# Valproic Acid-Induced Gait Disturbance and Cognitive Impairment that was Reversible with Discontinuation of Medication

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**Dedications**

Dedicated to my wife: Jana Evans, RN and my daughter Ansley Evans

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Also dedicated to the amazing clinical staff at Banner Alzheimer Institute

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And finally, dedicated to my great-grandmother Edwina Leffue who passed of Alzheimer Disease in 2006 after teaching me that “dogma is like a shoe: wear the style that fits you but don’t force others to wear your shoes, because they likely won’t fit.”

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**Abstract**

Clinicians should be aware that treating patients with Valproic Acid (VPA) can cause cognitive and neurological decline in a small percentage of patients. A 67-year-old female with urinary incontinence, who had taken VPA without major complaints for 15 years to control her seizures, presented with abnormal gait and cognitive impairment that was significantly impacting her day-to-day level of functioning. Initially normal pressure hydrocephalus was suspected, but large volume LP did not show significant improvements in gait or cognition. Discontinuation of VPA reversed her symptoms over the next two months. The hypothesis of this project was that clinical judgment combined with objective criteria could be used to support the argument that this patient's symptoms were likely an adverse drug reaction to VPA. The Naranjo adverse drug reaction scale was used as an objective measure and indicated that this patient's likelihood of an adverse drug reaction to VPA was "probable". Imaging findings consistent with the literature demonstrated reversible cortical pseudoatrophy and enlargement of the lateral ventricles, although changes in ventricular size did not reach statistical significance by two-tailed t-test. This case exemplifies the adverse effects of VPA, which can cause reversible neurological symptoms even in long-term treated patients and can present as parkinsonism or other dementia syndromes such as normal pressure hydrocephalus.

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## Introduction

Although the common anticonvulsant valproic acid (VPA) is generally considered a safe medication in the elderly[1], there are previous reports of patients developing reversible cognitive decline or reversible parkinsonism, often both[2-22]. These symptoms can occur even with a valproate drug level within therapeutic ranges. Common imaging findings among these reports are reversible cortical pseudoatrophy and enlargement of the lateral ventricles[3,4,11,13,18,20,23]. There are currently no reports in the literature of a patient with an adverse drug reaction (ADR) to VPA who presented with signs and symptoms typical for patients with normal pressure hydrocephalus (NPH).

Cognitive dysfunction encountered immediately after starting VPA therapy is typically attributed to hyperammonemic encephalopathy since it is well-recognized that VPA enters into mitochondrial metabolic pathways and can disrupt the urea cycle. Typically valproate-induced encephalopathy is associated with hyperammonemia; however up to 10% of patients with neurological symptoms may have a normal ammonia level[24]. Since only some patients on VPA develop hyperammonemic encephalopathy, it is thought that a genetic defect causing excess toxic metabolites to accumulate in the mitochondria must be present. The pathogenesis of this phenomenon is thought to be caused by valproyl-CoA's direct inhibition of n-acetylglutamate (NAG) synthase[25]. Valproyl-CoA is a metabolite of VPA that is present in the mitochondrion. Since NAG allosterically activates carbamoyl-phosphate synthase 1 (CPS-1) and CPS-1 is the first key enzyme involved in the urea cycle, NAG's absence results in an acquired urea cycle defect leading to hyperammonemia.

This patient did not have typical parkinsonian features to suggest valproate-induced parkinsonism and she did not have an elevated ammonia level to suggest valproate-induced hyperammonemic encephalopathy; however, she still had reversible neurological symptoms with drug discontinuation. The aims and rationale for presenting this unique case report are three-fold:

1. To describe the typical patient and this patient's unique reversible neurologic symptoms secondary to VPA, and use objective tools as evidence to support that this patient's symptoms were an ADR to VPA
2. To report a patient with an ADR to VPA who presented with symptoms more typical of NPH, distinct from those currently in the literature which consist mainly of parkinsonism and hyperammonemic encephalopathy
3. To reinforce that the neurologic symptoms secondary to VPA can occur even in long-term treated patients and that symptom onset is not always temporally associated with initiation of pharmacotherapy

The hypothesis that this project addresses is: There are objective ways to approach adverse drug reactions and these objective clinical tools should be used as a supplement to clinical judgment. To do this, Naranjo's ADR scale was used to assess the strength of the claim "this patient's symptoms are attributable to an ADR to VPA." Also, statistical methods were applied to measurements obtained by a radiologist blinded to the patient's clinical history to determine if MRI changes reached statistical significance.

