Valproate-associated parkinsonism – a critical review of the literature

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Abstract

Valproate (VPA) was first approved as an antiepileptic drug in 1962. It has since also become established as a mood stabiliser and as prophylaxis for migraine. In 1979, Lautin published the first description of a VPA-associated extrapyramidal syndrome. Many cases of VPA-associated parkinsonism have subsequently been published, but uncertainties remain concerning its prevalence, risk factors and prognosis. The aim of this review was to provide a critical review of the existing literature on VPA-associated parkinsonism and to discuss possible mechanisms. Literature databases were searched systematically. The quality of the evidence was assessed and probability of causation was examined using the Naranjo score. We identified a total of 116 patients with VPA-associated parkinsonism published in case reports, case series and systematic analyses. Prevalence rates ranged widely, between 1.4% and 75% of patients on VPA. There was great heterogeneity with regard to clinical presentation, age of onset, VPA dose, concomitant conditions and imaging findings. In all patients apart from three, VPA plasma levels were within or even below the recommended reference range when the parkinsonism occurred. Parkinsonism was reversible in the majority of patients, although recovery was often prolonged and sometimes incomplete. A dopaminergic deficit was confirmed in three of six patients investigated with dopamine transporter imaging. Seven of 14 patients who were treated with dopaminergic medication had a good response. The Naranjo score ranged from 0 to 7 (median: 5.0). Several pathophysiological mechanisms including altered gene expression and neurotransmitter signalling, enhanced neurodegeneration or unmasking subclinical dopaminergic degeneration could theoretically lead to VPA-associated parkinsonism. Further studies are warranted to elucidate this entity and its underlying pathophysiology.

Key points

- Although valproate-induced parkinsonism is widely accepted as an entity, it has become clear that its phenotype is quite heterogenous and that there are still uncertainties regarding clinical presentation, frequency, risk factors, course and outcome.
- Several potential pathophysiological mechanisms that could theoretically lead to parkinsonian features with valproate are discussed.

1. Introduction

Valproate (VPA) was first approved in 1962 for treating epilepsy [1]. It subsequently became established not only as one of the standard antiepileptic drugs but also as a mood stabiliser and for migraine prophylaxis [2, 3]. Chemically, VPA is a small branched fatty acid which is thought to block voltage-dependent sodium channels and to increase the levels of γ-aminobutyric acid (GABA) by inhibiting GABA degradation enzymes, probably by the inhibition of succinyl semiadenylate dehydrogenase and GABA transaminase [4, 5]. Apart from these short-term metabolic changes, there is growing evidence for associated long-term effects that require several weeks to become established, and that might even persist beyond the cessation of VPA intake [4]. The spectrum of VPA is wide and includes weight gain, hair loss, bruising/bleeding, tremor, hyperammonaemia presenting as encephalopathy associated with liver failure and pancreatitis [6-11]. Parkinsonism is another adverse drug reaction (ADR) that has been reported to occur with VPA. The first published case of an extrapyramidal syndrome with VPA was in 1979, by Lautin et al. [12]. Several case series, case reports and smaller studies focusing on VPA-associated parkinsonism have been published since. Despite the considerable number of publications on this topic, current evidence supporting the association of VPA and parkinsonism is still limited. It should be noted that, in 2011, Mahmoud and Tampi provided a review of VPA-associated parkinsonism [13], but they focused only on elderly patients. The aims of this paper are to provide a comprehensive and critical review of the existing literature and to discuss possible hypotheses for the mechanism of VPA-associated parkinsonism.

2. Literature search methodology

2.1 Search Strategy

Literature databases (PubMed/Medline, EMBASE, Cochrane Library, SciSearch) were searched systematically using the terms “extrapyramidal or parkinson$” (to include parkinson, parkinsonism and Parkinson’s) and “(valproate, valproic or divalproex)”. We also performed a

search for conference papers (published as abstracts in major topic journals). Articles were included in this review if the authors made the clinical diagnosis of parkinsonism in their patients, although the diagnostic criteria were not always clearly stated. Only articles published in English were considered. The reference lists of all relevant articles were screened for other publications that might have been missed by the database search. The abstracts of all articles were reviewed, and relevant articles were chosen for further evaluation on the basis of the information provided.

