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Vestibular signs of thiamine deficiency during the early phase of suspected Wernicke encephalopathy

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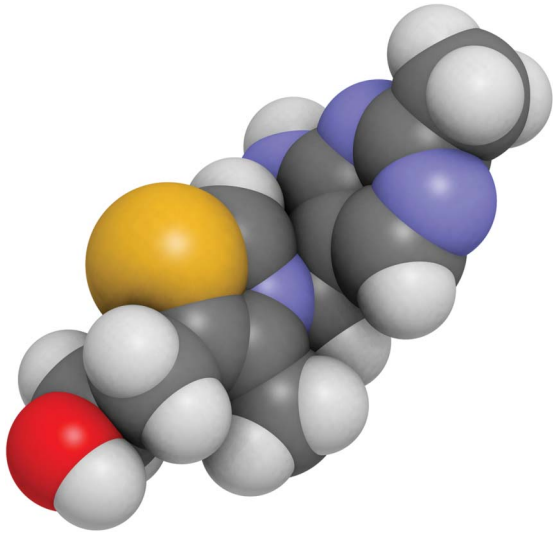
Summary

Non-encephalopathic presentations of CNS thiamine deficiency may be difficult to diagnose. We describe neuro-otologic findings of Wernicke syndrome in 5 patients with vestibular manifestations. Diagnosis was confirmed by low serum levels, response to replacement, and brain MRI to exclude other causes. All had bilaterally abnormal horizontal head impulse vestibulo-ocular reflex (VOR) responses and pathologic gaze-evoked nystagmus, without encephalopathy. After thiamine replacement, 4 had total resolution of vestibular and oculomotor findings. Novel findings included 2 patients whose VOR function improved within minutes of IV repletion and 1 whose recovery was documented by serial quantitative recordings. Early diagnosis of Wernicke by examining vestibular reflexes and prompt IV treatment might prevent encephalopathy and other neurologic or systemic complications of thiamine depletion.



The complete Wernicke encephalopathy triad includes ophthalmoplegia, ataxia, and encephalopathy. In their seminal 1971 study, Victor, Adams, and Collins[1] defined the clinical presentation and neuropathology of classic Wernicke in 232 cases. Altered mental status was present in 90%. Ocular findings were noted in 96% (228/232). Nystagmus was the most common ocular finding (87%, 198/228), and

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horizontal, bilateral gaze-evoked nystagmus the most common form, occurring in 97% (192/198). This form of nystagmus suggests failure of the oculomotor pathways for horizontal gaze-holding.[2] Nystagmus was the only ocular feature in 65% (151/232). Vestibular reflexes were not tested clinically, as the bedside head impulse test of vestibulo-ocular reflex (VOR) function was not described by Halmagyi and Curthoys[3] until 1988. Depending on the direction of the head impulse applied, this test can assess each component of the VOR,[4] including the horizontal VOR (h-VOR) and vertical VOR (v-VOR) canal plane responses. These tests can now be readily applied to patients with thiamine deficiency at the bedside.

In animal models of thiamine deficiency, bilateral, symmetric lesions of the vestibular nuclei are a consistent finding.[5] The most common human vestibular finding in Wernicke is bilateral vestibular hypofunction, occurring in 54/60 (90%) of previously reported cases.[6–9] Although some of these apparently had normal mentation,[7] most had comorbid encephalopathy.[6,8,9] In the only 2 prior reported cases where high-acceleration bedside head impulse testing was performed, it revealed dissociated h-VOR deficits localizing to the horizontal semicircular canal afferents (presumably within the brainstem vestibular nuclei), leaving v-VOR responses unaffected.[9] It appears VOR recovery may take weeks to months after IM followed by oral thiamine repletion.[6] We report rapid improvement of the VOR gain after high-dose, IV thiamine treatment.

Vestibular findings in the pre-encephalopathy phase, despite their potential value to assist early diagnosis and enable early treatment before severe neurologic morbidity occurs, are not widely known. We sought to report our experience with 5 nonencephalopathic, thiamine-deficient patients presenting with predominantly vestibular symptoms and signs, including 2 novel clinical findings: a patient who presented with a central mimic of an acute peripheral vestibulopathy (pseudo-neuritis[10]) and 2 patients with dramatic and immediate resolution of h-VOR deficits in response to high-dose IV thiamine repletion.