An abbreviated case report was published in *Seizure* in October of 2011 **(see appendix 1)**, and the impact of this topic is already apparent. A medical resident at Banner Good Samaritan Medical Center in Phoenix, AZ contacted the author of this project with a question regarding her patient. The patient was an ambulatory adult with a mood disorder being treated with an atypical antipsychotic and valproate that had slowly begun to develop parkinsonism. The clinical team was given guidance on the case that reminded them that atypical antipsychotics are more commonly associated with parkinsonism than VPA. They were also advised that in order to clinically diagnose an ADR to a medication, the withdrawal of the presumed offending agent could be attempted while monitoring closely for improvement of symptoms. Finally, they were informed of the radiopharmaceutical process

of differentiating drug-induced parkinsonism from Parkinson Disease (PD), as a DaTSCAN can identify loss of dopaminergic neurons in PD.

**Research Materials and Methods**

This project primarily consisted of a review of the patient's chart at Banner Alzheimer Institute (BAI), a literature review on the subject of the VPA and reversible neurologic symptoms, and frequent communication with the parties interested in the progress of the project (UA College of Medicine – Phoenix Scholarly Project Committees, BAI physicians, local physicians, and basic science researchers interested in studying the patient's genetic make-up). Funding was requested to analyze the mtDNA make up of this patient, as a similar patient had a mtDNA mutation identified[3]. Unfortunately the funding available for this ancillary project was insufficient and genetic studies were never performed.

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[26]. 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 or less)". This patient scored a 6, indicating that this was a probable ADR **(see table 1)**. This evidence supported the clinical suspicion that this was indeed an ADR to VPA.

NPH was considered to be the most likely diagnosis after the initial history and physical was performed by the clinical staff at BAI and the MRI of the patient was reviewed. To monitor the patient's enlarged lateral ventricles vs. hydrocephalus ex-vacuo, MRI studies were performed. After reviewing the literature, it was noted that enlargement of the ventricles and cortical pseudoatrophy are sometimes seen in VPA ADR patients[3,4,11,13,18,20,23]. To objectively evaluate the possible resolution of the patient's MRI findings, a radiologist blinded to the clinical history performed ventricular measurements. P-values were calculated by comparing the measurements of MRI ventricle size done during VPA therapy

## Table 1 – Naranjo ADR Questionnaire

| Naranjo Questionnaire | Answer | Point values possible | This patient's value |
|---|---|---|---|
| **Are there previous conclusive reports on this reaction?** | Yes | Yes = +1<br>No = 0<br>Do not know = 0 | +1 |
| **Did the ADR appear after the suspected drug was given?** | Yes | Yes = +2<br>No = -1<br>Do not know = 0 | +2 |
| **Did the ADR improve when the drug was discontinued or a specific antagonist was given?** | Yes | Yes = +1<br>No = 0<br>Do not know = 0 | +1 |
| **Did the ADR appear when the drug was readministered?** | Do not know | Yes = +2<br>No = -1<br>Do not know = 0 | 0 |
| **Are there alternative causes that could have caused the ADR?*** | Do not know | Yes = -1<br>No = +2<br>Do not know = 0 | 0 |
| **Did the ADR reappear when a placebo was given?** | Do not know | Yes = -1<br>No = +1<br>Do not know = 0 | 0 |
| **Was the drug detected in any body fluid in toxic concentrations?** | No | Yes = +1<br>No = 0<br>Do not know = 0 | 0 |
| **Was the ADR more severe when the dose was increased or less severe when the dose was decreased?** | Yes | Yes = +1<br>No = 0<br>Do not know = 0 | +1 |
| **Did the patient have a similar ADR to the same or similar drugs in any previous exposure?** | No | Yes = +1<br>No = 0<br>Do not know = 0 | 0 |
| **Was the ADR confirmed by any objective evidence?** | Yes | Yes = +1<br>No = 0<br>Do not know = 0 | +1 |

