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Reversible Pseudoatrophy of the Brain and Mental Deterioration Associated with Valproate Treatment

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Summary: *Purpose:* To describe an 11-year-old girl with symptomatic localization-related epilepsy and normal intelligence who developed reversible mental deterioration and pseudoatrophic brain changes while receiving valproate (VPA).

Methods: Assessment of mental function using Wechsler Intelligence Scale for Children—III (WISC) and Raven's Progressive Matrices (PM), EEG recordings while awake and asleep, and brain magnetic resonance imaging (MRI), were performed at the beginning of VPA therapy, after 2 years and 8 months of treatment and following VPA discontinuation.

Results: After 2 years and 6 months on VPA (≤26 mg/kg/day) the girl insidiously developed mental deterioration (loss of 18 IQ points and drop in age-adjusted PM score from the 95th to the 50th percentile) associated with MRI-documented pseudoatrophy of the brain. Onset of severe cognitive impairment coincided with serum VPA concentrations near 100 μg/ml. There were no other manifestations of drug toxicity or hyperammonemia. Background EEG activity was normal. Reduction of VPA dosage and subsequent discontinuation 4 months later resulted in disappearance of clinical symptoms with a 20-point improvement at IQ testing and recovery of previous PM score. Repeat MRI showed disappearance of pseudoatrophic changes.

Conclusions: The striking cognitive improvement and reversal of pseudoatrophic brain changes following VPA discontinuation strongly suggest a drug-induced condition. Based on this and previous reports, the syndrome of VPA-associated mental deterioration and pseudoatrophy of the brain appears to encompass different but possibly related clinical entities, which include parkinsonism with cognitive deterioration, mental deterioration with signs of VPA-toxicity, and isolated mental deterioration, as seen in our patient. A drug-induced effect should be considered whenever cognitive deterioration and imaging findings of brain atrophy occur in VPA-treated patients. **Key Words:** Valproate—MRI—Brain pseudoatrophy—Mental deterioration.

Valproate (VPA) is associated with fewer adverse neurological effects than other antiepileptic drugs (1). Severe neurological side effects such as VPA-induced encephalopathy with or without hyperammonemia (2,3), extrapyramidal disorders (4,5), and reversible dementia (6–9) are rare. We report on an 11-year-old girl with nonsevere epilepsy, in whom mental deterioration with pseudoatrophy of the brain developed insidiously after 2 years on VPA. The condition was not associated with other signs of toxicity or hyperammonemia and was rapidly reversible upon VPA discontinuation.

CASE REPORT

This 11-year-old girl was born with mild perinatal suffering (Apgar score 5–9) after a normal pregnancy. Developmental milestones were normal. At age 6 years she experienced her first, sleep related, brief generalized clonic seizure. The electroencephalogram (EEG) revealed infrequent sharp waves over the right frontotemporal region. Phenobarbital (PB) was introduced at a dosage of 4 mg/kg/day, with serum levels of 12 μg/ml. Magnetic resonance imaging (MRI) revealed mild ventricular enlargement (Fig. 1A). After a second similar seizure at the age of 7 years, PB dosage was increased to 6 mg/kg/day (serum level 28 μg/ml). The EEG showed normal background activity, infrequent bilateral frontal spike and wave complexes and repetitive left occipital spikes, which were mildly activated during sleep. Behavior was normal and school performance was excellent. Two follow-up EEGs at age 7 and 8 years revealed normal background activity and a marked increase in interictal abnormalities, with diffuse discharges of rhythmic spike and slow wave complexes, lasting for up to 6 s, without any detectable clinical manifestations. The discharges showed further activation during slow wave sleep, occupying almost 25% of the traces (2–3 h afternoon sleep recordings).

