EEG and PET Changes in Anti-*N*-Methyl-D-Aspartic Acid Receptor Encephalitis

To the Editor: A-30-year-old woman with no prior medical history presented with a 2-week history of headaches, progressive encephalopathy, and dysautonomia. She was found to exhibit intermittent episodes of bizarre behavior characterized by moaning, crying, screaming, teeth clenching, and posturing without any surface EEG correlate. Her serum (1:10, normal<1:10) and CSF (1:5, normal<1:1) anti-*N*-methyl-D-asparate (NMDA) receptor antibodies were positive, while CSF Purkinje cell cytoplasmic antibody type 1 and 2; anti-neuronal nuclear AB type 1, 2, and 3; anti-glial nuclear AB type 1; amphiphysin AB; CRMP-5-IgG and blood anti-Ri; anti-Hu; anti-Ma1 and Ma2; anti-CV2; anti-YO; anti-Zic4; anti-amphiphysin; anti-alpha 3AChR; anti-LGI1; anti-VGCC; anti-VGKC; and anti-CASPR2 were negative. No primary tumor was identified on whole-body PET scan, and [^{18}F] fluorodeoxyglucose (FDG) uptake in bilateral adnexa was thought to be physiological. A PET scan of her brain showed occipital and superior parietal hypometabolism bilaterally (Figure 1). While continuous EEG revealed no overt seizure activity, "extreme delta brush" pattern and rhythmic delta activity with superimposed rhythmic beta activity were noted (Figure 2).

An FDG PET brain scan showing relative frontal and temporal glucose hypermetabolism associated with occipital hypometabolism (increased frontotemporal-to-occipital gradient) and extreme delta brush pattern on EEG has been reported in patients with NMDA-receptor antibody encephalitis (1, 2). Although abnormalities in brain FDG-PET have been reported to occur in autoimmune encephalitis of various etiologies as well as in neurodegenerative disorders such as frontotemporal dementias, in anti-NMDA encephalitis the fronto- and temporo-to-occipital gradient of cerebral FDG uptake correlates with disease severity and is reported to normalize after recovery (1). Recognition of these patterns in the appropriate clinical setting may therefore aid in the timely diagnosis of patients presenting with anti-NMDA receptor encephalitis.

FIGURE 1. [^{18}F]Fluorodeoxyglucose PET Scan Showing Relative Frontal and Temporal Glucose Hypermetabolism Associated With Occipital Hypometabolism (Increased Frontotemporal-to-Occipital Gradient)

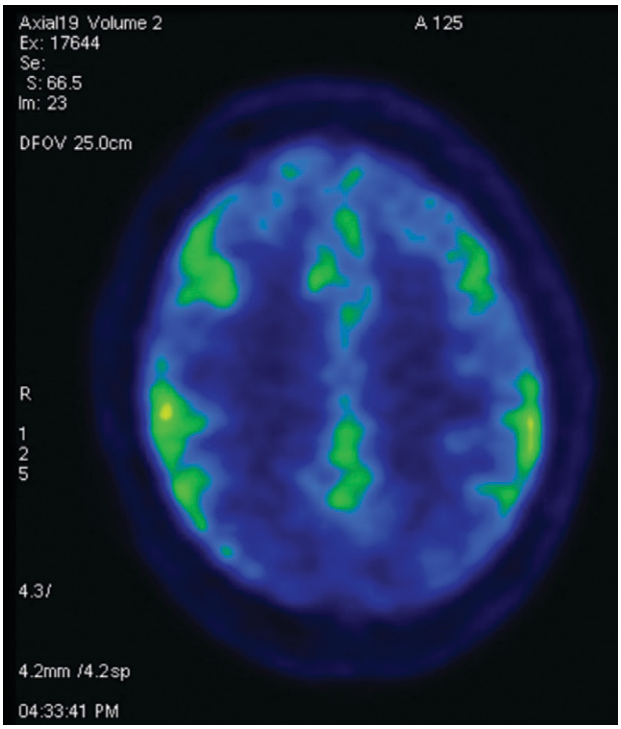
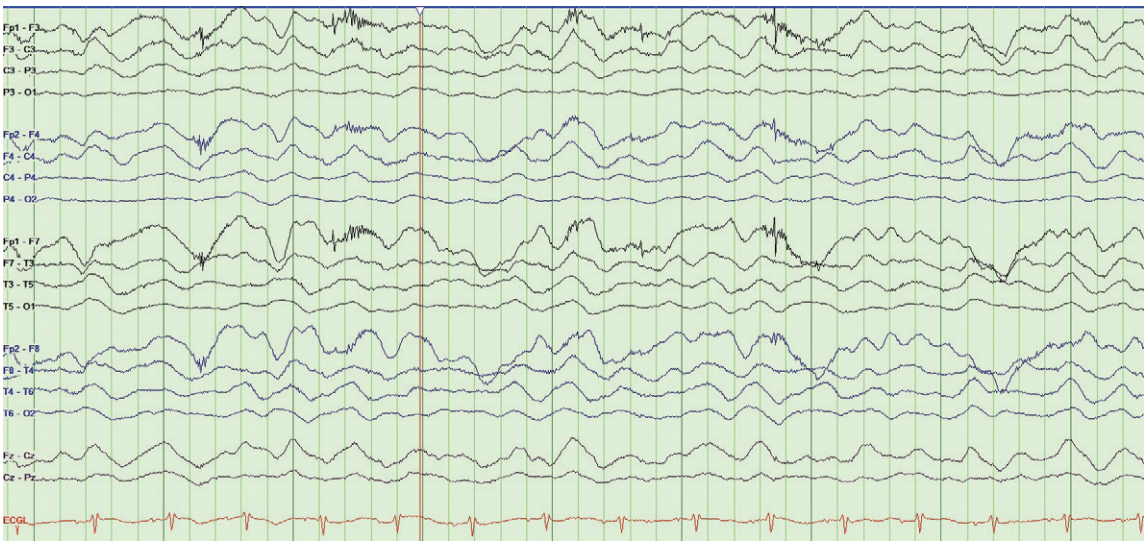