In the second step, all relevant articles were analysed for the following information: number of patients with parkinsonism, patient age and sex, indication for VPA, VPA dose and plasma levels, clinical presentation, duration of VPA intake at onset of parkinsonism, outcome after stopping VPA, use of dopaminergic medication for treatment of the associated parkinsonian symptoms, concurrent conditions and medication intake; the Unified Parkinson's Disease Rating Scale (UPDRS III; scale range: 0-108 points) scores were retrieved (where provided). If dopaminergic drugs were used, the levodopa equivalence dose was calculated [14]. Publications were also searched for computed tomography (CT), magnetic resonance imaging (MRI), [^{123}I]-Ioflupane (DATScan^{TM}) and [^{123}I]beta-CIT (2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane) SPECT findings. The quality of the articles was assessed according to the classification of evidence of the American Academy of Neurology [15] and the Naranjo score aiming at estimating the likelihood of a causal relationship between a drug and putative adverse effect was calculated for each case based on the information provided [16]. Calculation was omitted if the cases of VPA-associated parkinsonism were part of a larger cohort and not enough clinical information on the individual cases was available.

The Naranjo score ranges from 0 to 13, with higher scores indicating a higher probability of a causal relationship [16]. The score ranges are classified as follows: scores of >=9 indicate a definitive ADR, scores from 5 to 8 a probable ADR, scores between 1 and 4 a possible ADR, and 0 is considered as a doubtful ADR. Descriptive statistics (mean or median, range) were used to present data in a systematic way. Relevant data were harmonized to a single unit (to mg/l for

plasma levels, months for treatment duration and years for age) to allow comparisons and statistical analysis. The data were extracted and reviewed by the same person (F.Br.)

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3. Literature search results

3.1 Selection of Studies and Patient Populations

We identified 32 publications with a total of 116 patients who were diagnosed as developing parkinsonism with VPA (see table 1). Three publications fulfilled the criteria for class III evidence [17-19], whereas all other publications were classified as class IV evidence. One article was only available in abstract form [20]. In another publication, the patient described was on a combination of VPA and carbamazepine but the parkinsonism occurred in clear temporal relationship to the introduction of carbamazepine and disappeared after stopping it [21]. Because the authors could not exclude the possibility that the interaction between CBZ and VPA had led to the clinical presentation, we also included this case report. Three cases were published as conference papers [22-24]. Among the 32 publications identified, there were 18 case reports [12, 20, 21, 23-37], 5 case series with a total of 20 patients [38-41] and 9 systematic analyses with a total of 78 patients [17-19, 22, 42-46]. As far as we could determine, no patient was included in more than one of these studies, i.e. there was no "double counting". The prevalence was systematically determined in five articles and was found to be between 1.4% and 10.7% [17-19, 45, 46]. The largest number of cases was reported by Armon et al. who assessed motor, cognitive and hearing adverse effects [43]. They reported that 27 of 36 patients treated with VPA (i.e. 75%) developed parkinsonism. Notably, this cases series accounts for about one quarter of all cases identified by our literature search.

