), Hôpital Necker Enfants-Malades, Paris, France.

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Address correspondence and reprint requests to Dr. Helene Verhelst, De Pintelaan 185, B-9000 Gent, Belgium; helene.verhelst@ugent.be

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- Nichols KE, Ma CS, Cannons JL, Schwartzberg PL, Tangye SG. Molecular and cellular pathogenesis of X-linked lymphoproliferative disease. *Immunol Rev* 2005; 203:180–199.
- Seemayer TA, Gross TG, Egeler RM, et al. X-linked lymphoproliferative disease: twenty-five years after the discovery. *Pediatr Res* 1995;38:471–478.
- Dutz JP, Benoit L, Wang X, et al. Lymphocytic vasculitis in X-linked lymphoproliferative disease. *Blood* 2001;97: 95–100.
- Kanegane H, Ito Y, Ohshima K, et al. X-linked lymphoproliferative syndrome presenting with systemic lymphocytic vasculitis. *Am J Hematol* 2005;78:130–133.
- Lankester AC, Visser LFA, Hartwig NG, et al. Allogeneic stem cell transplantation in X-linked lymphoproliferative disease: two cases in one family and review of the literature. *Bone Marrow Transplant* 2005;36:99–105.
- Mochizuki Y, Mizutani T, Isozaki E, Ohtake T, Takahashi Y. Acute limbic encephalitis: a new entity? *Neurosci Lett* 2006;394:5–8.
- Munshi SK, Thanvi B, Chin SK, Hubbard I, Fletcher A, Vallance TR. Paraneoplastic limbic encephalitis: case report and review of literature. *Age Ageing* 2005;34:190–193.

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