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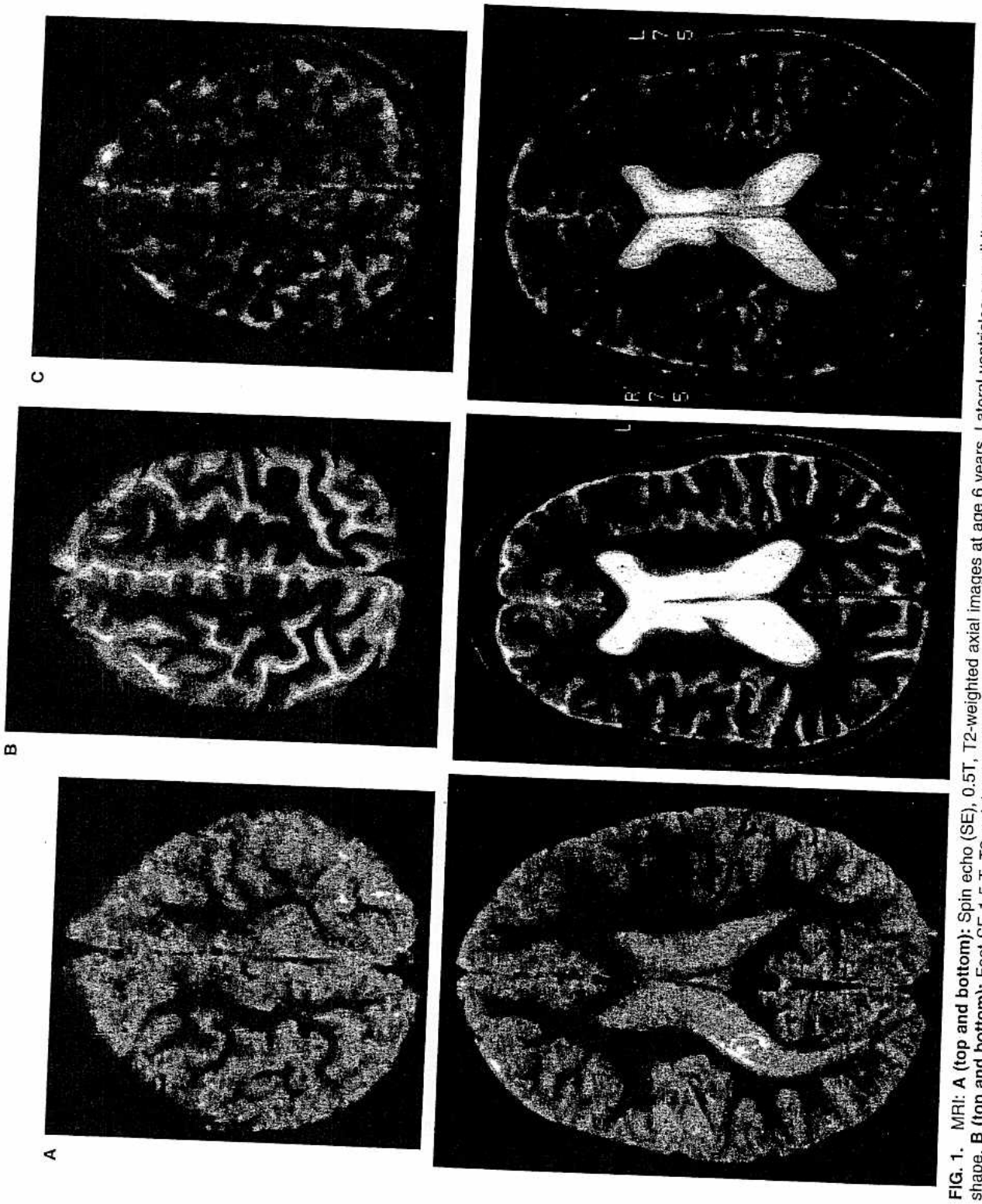

FIG. 1. MRI: **A (top and bottom):** Spin echo (SE), 0.5T, T2-weighted axial images at age 6 years. Lateral ventricles are mildly enlarged, with a normal shape. **B (top and bottom):** Fast SE 1.5 T, T2-weighted axial images obtained at age 10 years 8 months. Marked enlargement of lateral ventricles with rounding of the ventricular cavities. Pericerebral subarachnoid spaces are also enlarged. **C (top and bottom):** Fast SE 1.5T, T2-weighted axial images obtained at age 11 years 3 months. The size of ventricles and subarachnoid spaces is greatly reduced in comparison to the previous MRI (B).

