Contemporary Encephalitis Lethargica: Phenotype, laboratory findings and treatment outcomes

Introduction

Encephalitis Lethargica (EL; von Economo’s disease) is a complex neurological disease first described in detail at the beginning of the 20th century by neurologist Constantin von Economo [36] during an outbreak that claimed thousands of lives [7]. Lethargy, sleep cycle disturbances, extrapyramidal symptoms, psychiatric manifestations, ocular features and cardio-respiratory abnormalities were the clinical highlights of the original descriptions of EL. Although there have been no further epidemics of EL, a number of reports show that cases of EL are still encountered regularly in both pediatric and adult populations [1, 8, 13, 14, 24, 26, 28, 31, 38].

Abstract

Background Encephalitis lethargica (EL) is a CNS disorder that manifests with lethargy, sleep cycle disturbances, extrapyramidal symptomatology, neuropsychiatric manifestations, ocular features and cardio-respiratory abnormalities. Although there have been no reported outbreaks of EL recently, a number of reports show that cases of EL are still encountered regularly. Against this background we conducted a study aiming to elucidate the clinical characteristics, describe laboratory/neuroimaging findings (MRI, PET) and present treatment options and outcomes in sporadic EL.

Methods Patients were diagnosed over a period of 3 years using proposed diagnostic criteria. Extensive laboratory and imaging tests were performed for exclusion of other causes. Anti-neuronal antibodies against human basal ganglia were detected with western immunoblotting and 18F-FDG PET imaging was performed. Selected cases were videotaped.

Results Our patients (M/F: 5/3) ranged from 2–28 years (mean 9.3 ± 9.5). Encephalopathy, sleep disturbances and extrapyramidal symptoms were present in all cases. Laboratory investigations revealed CSF leukocytosis in 5/8 patients and anti-BG Ab in 4/7 patients. MRIs revealed structural abnormalities in 7/8 cases. 18F-FDG PET showed basal ganglionic hypermetabolism in 4/7 patients. Treatment approaches included immunomodulating and symptomatic therapies. We report no mortality from EL in our series.

Conclusions There seems to be little doubt that cases of EL still occur. Diagnosis may be based on clinical suspicion and laboratory/imaging tests may lead to early initiation of immunomodulating and supporting therapies. We suggest that in addition to anti-BG Abs FDG PET should be considered as a diagnostic tool for EL.

Key words Encephalitis Lethargica · MRI · PET · anti-basal ganglia antibodies · treatment
The etiology of EL remains unknown. The possible pivotal role of autoimmunity in the pathogenesis of EL was highlighted with the outbreak of EL [27] that followed the early 20th century influenza virus pandemic [19]. The presence of anti-basal ganglia neuronal antibodies in sera, oligoclonal banding in cerebrospinal fluid of EL patients [8], steroid response [22] and negative virological tests [8] further implicate autoimmunity in the pathogenesis of EL.

Imaging studies on contemporary cases of EL have suggested structural involvement of the basal ganglia in about 40% of cases [8]. Single-case positron emission tomography (PET) studies have delivered conflicting results [3, 11]. One of these reports raised the possibility that an immunological reaction directed against the basal ganglia may explain an increased striatal metabolism detected with 18F-FDG PET [12].

In an attempt to better define disease-related parameters in EL we report a series of consecutive patients and present clinical, immunological and imaging findings.

Methods

Patients were initially diagnosed at or referred to the Department of Neurology, University of Miami, Miller School of Medicine at Jackson Memorial Hospital, Miami, FL, between September 2003 and December 2006 with new-onset EL symptomatology consisting of an encephalopathy, a movement disorder with associated sleep disturbance, lethargy, and neuropsychiatric symptoms. Diagnosis was based on proposed clinical criteria for EL [13, 26]. Patients were classified into three subtypes (somnolent, hyperkinetic and akinetic) according to their clinical characteristics [36]. Standard laboratory tests including CSF analysis (including oligoclonal bands) and screening for known infectious, inflammatory and metabolic cerebral disorders were performed. Anti-neuronal antibodies against human basal ganglia were detected with western immunoblotting using methods previously described [8]. Electroencephalography (EEG) and brain magnetic resonance imaging (MRI) were conducted using standard methods.

18F-FDG PET imaging was performed using a C-PET Plus (Philips Medical Systems, Cleveland, OH) dedicated ring detector PET scanner, using standard brain protocol. The patients relaxed for 20 minutes in a quite room with dim lights and were subsequently injected intravenously with 0.053 mCi/kg of 18F-FDG. Scanning was performed 45 minutes post-injection for 40 minutes of imaging time. The images were attenuation corrected using a transmission scan from a 137Cs rotating point source and were reconstructed using the manufacturer’s software, with an iterative (OSEM) algorithm into 128 x 128 matrices of isotropic voxels with slice thickness of 2 mm. The reconstructed transaxial slices were realigned to yield sagittal and coronal images; three-dimensional volume-rendered images were also generated for review.

Case summaries

Case 1 (somnolent type)

A 15-year-old previously healthy female presented with a 4-day history of headaches followed by a 2-day history of mental status deterioration and somnolence. Soon after admission the patient developed focal seizures with secondary generalization and deteriorated rapidly becoming unresponsive to external stimuli. Bilateral pyramidal tract involvement with hyperreflexia was noted (R>L). She also developed choreiform movements initially of the upper limbs and orobuccal areas but later involving the entire body. Choreiform movements were somewhat responsive to tetrabenazine (150 mg/d), after failing to respond to trihexyphenidyl or haloperidol. The patient also developed several episodes of oculargrycises, rigidity and dystonia. Significant sleep and wake cycle alterations were noted, as well as “storming,” with episodes of hyperthermia, hypertension and tachycardia, requiring beta-blockers (propranolol). Treatment with IVIg (2 g/kg) and high doses of IV methylprednisolone (250 mg q 8 h) was initiated.

CSF analysis revealed leukocytosis. Other detailed infectious, metabolic, toxic, and immunologic work-ups were negative. Her initial brain MRI showed bilateral thalamic signal abnormalities (Fig. 1 A). Follow-up MRI only revealed mild atrophy. Her PET scan was normal and EEG showed generalized slowing with poor organization but no epileptiform activity.

The patient slowly regained motor and verbal func-