



CASE REPORT

Parkinsonism Due to the Use of Long-Term High-Dose Valproic Acid in an Elderly Patient with Mania Syndrome: A Case Report and Literature Review

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ABSTRACT

Valproic acid (VPA) is used as a mood stabilizer in the treatment of bipolar disorder and is commonly associated with central nervous system side effects. The most common side effect is tremor due to dose, while parkinsonism is a less common side effect. Among psychiatric patients, there are few reports of recurrent parkinsonism attributed to VPA use. However, in the literature, especially among neurological patients, VPA is one of the main important causes of Parkinsonism. Furthermore, the relationship between VPA treatment dose and parkinsonism symptom severity is uncertain. 72-year-old male patient has been followed-up for 30 years with a diagnosis of bipolar disorder and has been receiving a treatment of VPA. After VPA treatment was started, complaints of impairment in speech, walking with small steps, slowed movements, and imbalance which had gradually increased, started within the last 10 years. The patient was admitted to the clinic and assessed for secondary parkinsonism. VPA treatment of the patient was stopped since he was thought to have secondary parkinsonism associated with medication. 4 days after the VPA medication was stopped, it was seen that there was a decrease in bending forward posture and regression in dysphagia and the patient was seen to walk alone without any support. Based on this case, it can be put forward that addressing psychiatry patients who have a long-term use of VPA in terms of parkinsonism symptoms can be significant in terms of not overlooking this side effect that can disrupt the quality of life and also in terms of early diagnosis and treatment.

Keywords: Valproic acid, parkinsonism, bipolar disorder, mood stabilizer, adverse effect, elderly

INTRODUCTION

Parkinsonism is a type of movement disorder that can be a result of various neuropathological and pharmacological problems. Degeneration of nigrostriatal dopamine (DA) neurons is main mechanism of idiopathic Parkinson's diseases (1). Parkinsonism symptoms also can be induced

or exacerbated by various drugs, this situation is defined as drug-induced parkinsonism (DIP) (2). In psychiatric clinics, this drug reaction also caused by other psychotropic drugs, fluoxetine and other antidepressants, lithium and antiepileptic drugs including valproic acid (VPA) (3).

Valproic acid (VPA) is an important treatment option especially in elderly patients and it is frequently used as mood stabilizer in the treatment of bipolar disorder and in the treatment of epilepsy and agitation in dementia (4). Although the mechanism of action of valproate is not fully understood, blockade of voltage-dependent sodium

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currents and increased brain levels of gamma-aminobutyric acid (GABA), known as underlying important mechanisms (5). However, given the various experimental and clinical effects of valproate, a great number of neurological side effects have been reported with the VPA use. The most frequent of these side effects is tremor, which is seen in 6-45% of the patients. Parkinsonism is one of the less common side effects of VPA treatment (4). According to Easterford's study, DIP has been observed in up to 6% of long term users of VPA patients (6). When we look at the underlying mechanism of VPA-induced parkinsonism, toxic effect on neurons, altered gene expressions, neurotransmitter signalling and mitochondrial dysfunction, unmasking subclinical dopaminergic degeneration, co-occurrence with PD a possible mechanism as VPA may affect complex activity in the electron transport chain of mitochondrias also alternative mechanism is GABAergic activity on the basal ganglia (7).

Case reports and studies about recurrent parkinsonism attributed to VPA are mostly on epilepsy patients and there are few numbers of case reports on this issue in psychiatric patient population. However, in literature VPA is shown as one of the important reasons of parkinsonism attributed to medication (8). In addition, the relationship between VPA treatment dose and parkinsonism symptom severity is uncertain in limited number of cases reported (9).

Due to its nature that can disrupt life quality, in addition to being recurrent, the realization of this condition in psychiatry patients who have used long-term VPA is important in terms of early diagnosis and treatment. In this case report, it was thought that parkinsonism symptoms in a patient followed-up with the diagnosis of bipolar disorder could be associated with long-term and high-dose VPA use and with the discontinuation of the drug, symptoms were found to regress. Within this context; here, we aim to attract attention to this side effect resulting from VPA use, which is argued to be one of the important reasons for parkinsonism, although rare, and which may be overlooked in psychiatry patients, although relatively better known in neurology.

CASE PRESENTATION

72-year-old male patient who is married has been followed up for 30 years with a diagnosis of bipolar disorder and has been receiving a treatment of Valproic acid (VPA) 2500 mg/day, lithium carbonate 900 mg/day for the last 15 years. After VPA treatment was started, complaints of impairment in speech, walking with small steps, slowed movements and imbalance which had gradually increased, started within the last 10 years. However the patient never stopped using VPA during past ten years. The patient, who was not able to get up from bed alone for the last 15 days had dysphagia and frequent falls. For the last 10 days, complaints of talking too much, irritability, energy increase and insomnia were added to these complaints.