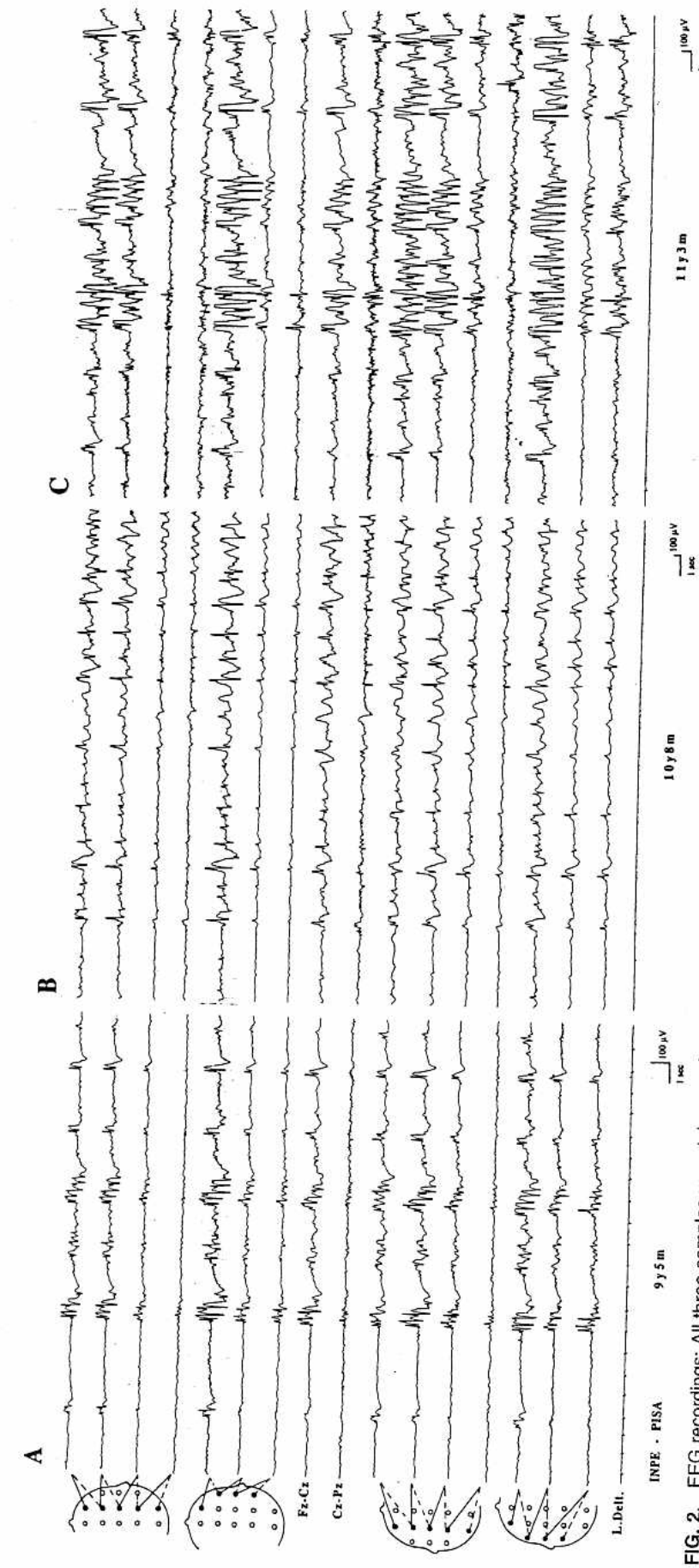

FIG. 2. EEG recordings: All three samples were taken as the patient was falling asleep, the moment with the maximum degree of activation of interictal discharges. Note that the gain of the EEG signal is different from one recording to the next. **A:** Recording obtained at age 9 years 5 months. Bilateral frontocentral spike and wave and slow spike and wave discharges appear in short, diffuse, rhythmic bursts. **B:** Similar abnormalities are present at age 10 years 8 months, although spike and wave discharges are less rhythmic. **C:** At age 11 years 3 months, the patient is on phenobarbital monotherapy, after discontinuation of Valproate. A tendency of spike and wave complexes to be rhythmic is again observed.

VPA 20 mg/kg/day was added, resulting in serum levels of 23 μg/ml for PB and 65 μg/ml for VPA. The Wechsler Intelligence Scale for Children–III (WICS) at age 8 years, 4 months showed a full-scale-IQ of 90 (verbal 85, performance 98). Raven's Progressive Matrices (PM 47) score was 25/36 (95th age-adjusted percentile, AAP). PB was discontinued and VPA increased to 26 mg/kg/day, with serum levels of 99 μg/ml and 84 μg/ml at age 8 years, 9 months, and 9 years, 5 months, respectively. No appreciable reduction in interictal EEG discharges was observed either while awake or asleep (Fig. 2A). Moderate learning difficulties, ascribed mainly to poor concentration and memory, were reported by the parents and teachers. Since these symptoms were considered as possibly related to the severe interictal EEG abnormalities, sequential add-on therapy with clobazam and ethosuximide was tried. These drugs produced no lasting clinical or EEG improvement. VPA monotherapy was therefore reinstituted, at an unchanged dosage of 26 mg/kg/day (900 mg/day).