***The question "Are there alternative causes that could have caused the ADR?" is reported to be the question with the most disagreement among raters. Since many of the alternative causes were ruled out with testing, it is possible that some raters would have responded 'No'. Conversely, there are other individuals that may have responded 'Yes' as the patient was started on citalopram at the same time indicating that pseudodementia could have accounted for cognitive changes. Also, after CVA, citalopram has shown to improve motor function in a study[29], which is a remote possibility that could have account for the improved gait in our patient. Negative large volume LP also does not definitively rule out normal pressure hydrocephalus. Regardless of the decision to choose 'Yes', 'No', or 'Don't know' on this particular question the patient's final score would remain in the 5-8 range, indicating that the ADR was "probable".**

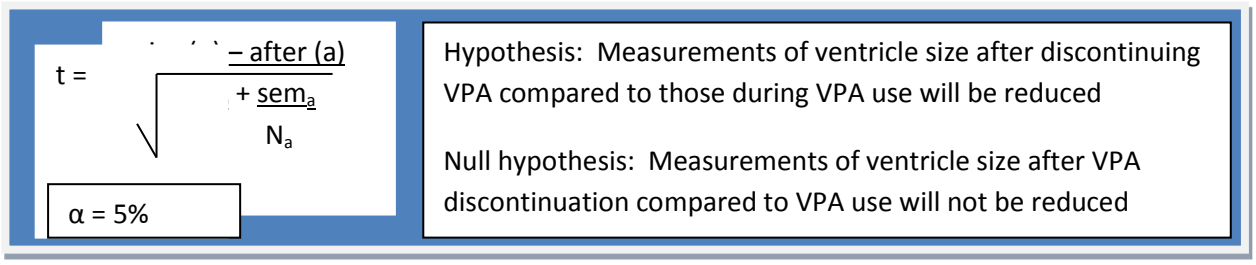
compared to MRI ventricle measurements done after VPA had been discontinued **(see table 2).** A two-tailed t-test was used to calculate significance and an alpha value of 5% was chosen **(see figure 1).**

## Table 2 – MRI measurements and calculated statistical p-values

| Time of MRI | 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 |
| ***Mean** prior **data*** | *42.167* | *40.533* | *79.767* | *79.3* |
| **4 months** after | 43.5 | 41.4 | 78.2 | 80.4 |
| **p-value (fig. 1)** | 0.28662 | 0.83238 | 0.66945 | 0.73234 |

Ventricular measurements before and after cessation of VPA. **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.

## Figure 1 – Statistics: two-tailed t-test



**Case Report and Results**

A 67-year-old woman saw her neurologist because she had recently had a seizure-like episode and developed increasing difficulty with cognitive tasks, worsening gait, and urinary incontinence. She had been seizure-free for more approximately 15 years prior to this. Her previous MRI brain scan showed central white matter volume loss, mildly diffuse cerebral and cerebellar volume loss without lobar preference, and prominence of the lateral ventricles relative to the cortical sulci. The radiologist's impression was age-appropriate senescent changes with mild prominence of the lateral ventricles, and he could not exclude NPH. Her general neurologist increased her dose of VPA due to her recent seizure-like activity, and she was then referred to the BAI memory disorders clinic by the neurologist for a second opinion. All clinical care, physical examinations, and large volume LP procedures were performed by the medical staff at BAI.

A complete history and physical examination produced additional subjective data and objective findings. The patient reported significant decline in her normal functioning in her occupation and her personal life. Some of her complaints included forgetting the day of the week, leaving her car running after arriving to work, misplacing items, generalized disorganization, loss of muscle strength and a progressively deteriorating "slowed and shuffling walk", difficulty parking her car, inability to drive due to concerns about seizures and her overall condition, lack of energy, and depression. Her medical history was significant for hypothyroidism, hypertension, gastroesophageal reflux disease, osteoporosis, and a seizure disorder that was diagnosed in the 1970's. The patient has suffered urinary incontinence for the past 2 years as well.

The general physical examination was unremarkable, but the neurological examination was abnormal. The patient exhibited decreased bilateral hearing to finger rub despite using hearing aids. Her bilateral iliopsoas muscles had give-way weakness and her gait was somewhat abnormal with outwardly rotated feet and a mildly wide-based stance.

She exhibited a right palmomental reflex. The patient did not have a tremor. She scored a 27/30 on the MMSE, and all three of her errors were related to recall memory. Although this score is normal, the patient met criteria for dementia due to her progressive decline in occupational functioning for cognitive reasons. Based on her clinical history, a large volume spinal tap and neuropsychological testing were done to pursue the working diagnosis of NPH.