Psychometric scales

Young Mania Rating Scale (YMRS): This scale was 11-item developed by Young et al. (10) in 1978. Every item is rated on a 0–4 scale. The rating of severity is based on both the patient's declaration during the last 48 hours also the clinician's impressions about the patient during the session. The Turkish validity and reliability study was made by Karadağ et al. 2002 (11).

Mini Mental State (MMS) Examination: Mini Mental State (MMS) examination was first introduced by Folstein et al. in 1975 (12) in order to obtain an examination method to measure cognitive performance in quantitative form. Orientation, recording memory, attention and calculation were all evaluated, The reliability and validity of the Turkish version was conducted by Güngen et al. 2002 (13).

United Parkinson Disease Rating Scale (UPDRS): United Parkinson Disease Rating Scale (UPDRS) is a scale that was developed to monitor parkinson disease related disability and impairment. The scale has four subscales, derived from pre-existing scales. These are mental state of patients, behavior and mental state, activities of daily living, motor function and treatment complications. Total 42 items were scored between 0-4. High scores indicating more severe impairment. Turkish versions' reliability and validity has been conducted by Akbostancı et al. in 2000 (14).

The patient's psychiatric examination revealed increased speed of speech, the patient was elaborative and

distracted, his affect was anxious, he had increased exhilarated mood, and his thoughts had anxieties about loss of functionality. He had decreased appetite and need for sleep. Scale scores of the patient who was hospitalized with a diagnosis of bipolar disorder-mania attack, secondary parkinsonism were as follows: Young Mania Rating Scale (YMRS): 18, United Parkinson Disease Rating Scale (UPDRS) 3rd part motor score was 24. His neurological examination showed slight tremor on tongue and eyelids, his physical examination showed bradykinesia, mild cogwheel rigidity, and decrease in associated arm movements while walking. In his routine blood tests, his total blood count, liver function tests, renal function tests, lipid profile, serum electrolytes, calcium and phosphate, creatine phosphokinase, serum ammonia levels, lung radiography, and electrocardiography (ECG) results were all unremarkable. His mini mental test score was 28/30. As a result of his brain computerized tomography in 2012, brain magnetic resonance imaging (MRI) was performed and his MMRI came as ventricle size in proportion with cerebral atrophy. Quetiapine 100 mg/day therapy was started due to psychomotor accelerating symptoms and on the sixth day of the therapy, the dose was gradually increased to 400

mg/day. VPA treatment of the patient was stopped since he was thought to have secondary Parkinsonism associated with medication. 4 days after the VPA medication was stopped, it was seen that there was a decrease in the bent forward posture and regression in dysphagia and the patient was seen to walk alone without any support. In the examination on the sixth day of his hospitalization, no tremor, rigidity or bradykinesia were seen. In the scale assessment, UPDRS 3rd part motor score decreased to 14. Turkish version of Naranjo Adverse Drug Reactions Probability Scale was administered and the score was 6, indicating probable association with VPA use (15). Written consent was taken for the case report.

DISCUSSION

VPA, which is used as a mood regulator in the treatment of bipolar disorder treatment, shows common side effects on central nervous system. Parkinsonism is one of the rare side effects of VPA treatment (16). This syndrome, which was first defined by Lautin et al. has been defined with clinical symptoms such as bradykinesia, rigidity, postural instability, and resting tremor (16). In this case report, it

Table 1: Table of the cases of VPA-induced parkinsonism in psychiatric diseases

Case(year)	Age	Gender	Reason for VPA	VPA dosage	VPA blood levels	Approximate time from usage until parkinsonian symptoms appeared or worsened	Time from discontinuation until clinical improvement/resolution
1 (Wils and Golük e-Willemse 1977)	70	F	Bipolar affective disorder	750 mg daily	48-52 mg/mL	10days	Not specified
2. (De Dios et al.2011)	66	F	Bipolar affective disorder	1500 mg/daily	78mg/mL	3 years	Not specified
3 (Silver and Factor 2013)	72	F	Depression	1000 mg/daily	Not specified	1.5 years	3 days
4. (Silver and Factor 2013)	44	F	Depression	250 mg/daily	Not specified	2.5 years	2 years
5. (Silver and Factor 2013)	74	M	Bipolar affective disorder	1500 mg/daily	Not specified	3 years	4 month
6. (Ricard et al. 1979)	58	M	Bipolar affective disorder	1000 mg/daily	79 mg/mL	7 month	1 year
7. (Lautin et al.1979)	52	M	Schizophrenia	1000 mg/daily	Not specified	4 days	2 days
8. Sameer et al.2014	71	F	Bipolar affective disorder	1250 mg/daily	Not specified	8 years	2 month
9. (Tada et al. 2016)	75	F	Bipolar affective disorder	1000 mg/daily	Not specified	6 month	Not specified