When the patient was 10 years old, lamotrigine (LTG) at a maintenance dosage of 6 mg/kg/day (200 mg/day) was added. Serum VPA levels were 101 μg/ml and blood ammonia was 58 μg/dl (normal range 45–80 μg/dl). Because of the patient's progressive learning difficulties and decreased alertness, VPA dosage was reduced to 23 mg/kg/day (800 mg/day), resulting in serum levels of 95 μg/ml. At the age of 10 years, 6 months, the girl showed progressive deterioration in cognitive functions, lack of interest in surroundings, marked decline in school performance, memory loss, disorientation to place and time, and praxic difficulties. Neurologic examination was normal, except for marginal unsteadiness of gait. Serum VPA levels on two separate occasions within one month were 106 μg/ml, and ammonia levels were 67 μg/dl.

At age 10 years 8 months, repeat IQ testing (WISC) showed a full-scale IQ of 72 (verbal 72, performance 75) while PM 47 score was 24/36 (50th AAP). EEG during wakefulness and sleep was unchanged as compared with previous recordings (Fig. 2B). MRI revealed a diffuse enlargement of subarchnoid spaces, with generalized ventriculomegaly and rounding of ventricular walls (Fig. 1B). There was no appreciable modification of pericerebellar subarachnoid spaces.

Alerted by reports suggesting a possible association between VPA and reversible pseudoatrophy of the brain (7,9), we reduced VPA dosage to '17 mg/kg/day (600 mg/day, serum levels 64 μg/ml). Within 10 days the decreased dosage produced dramatic cognitive and behavioral improvement. LTG was later substituted by PB (1.5 mg/kg/day). At age 11 years, VPA discontinuation was followed within 2 weeks by further mild cognitive improvement. At the age of 11 years, 3 months, serum PB level was 15 μg/ml. MRI revealed marked-reduction in the widening of pericerebral subarachoid spaces and of the ventricular system (Fig. 1C). Repeat testing showed a full-scale WISC IQ of 92 (verbal 92, performance 95) and a PM 47 score of 33/36 (>95th AAP). Neurological examination was normal. EEG showed normal background activity and diffuse slow spike and wave abnormalities, still occupying about 25% of slow wave sleep (Fig. 2C).

DISCUSSION

The striking mental deterioration observed in our patient, its progressive course, and the appearance of MRI findings consistent with marked brain atrophy, were suggestive of a progressive degenerative disorder. However, at least two lines of evidence suggest that the clinical and imaging abnormalities represented an unusual and probably dose-dependent manifestation of VPA toxicity. First, cognitive functioning and behavior showed a striking improvement within a few days of reducing VPA dosage, and a repeat MRI performed 5 months after drug discontinuation revealed disappearance of pseudoatrophic changes. Second, an association of VPA with reversible severe cognitive deterioration and pseudoatrophy of the brain has recently been suggested in other patients (5,7–10). The possibility that pseudoatrophic changes may be related to LTG comedication cannot be fully excluded. This is unlikely, however, as mental deterioration preceded the introduction of LTG and regressed after the reduction in serum VPA levels, without changesin LTG dosage. The role of paroxysmal interictal EEG abnormalities as a cause of cognitive dysfunction can be reasonably excluded because, although severe and greatly activated during sleep, they did not occupy >25% of slow wave sleep and persisted unchanged when mental function improved after VPA discontinuation.

There are some similarities between our patient and the 3 patients with epilepsy previously described by McLachlan (7) and by Papazian et al. (9). These include the pediatric age and development of progressive mental deterioration as the main presenting symptom (with an IQ loss between 18 and 26 IQ points), persistence of normal background EEG activity and reversibility of clinical manifestations, as well as imaging evidence of brain pseudoatrophy after discontinuation of VPA. The previous reports were remarkable also for the simultaneous presence of other manifestations of overdosage such as tremor, weight gain, hair changes, ataxia, and nystagmus, which led to prompt diagnosis of VPA intoxication. A wide range of associated neurological symptoms and signs, especially parkinsonism, was also described recently in 15 VPA-treated adults with "dementia-like" syndrome, many of whom improved after discontinuation of therapy. In the latter study, a repeat CT scan was obtained in only 2 patients, revealing regression of pseudoatrophic changes in both. Seven addi-