In the time between the initial visit and the lumbar puncture, the patient reported her symptoms were worsening. The patient tolerated the lumbar puncture, although she did develop a headache during the procedure. Her intracranial pressure was normal while supine at 15 cm of water. When the headache was reported, 29 ml of clear CSF had been removed. There was an insignificant, equivocal improvement in gait and cognition after the procedure **(see table 3)**. Due to the equivocal results, the decision to place a shunt to treat NPH was delayed and the patient was referred to be seen at a NPH specialty clinic for further evaluation.

The laboratory data obtained from the patient's CSF are shown **(see table 4)**. The results showed no evidence of infection, hyperammonemia, or neurologic disease. The CSF was also sent in for testing of Alzheimer Disease (AD) biomarkers, but the results were not consistent with AD. Interestingly, her levels of P-tau, T-tau, and AB42 in the AD biomarker workup were consistent with idiopathic NPH[27].

The patient began a physical therapy regimen three times per week to treat her gait abnormality and lower extremity weakness. Her progress notes, along with those documented at the memory disorders clinic, are summarized in a table **(see table 5)**. Two months after the first visit, the patient presented for a follow up at the memory disorders clinic. She had stopped working completely due to subjective worsening of her condition; but, objectively, her condition was stable and similar to her first visit. Results from neuropsychological testing were received, and a "markedly slow speed of mental

**Table 3 - Neuropsychological testing and gait evaluations pre- and post-LP**

| Results | **Time** | **Turns** | **Distance** | **Gait** | **MOCA*** |
|---|---|---|---|---|---|
| **Before LP** | Walked for 27 seconds | 10 | 51-53 ft | Magnetic type, mild | 18/30 |
| **After LP** | Walked for 27 seconds | 15 | 48-49 ft | Magnetic type, mild | 21/30 |

| MOCA Score Breakdown | **Visuospatial/executive** | | **Naming** | **Attention** | **Language** |
|---|---|---|---|---|---|
| **Total before LP = 18** | 4/5 | | 3/3 | 4/6 | 1/3 |
| **After LP = 21** | 3/5 | | 3/3 | 6/6 | 2/3 |
| | **Abstraction** | Memory | Recall | Orientation | |
| | **0/2** | 0/0 | 0/5 | 6/6 | |
| | **1/2** | 0/0 | 0/5 | 6/6 | |

*MOCA = Montreal Cognitive Assessment

**Table 4 - Laboratory data**

| Test | In range value | Reference | Mean ± SD values of idiopathic NPH patients[27] |
|---|---|---|---|
| **Protein, CSF** | 31 mg/dl | 15-45 mg/dl | |
| **Glucose, CSF** | 55 mg/dl | 40-70 mg/dl | |
| **Oligoclonal bands IgG, CSF** | Multiple bands in CSF and serum | No bands | |
| **IgG Synthesis rate/index** | Unremarkable | Unremarkable | |
| **Diff, CSF (color)** | Colorless | Colorless | |
| **Diff, CSF (appearance)** | Clear | Clear | |
| **Diff, CSF (WBC)** | 0 | 0-5 /mm3 | |
| **Diff, CSF (RBC)** | 0 | None /mm3 | |
| **Gram stain, CSF** | No WBC or organisms seen | No abnormalities | |
| **Culture** | No growth | No growth | |
| **Ammonia** | 30 µmol/L | 11-35 µmol/L | |
| **AB42** | 491.4 pg/ml | See ATI | 503 ± 103 |
| **T-Tau** | 143.35 pg/ml | See ATI | 171 ± 68 |
| **P-Tau** | 32.35 pg/ml | < 61 pg/ml | 33 ± 10 |
| **ATI (ratio that accounts for AB42 and T-Tau)** | 1.20 | > 1.0 | |

## Table 5 – Patient's symptoms and recovery progress

| General date/time | Able to drive ? | Able to work ? | Tinetti score* (risk of falls) | Objective* improvement? /Subjective* improvement? | Depression? | Urinary incontinence | Gait | Cognition (MMSE) |
|---|---|---|---|---|---|---|---|---|
| **Initial visit** | No | Yes | 14/28, high fall risk | N/A | Yes | Yes | Wide-based, Outwardly rotated feet | Mild changes in cognition (27) |
| **First follow up visit** | No | No | 23/28, moderate fall risk | yes/no | Yes | Yes | Mildly wide-based, some LE external rotation | No change |
| **‡** | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ |
| **Second follow up visit** | Yes | Yes | 26/28, low fall risk | yes/yes (50% improvement reported by pt) | No | Somewhat improved | Relatively normal gait | Husband states - improved |
| **Deferment of care** | Yes | Yes | 27/28, low fall risk | yes/yes (90% improvement reported by pt) | No | Urinary incontinence persists | Normal | Normal, no cognitive deficits |

