Case Report

Valproic Acid-Induced Normal Pressure Hydrocephalus in a Tertiary Care Hospital

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Abstract

Behavioral and psychological symptoms of dementia (BPSD) are a common psychological disorder in the geriatric population with dementia. The causes and risk factors are multiple, and they include biological, psychological, and environmental variables. The combination of these symptoms, rather than any specific factor, explains the occurrence of BPSD in an individual patient. Treatment is targeted to a specific symptom; anticonvulsants such as valproic acid (VPA), carbamazepine, and anti-psychotics have been used to treat agitation in elderly patients. Atypical antipsychotics are used to treat psychosis, and Selective Serotonin Reuptake inhibitors are used to treat depression and anxiety. VPA is dosed using the weight-based dosing approach, which is usually found to be very safe and effective in elderly patients. However, in certain cases, it has also been known to produce reversible neurological symptoms such as dementia, altered sensorium, psychological disturbances, and normal pressure hydrocephalus (NPH) on its prolonged use. The present case report is unique as we identified that an elderly patient with a history hypertension, type 2 Diabetes and asthma, and BPSD was diagnosed with NPH after a short-term treatment with Divalproex sodium-125 mg which is once daily which was added on to his on-going therapy to better control his symptoms.

Keywords: Adverse effect, case report, divalproex sodium

Introduction

Behavioral and psychological symptoms of dementia (BPSD) represent various groups of non-cognitive symptoms and behaviors occurring in subjects with dementia. Mood stabilizers are the drug of choice in variant BPSD.[1] Several abnormal symptoms and signs related to motor and cognitive function impairment, including dementia syndromes, normal pressure hydrocephalus (NPH), have been reported in patients on long-term valproic acid (VPA) therapy.[2,3] This one of the very rare cases reported. The total number of cases that have been reported in a reliable resource with confirmed NPH are four or five.

Case Report

This was a case identified during regular ward round activities which was found to have a rare Adverse reaction to a short-term therapy with VPA hence the details and laboratory Reports were collected to provide enough information to form a case report. A single-case was included in this study to showcase the rare event of VPA-induced NPH was included.

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An 80-year-old male who is a known case of hypertension, diabetes mellitus– Type 2 for 5 years, bronchial asthma, and BPSD was admitted with a history of difficulty in walking and bilateral swaying on sitting since a day. The patient was on enalapril 5 mg/day for hypertension and Neb. Duolin for bronchial asthma. For BPSD the initial dose of T. Quetiapine was 50mg/day. Following the diagnosis with NPH and acute encephalopathy, Divalproex sodium was stopped, and the dose of T. Quetiapine was slightly increased to 100mg/day and later to 125mg/day." He was started on divalproex 125mg recently approximately from the past 2 months for better control of the symptoms.

The computed tomography of the brain showed dilation of the ventricular system with reduced callosal angle suggestive of

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NPH. It also showed age-related diffuse cerebral atrophy with small vessel ischemic changes. The Electroencephalogram showed diffuse severe encephalopathy. Following the diagnosis with NPH and acute encephalopathy, divalproex sodium was stopped, and the dose of quetiapine was slightly increased to 100 mg/day and later to 125 mg/day, dopamine 110 mg/day, and donepezil + Memantine 5 mg for BPSD and to better control symptom. The symptoms improved within a week, and the patient was discharged.

All relevant laboratory investigations, including liver function test, renal function test, were found to be normal. However, hematological reports suggested beta-thalassemia trait (Hb: 9.7 g/dl).

Causality assessment using Naranjo adverse drug reaction probability scale and WHO-UMC causality system showed probable correlation with the adverse reaction. The severity of the adverse event assessed using Hartwig *et al*. scale suggested Level 4a as the patient was admitted due to symptoms of NPH (Level 4a states that the patient is hospitalized because of the adverse event).

Discussion

BPSD encompasses signs and symptoms regarding behavior, mood, and perception or thought content that frequently occurs in patients with dementia. The clinical opinion suggests that the first-line treatment for agitated delusion in dementia is monotherapy with an antipsychotic; and the second-line treatment a combination of antipsychotics with a mood stabilizer. Several uncontrolled open trials, case reports, or case series have suggested the efficacy and supported the use of VPA in variant BPSD, although few Randomized Controlled Trials have shown conflicting outcomes.[1]

In rare situations, VPA has been known to cause a severe and potentially lethal state of hyperammonemia with encephalopathy. It is the result of a dose-independent increase in ammonia levels. The mechanism of VPA causing hyperammonemia is considered to be due to its ability to cause impairment in the body's usual fatty acid metabolism leading to disruption in the urea cycle, causing high serum ammonia levels.[4]

On reaching the clinical threshold, lethargy is the most common symptom, though seizures, focal neurologic deficits, and even coma may also be possible. It can occur even in patients with normal hepatic function, normal loading doses, chronic stable doses, and normal serum drug levels.[5]

VPA is also known to cause cognitive decline and Parkinson's like symptoms, but these are found to be reversible with dose reduction or discontinuation of the medication. Imaging techniques have demonstrated reversible cortical pseudo atrophy and of the lateral ventricles as an adverse effect of VPA that can present as dementia syndrome such as NPH in patients on VPA for a long duration.[1,2]

Mechanism involved

The neuronal model using SY5Y neuroblastoma cells as employed by Qian *et al*.[6] found that VPA reduced cell proliferation and neurite outgrowth. It was also found to reduce mRNA and protein levels of a neurofilament 160. The adverse effects were found to be reversible within 2 days of reducing or completely stopping of VPA.

