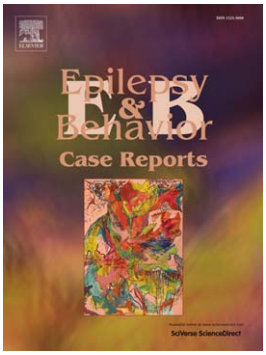

Non-Hyperammonaemic Valproate encephalopathy after 20 years of treatment

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Non-Hyperammonaemic Valproate encephalopathy after 20years of treatment

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Abstract:

Sodium valproate is a commonly used anti-epileptic drug with broad indications for different seizure-types and epilepsy syndromes. Well-recognised side effects include weight gain, tremor, dizziness, and unsteadiness. Non-hyperammonaemic parkinsonism, with or without cognitive impairment, is a rare adverse effect of sodium valproate. We present the case of a 60-year lady with a generalized seizure disorder, treated with phenytoin, valproate, lamotrigine and clonazepam. Following withdrawal of phenytoin she developed an akinetic-rigid syndrome, with ataxia and marked cognitive impairment. Extensive investigation failed to identify a cause. Serum ammonia and valproate levels were normal. Hypothesizing this might be valproate encephalopathy, valproate was rapidly substituted with levetiracetam. Her severe motor symptoms resolved within two weeks and cognitive impairment markedly improved. Valproate-induced encephalopathy, with or without hyperammonaemia and liver toxicity are typically recognizable for their temporal relation between the start of therapy with valproate and emergence of the clinical syndrome. Reversible disorders of motor function and cognition attributable to valproate are well described, but few cases have been reported presenting years after starting treatment. Given the insidious progression, delayed onset, lack of association with drug levels or presence of hyperammonaemia, a low index of suspicion is needed to make the diagnosis.

1.0 **Introduction:**

Serious adverse events in patients treated with sodium valproate are uncommon. The risk of such events occurring is considerably increased when valproate is administered as part of a poly-therapy regimen, in the very young (under two years of age), and in those with unsuspected defects of the urea cycle [1]. Many of the adverse events that arise with sodium valproate are quickly detected because of the temporal association between starting the drug and the onset of symptoms, which may range from weight-gain and tremor, to the more serious apathy and drowsiness seen in hyperammonaemic valproate-encephalopathy or valproate-induced liver toxicity. Non-hyperammonaemic parkinsonism, with or without cognitive impairment, is a rare adverse effect of sodium valproate therapy. We report the case of a woman who developed an akinetic rigid syndrome with ataxia and cognitive impairment after many years of treatment on a stable dose of sodium valproate, and review of the relevant literature.

2.0 Case Report:

A 60-year old woman was referred to our epilepsy clinic for follow up of her childhood onset epilepsy, characterized by absences, generalised tonic-clonic seizures, and possible myoclonic jerks. Videotelemetry recording undertaken to confirm syndromic classification showed interictal spike wave and polyspike wave complexes, supporting the diagnosis of an idiopathic (genetic) generalized epilepsy. She had been seizure-free prior to referral for 20 years on a combination of clonazepam (total daily dose of 1.5mg), sodium valproate (total daily dose of 1700mg), lamotrigine (total daily dose of 100mg) and phenytoin (total daily dose of 200mg). She also had longstanding anxiety and depression, and breast cancer diagnosed in 2003, treated with wide local excision and local radiotherapy. She has one son with learning disabilities and lives with her mother who is well at 94 years of age.

In view of her ongoing seizure freedom, the EEG findings and to simplify her drug regime, phenytoin was gradually withdrawn and stopped. Two months later, she complained of new confusion and unsteadiness, with falls, intermittent slurring of speech and a change in handwriting. She was noted to have a mild, bilateral upper limb tremor. Her drug levels were within therapeutic range.

Her symptoms progressed resulting in several presentations to her local emergency department with recurrent falls and on one occasion a fractured pubic ramus. When assessed again in the epilepsy clinic she was noted to have hypomimia and dysarthria, with rest tremor and cogwheel rigidity, in keeping with a Parkinsonian syndrome. She could not stand unaided and had a broad-based, shuffling gait. Her mother reported the patient was more forgetful, missing appointments and repeatedly asking what time of the day it was.

Blood investigations, including vitamin B12 and folate, anti-neuronal and paraneoplastic antibodies, were all within normal limits or negative. Notably, serum Valproate level was 99mg/L, serum

ammonia was 17umol/l (normal range 9-30umol/l) and liver function tests were normal. Lamotrigine level was 12mg/L (range 3-15mg/L) and Phenytoin was undetected. Analysis of cerebrospinal fluid was unremarkable and biomarkers for prion disease were negative. Magnetic resonance imaging of the brain showed a degree of generalized cerebral and cerebellar atrophy. The hippocampi were thought to be a little small, possibly with middle cerebellar peduncle and pontine atrophy. Electroencephalogram showed mild slow background with no evidence of subclinical seizures. She scored 75/100 on the Addenbrooke's Cognitive Examination (ACE-R), which was much lower compared to formal neuropsychometric assessments performed in 1989 and 2011, which showed essentially normal profiles.

Given the unusual clinical picture of progressive akinetic-rigid syndrome, ataxia and cognitive decline, and the timing of symptoms following withdrawal of phenytoin, it was hypothesized this may represent non-hyperammonaemic valproate encephalopathy.

The patient was admitted to our Neurology ward for rapid replacement of valproate with levetiracetam. On admission her Unified Parkinson's Disease Rating Scale score was 48 and ACE-R score was 49/100. The drug changes were made successfully over a few days without seizure relapse. Resolution of the extrapyramidal movement disorder and improvement of her cognitive impairment was noted by two weeks following withdrawal of valproate. ACE-R score improved to 89/100 by the time of discharge. Outpatient review has shown ongoing improvements regaining full independence for activities of daily living and she has remained seizure free since.