*Data from physical therapy center notes

‡At this point, VPA was stopped. Patient was started on levetiracetam and citalopram.

information processing" reported by the psychologist supported the working diagnosis of NPH. The patient was given a referral for possible depression and a PET scan was ordered to see if the pattern was consistent with AD or frontotemporal dementia (FTD). As an afterthought, the patient was contacted and instructed to taper off VPA and start on Levetiracetam. This decision was made after searching for clinical guidance from the literature[2,3,4]. The patient was also started on citalopram for her depressed mood.

A month after discontinuing VPA, the PET scan results were received and revealed decreased metabolic activity in the periventricular region bilaterally, more pronounced on the right side. There was also decreased metabolic activity on the right anterior parietal region, a few scattered areas of decreased metabolic activity in the frontal region on the right side, and very small metabolic activity decreases noted on the left anterior and left frontal regions. It was also again noted that the ventricles appeared enlarged. These patterns of metabolic abnormality did not fit the typical patterns of AD or FTD**.** AD typically shows hypometabolism in the posterior temporoparietal association cortex and the posterior cingulated cortex while FTD typically shows hypometabolism in the frontal lobes, the anterior temporal cortex, and the anterior cingulate cortex[28]. Also around this time, significant improvement was reported by the physical therapy facility. Similar improvement was noted a few weeks later during the patient's second follow up visit.

When the patient presented at the NPH clinic she was referred to, the physician performed a complete history and physical. Her gait was essentially normal, cognition good, and physical examination unremarkable. It was determined that she had such remarkable improvement that she would not be candidate for shunt placement. A final MRI was taken approximately two months later to monitor treatment. Compared to the MRI performed just prior to the patient's initial visit, the patient's left and right lateral ventricles both decreased in size; however, the width of the anterior and posterior horns increased in size slightly. The cortical atrophy mentioned in the previous MRI was no longer noted. The reduction of lateral ventricle size did not reach statistical significance.

Currently, the patient remains cognitively normal without gait disturbance over 3 years after discontinuing VPA. She describes the 15 years that she was on VPA as a period of her life in which she was recognizably more impaired in her cognition. She states that her friends say that they have the "old her" back. Her ability to complete her activities of daily living has improved significantly. Her urinary symptoms never improved and are likely related to an unrelated diagnosis of stress incontinence. In the 3 years since her discontinuation of VPA, she has had multiple episodes of TIA and has been referred to a vascular neurologist to work up her underlying atherosclerosis. It is unlikely that her vascular disease contributed to the reversible cognitive decline and gait disturbance reported in this paper.

**Discussion**

Likely most widely considered the recognized cause of neuropsychiatric changes related to Valproate use is hyperammonemic encephalopathy. Valproate-induced encephalopathy has also been considered to be the pathophysiology of neuropsychiatric changes even in patients without hyperammonemia. Valproyl-CoA directly inhibits NAG to cause hyperammonemia which leads to elevations of glutamine levels and decreased levels of myoinositol levels in the brain. In examining deadly toxic overdoses with VPA the fatal complication is usually cerebral edema, likely secondary to the increased glutamine that increases intracellular osmolarity and results in astrocyte swelling[24].

An alternative proposed mechanism of the cognitive decline seen in these patients is a mtDNA mutation. Since VPA enters mitochondrial metabolic pathways, a clinically silent mutation could become overt when a new drug or metabolite is introduced. There is clinical evidence of MELAS (a mtDNA inherited disease) being triggered by VPA therapy[30]. One case with similar clinical and imaging findings found a mtDNA mutation in the patient that was absent in 101 control subjects[3]. This would explain the idiosyncratic nature of this poorly documented drug side effect. Also, since mtDNA mutations are heteroplasmic it would explain the highly variable clinical timeline of symptom appearance in these patients. Heteroplasmy describes a phenomenon in which some or many copies of mtDNA can be affected by a mutation, which is supported by the finding that symptom onset in this condition can range from weeks (higher frequency of mtDNA mutation) to years to decades (lower frequency of mtDNA mutation). It is possible that this patient's hearing loss, poor vision, and epilepsy are all related to an undiagnosed mtDNA mutation syndrome since these are all common features. The patient's mother and her maternal uncle both had epilepsy and also decreased hearing requiring hearing aids at a young age, which increases the suspicion of mtDNA mutations as they follow maternal inheritance patterns. However, the suspicion of a mtDNA mutation was not pursued and no genetic studies were performed. The lack of genetic studies is the major limitation of this study. It is also

