Case report

Encephalopathy and myoclonus triggered by valproic acid

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Abstract

In recent years, the use of valproic acid (VPA) as a mood-stabilizing agent has continuously increased. Although VPA usually is well tolerated, its use in combination with other psychotropic compounds might bear an elevated risk of adverse reactions. Here, we present the case of a 42-year-old male suffering from treatment-resistant psychotic depression, who was prescribed VPA additionally to lithium, clomipramine, flupentixol and risperidone. By doing so, he developed myoclonus, tremor and encephalopathy with sedation and marked EEG background slowing. Most notably, these side effects occurred in the presence of normal VPA and ammonia serum concentrations. On VPA discontinuation, all symptoms vanished and EEG normalized. We thus suggest that direct VPA-induced encephalopathy in the absence of ammonemia does exist, in this case probably facilitated by psychotropic polypharmacy.

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1. Introduction

The anticonvulsant drug valproic acid (VPA) is a commonly used mood stabilizer, suggested to be especially effective in atypical bipolar disorder. Especially when used with other treatment regimes, it is thought to exert synergistic, additive effects (Bowden, 2003). It is generally well tolerated in patients with no underlying brain or metabolic pathology. In those conditions however, as well as when used in a polypharmacy regime, adverse CNS effects occur more frequently, which include extrapyramidal motor symptoms (EPMS) and cognitive decline (Armon et al., 1996; Reif et al., 2003), stupor and encephalopathy with neurological symptoms (Perucca, 2002). The latter usually is associated with ammonemia (Verrotti et al., 2002), reflecting hepatic dysfunction due to—presumably idiosyncratic—liver toxicity of VPA. Here, we report on a case in which encephalopathy with severe EEG alterations and myoclonus acutely developed on VPA dose loading in the absence of ammonemia.

Abbreviations: EPMS, extrapyramidal motor symptoms; VPA, valproic acid.

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2. Case report

2.1. Present history

Mr. S., a 42-year-old worker from the former GUS, suffered for 2 years from a prolonged episode of psychotic depression. Besides depressed mood and lack of drive, he had mood-congruent delusions of being poisoned by other people; no hallucinations were present. His medical history was empty except for obesity and mild diabetes mellitus treated with acarbose; in particular, there was no history for head trauma or neurological disorders. He had no past psychiatric history except for potentially harmful alcohol abuse; however, there were no sequelae and he was teetotal since psychotropic medication was introduced in 2001. At that time, he was treated with amitriptyline, flupentixol, mirtazapine and lithium. His EEG then was entirely normal with a background rhythm of 11 Hz. As his situation only partially responded to this medication, he was readmitted several times to our department. He was additionally treated with risperidone, which improved his condition, but he never completely remitted. Following his last discharge in partial remission, he presented 3 weeks later with depressed mood and ideas of being poisoned. On admission, he was treated
with lithium, risperidone and amitriptyline. We increased risperidone dosage to 4 mg/day, added flupentixol (10 mg) and substituted amitriptyline by clomipramine (225 mg), which slightly improved his condition. All drugs were well tolerated. As he continuously suffered from an atypical depression with persecutory delusions, a treatment attempt with VPA was initiated (day 1, 500 mg; day 2, 1000 mg; day 3 and thereafter, 2000 mg corresponding to 20 mg/kg).

2.2. Valproic-acid induced encephalopathy and myoclonus

At the seventh day of VPA treatment, Mr. S. appeared markedly sedated. He complained about tremor and symmetric myoclonus of the upper extremities, which was confirmed by neurological examination. No other symptoms were present, especially no other neurological signs like asterixis, gait disturbances, confusion or nausea. Routine laboratory parameters including liver enzymes were entirely normal, both clomipramine and VPA serum levels were in the normal range (96 ng/ml clomipramine and 40 ng/ml desmethyclomipramine; 102 mg/l VPA; both have been measured by HPLC) as were lithium concentrations, which remained constant between 0.67 and 0.87 mmol/l. Ammonia was insignificantly elevated (96 μg/dl; normal range in our laboratory: 19–87 μg/dl), and carnitine was in the normal range (45 μmol/l). The EEG showed a prominent, generalized slowing with theta-/delta-rhythm (basal frequency, 2.5 Hz) during the whole recording of 13 min (Fig. 1A). VPA was discontinued, and 2 days later, sedation, tremor and myoclonus were no longer present. Fourteen days after VPA discontinuation, the EEG was only slightly altered (background rhythm, 7–8 Hz) with intermittent, generalized theta waves (Fig. 1B). Another 2 weeks later, EEG was normal (basal frequency, 8–9 Hz; Fig. 1C) and similar to baseline. All other psychotropic medications (lithium, clomipramine, risperidone, and flupentixol) remained unchanged and were well tolerated.

