VALPROATE-INDUCED PARKINSONISM IN EPILEPSY PATIENT – A CASE REPORT

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Summary. Valproate (VPA) is one of the most commonly used anti-epileptic drugs troughout the world. It is generally considered to have a good safety profil. Among the side effects due to valproate administration, parkinsonism is the rarest in frequency. This side effect is often unsuspected. Clinical features of valproate-induced parkinsonism (VPA-P) can mimic Parkinson's disease and may be confusing especially when they occur in older men. A case of a 75-year-old man with ten years history of epilepsy treated with Depakine Chrono who developed parkinsonism in the last two years is described. Antiparkinsonian treatment with Madopar HBS even in high dosage was ineffective. The characteristics and possible mechanisms of VPA-P are described. Despite the good safety of VPA therapy for several years, clinicians should have a high suspicion for VPA-P especially in old patients and this possibility should be considered in the differential diagnosis.

Key words: *valproate, epilepsy, parkinsonism*

INTRODUCTION

Over the past 20 years, the treatment of epilepsy has undergone tremendous changes. New drugs have been introduced and neurologists have a vast armamentarium to treat epileptic seizures. Among antiepileptic drugs of first choice, valproate (VPA) is one of the most effective [8, 12, 16]. It is also one of the most commonly used antiepileptic drugs throughout the world [16]. It is generally considered to have a good safety profile [8, 16]. VPA indications incude a wide range of epileptic seizures such as primary generalized tonic–clonic seizures, absences, epileptic myoclonus, atonic seizures, photosensitive epilepsy (part of the syndrome of primery generalized epilepsy) and Lenox–Gastaut syn-

drome [8, 16]. It is also useful in patients with partial seizures, West syndrome and febrile convulsions. Serum level estimations can be made but there is a poor relationship between level and effect [8, 16] There is little point in a rigid adherence to the so-called therapeutic range (300-700 mmol/l). The VPA levels fluctuate widely during a 24 h period, even on three times daily dosage, and the antiepileptic effectiveness is not influenced by these fluctuations [16]. The controlled–release formulation lessens this fluctuation, but does not improve seizure control nor does lessen side effects and there seems to be a little justification for its wide usage [16]. Because of the lack of correlation between serum level and effect serum level monitoring is not generally clinically useful [9, 16].

Among the side-effects attributed to VPA administration, the production of parkinsonian syndrome is very uncommon [16]. That's why this side effect is often unsuspected. Clinical features of VPA–induced parkinsonism can mimic Parkinson's disease and may be confusing especially when they occur in older patients. Confirmation of this is our case report described below.

CASE REPORT

A 75–year-old-man (№ 420/ 12.11.2007) was examined as out-patient at the Medical Center for Neurology and Neurosurgery of Military Medical Academy in Sofia in November 2007 because of an comorbidity of epilepsy and parkinsonism. Since 1997, tonic-clonic epileptic seizures occurred. Depakine chrono at daily dosage of 1000 mg two times daily (b.i.d.) had been instituted as monotherapy with good clinical response. Since 2005, the patient developed a progressive syndrome characterized by tremor (confined to the four extremities), trunk and limb rigidity, motor slowness and hypomimia. Clinically, parkinsonism had been diagnosed. Madopar HBS had been started at a low dosage and gradually increased to a daily dosage of 730 mg three times daily (t.i.d.), because of the lack of satisfactory therapeutic response. At that time Depakine chrono daily dosage has been maintained unchanged.

Family history and past history were negative for neurologic disorders such as Parkinson's disease. Serum level of Depakine chrono was within the therapeutic range (510 mmol/l). EEG showed a low amplitude activity in the theta and beta ranges, without epileptic discharges. Brain MRI (magnetic resonance imaging) was normal.

DISCUSSION

Association of epilepsy and parkinsonism is not frequent [12]. VPA is well tolerated anti-epileptic drug [8]. Among its side-effects, VPA–induced parkinsonism is extremely rare – 1,37% [6, 7, 13].

The mode of action of VPA is thoroughly associated with the effects of GABA. VPA enhances GABA inhibition but this effect is only observed at high concentrations [16]. VPA increases the synthesis of GABA by stimulating glutamic acid decarboxylase and inhibits GABA degrading enzymes and succinate semialdehyde dehydrogenase [8]. VPA also inhibits the threshold for calcium and potassium conductance [8, 16].

We analysed the characteristics of VPA–induced parkinsonism (VPA–P) and we found that they are some peculiarities:

– VPA–P develops in patients who have not had a previous adverse reaction to VPA and who have had a favorable therapeutic response [15] for years as it was in our case report;

– VPA–P develops several days [1], months [11] or years after the initiation of VPA therapy;

– VPA–P is not an age-dependent process [15]. Parkinson's syndrome may develop in every age: in children (very uncommon) as well as in older patients [1, 15];

– VPA–P is reversible after reducing the dosage of VPA [1, 17] or discontinuation of treatment and changing to another anti-epileptic drug [11, 15];

– Improvement of VPA–P may occur 3 or 6 months after discontinuation of VPA [2, 7, 10];

– Improvement of VPA –P is greatest in patients who have been affected most [2];

– VPA–P is not dosage-related and serum levels of VPA doses do not represent a precipitating factor [6];

– Antiparkinsonian treatment of VPA-P is not effective in most cases even in high dosage.

All these characteristics of VPA-P show that VPA action remains not fully understood.

The underlying mechanisms of VPA-P remain unclear. Some side-effects of VPA related to the VPA-P may be associated with the role of GABA-containing neurons in the basal ganglia [4, 5] and GABA-mediated mechanisms [4, 5, 7]. A massive inhibitory effect of GABA on the dopaminergic routes is possible to develop VPA-P in some patients [15]. Inherited susceptibility may play a certain role. The pathophysiology of neuroleptic-induced parkinsonism involves the blocade of D2 (dopamine type 2) receptors in the nucleus caudatus at the termination of the nigrostriatal dopamine neurons, the same neurons that degenerate in idiopathic Parkinson's disease. Is it possible VPA-P and neuroleptic-induced parcinsonism to have common mechanisms and VPA to act as dopamine receptor antagonist? The normal SPECT examination in several patients with VPA-induced parkinsonism suggests that the mechanism of VPA-P is not related to the loss of dopaminergic

neurons [3]. The reversibility of VPA-P after VPA discontinuation supports the possibility of transitory perturbed VPA metabolism [14, 16]. Recently, it was found that VPA may affect signalling systems like the Wnt/beta – catenin and ERK pathways and interfere with inositol and arachidonate metabolism [14]. VPA treatment also produces alternation in the expression of multiple genes, many of which are involved in transcription regulation, ion homeostasis and signal transduction [14]. These alterations may well be relevant to the side effects of VPA. But most questions related to the characteristics of VPA-P remain without answers for the time being.

CONCLUSIONS

Because VPA-P is a very rare toxic side effect of VPA treatment, it is not always recognized at time, and inadequate therapy may be initated. Despite the good safety of VPA therapy for several years, clinicians should have a high suspicion for VPA-P especially in old patients and this possibility should be considered in the differential diagnosis.

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