impossible to diagnose a mtDNA mutation clinically since symptoms among these types of diseases are extremely variable and significant overlap does occur. It has been reported that reversible valproate-induced sensorineural hearing loss can occur[31], although our patient's hearing did not improve.

GABA pathway disturbance leading to dopamine inhibition has also been hypothesized[16]. Evidence indicates that GABA mediates dopaminergic function in the substantia nigra[32]. 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 itself[33], may cause a transient inhibitory effect on dopaminergic pathways.

A novel mechanistic explanation has been presented after a cellular study involving VPA's action on neuroblastoma cells produced results strikingly similar to the reversible nature of valproate-induced cognitive decline. The study showed that VPA reduced neurite outgrowth and also reduced cell proliferation during part of the treatment. This inhibitory effect on neurons was completely reversed two days after VPA treatment was ceased[34]. The reversible inhibition after VPA exposure of these neural cells is very similar to the reversible cognitive decline in these types of patients, and it also aligns well with the common neuroimaging findings of pseudoatrophy.

In summary, our patient gradually developed dementia symptoms and a mild gait disturbance after 15 years of VPA use for a generalized seizure disorder. About two months after discontinuation of VPA, her cognition and gait returned to normal. On brain MRI there appears to be a trend of enlarging ventricles while on VPA, and reduction after VPA cessation but this trend did not reach statistical significance. Because the reversal of cognitive decline and gait disturbance occurred shortly after discontinuing Valproate, a Valproate-induced syndrome is the likely cause of symptoms in our patient. This is supported by a Naranjo adverse drug reaction score of 6, which makes the patient's symptoms attributable to VPA "probable". Although it is generally considered a safe

medication, there are many reports of patients developing reversible cognitive decline and reversible Parkinsonism while taking Valproate. This patient illustrates an interesting case of Valproate-induced cognitive decline and gait changes similar to many of the previously published case reports[2-22]. However, this case also contributes two novel nuances to the literature: the development of symptoms after a prolonged 15 year exposure to VPA and the clinical picture more fitting of NPH than parkinsonism.

**Future Directions**

This patient's clinical features suggest that the underlying defect was likely of genetic and, more specifically, of mtDNA origin. A case series of similar patients with reversible valproate-induced neurologic effects could be studied and their mtDNA could be analyzed. If genetic studies cannot be done, the case series patients could be asked about other symptoms of mtDNA disease, such as epilepsy, sensorineural hearing loss, myopathy, and other mtDNA associated neurologic symptoms that follow a maternal inheritance pattern. If the reported frequency is high enough, it would be wise to formally study the mtDNA of these patients to better understand the genetics of this pathophysiology.

## Conclusions

This patient serves as an example that the potential adverse effects of Valproate can cause reversible neurological symptoms even in long-term treated patients. Due to this patient's complicated and unique clinical presentation, it is important that clinicians be aware of how valproate-induced gait disturbance and dementia can masquerade as parkinsonism, toxic encephalopathy, Alzheimer disease, normal pressure hydrocephalus, and other neurologic diseases. Recognizing this clinical scenario may allow clinicians to relieve a patient's worry of neurodegenerative disease etiology, avoid recommending unnecessary surgeries or treatment, and, most importantly, reverse the condition.