Considering all the publications together, of those patients for whom gender was stated, 41.4% were male (24/58) and 58.6% female (34/58). The median age, calculated from the 90 patients for whom information was available, was 63.5 years (range: 12 to 82). In the majority of cases

(n=79), epilepsy was the primary indication for prescribing VPA. The other reasons for prescribing VPA were bipolar disorder (n=4), depression (n=2), schizophrenia (n=1), psychiatric complications due to an underlying neurodegenerative disorder (n=2) and a myoclonic disorder after an acute illness (n=1). The median VPA dose was 1250 mg (n=60; range: 250-3000 mg) and median duration on VPA until the onset of parkinsonism was 34.2 months (n=54; range: 0.1-360 months). Only 3/37 patients were reported as having excessive VPA plasma levels (112, 115 and 121 mg/ml, respectively), when the parkinsonism occured, while for 33/37 patients plasma levels were within the recommended reference range for treating epilepsy (40-100 mg/l) [47] and for 1/37 below this range (25.3 mg/l) [37]. In some patients, the plasma levels were just reported as being "normal" (n=8; [35, 45, 46]) or "below the therapeutic range" (n=1; [27]) without providing further details regarding the exact levels. In another 6 patients, only the mean for the whole population was provided [17].

3.2 Clinical Presentation and Course of the Parkinsonism

The clinical presentation was quite heterogeneous among the cases. It included various combinations of akinesia and hypokinesia, micrographia, increased muscle tone (i.e. rigidity) or cogwheel rigidity, dysarthria, resting, action and postural tremor, walking difficulties, festination, postural instability, upgaze restriction, cerebellar features, pyramidal signs, autonomic features, mainly urinary incontinence, and drooling and dysphagia. Cognitive impairment, including bradyphrenia, disorientation and apraxia, agnosia or aphasia, either as a new clinical feature or as a deterioration of a pre-existing dementia, were sometimes described as an accompanying feature. The severity of the clinical presentation also covered a wide range from mild to very severe with dementia and complete loss of physical independence (including being wheelchair bound or bedridden). The UPDRS III scores [48] were provided for 31 patients, with a median of 18 points (range: 4-98). Information on comorbidities other than the indication for VPA prescription was

available for 29 patients and included conditions with predominant basal ganglia involvement, such as probable Parkinson disease (PD), multiple system atrophy (MSA), vascular parkinsonism, pre-existing tremor conditions or Huntington disease, and other comorbidities such as urinary tract infection, acute illness due to urosepsis, systemic lupus erythematosus with secondary renal failure, history of head trauma, depression, cerebral inflammatory granuloma, functional overlay, coeliac disease, chronic renal impairment, depression, cerebral palsy, neurofibromatosis, alcoholism, arterial hypertension, hypercholesterolaemia, stroke, cerebral lymphoma, breast cancer, meningioma, arachnoid cyst, gout, diabetes, pre-existing dementia and mental retardation. A history of previous or concomitant intake of neuroleptic medication was reported for nine patients. In another patient, metoclopramide and haloperidol were added five and ten days, respectively, after stopping the VPA. It should be noted that both anti-dopaminergic agents led to a re-occurrence of the same extrapyramidal features as with VPA. However, in contrast to the clinical presentation with VPA, the extrapyramidal features then responded to trihexyphenidyl [12].

VPA was reported as having been stopped in 71 of the 116 patients. The parkinsonian features improved and/or resolved in 67/71 upon discontinuation of the drug. The latency of improvement after stopping VPA was provided for 38 cases and was 4.5 months on average (range: 0.1-24 months). For the other 33 cases, either no exact time frame was provided in the article or the latency until improvement was just stated approximately (e.g. “improvement within 1 year”). Dopaminergic treatment, mostly levodopa, was tried in 16/116 patients and was judged as being effective in 7/16 patients. One patient was started on bromocryptine, but no details regarding treatment response were provided. Another patient was reported to be unresponsive to levodopa, but the exact dose was not provided. Also, it should be noted that in three of the seven unresponsive cases, only a levodopa challenge was performed (with a single dose of 200 mg levodopa). In the seven who responded, the median levodopa equivalence dose was 350 mg (range: 300-600 mg). In seven patients who did not benefit the median dose was 300 mg (range:

200-730 mg). This difference was not statistically significant. Dyskinesias occurred in one single patient, with a latency of 4 months. Dyskinesias were reversible upon stopping levodopa and after complete resolution of the extrapyramidal syndrome.