METHODS

We conducted a retrospective chart review of 5 cases of thiamine deficiency presenting with vestibular findings to a single center (July 2008–October 2011). The study was approved by the University of Illinois College of Medicine at Peoria Institutional Review Board. All patients underwent clinical neurologic, neuro-ophthalmologic, and neurovestibular evaluation. VOR testing was performed by clinical head impulse testing in all 5, by video-nystagmography during caloric testing in 2, and by video head impulse testing[11] in 1. The h-VOR response to high-dose IV thiamine was tested in 3 patients. Testing was incomplete because of the acute nature of the illness. Serum thiamine, folate, and vitamin B_{12} levels were measured. Brain MRI (with/without contrast enhancement) was obtained in all 5 patients within 24 hours of initial examination. Final diagnoses were confirmed by low or borderline serum thiamine levels, normal B_{12} levels, response to therapy, and exclusion of other diagnostic possibilities. All patients were followed for at least 3 months post treatment.

RESULTS

Patient demographic and clinical features are listed in the table. All 5 were at high risk for nutritional deficiency. No patients were taking metronidazole, which may produce a syndrome

Table Clinical characteristics of 5 patients with nonencephalopathic vestibular Wernicke syndrome

Case	Presumed etiology	Age, y/ sex/race	Symptoms	VOR responses[a]	Nystagmus[b]	Gait/ limb ataxia	Other nonvestibular features	Thiamine, nmol/L (normal 87–280)	Folate, ng/mL (normal 7.2–15.4)	MRI results and timing after symptom onset
1	Chronic alcoholism	55/M/C	Mild gait unsteadiness; falls; decreased visual acuity; oscillopsia	Bilaterally abnormal h-HIT; hypoactive caloric VORs (slow phases <5°/s)	Bilateral horizontal gaze-evoked; no vertical gaze evoked; no rebound	Mild/ absent	Bilateral optic neuropathy; decreased visual acuity; ceco-central scotomas	69	6.8	Normal; 4 weeks
2	Chronic alcoholism	50/F/C	Acute vertigo with severe nausea, vomiting; considerable postural instability and gait unsteadiness	Bilaterally abnormal h-HIT; normal v-HIT; hypoactive caloric VORs (slow phases <5°/s)	Bilateral horizontal gaze-evoked; no vertical gaze evoked; no rebound	Severe/ absent	None	88	2.9	Normal; 72 hours
3	Gastric bypass with prolonged vomiting (5 months post); weight loss 157 lb	39/F/C	Severe vomiting; diplopia; oscillopsia	Bilaterally abnormal h-HIT	Bilateral horizontal gaze-evoked; no vertical gaze evoked; no rebound	ND (leg edema)/ absent	Left abducens paresis; lower extremity lymphedema (no heart failure)	30	2.4	Abnormal (midline brainstem, thalamic FLAIR/T2 hyperintensities); 5 days
4	Gastric bypass with prolonged vomiting (3 months post); weight loss 150 lb	60/M/C	Mild gait unsteadiness; mild diplopia at distance left; oscillopsia	Borderline abnormal bilateral h-HIT (subtle refixations, obvious deficit by VOG); normal v-HIT	Bilateral horizontal gaze-evoked; no vertical gaze evoked; no rebound	Mild/ absent	6 prism diopter esotropia	21	8.5	Normal; 72 hours
5	Gastric bypass with prolonged vomiting (4 months post); weight loss 120 lb	37/F/C	Severe postural instability and gait unsteadiness, falls (walks only with walker); oscillopsia	Bilaterally abnormal h-HIT; borderline abnormal upward v-HIT	Downbeating in primary gaze; oblique down-right in right gaze and oblique down-left in left gaze	Severe/ absent	None	55	ND	Abnormal (periventricular hemispheric FLAIR/ T2 hyperintensities, presumed incidental); 2 months

Abbreviations: C = Caucasian, non-Hispanic; FLAIR = fluid-attenuated inversion recovery; h-HIT = horizontal head impulse test; ND = not done; v-HIT = vertical head impulse test; VOG = video-oculography; VOR = vestibulo-ocular reflex.

[a] v-HIT VOR responses were only tested in cases 2, 4, and 5; caloric VOR responses were only tested in cases 1 and 2.