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**Appendix – Case report published in 2011**

Seizure

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# Reversible dementia and gait disturbance after prolonged use of valproic acid

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ABSTRACT

**Valproic acid (VPA) has been reported to cause cognitive decline and parkinsonism that are reversed with cessation of medication. Common imaging findings among these reports demonstrate reversible cortical pseudoatrophy and enlargement of the lateral ventricles. This case exemplifies these adverse effects of VPA which can cause reversible neurological symptoms even in long-term treated patients and can present as dementia syndromes such as normal pressure hydrocephalus.**



## 1. Introduction

Although VPA is generally considered a safe medication in the elderly,[1] there are previous reports of patients developing reversible cognitive decline or reversible parkinsonism, often both.[2–22] Common imaging findings among these reports are reversible cortical pseudoatrophy and enlargement of the lateral ventricles.[3,4,11,13,18,20,23] Here we describe an epilepsy patient treated with VPA for 15 years who presented to a Memory Disorders Clinic to be evaluated for normal pressure hydrocephalus due to a cognitive decline, gait changes, urinary incontinence, and ventriculomegaly on brain imaging. All clinical symptoms were reversed with cessation of VPA.

## 2. Case report

A 65-year-old woman with a generalized seizure disorder which began at age 25 presented to a Memory Disorders Clinic complaining of confusion. Medical records from the time of epilepsy diagnosis could not be obtained to further characterize her seizure type. After her first seizure she was treated with phenytoin for two years and subsequently had trials of monotherapy with Phenobarbital and carbamazepine. Since valproic acid (VPA) was initiated approximately at age 50 she has been seizure-free with an average daily dose of 1 g. No attempts of VPA discontinuation were made. At age 63, she gradually developed a gait disturbance, urinary incontinence, and worsening cognitive impairment that began affecting her normal functioning in her occupational and personal life over a two year period. Formal cognitive testing displayed significantly impaired memory ability as well as impaired executive function, visual perception, and a markedly slowed speed of mental information processing with intact language abilities. The remainder of her neurological examination was normal except for a moderately slow wide-based gait with bilateral outward foot rotation requiring use of a walker.

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 that started in his early 60s.

VPA blood levels were stable (78–85 mg/mL) and within the therapeutic range. An ammonia level was normal (30 mmol/L). 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 benefit gait or cognitive measures. During the procedure the patient developed a severe positional headache. CSF studies were normal with no evidence of infection or inflammation. CSF levels of Aβ42 (491.4 pg/mL) and phosphorylated-tau (32.35 pg/mL) were not consistent with Alzheimer's disease. An FDG PET scan revealed hypometabolism

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Table 1
Ventricular measurements before and after cessation of VPA. 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.

| 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 |

in the bilateral periventricular regions, right anterior parietal region, and few small scattered areas of decreased metabolic activity in the right frontal region. This pattern is not consistent with Alzheimer's disease.

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 reduction of ventricular size (see Table 1). On 3 out of 4 measures 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.

## 3. Discussion

Our patient gradually developed dementia symptoms and a gait disturbance after 15 years of VPA use. About two months after discontinuation of VPA, her cognition and gait returned to normal, implicating a VPA-induced syndrome. Although she also presented with urinary incontinence, it appears due to an unrelated urologic disorder.

A possible mechanistic explanation involves inhibition of neurite outgrowth. Using SY5Y neuroblastoma cells as a neuronal model, Qian et al. found that therapeutic plasma levels of VPA reduced cell proliferation and neurite outgrowth.[24] VPA also reduced mRNA and protein levels of neurofilament 160 (NF160). These effects were reversed after 2 days of cessation of VPA exposure.

GABA pathway disturbance leading to dopamine inhibition has also been hypothesized.[16] Evidence indicates that GABA mediates dopaminergic function in the substantia nigra.[25] 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,[26] may cause a transient inhibitory effect on dopaminergic pathways.

Another proposed mechanism of the reversible cognitive decline seen in these patients taking VPA is a mitochondrial DNA (mtDNA) mutation. Since VPA enters mitochondrial metabolism pathways, a clinically silent mutation could become overt when a new drug or drug metabolite is introduced.[27] 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 $\longrightarrow$ Ser mutation in the MTATP8 gene.[3] Such a mutation could explain the idiosyncratic nature of this drug side effect. Also, since mtDNA mutations are heteroplasmic, it would explain the highly variable clinical timeline of symptom appear- ance.

It is possible that our patient's hearing loss and epilepsy are all related to an undiagnosed mtDNA mutation syndrome, which is supported by the family history of idiopathic generalized seizures and hearing loss that follows a pattern of maternal inheritance. In our patient, genetic testing was not performed. VPA-induced reversible sensorineural hearing loss has also been reported,[28] but cessation of VPA had no effect on hearing in our patient.

## 4. Conclusion

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

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