Case Definition of Encephalitis May Misdiagnose Congenital Urea Cycle Disorders

To the Editor—We read with interest the recent article by Venkatesan et al [1], which proposes a consensus guideline of the International Encephalitis Consortium for case definition and diagnostic algorithms in encephalitis. The authors define encephalitis as inflammation of the brain parenchyma associated with neurologic dysfunction, diagnosed on the basis of selected clinical, laboratory, electroencephalographic, and neuroimaging features. Confirmed encephalitis or encephalopathy of presumed infectious or autoimmune etiology requires 1 major criterion (altered mental status) and 3 or more minor criteria (fever, seizures and new onset of focal neurologic findings, cerebral spinal fluid pleocytosis, abnormality on neuroimaging or electroencephalography consistent with encephalitis). In our experience, late-onset inborn urea cycle disorders (UCDs) often mimic encephalitis [2,3], and determination of blood ammonia level must be added to the initial routine screening for encephalitis.

UCDs are inborn errors of nitrogen detoxification that cause hyperammonemia, astrocyte swelling, and brain edema. They are probably underdiagnosed, and their prevalence may exceed the current estimates of from 1 in 8000 to 1 in 44 000 births [4]. In late-onset forms, the first recognized clinical episode may be delayed for months or years, even until adulthood, after a prolonged symptom-free period. Hyperammonemic crises are frequently triggered by catabolic events such as infectious diseases [5,6] and are often misdiagnosed as encephalitis. Within a few days, most patients develop a decreased level of consciousness associated with acute neurological signs, such as tremors and status epilepticus, vomiting, and fever [2,6,7]. Electroencephalogram classically shows bilateral slow delta waves and is frequently interpreted as suspicious for encephalitis [2,3]. Neuroimaging findings are variable, from no abnormality to varying degrees of white matter injury without specific localization, basal ganglia hyperintensity, and multifocal edema, most often consistent with encephalitis. All findings could be symmetric or asymmetric, sometimes mimicking the finding of herpes simplex encephalitis [8]. Magnetic resonance spectroscopy may be discriminant, showing increased peaks of glutamine and glutamate, 2 toxic molecules that are involved in the physiopathology of brain injury in UCDs; however, this investigation is not commonly performed. Cerebrospinal fluid examination is usually normal, but pleocytosis has been reported in some cases [3]. Finally, the clinical presentation of late-onset UCD patients is usually in accordance with the definition of “encephalitis” reported by Venkatesan et al. However, acute hyperammonemic crises need specific therapies, and prognosis has been clearly improved by new treatments that involve the use of alternative pathways of nitrogen excretion. Thus, prompt recognition of a UCD and initiation without delay of specific therapies result in survival in the majority of late-onset patients [9]. In contrast, delayed initial diagnosis may adversely affect the outcome, with a high mortality rate [6]. Additionally, misdiagnosing a congenital disorder may have deleterious consequences for the patient and family. For these reasons, we think that determination of plasma ammonia level, which is a simple test that can be performed anywhere, should be added to the initial routine screening for encephalitis and may improve case definition and prognosis.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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