Molecular mechanism

This mutation describes and validates the peculiar feature of this adverse reaction. In addition, the mutations in the mitochondrial DNA are heteroplasmic, which validates the

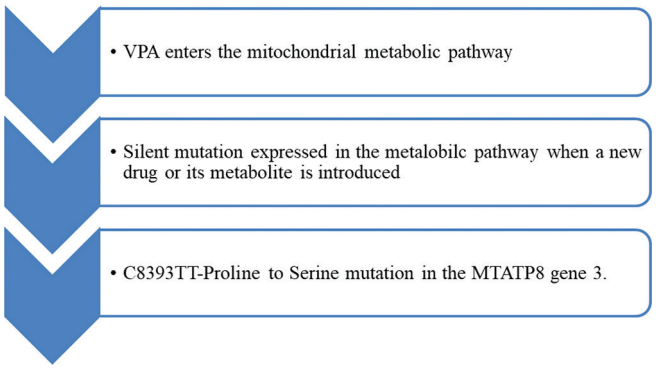

Figure 1: Silent mutation mechanism

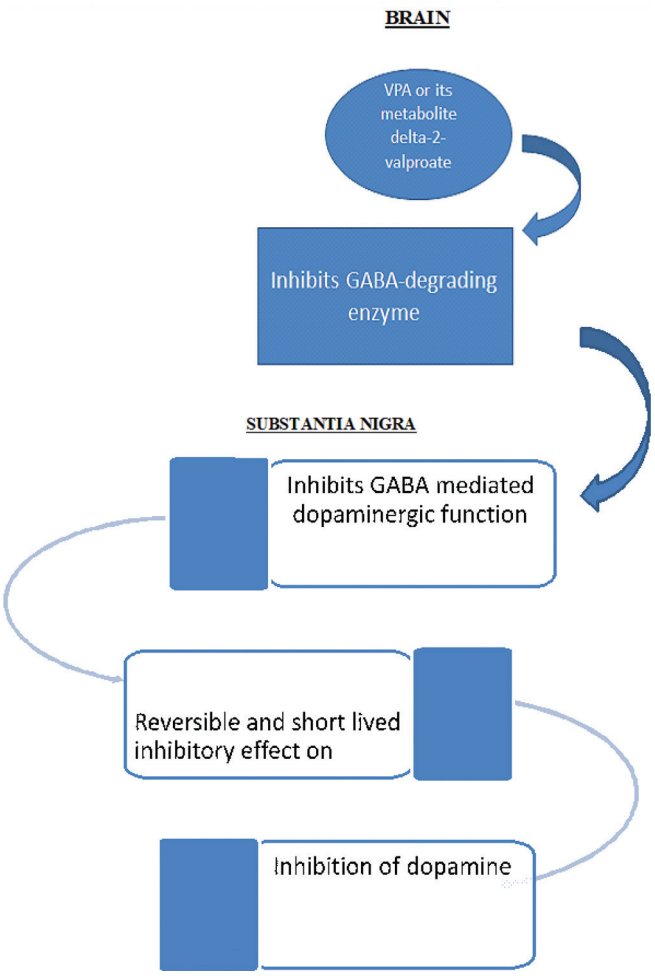

Figure 2: GABAnergic pathway inhibition mechanism

Table 1: Comparison of various case reports

	Age	Dose of valproic acid	Duration of therapy	Concurrent therapy	Adverse effects	Diagnostic techniques	Time taken to reverse symptoms after de challenge
Present case	80	125 mg/day	2 months	Quetipine-50 mg BID Enalapril 5 mg	Gait disturbance and swaying on sitting confirmed NPH	*CT – Brain*: Dilation of the ventricular system EEG: Severe encephalopathy	1 week
Case report 1[7]	65	1000 mg/day	15 years	Phenytoin for 2 years Monotherapy with Phenobarbital and carbamazepine	Reversible dementia, cognitive impairment and gait disturbance evaluated for NPH	MRI: Ventricular measurements before and after cessation of VPA showed enlargement of the ventricles	2 months
Case report 2[9]	67	1000 mg/day	8 years	Venlafaxine 150 mg/day	Cognitive impairment, gait disturbance, dyskinesia, and urinary incontinence	MRI shows enlarged ventricles and some cortical atrophy confirmed NPH	8-0 weeks

NPH=Normal pressure hydrocephalus, MRI=Magnetic resonance imaging

variable timeline for expression and appearance of symptoms [Figure 1].[6,7]

Alternate mechanism

Table 1 compares various case reports on VPA-induced NPH or cognitive impairment with the present case to provide a better understanding of the adverse event its duration and the diagnosis [Figure 2].[6-8]

The above-mentioned case reports have showed the behavioral and cognitive side effects of VPA in geriatric patients. Geriatric patients are more sensitive to the side effects of the medications and are at a higher risk of developing medical complications due to multiple comorbidities. Literature also states that geriatric patients require closer monitoring when treated with VPA regardless of the duration of the therapy as they are more prone to its side effect.

In our case, an anticonvulsant mood stabilizer, VPA, was added to the therapy in addition to antipsychotic (quetiapine) in an attempt to better control the symptoms of BPSD, but VPA caused its untoward side effect of NPH, resulting in worsening of his agitation and behavioral symptoms. The duration from the initiation of therapy to the adverse effect of VPA was 2 months, unlike the other mentioned case reports in which the adverse effect was seen only on prolonged use of VPA.

Conclusion

This case report demonstrates the adverse effect of VPA in elderly patients with BPSD even after a short-term treatment and that if anticonvulsants or mood stabilizers have to be administered should be monitored appropriately. It also suggests that antipsychotics are the preferred line of treatment for BPSD when compared to anticonvulsants.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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