Treated with a mood stabilizer, he becomes incontinent and walks oddly

Suneeta Kumari, MD, MPH, R. Sridhar, MD, and Murali Rao, MD

Mr. X, age 67, develops cognitive impairment, gait disturbance, and urinary incontinence. He has been taking valproic acid for 8 years to treat bipolar depression. What is your diagnosis?

CASE Rapid decline

Mr. X, age 67, is a businessman who had a diagnosis of bipolar depression 8 years ago, and who is being evaluated now for new-onset cognitive impairment, gait disturbance that resembles child-like steps, dyskinesia, and urinary incontinence of approximately 2 months' duration. He has been treated for bipolar depression with valproic acid, 1,000 mg/d, and venlafaxine, 150 mg/d, without complaint until now, since the diagnosis was made 8 years ago. The serum valproic acid level, tested every month, is within the therapeutic range; liver function tests, ordered every 6 months, also are within the normal range.

Mr. X has become confined to his bedroom and needs assistance to walk. He has to be lifted to a standing position by 2 attendants, who bear his weight and instruct him to take one step at a time. He wears a diaper and needs assistance shaving, showering, and getting dressed. When the treatment team asks him about his condition, Mr. X turns to his wife to respond on his behalf. He is slow to speak and struggles to remember the details about his condition or the duration of his disability.

Mr. X is referred to a neurologist, based on cognitive impairment and gait disturbance, who orders an MRI scan of the brain that shows enlarged ventricles and some cortical atrophy (***Figure 1, page 66***). A neurosurgeon removes approximately 25 mL of CSF as a diagnostic and therapeutic intervention.

Videography of his ambulation, recorded before and after the CSF tap, shows slight improvement in gait. Mr. X is seen by a neurosurgery team, who recommends that he receive a ventriculoperitoneal shunt for hydrocephalus.

While awaiting surgical treatment, Mr. X's psychotropic medications are withheld, and he is closely monitored for reemergence of psychiatric symptoms. Mr. X shows gradual but significant improvement in his gait within 8 to 10 weeks. His dyskinesia improves significantly, as does his cognitive function.

What additional testing is recommended beyond MRI?

a) complete blood count with differential
b) blood ammonia level
c) neuropsychological evaluation
d) APOE-e4 genetic testing
e) all the above

continued

Dr. Kumari is Project Manager at the Department of Psychiatry and Behavioral Sciences, Howard University Hospital, Washington, DC. Dr. Sridhar is Medical Director, Vatsalya Hospital, Mysore, India. Dr. Rao is Professor and Chair, Department of Psychiatry and Behavioral Sciences, Loyola University, Chicago, Illinois.

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How would you handle this case?

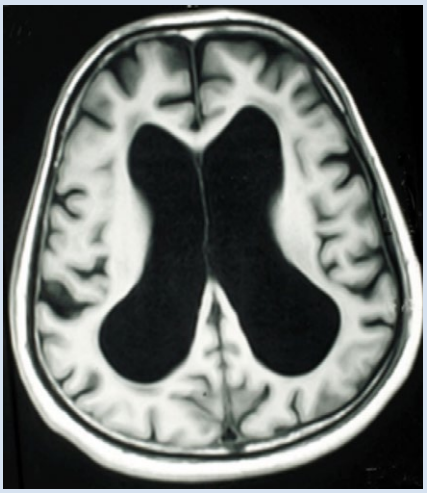
Answer the challenge questions throughout this article

Clinical Point

Although there is no one type of gait disturbance indicative of NPH, it often is described as shuffling, magnetic, and wide-based

Figure 1

Findings on MRI at current presentation



The authors' observations

Normal pressure hydrocephalus (NPH) is characterized by gait disturbance, dementia, or urinary incontinence that is associated with dilation of the brain's ventricular system with normal opening CSF pressure (***Table 1, page 68***). Several studies have reported that patients with NPH might exhibit neuropsychiatric symptoms,[1-4] possibly related to alterations in central neurotransmitter activity.[5] NPH patients could present with symptoms reflecting frontal dominance (***Table 2,***[6-9] ***page 68***). In a study of 35 patients with idiopathic NPH in a tertiary hospital in Brazil,[10] psychiatric symptoms were established by formal psychiatric evaluation in 71%, notably anxiety, depression, and psychotic syndromes.

Mechanism responsible for gait disturbance

Gait disturbance typically is the first and most prominent symptom of the NPH triad. Gait disturbance in NPH can be progressive because of expansion of the ventricular system, mainly the lateral ventricles, leading to pressure on the corticospinal motor fibers descending to the lumbosacral spinal cord. Although there is no one type of gait disturbance indicative of NPH, it often is described as shuffling, magnetic, and wide-based.[11] Slowness of gait and gait imbalance or disequilibrium are common and more likely to respond to shunting.[12]

Drug-induced gait disturbance is likely to result in parkinsonian symptoms.[13] A possible mechanism involves inhibition of neurite outgrowth. Qian et al[14] found that therapeutic plasma levels of valproic acid reduced cell proliferation and neurite outgrowth, using SY5Y neuroblastoma cells as a neuronal model. Researchers also reported that valproic acid reduced mRNA and protein levels of neurofilament 160; a possible mechanistic explanation involves inhibition of neurite outgrowth that leads to gait disturbance. These effects reversed 2 days after stopping valproic acid.