[b] Bilateral, horizontal, gaze-evoked nystagmus (also called direction-changing horizontal gaze-evoked nystagmus, i.e., right-beating in right gaze, left-beating in left gaze) is a sign of failure of gaze-holding mechanisms localized to the brainstem or cerebellum.[2] It can occur with unilateral acute central lesions[21] (in which case it is often asymmetric), but is most commonly seen with bilateral central lesions (in which case it is typically symmetric). Some patients with gaze-holding failure also have rebound nystagmus (nystagmus that beats one direction in eccentric gaze and briefly reverses direction on return to straight-ahead gaze) or vertical gaze-evoked nystagmus (upbeat in upgaze and downbeat in downgaze). In patients with lesions causing gaze-holding failure, involvement of additional pathways may also lead to spontaneous vertical (upbeat or downbeat) nystagmus in straight-ahead gaze. In such cases, an oblique nystagmus may appear in lateral gaze as a combination of spontaneous and gaze-evoked components.

similar to Wernicke.[12] All patients had normal orientation and sensorium, had a normal Mini-Mental State Examination score (30/30), and were able to provide a coherent medical history and cooperate with the neurologic examination. One presented with an acute vestibular syndrome characterized by acute, persistent, vertigo, with severe vomiting and gait ataxia for 48 hours, mimicking vestibular neuritis or stroke (case 2). The others presented with subacute, progressive symptoms dominated by postural instability (difficulty standing), gait unsteadiness, falls, and oscillopsia. Case 3 had severe lymphedema precluding examination of posture and gait.

Pathologic horizontal gaze-evoked nystagmus (right-beating in right gaze and left-beating in left gaze) and bilaterally abnormal horizontal head impulse tests were found in all 5 patients. In 3 where v-VOR responses were tested (cases 2, 4, 5), 2 (cases 2, 4) clearly had dissociated loss of h-VOR function with spared v-VOR function (video 1 at Neurology.org/cp). One patient (case 5) with primary gaze downbeat nystagmus appeared clinically to have decreased upward VOR gain; however, without quantitative analysis, this might simply have reflected a normal downward nystagmus fast phase. Brain MRI performed when the patients were first examined was normal in 3 patients (cases 1, 2, 4). Case 3 had areas of increased fluid-attenuated inversion recovery/T2 signal in the midline thalami, upper midbrain, and pons, consistent with Wernicke. Case 5 had nonspecific hemispheric leukoaraiosis.

Video
neurology.org/cp

We suspected thiamine deficiency in all 5 patients; 2 had a history of chronic alcoholism. Two bypass patients had a duodenal switch (case 3, 5 months, and case 4, 3 months prior to the clinical onset of thiamine deficiency). In 1 bypass patient (case 5), we had no detailed record of the specific surgical procedure performed 4 months prior to presentation. Weight loss ranged from 120 to 157 pounds. Case 3 had a 10-day history of daily, frequent vomiting due to a postprocedure stomach kink before the onset of neurologic symptoms. Case 4 had nausea and vomiting right after the procedure, which he attributed to the vitamin supplements he was prescribed, so he chose to discontinue taking the supplements. Case 5 had recurrent, frequent vomiting beginning 1 month after the procedure. We obtained baseline serum levels of thiamine in all cases and ordered a head MRI, which was obtained within 24 hours after initial evaluation in all 5 cases.