3.0 Discussion:

Sodium valproate is a widely used anti-epileptic drug used for a broad range of epilepsy syndromes and seizure-types. Tremor is a common adverse effect of valproate on the central nervous system, with less common side effects including headache, blurred vision, dizziness, nystagmus, and unsteadiness [1]. Occurrence of these and more serious adverse events during treatment with valproate is influenced by co-administration of other drugs that influence valproate pharmacokinetics and pharmacodynamics, underlying disorders of the urea cycle, and individual susceptibility to adverse events.

Valproate-associated encephalopathy is a well-recognised adverse event, often associated with hyperammonaemia and typified by the development of apathy, drowsiness and impaired cognition. This idiosyncratic reaction is by definition unpredictable and not always associated with valproate dose or plasma levels, abnormal liver function, or raised serum ammonia levels. It has often been described occurring shortly after the introduction of sodium valproate, with rapid resolution of encephalopathy following withdrawal of the drug [2]. Valproate-induced liver toxicity is rare, occurring in roughly 1 in 20,000 patients. It typically presents with apathy, drowsiness, vomiting, and increased seizure frequency. Deranged liver function tests may lag the clinical presentation, so

clinicians need to be aware of this serious adverse reaction and stop the drug if they suspect the diagnosis [1].

Less well-recognised is valproate-associated encephalopathy without hyperammonaemia presenting with a parkinsonian syndrome, with or without cognitive impairment. To date 28 adult patients have been described in the literature presenting with an akinetic-rigid syndrome that resolved on stopping sodium valproate [3–5]. Typically symptoms developed shortly after starting or increasing the dose of sodium valproate (10 days to one week). Few of the reported cases developed symptoms after years of stable treatment [3,4]. To our knowledge our case is the first to be reported in which symptoms developed after 20 years on a stable dose. Given the insidious progression of symptoms and lack of association with valproate dosage, drug levels, or presence of hyperammonaemia, a low index of suspicion is needed to make the diagnosis of valproate-associated encephalopathy in patients presenting with an extra-pyramidal syndrome. As in our case, almost all patients who stopped valproate showed dramatic recovery within weeks, with most improvement seen within six months.

The mechanisms by which sodium valproate causes encephalopathy and parkinsonism remain unknown but are likely to be multiple [3]. Commonly cited mechanisms include effects on mitochondrial metabolism by inhibition of mitochondrial fatty acid B-oxidation and effects on the urea cycle, and through inhibition of GABA degradation within the basal ganglia. Paradoxically, valproate has been used to improve symptoms of parkinsonism without adverse effect [3]. A number of reported cases had normal SPECT imaging suggesting that valproate does not cause parkinsonism through loss of dopaminergic neurons [3], but some patients do appear to respond to dopamine replacement therapy [4,5].

It is difficult to know what role our patient's other anti-epileptic medication may have played in her clinical presentation. Phenytoin had been stopped entirely just before the onset of her symptoms. Phenytoin is known to increase valproate metabolism and we hypothesized that withdrawal of phenytoin may have led to a relative rise in valproate levels, even though these remained within the therapeutic range. There is a well-recognised interaction between lamotrigine and valproate, with valproate increasing lamotrigine levels by slowing its metabolism, while lamotrigine may increase metabolism of valproate by inducing liver enzymes. It is unclear what contribution, if any, lamotrigine may have had to the clinical picture we observed in our patient.

Interpretation of ammonia levels reported in the context of valproate encephalopathy is challenging. Many reports and case series do not report ammonia levels and differences in methodology make their interpretation difficult. In animal studies the presence of valproate lowers levels of ammonia required to cause encephalopathy compared to animals not given valproate [6]. Administration of carnitine allows higher levels of serum ammonia to be tolerated without causing encephalopathy, an effect that is diminished in the presence of valproate.

4.0 Conclusion:

Many practitioners are familiar with valproate encephalopathy presenting with fluctuating level of consciousness, with or without raised ammonia levels and impaired liver function. Although our case had many of the clinical features of Parkinsonism, including rest tremor, hypomimia, bradykinesia, and cogwheel rigidity, her marked ataxia and rapidly evolving cognitive impairment made us suspicious for an alternative cause of her symptoms. Our case highlights a less well-recognised presentation of valproate encephalopathy, which resolved on withdrawal of the drug.

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References

[1]. Perucca E. Pharmacological and Therapeutic Properties of Valproate. CNS Drugs. 2002 Oct 1;16(10):695–714.

[2]. Verrotti A, Trotta D, Morgese G, Chiarelli F. Valproate-Induced Hyperammonemic Encephalopathy. Metab Brain Dis [Internet]. 2002 Dec;17(4).

[3]. Mahmoud F, Tampi RR. Valproic acid-induced parkinsonism in the elderly: a comprehensive review of the literature. Am J Geriatr Pharmacother. 2011 Dec;9(6):405–12.

[4]. Silver M, Factor SA. Valproic acid-induced parkinsonism: levodopa responsiveness with dyskinesia. Parkinsonism Relat Disord. 2013 Aug;19(8):758–60.

[5]. Tada H, Ogihara T, Nakamura T, Sasayama D, Sugiyama N, Takahashi Y, et al. A case of severe parkinsonism in an elderly person induced by valproic acid. Psychogeriatrics. 2016 Jan 1; 1-2.

[6]. Stephens JR, Levy RH. Effects of valproate and citrulline on ammonium-induced encephalopathy. Epilepsia. 1994 Feb;35(1):164–71.