3.3 Neuroimaging Results

Information on imaging was available in 33 patients. Imaging modalities included MRI in 12 patients, CT in 16 patients, and scans of unspecified modality (MRI or CT) in another 5 patients. 17/33 patients were reported as having abnormal radiological findings, which included white matter changes, various degrees of cortical/subcortical atrophy with concomitant ventricular enlargement, and lacunar infarcts in the cerebellum, pons and the basal ganglia. Follow-up scans were reported in three patients; the brain atrophy was reversible in one of these patients. In one of the two other cases, the scan was normal both with the VPA and after it had been stopped. In the other case pathological enlargement of the ventricles persisted despite stopping VPA. In the study by Armon et al., 11 out of 16 patients with neurological adverse effects following VPA intake were reported as showing progressive or new cerebral atrophy with VPA. However, it remains unclear which of them eventually had developed parkinsonism. Four patients had a DATScan™ and another two had a beta-CIT SPECT scan. These scans revealed a presynaptic dopaminergic deficit in three of the six patients. The three with an abnormal scan had a median age of 67 years (range: 65-87 years) and the three with a normal scan a median age of 75 years (range: 65-75 years). However, this age difference was not statistically significant. Onofrj et al. performed a 99mTc-bicisate SPECT in two patients [38]. The scans revealed reduced blood flow in the right temporal lobe, and both the left frontal and temporal lobe, respectively. In a case report by Evans et al. fluorodeoxyglucose (18F)-PET revealed hypometabolism in the bilateral periventricular, right-sided anterior parietal and frontal regions [26]. Tada et al. reported a frontal blood flow reduction on a cerebral blood flow scan, but the authors did not provide further information regarding the tracer used [37].

3.4. Naranjo score

The median Naranjo score was 5.0 with a range from 0 to 7 (n=59).

4. Discussion

We reviewed and summarized the existing literature on VPA-associated parkinsonism. In 2011, Mahmoud and Tampi reviewed this issue [13], but they focused only on the elderly and did not review the literature as systematically as we did it here (although our review does not fulfil the PRISMA criteria for a systematic review due to the lack of well designed randomized-controlled trials [49]). In our literature search, we identified 32 relevant publications, comprising case reports, case series and systematic analyses with a total of 116 patients. We aimed at characterizing this entity with regard to frequency and clinical features on the basis of the existing literature.

The prevalence rates indicated in the systematic analyses included covered a wide range from 1.4% up to 75% of patients treated with VPA, with a slightly higher preponderance of women. The majority of authors, however, suggested rates lower than 10%. By far the most common primary diagnosis, which led to the prescription of VPA, was epilepsy, followed by various psychiatric conditions such as bipolar disorder or schizophrenia. With regard to clinical presentation, the reports of VPA-associated parkinsonism were very heterogeneous. There was a wide range of age at onset, latency from treatment initiation to first presentation and symptom severity (with some patients even becoming bedridden). It was striking that, even in very severe cases with a history of many years of neurological complications, symptoms could often be reversed after stopping VPA. Imaging techniques to prove a dopaminergic deficit (DATScan™, beta-CIT SPECT) revealed mixed results, showing a dopaminergic deficit in half of the patients. Response to dopaminergic treatment, mainly levodopa, varied from none to excellent. When VPA plasma levels were measured, in almost all cases they were within the reference range as

suggested by the International League Against Epilepsy [47]. The possibility of a relationship between parkinsonism and VPA level was investigated systematically in only one study but no correlation was found [46] and parkinsonism was also reported in patients on VPA doses as low as 250 mg per day. Of note, the typical maximum recommended dose for epilepsy is 2.4 g daily.