was found that following the initiation of VPA treatment, gradually increased speech impairment, walking with small steps, slow movements and imbalance. Patient's neurological examination showed slight tremor on tongue and eyelids, bradykinesia, mild cogwheel rigidity, decrease in associated arm movements while walking. Within this context, the existing parkinsonian symptoms were assessed as secondary to VPA treatment.

Literature databases were searched systematically; Brugger et al. identified a total of 116 patients with valproate-associated parkinsonism published in case reports, case series and systematic analyses (7). There are a total of 9 cases followed with a diagnosis of psychiatric diseases and defined as parkinsonism associated with use of VPA. Six of these cases are followed with a diagnosis of bipolar disorder. Parkinsonism symptoms had developed within 6 months-8 years of VPA initiation and the daily VPA dose reported changes between 250-1500 mg/day (8, 9, 16-20) (Table 1). In this case, Parkinson symptoms, gradually increasing after VPA treatment taken daily as 2500 mg/day for 15 years were found. The report by Althauda et al. (2015) that parkinsonism symptoms were seen in a 65-year-old male patient diagnosed with epilepsy after using 3000mg/day VPA for 8 years supported the association between high-dose and long-term VPA use and parkinsonism, similar to the one in this present case (4). However, it has been reported in literature that the association between VPA dose and parkinsonism symptom severity is vague. While the development of symptoms after the initiation of VPA treatment is unpredictable, the severity of symptoms and plasma level are not associated. Although the recovery is seen in many of the cases after medication is stopped, parkinsonism symptoms might continue in some cases (4). The onset of symptoms can be seen months-years after VPA treatment is initiated and clinical recovery can occur within days or months after VPA treatment is stopped (9). However most cases showed improvement with the discontinuation of the drug, but the rate and extent of improvement was unpredictable (21). In this case, another finding that supports the symptoms of Parkinsonism associated with VPA is the regression in symptoms after the medication is stopped. Psychiatric cases in literature

have reported that parkinsonism symptoms regress within a period between 4 days and 8 years after VPA medication is stopped (8, 9, 16-20) (Table 1). Consistent with the literature, it was seen in our case that parkinsonism symptoms regressed within 4 days after VPA medication was stopped.

VPA-induced parkinsonism develops several days, months or years after the initiation of VPA therapy; in some studies claimed that, especially appears chronic use, especially at higher doses, may cause an increase in the GABAergic inhibitory activity that has been implicated in the symptom of bradykinesia (22). As in this case; advanced age is major risk factor. Other risk factors were reported as being a woman, genetic variants, preexisting movement disorders, and cigarette smoking. DA antagonists and DA-depleting agents, fluoxetine and other antidepressants, lithium that are used as antipsychotic drugs are the most common causes of drug-induced parkinsonism (3). In this present case, lithium had been used as well as VPA.

Although parkinsonism secondary to VPA use is rare, it has been shown as one of the important reasons of parkinsonism attributed to medication. These side effects, which are more frequently observed and well-known among neurological patients, are rare in psychiatry and thus they can be overlooked. In psychiatric patients, when patients have VPA use or when they are admitted with symptoms of parkinsonism and can be thought to have Parkinson's disease, this medication attributed side effect should be kept in mind. Besides the difficulty of differentiating between parkinsonism symptoms secondary to medication and idiopathic Parkinson's disease, the management of the disease and the differences between their courses are important (23). Although it is stated in literature that there are studies for developing clinical ways to make this differentiation, it has been stated that even when the clinical appearance is fully met in the last phase of the diseases, diagnosis accuracy for idiopathic Parkinson's disease does not reach 100% (24). This situation results from the lack of biological markers that can find out the basic mechanism in the emergence of Parkinson's disease (22). Although this case is not complex from this perspective, the problem of

differentiating between idiopathic and medication attributed parkinsonism can create a problem during clinical follow-up. In such cases, when there are doubts about the drug, it can be recommended to discontinue the drug and observe the change in symptoms although this may prolong the duration of treatment.

Based on this case, it can be speculated that in patients with long-term use of VPA, parkinsonism symptoms can be significant in terms of not overlooking this side effect that can disrupt the quality of life and also in terms of early diagnosis and treatment.

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