CNS involvement in systemic lupus erythematosus: a case with remarkable histopathological findings

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Case report
A 38 year old man was admitted in a subcomatose condition. According to the accompanying family, his current state had developed the night before. The patient was known to have had systemic lupus erythematosus (SLE) for 10 years. The diagnosis was based on a history of characteristic skin lesions, pleuritis, pericarditis, arthritis, antinuclear antibody, anti-Sm antibody, and hypocomplementaemia. His spleen had been removed in his adolescence as treatment for idiopathic thrombocytopenic purpura, diagnosed before the onset of SLE. Currently, he was taking 10 mg prednisone daily, started a week ago because of deteriorating skin lesions.

Physical examination showed a Glasgow Coma Score of 1-4-2. His body temperature and blood pressure were normal. Abdominal and thoracic examination did not disclose abnormalities. No signs of meningeal inflammation were present. The pupils were equally large and reacted adequately to light stimuli. Symmetrical retractions of the limbs occurred after inflicting pain stimuli. The right sided reflex of the quadriceps was higher than the left. A right sided Babinski’s sign was noted. At the emergency ward the patient developed tonic-clonic seizures.

Laboratory testing showed an erythrocyte sedimentation rate (ESR) of 32 mm/1st h and a normal haematological survey. Antinuclear antibodies and anti-dsDNA were present and no recent immune response against neurotropic viruses could be detected. Antiphospholipid antibodies were absent. Computed tomography as well as magnetic resonance imaging scanning of the brain and a chest x ray examination were normal. The cerebrospinal fluid (CSF) was clear with a normal opening pressure and contained 36 mononuclear cells/mm³. Protein content of the CSF was 3.85 g/l (normal range 0.15–0.45 g/l) and the IgG index was 1.3 (normal range 0.20–0.85). The albumen quotient was 36.3 (normal value <7.6). All CSF cultures were negative. Central nervous system (CNS)-SLE was diagnosed and 1000 mg methylprednisolone at three consecutive days and phenytoin was started.

The clinical course of the patient was complicated after three days by an opportunistic infection. The patient started antibiotics with benzylpenicillin and 1000 mg methylprednisolone at three consecutive days and phenytoin was started. At necropsy, both lungs contained several bronchopneumonic lesions, from which Klebsiella pneumoniae was cultured. No macroscopic signs of inflammation of the meninges were found. The dural sinuses were open. The cerebrum did not show oedema, signs of herniation, infarctions, or neoplastic changes. Microscopically, the subarachnoidal space and the perivascular spaces in the parenchyma were invaded with T lymphocytes. Several venes and venules showed invasion of lymphocytes within the vascular wall, associated with fragmented nuclei and fibrinoid material (figs 1A and 1B). Arteries and arteriolae were not affected. Amyloid staining was negative, IgM was present around several vessels. No intravascular microthrombi, infarctions, or gliosis lesions were discovered. When the immunoperoxidase technique was used, cytoplasmic and nuclear staining of neuronal cells occurred after incubating microscopic preparations of normal human and murine cerebrum or cerebellum with serum of the patient (fig 2). Astrocytes and—in a separate assay—Hep-2 cells did not show cytoplasmic staining, indicating that the staining was neuron specific.

Discussion
Cerebral perivascular and interstitial infiltrates can be detected in a number of pathological situations, including viral infections and paraneoplastic encephalomyelitis. The lack of signs of meningeal inflammation, the normal body temperature, and the absence of increased titres of antibodies against neurotropic viruses at admission indicated that a viral origin of the symptoms is less likely. The Streptococcus and Klebsiella pneumoniae infections were considered to be concomitant disease, because these infections cannot be held accountable for the comatose state at admission. Moreover, the absence of polynuclear cells in the CSF excluded bacterial infections of the CNS. The presence of paraneoplastic encephalomyelitis is less likely because of the lack of anti-Hu antibodies and the absence of a lung tumour at necropsy.

The most likely explanation for the histopathological findings is vasculitis due to SLE. In the case series describing the histopathological correlates of neuropsychiatric SLE, the incidence of cerebral vasculitis ranges from 4% to 12%. In none of these series was the exclusive occurrence of cerebral phlebitis reported.
The aetiopathogenesis of the CNS manifestations in this patient is clarified by the analysis of the CSF. The very high albumen quotient is indicative of a breach in the blood-brain barrier. The IgG index was moderately raised; the reliability of this ratio as an indicator for intrathecal production of IgG might be corrupted by the extremely high protein levels in the CSF. Cerebral phlebitis is a realistic cause of a defective blood-brain barrier. Incubation of normal human and murine cerebrum and cerebellum with serum of the patient indicated the presence of antineuronal antibodies, suggesting that by leakage through the blood-brain barrier, antineuronal antibodies could gain access to the neuronal tissue. This mechanism has been implicated in the pathogenesis of a number of diseases. In Rasmussen’s encephalitis, antibodies to a glutamate receptor are thought to be pathogenic, whereas in SLE and primary Sjögren’s syndrome with CNS involvement, non-specific antineuronal antibodies have been detected.7–11

The lesson
- Cerebral phlebitis can allow antineuronal antibodies to gain access to the central nervous system in primary neuropsychiatric manifestations of SLE.
- The use of normal frozen murine and human cerebrum and cerebellum for the detection of antineuronal antibodies in patients with neuropsychiatric SLE merits further investigation.

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8 Leach JP, Chadwick DW, Miles JB, Hart JK. Improvement in adult-onset Rasmussen’s encephalitis with long-term immunomodulatory therapy. Neurology 1999;52:738–42.