3. Discussion

We suggest that severe EEG slowing with concomitant sedation, tremor and myoclonus was due to VPA administration as all of those symptoms disappeared within a few days upon VPA discontinuation. Altered states of consciousness, tremor and EEG alterations may occur in hepatic encephalopathy due to VPA treatment. However, ammonia levels were only slightly elevated, and all other routine laboratory parameters were entirely normal. Moreover, plasma carnitine was in the normal range, thus excluding hypocarnitinemia as an underlying pathology as previously suggested (Averbuch-Heller et al., 1994; Verrotti et al., 2002). VPA serum concentrations were in the upper normal range, thus hepatic encephalopathy as well as VPA intoxication cannot explain EEG abnormalities and neurologic symptoms. Treatment with other anticonvulsant compounds (e.g., phenobarbital or carbamazepine), which is also frequently observed in VPA-induced encephalopathy, was not accomplished in this patient. Therefore, none of the previously known risk factors for VPA-associated encephalopathy were present and adverse effects may be explained by a direct action of VPA on brain function, as previously suggested (Gastaut and lemo, 1982), probably facilitated by the patient’s past alcohol abuse. The latter might have predisposed the patient to VPA-induced encephalopathy either by impairing liver function or by promoting alcohol-induced brain pathologies. However, routine examinations (laboratory measures, cranial CT) did not argue for both of this. The use of other psychoactive compounds might have also contributed to the observed symptoms, probably by pharmacodynamic interactions on the serum level of one of the substances. However, both lithium and clomipramine/desmethylclomipramine were entirely in the normal range; elevation of the concentration of clomipramine and its metabolite, which can occur due to VPA administration (DeToledo et al., 1997; Fehr et al., 2000), thus can be excluded as a cause of CNS symptoms in our case. Flupentixol and risperidone concentrations have not been determined, yet it seems unlikely that these drugs caused the
observed side effects, as no parkinsonism was present. Nevertheless, intoxication—as an effect of drug interactions—despite normal serum levels of the used drugs remains a possibility we cannot entirely rule out. With respect to this, clues can be pertained by animal studies showing that VPA treatment can produce lesions in the blood–brain barrier (Sobaniec-Lotowska and Sobaniec, 1996), which might result in elevated drug concentrations in the brain. Alternatively or additionally, this might lead to cerebral accumulation of toxic substances, including ammonia.

Especially the presence of myoclonus in the presented patient is counterintuitive, as VPA per se is an anti-myoclonic agent. One case series reported on the presence of negative myoclonus in VPA-induced stupor (Aguglia et al., 1995). Similar to our case, EEG of those six patients showed diffuse cerebral dysfunction with background posterior slowing, although not as prominent as in the present case. Furthermore, all of the reported patients had clearly elevated ammonia levels (200–700% of the upper normal range). Reports on VPA-induced EEG slowing, or myoclonus, in the absence of ammonemia are rare. Recently, a case was published in which diffuse background EEG slowing upon rapid VPA dose loading was described; the patient was co-medicated with carbamazepine, and VPA, carbamazepine and ammonia levels were in the normal range (Chen et al., 2001). In another case, EEG background slowing was observed in a VPA-treated 4-year-old boy. However, this was paralleled by pure red-cell aplasia rendering direct VPA-mediated encephalopathy unlikely (Farkas et al., 2000). Moreover, seven cases of stuporous states associated with VPA dose loading were reported by Gastaut and Jemolo (1982), in whom also a slowing of EEG with predominant delta activity was observed, although ammonia levels were not reported. Rottach et al. (2000) reported on a patient with VPA-associated encephalopathy with seizures in the absence of hyperammonemia (carnitine has not been determined), similar to our patient. EEG slowing was present as well and all symptoms vanished upon discontinuation. Finally, a case series aiming at the determination of CSF glutamine levels in VPA encephalopathy reported two out of seven patients with encephalopathy and EEG slowing to have normal ammonia levels (Vossler et al., 2002). No carnitine levels were stated. Thus, from the cases reported in the literature including the present study, VPA-induced encephalopathy or myoclonus seem to be rare. Given the normal laboratory measures in our case, EEG monitoring is the appropriate means to diagnose these adverse effects.

4. Conclusion

We suggest that direct encephalopathy by valproic acid does exist, also in the absence of hyperammonemia or hypocarnitinemia, and it is accompanied by EEG slowing, somnolence and probably tremor and myoclonus. This conclusion is limited by the fact that we report on a single case, especially as valproic acid is usually well tolerated and the described symptoms are rare side effects. Multiple psychotropic medication, drug interactions and relatively rapid dose titration however might have contributed to the adverse reaction. We thus argue that VPA in conditions of polypharmacy, including not only anticonvulsants but also other psychoactive compounds, should be used cautiously and that such patients should be carefully evaluated for VPA-dependent side effects including EEG measurements as previously suggested (Rottach et al., 2000).

References