FIGURE 2. EEG of "Extreme Delta Brush" Pattern[a]



[a] Rhythmic delta activity at 1–3 Hz with superimposed bursts of rhythmic beta frequency activity "riding" on the top of the delta waves.

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Serotonin Toxicity in a CYP2D6 Poor Metabolizer, Initially Diagnosed As a Drug-Resistant Major Depression

To the Editor: We report a case of serotonin toxicity related to a CYP2D6 poor metabolizer, initially diagnosed as drug-resistant depression.

A 48-year-old Caucasian man, with no somatic disorder and no familial psychiatric history, underwent a major depressive episode 5 years ago and started citalopram (partially metabolized by CYP2D6, mainly CYP2C19/3A4), 20 mg/day increased to 40 mg/day. Simultaneously, he developed a bilateral resting hand tremor that was treated efficiently by atenolol, 20 mg/day. Moreover, major asthenia and anxiety persisted. Citalopram was switched to venlafaxine XR (mainly metabolized by CYP2D6), 75 mg/day progressively increased to 300 mg/day. He reported no improvement and his asthenia increased.

He was admitted to our psychiatric department with major anxiety, asthenia, and difficulties falling asleep. He reported no sadness, social withdrawal, anhedonia, or suicidal ideation. Physically, he presented with hypertonia, diaphoresis, chronic sustained secretory diarrhea, ankle clonus, and patellar hyperreflexia. The results of blood serum screening (including thyroid hormones, glycemia, and calcemia) and cerebral contrast MRI were normal. His Hamilton Depression Rating Scale (HAM-D) score was 23; however, six items indicated anxiety or somatic symptoms. All symptoms evoked moderate serotonin toxicity rather than resistant major depressive episode.

Further investigation revealed a markedly higher than expected trough venlafaxine (V) plasma concentration (900 ng/ml) and undetectable *O*-desmethylvenlafaxine (ODV), its predominant metabolite (<50 ng/ml), whereas the therapeutic range is 150–400 ng/ml (V+ODV). The ODV/V ratio was <0.055. Comedication with oxazepam could not explain such levels. CYP2D6 and CYP2C19 genotyping routinely performed in our laboratory (alleles *CYP2D6*3,*4,*5,*6,x2N, CYP2C19*17*) showed *CYP2D6*4/*4* corresponding to a poor metabolizer phenotype. Thus, chronic serotonin toxicity caused by CYP2D6 poor metabolizer was diagnosed.

The dosage of venlafaxine XR was decreased to 37.5 mg/day. Dramatic improvement of symptoms, including hand tremor (even after stopping atenolol), was observed within 2 weeks, and his HAM-D score decreased to 6. Trough venlafaxine concentration decreased to 250 ng/ml and ODV remained undetectable. No depressive relapse had occurred after 12 weeks.

While well known in its dramatic form (serotonin syndrome), serotonin toxicity is less diagnosed in its moderate and chronic form (1), in which some symptoms, such as tremor, diaphoresis, and anxiety could be mistaken for depressive ones.

Serotonin toxicity has been previously reported with venlafaxine but in its severe form, with rapid onset, suggesting no CYP2D6 activity (2). ODV/V ratio below 0.3 has been associated with CYP2D6 poor metabolizer and side effects (3).

Consequently, for depressed patients with persistent symptoms, physical examination is essential to detect signs of serotonin toxicity (spontaneous clonus—the most specific sign—mydriasis, tremor, hyperreflexia, and akathisia). In addition, physical symptoms in a major depressive episode should incite antidepressant monitoring from an early stage and *CYP2D6* genotyping if elevated. Such tests could help clinicians diagnose serotonin toxicity and give the right antidepressant drug and dosage to the right patients.

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