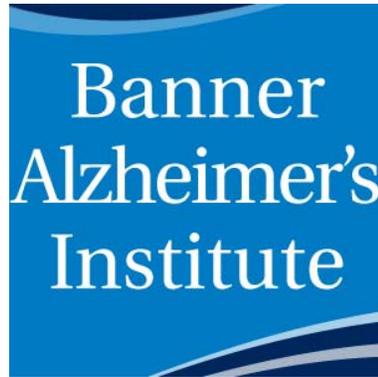


Reversible dementia and gait disturbance after prolonged use of valproic acid

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Intro

- Although Valproic acid (VPA) is generally considered a safe medication in the elderly, there are previous reports of patients developing reversible cognitive decline or reversible parkinsonism, often both¹
- The most common cause for cognitive dysfunction in patients taking VPA is hyperammonemic encephalopathy, which is a toxic cognitive impairment caused by VPA. The pathophysiology is attributed to the accumulation of Valproyl-CoA in the mitochondria which inhibits n-acetylglutamate synthase (NAG). NAG is an inducer of CPS-I, the first enzyme involved in the urea cycle²
- The Naranjo adverse drug reaction scale can be used as an objective tool to determine whether a patient's symptoms can be attributed by an adverse drug reaction (ADR) by answering a questionnaire³
- Common imaging findings among similar case reports are reversible cortical pseudoatrophy and enlargement of the lateral ventricles¹

Case

- A 65-year-old woman with a generalized seizure disorder which began at age 25 presented to a Memory Disorders Clinic complaining of confusion and difficulty walking. Since valproic acid (VPA) was initiated approximately at age 50 she has been seizure-free with an average daily dose of 1 g
- Incidentally, the patient has a history of gradual hearing loss of unknown etiology starting in her early 50s. Her mother and maternal uncle also had a similar pattern of hearing loss. The same maternal uncle has a "generalized seizure disorder" of unknown etiology
- VPA and ammonia levels were therapeutic and normal, respectively. A brain MRI revealed mild prominence of the lateral ventricles concerning for normal pressure hydrocephalus, however significant sulcal atrophy was also observed
- Given the apparent dementia, urinary incontinence, gait changes, and an MRI suggestive of enlarged ventricles, a workup for normal pressure hydrocephalus was pursued. A large volume lumbar puncture (29 mL of CSF was expressed) did not significantly benefit gait or cognitive measures
- VPA was changed to levetiracetam without incident. Cognition and gait disturbance gradually normalized over the following two months. A brain MRI 4 months after cessation of VPA showed possible, but not significant, reduction of ventricular size (see table 1)

Methods / Results

- As dementia and gait disturbance in an elderly patient could be due to a wide variety of causes, her clinical history was evaluated with the Naranjo adverse drug reaction (ADR) scale. This scale determines the probability that a patient's clinical syndrome is related to an ADR in a more objective manner than clinical judgment alone
- The likelihoods are reported quantitatively with an associated qualitative modifier for score ranges, which include: "definite (9 or more), probable (5-8), possible (1-4), doubtful (0)". This patient scored a 5, indicating an ADR to VPA is **probable**
- The specific questions of the Naranjo ADR questionnaire³ are:
 - "Did the ADR improve when the drug was discontinued or a specific antagonist was given? **Yes, +1**"
 - "Was the ADR more/less severe when the dose was increased/decreased? **Yes, +1**"
 - "Are there previous conclusive reports on this reaction? **Yes, +1**"
 - "Did the ADR appear after the suspected drug was given? **Yes, +2**"
 - "Was the ADR confirmed by any objective evidence? **Yes, +1**"
 - "Did the ADR appear when the drug was readministered? **n/a**"
 - "Are there alternative causes that could have caused the ADR? **Yes, -1. NPH may have caused the patient's symptoms despite a negative large volume LP, though unlikely**"
 - "Did the ADR reappear when a placebo was given? **n/a**"
 - "Was the drug detected in any body fluid in toxic concentrations? **No, +0**"
 - "Did the patient have a similar ADR to the same or similar drugs in any previous exposure? **No, +0**"

Discussion

- A proposed mechanism of the reversible cognitive decline seen in these patients taking VPA is a mitochondrial DNA (mtDNA) mutation. One of the reported cases of VPA-induced non-hyperammonemic reversible cognitive decline describes a pediatric patient who was found to have a C8393TT-Pro→Ser mutation in the MTATP8 gene⁴. Also, since mtDNA mutations are heteroplasmic, it would explain the highly variable clinical timeline of symptom appearance. The patient's hearing loss and epilepsy are suggestive of a mtDNA mutation syndrome, especially with her family history of similar symptoms that followed a maternal inheritance pattern. Unfortunately, in our patient genetic testing was not performed
- Evidence indicates that GABA mediates dopaminergic function in the substantia nigra. VPA or a metabolite of VPA such as delta-2-valproate, which may be a more potent inhibitor of the human brain GABA-degrading enzyme than VPA, may cause a transient inhibitory effect on dopaminergic pathways⁵
- VPA has also been shown to reversibly inhibit neurite outgrowth in a cellular study⁶

Conclusion

- This case exemplifies one of the adverse effects of VPA, which can cause reversible neurological symptoms even in long-term treated patients. Clinicians should be aware of how valproate-induced cognitive impairment and gait disturbance can masquerade as dementia syndromes such as Alzheimer's disease or normal pressure hydrocephalus, especially when pseudoatrophy is present. Recognizing this clinical scenario can allow clinicians to avoid unnecessary tests or treatments, and possibly reverse the condition.

References

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Time of MRI (months)	Measurement (mm)			
	1	2	3	4
57 months prior	41.4	37.1	76.8	76.7
21 months prior	42.1	41.3	80.3	79.7
7 months prior	43.0	43.2	82.2	81.5
4 months after	43.5	41.4	78.2	80.4

Table 1 Ventricular measurements before and after cessation of VPA. On 3 out of 4 measurements of ventricle size, numeric reductions were seen 4 months after cessation of VPA. The ventricular measurements were performed by a radiologist blinded to the clinical history.

Measure 1: transverse diameter between lateralmost portions of the frontal horns of the lateral ventricles at the level of the head of caudate by axial plane. **Measure 2:** transverse diameter of frontal horns of the lateral ventricle by coronal plane at the level of the hypothalamus. **Measure 3:** greatest anteroposterior diameter of the right lateral ventricle by sagittal plane. **Measure 4:** greatest anteroposterior diameter of the left lateral ventricle by sagittal plane.

p-values: 1 = 0.29; 2 = 0.83; 3 = 0.67; 4 = 0.73. No statistically significant change after VPA cessation.