Another possible mechanism is related to γ-aminobutyric acid (GABA) pathway disturbance leading to dopamine inhibition. This postulates that valproic acid or a metabolite of valproic acid, such as Δ-2-valproate, which may be a more potent inhibitor of the GABA-degrading enzyme than valproic acid, could cause a transient inhibitory effect on dopaminergic pathways.[15]

Mechanism of mood stabilizer action

Valproic acid is incorporated into neuronal membranes in a saturable manner and appears to displace naturally occurring branched-chain phospholipids.[16] Chronic valproic acid use reduces protein kinase C (PKC) activity in patients with mania.[17] Elevated PKC activity has been observed in patients with mania and in animal models of mania.[18] Valproic acid has antioxidant effects and has reversed early DNA damage caused by amphetamine in an animal model of mania.[19] Valproic acid and lithium both

reduce inositol biosynthesis; the mechanism of action for valproic acid is unique, however, resulting from decreased myo-inositol-1-phosphate synthase inhibition.[20]

There is not a strong correlation between serum valproic acid levels and antimanic effects, but levels in the range of 50 to 150 µg/mL generally are required for therapeutic effect.

Neuropsychiatric adverse effects of valproic acid

With most antiepileptic drugs, adverse effects mainly are dose-related and include sedation, drowsiness, incoordination, nausea, and fatigue. Careful dose titration can reduce the risk of these adverse effects. Research on mothers with epilepsy has shown an association between valproic acid exposure in utero and lower IQ and a higher prevalence of autism spectrum disorder in children.[21]

Adverse effects on cognitive functioning are infrequent; valproic acid improves cognition in select patients.[22] In a 20-week randomized, observer-blinded, parallel-group trial, adding valproic acid to carbamazepine resulted in improvement in short-term verbal memory.[23] In a group of geriatric patients (mean age 77 years), no adverse cognitive effects were observed with valproic acid use.[24]

Masmoudi et al[25] evaluated dementia and extrapyramidal symptoms associated with long-term valproic acid use. Among the side effects attributed to valproic acid, parkinsonian syndromes and cognitive impairment were not commonly reported. In a prospec-

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Unusual appearances of NPH symptoms could hinder early diagnosis and proper treatment

Table 1

Essential features when considering a diagnosis of normal pressure hydrocephalus

Clinical features	• Cognitive impairment • Gait disturbance • Urinary incontinence
Diagnostic criteria	• CSF normal opening pressure • MRI changes: Dilation of ventricular system with or without cortical changes • Reversal of neurological complications after CSF tap
Differential diagnosis	• Age-related major neurocognitive disorder (Alzheimer's dementia) • CNS infection • Drug interaction • Intracranial neoplasm • Parkinson's disease • Valproic acid-induced encephalopathy

Table 2

Signs and symptoms of frontal dominance in normal-pressure hydrocephalus

Aggression
Anxiety
Delusional states
Depression
Hallucinations
Mania
Obsessive-compulsive disorder
Othello syndrome[a]
Personality changes
Psychotic syndromes
Shoplifting

[a]A content-specific delusion characterized by the fixed false belief that one's partner has been or is unfaithful

Source: References 6-9

tive study, Armon et al[26] found several abnormal symptoms and signs related to motor and cognitive function impairment in patients on long-term valproic acid therapy. These side effects might be related to a disturbance in the GABAergic pathways in the basal ganglia system. Note that Δ2-valproic acid, a metabolite of valproic acid, preferentially accumulates in select areas of the brain: the substantia nigra, superior and inferior colliculus, hippocampus, and medulla.

What is the next best step in management?

a) surgically implant a shunt
b) adjust the dosage of valproic acid
c) switch to monotherapy
d) switch to an alternative psychotropic medication
e) provide observation and follow-up

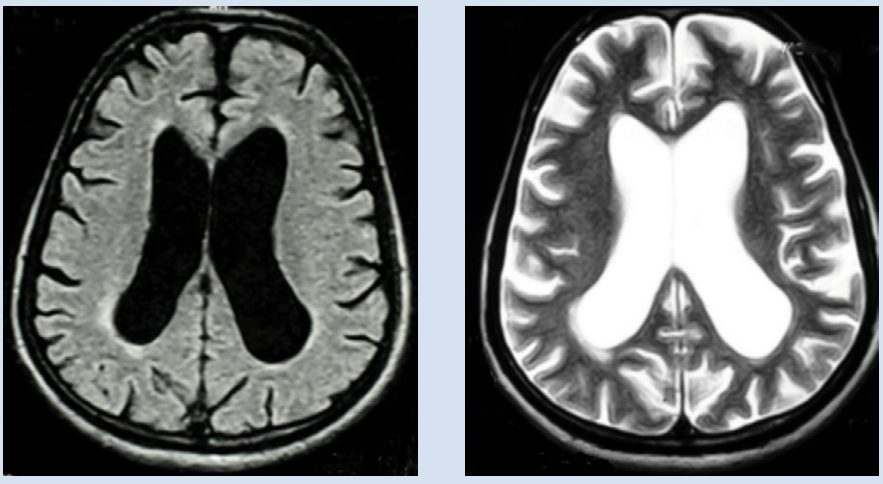
The authors' observations

Unusual appearances of NPH symptoms could hinder early diagnosis and proper treatment. Mr. X was taking valproic acid and venlafaxine for bipolar depression, without any complaints, and was asymptomatic for 8 years—until he developed symptoms of NPH.