Although the entity of VPA-associated parkinsonism seems to be widely accepted and recognized, numerous questions remain unanswered: First, the frequency is still unclear. In view of the very large numbers of patients receiving VPA, it would appear that either the frequency of parkinsonism is quite low or many cases go unrecognised. Second, the risk factors for developing VPA-associated parkinsonism remain unclear. There may be an individual genetic susceptibility, and possibly a "double-hit" mechanism consisting of an individual genetic susceptibly followed by exposure to the offending drug, as proposed for neuroleptic-associated parkinsonism, may apply [50]. Third, there was a broad spectrum of associated symptoms and we could not identify a single characteristic phenotype. Fourth, it remains unclear whether an underlying dopaminergic deficit is essential for developing VPA-associated parkinsonism, as only a small number of patients identified for this review underwent a DATscan^{TM} or beta-CIT scan. Fifth, the long-term outcome remains unknown, but would be of great interest with regard to managing these patients.

Beyond the clinical presentation, the underlying pathophysiology also remains unclear. Several mechanisms for the development of parkinsonism with VPA can be considered, as follows (2).

I.) Altered neurotransmitter signalling: VPA has a strong GABAergic effect [5]. GABA can inhibit dopaminergic activity in the substantia nigra [51] and excessive GABAergic activity in the globus pallidus externus can lead to overactivity of the indirect basal ganglia pathway [52, 53]. The observation by Lautin that anti-dopaminergic medications caused a similar clinical presentation as VPA in the same patient may moreover suggest common neuronal pathways associated with extrapyramidal adverse effects of these two drug classes [12]. The good response to levodopa in some cases reinforces the hypothesis of an involvement of the dopaminergic

pathway. The reversibility of symptoms after discontinuation of VPA would also be in line with disturbances on the transmitter signalling level.

II.) Altered gene expression: There are reports of patients requiring up to several weeks to recover after the VPA was discontinued. Because VPA has a relatively short half-life of six to eight hours [54], it has been argued that it would be unlikely that an increased GABAergic action alone could be responsible for the evolution of parkinsonism (although it should be noted that plasma half-life does not necessarily correlate with the brain effect of a neurotropic drug). It has been shown that VPA also activates various intracellular signalling pathways, which, in turn, switch on the transcription of numerous target genes [4]. For example, VPA activates the extracellular-regulated kinases (ERK) pathway, which is involved in synaptic plasticity, neurogenesis and neuronal survival [55, 56]. It should be noted that haloperidol, one of the most potent drugs to induce parkinsonism, acts in a similar way on the ERK signalling pathway [57]. It has also been shown that VPA upregulates the expression of the dopamine transporter and it could thus lead to increased transmitter re-uptake and decreased availability of dopamine in the synaptic cleft [58]. VPA has strong histone deacetylase activity and can thus regulate gene expression through modifying chromosomal acetylation status and subsequently of DNA packaging resulting in an increased accessibility of the transcriptional machinery to DNA [4]. This way of regulating gene expression by VPA has been shown for par-4, a protein involved in dopamine receptor signalling [59]. In summary, long-term effects of VPA might affect dopamine signalling by modulating the expression of involved proteins, possibly explaining the often prolonged recovery period.

III.) Unmasking subclinical dopaminergic degeneration: Two cases were proven to have a presynaptic dopaminergic deficit [28, 32] and one case was clinically diagnosed as having PD four years after stopping VPA [60]. This may point to the possibility either of unmasking subclinical dopaminergic degeneration or of the induction of dopaminergic degeneration in patients at risk when they take VPA. One explanation may be that in patients with a subclinical dopaminergic deficit, increased GABAergic activity or an altered gene expression leads to a breakdown of

compensatory processes in the basal ganglia networks and eventually to the evolution of a clinically manifest syndrome. Many of the patients with VPA-associated parkinsonism were also elderly or had concomitant neurological conditions such as dementia [43]. These observations could also point to the importance of an age-related or comorbidity-related decreased capacity to reverse toxic effects.