tional patients with VPA-associated mental deterioration, cerebral atrophy and pyramidal, extrapyramidal or cerebellar signs have been mentioned in abstract form (8,10). In at least 4 of these patients, CT scan abnormalities did not regress after drug discontinuation (10). Compared to the above reports, our patient appears to be unique in that mental impairment developed as an isolated manifestation, in the absence of other signs of drug toxicity. Reversible VPA-associated "dementia" without other toxic manifestations was previously described in a 21-year-old man, but imaging studies at the peak of the symptoms were not performed (6). Although the syndrome of reversible dementia and cerebral pseudoatrophy ascribed to VPA has also been reported in patients with benign rolandic epilepsy and apparently normal brain morphology (9), it cannot be excluded that in our patient its development was facilitated by pre-existing CNS abnormalities such as the slight alterations in the baseline MRI scan and the presence of symptomatic epilepsy with frequent EEG paroxysms during sleep. Although the specific question as to whether frequent spike-and-wave discharges during sleep can produce pseudoatrophy of the brain has never been specifically addressed, at present there is no evidence that such a possibility exists. In our patient, severe sleep-related interictal EEG discharges persisted unaltered after reversal of pseudoatrophic brain changes.

In at least 3 of the previously reported observations (7,9,10), mental deterioration developed shortly after introduction of VPA, while in many other cases (5,6,10) an insidious development was observed. In our patient, the condition developed insidiously about 2 years after initiation of VPA therapy with serum concentrations near or above the upper limit of the optimal range (100 μg/ml). A correlation between mental deterioration, shrinkage of the brain and high serum VPA concentration is further suggested by the remission of symptoms following a reduction in VPA dosage. As a confirmation of the concentration-dependent nature of the disorder, it is remarkable that in the children reported by McLachlan (7) and Papazian et al. (9), and in the patient without imaging data reported by Zaret and Cohen (6), serum VPA levels were near or above the 100 μg/ml limit.

Based on evaluation of all cases reported to date (5,7–10), the syndrome of VPA-induced mental deterioration and pseudoatrophy of the brain is likely to encompass different but possibly related clinical entities. These may range from parkinsonism with cognitive deterioration (5,10), to marked cognitive regression associated with more typical signs of VPA-toxicity (7,9) and to isolated severe metnal impairment without associated neurological signs (6, and our patient). The mechanisms by which high serum levels affect both function and morphology of the brain are obscure. Interference with pituitary adrenal function (7), metabolic alterations (9) or changes in blood brain barrier permeability (7) have been hypothesized, but their role remains speculative. Hyperammonemia, in particular, has been considered as a possible contributory factor, but in none of the patients in whom this parameter was measured, including our own, were abnormally high levels detected (6,9). Pseudoatrophy of the brain has also been associated with ACTH treatment in patients with infantile spasms, but even in this case the pathogenic mechanisms remain unclear (11).

The mechanisms involved notwithstanding, the findings discussed in this report have important implications. They suggest that in VPA-treated patients a drug effect should be considered whenever there is neuroimaging evidence of brain atrophy, progressive mental deterioration, or both, even if other manifestations of toxicity are lacking. Since there is no general awareness of this condition, physicians may be reluctant to ascribe an apparent structural change of the brain (and associated symptoms) to the underlying treatment, and the risk of underrecognition is substantial. As was the case initially in our patient, mental and behavioral deterioration may be ascribed erroneously to sleep-related interictal EEG abnormalities (12), which did not appear, however, to have played a role in producing either cognitive or pseudoatrophic brain changes.

The reversibility of clinical and imaging abnormalities after drug discontinuation is indispensable for a correct diagnosis. The finding of normal background EEG activity may be helpful in differentiating this condition from other disorders possibly associated with brain atrophy, even though in the syndrome of reversible dementia associated with parkinsonism a slowing in background EEG activity has been reported (5). Other conditions to be considered for differential diagnosis include VPA-induced stupor (2,13,14) with or without hyperammonemia (3,14), which can be differentiated because of lack of brain atrophy (unless preexistent), impairment of consciousness and, in some stuporous cases, clinical or EEG evidence of increased seizure activity.

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