In patients who have what can be considered classic symptoms of NPH and are taking valproic acid, consider discontinuing the drug on a trial basis before resorting to a more invasive procedure. This strategy could significantly reduce the cost of health

Figure 2

Findings on the patient's past MRI scans



MRI was performed 6 years earlier (left) and 10 years earlier (right)

care and contribute to the overall well-being of the patient.

NPH associated with chronic valproic acid use is rare, supported by only 1 case report[13] in our literature review. Based on the severity of symptoms and chance for misdiagnosis, it is essential to identify such cases and differentiate them from others with underlying neuropathology or a secondary cause, such as age-related dementia or Parkinson's disease, to avoid the burden of unnecessary diagnostic testing on the patient and physician.

Family history also is important in cases presenting with sensorineural hearing loss,[13] which follows a pattern of maternal inheritance. Consider genetic testing in such cases.

Earlier diagnosis of valproic acid-induced NPH enables specific interventions and treatment. Treatment of NPH includes one of several forms of shunting and appropriate neuroleptic therapy for behavioral symptoms. Although there is a significant risk (40% to 50%) of psychiatric and behavioral symptoms as a shunt-related complication, as many as 60% of operated patients showed objective improvement. This makes the diagnosis of NPH, and referral for appropriate surgical treatment of NPH, an important challenge to the psychiatrist.[27]

OUTCOME No reemergence

Findings on a repeat MRI 2.5 months after the CSF tap remain unchanged. Surgery is cancelled and medications are discontinued. Mr. X is advised to continue outpatient follow-up for monitoring of re-emerging symptoms of bipolar depression.

At a follow-up visit, Mr. X's condition has returned to baseline. He ambulates spontaneously and responds to questions without evidence of cognitive deficit. He no longer is incontinent.

Follow-up MRI is performed and indicated normal results.

Neuropsychological testing is deemed unnecessary because Mr. X has fully recovered from cognitive clouding (and there would be no baseline results against which to compare current findings). Based on the

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Treatment of NPH includes one of several forms of shunting and appropriate neuroleptic therapy for behavioral symptoms

medication history, the team concludes that prolonged use of valproic acid may have led to development of signs and symptoms of an NPH-like syndrome.

The authors' observations

Awareness of an association of NPH with neuropsychiatric changes is important for clinical psychiatrists because early assessment and appropriate intervention can prevent associated long-term complications. Valproic acid is considered a relatively safe medication with few neurologic side effects, but the association of an NPH-like syndrome with chronic valproic acid use, documented in this case report, emphasizes the importance of studying long-term consequences of using valproic acid in geriatric patients. More such case reports need to be evaluated to study the association of neuropsychiatric complications with chronic valproic use in the geriatric population.

Mr. X apparently had cerebral atrophy with enlarged ventricles that was consistently evident for 10 years (***Figure 2, page 69***), although he has been maintained on valproic acid for 8 years. What is intriguing in this case is that discontinuing valproic acid relieved the triad of incontinence, imbalance, and memory deficits indicative of NPH. Mr. X remains free of these symptoms.

Clinical Point

Early assessment of neuropsychiatric changes with NPH and appropriate intervention can prevent long-term complications

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Related Resources

- National Institute of Neurological Disorders and Stroke. NINDS Normal Pressure Hydrocephalus information page. http://www.ninds.nih.gov/disorders/normal_pressure_hydrocephalus/normal_pressure_hydrocephalus.htm.
- Israelsson H, Allard P, Eklund A, et al. Symptoms of depression are common in patients with idiopathic normal pressure hydrocephalus: the INPH-CRasH Study. Neurosurgery. 2016;78(2):161-168.

Drug Brand Names

Carbamazepine • Tegretol
Lithium • Eskalith, Lithobid
Valproic acid • Depakene
Venlafaxine • Effexor

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Clinical Point

It is intriguing that discontinuing valproic acid relieved the triad of incontinence, imbalance, and memory deficits that is indicative of NPH

Bottom Line

Identifying signs and symptoms of normal pressure hydrocephalus (NPH) and implementing effective treatment can be challenging. Psychiatric symptoms are common in the context of idiopathic NPH—making it crucial for psychiatrists to (1) evaluate patients who have symptoms of NPH while taking valproic acid therapy and (2) identify atypical cases through neuroimaging.