IV.) Enhanced neurodegeneration: Another possibility may be that VPA promotes ongoing neurodegenerative processes in the dopaminergic system [13], particularly on the mitochondrial level by inducing a state of cellular energy deficiency and increased oxidative stress [60]. Mutations in one of the PD genes could further increase the susceptibility of dopaminergic neurons to associated detrimental effects [61]. In line with this, disrupted mitochondrial function has also been proposed in the pathogenesis of Parkinson disease [62]. The notion of mitochondrial dysfunction secondary to VPA may also supported by the alleged observation of hearing loss, a common clinical sign in mitochondrial disorders, as a further adverse effect of VPA [43]. Of note, abnormalities in the putamen, as can also be observed in mitochondrial disorders such as complex I deficiency, were described in one of the case series [30, 63].

V.) Co-occurrence with PD: As the majority of the patients were older, the likelihood of developing coincidental PD is considerable. However, in most of the cases the first symptoms were recognized a few weeks to months after starting VPA and in many cases the parkinsonism recovered completely or improved significantly after stopping the drug, favouring a causal relationship.

To shed more light on the clinical presentation and pathophysiology, a systematic study in a large patient cohort with baseline assessments before starting on VPA and standardized assessments both while patients are taking VPA and for a follow-up period would be required. Methods should include validated clinical scores such as the UPDRS and cognitive tests. DATScans™ should be performed in those who develop parkinsonian features to establish whether there is a dopaminergic deficit [64]. Screening tests for risk factors for PD, such as REM sleep behaviour

disorder and hyposmia [65] and the inclusion of genetic risk factors, particularly for developing PD and mitochondrial disorders [66], might support the detection of patients at high risk of developing parkinsonism with VPA. Long-term follow-up of those who do develop VPA-associated parkinsonism will provide prognostic factors that may guide clinicians in the information they provide to patients in the future with regard to the outcome in those who discontinue VPA.

Our review has some limitations. There is a lack of consistency in reporting relevant information such as plasma levels, latency to evolution of symptoms after starting the dose and latency until improvement on stopping the drug. Therefore, it was sometimes difficult to compare the reports. Clinical descriptions were sometimes inadequate or inconclusive with regard to the clinical aspects of interest for this review. Furthermore, cases were followed up at different intervals. We identified eight systematic analyses, in which cases of VPA-associated parkinsonism were included. Although systematic analyses with larger number of patients are thought to provide higher level of evidence, they are usually at the expense of more detailed information on individual cases. Another limitation is the fact that authors previously used different definitions for parkinsonism. Whilst bradykinesia is now considered as the core feature [67], some authors, particularly in the older literature, used a combination of typical symptoms as diagnostic criteria without necessarily requiring the presence of bradykinesia. For example, Armon et al. described 26 patients with “parkinsonism”, but only 22 had bradykinesia [43] and in the study by Nouveilles et al. the presence of a typical resting tremor alone was sufficient for the diagnosis of parkinsonism [46]. Also, we cannot exclude that VPA-induced postural tremor, a frequent side effects with VPA treatment [9, 10], may have been misdiagnosed as parkinsonism by some authors thus leading to errors in case ascertainment. All these issues make it difficult to assess the incidence of VPA-associated parkinsonism accurately, but rates of 75% as suggested by Armon et al. are very likely to be an overestimate, since such a high rate is neither consistent with most published reports nor with clinical experience.

5. Conclusion

The clinical presentation of VPA-associated parkinsonism is heterogeneous and not yet well established. There are several possible pathophysiological mechanisms but the current literature does not allow any firm conclusions to be drawn. Prospective and systematic collection of relevant data from a large cohort of patients taking VPA may provide the answers to some of the unresolved questions. Although the symptoms are reversible in most cases of VPA-associated parkinsonism, the fact that some patients are left with residual deficits underscores the importance of gaining a better understanding of this entity.

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