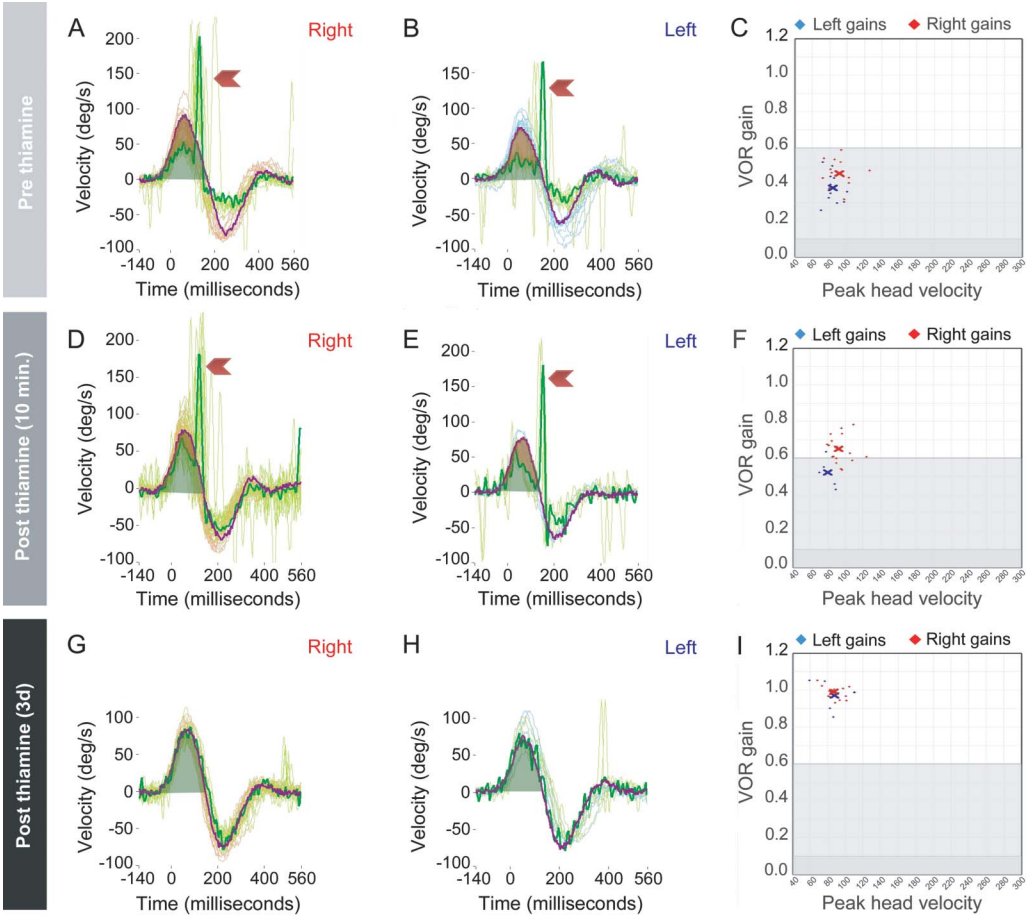
We began thiamine replacement following clinical examination. Thiamine levels were low or borderline in all 5 and folate levels were also low in 3 of 4 who were tested. Cases 1 and 2 received only oral thiamine replacement (100 mg daily). Cases 4 and 5 received an IV dose of 500 mg thiamine in 100 mL of normal saline given over a 5-minute period, followed by 100 mg/day orally. Case 3 had oral replacement followed by IV thiamine after partial improvement. Four had complete resolution of clinical findings and 1 had a partial response (case 5).

Two of 3 improved dramatically after IV thiamine. Case 3 with initial abducens palsy and abnormal MRI had partial improvement of the ophthalmoplegia after oral thiamine but remained nauseated with horizontal nystagmus and a bilaterally positive horizontal head impulse test. Her horizontal head impulse VOR normalized immediately after thiamine infusion (video 2) and she reported improvement of her symptoms in the ensuing hours. Case 4 had bilateral, horizontal gaze-evoked, direction-changing nystagmus; a subtle, 8-prism diopter esotropia in left gaze during cross-cover testing; and truncal ataxia; he also had mostly covert, corrective saccades[13] (video 3, figure). Covert corrective saccades in VOR-deficient subjects occur during the head rotation in a head impulse test of the VOR, rather than after the head comes to rest; when corrective saccades are covert, clinical head impulse testing (without quantitative recording equipment) can be falsely negative.[13] Following IV thiamine infusion, Case 4's quantitatively measured h-VOR improved immediately and normalized by day 3 (figure); horizontal nystagmus and truncal ataxia resolved the next morning. Case 5 did not have immediate improvement in her clinical findings with IV replacement, but improved gradually over the ensuing weeks; recovery was incomplete with residual nystagmus. In all patients, the h-VOR normalized.

DISCUSSION

Our results suggest that thiamine deficiency should be considered in patients with nutritional deprivation and unexplained acute or subacute vestibular symptoms, even absent encephalopathy.

Figure Quantitative head impulse testing in a patient with nonencephalopathic vestibular Wernicke syndrome



Rows show 3 time points for a single patient (case 4) before IV thiamine (row 1), 10 minutes after IV thiamine (row 2), and 3 days after IV thiamine (row 3). Column A (panels A, D, G) shows right-sided and B (panels B, E, H) shows left-sided vestibular reflex responses. In each of these panels, multiple impulses are displayed with a single impulse highlighted. The orange trace corresponds to head velocity and the green trace to eye velocity. Green shading denotes the area under the curve of the eye trace during the impulse. Red shading (panels A, B, D, E) denotes the difference in area under the curve between the head trace and the eye trace. This red shading represents reduced vestibulo-ocular reflex (VOR) gain, also shown as abnormally low results in the VOR gain plots (panels C, F). Red chevrons in these same panels point to rapid corrective ("refixation") saccades that are compensatory for the deficient vestibular response that fails to keep the eyes on target. Because these saccades occur during the head impulse (as opposed to after the head has come completely to rest), they are more difficult to detect clinically (compare video 3 to videos 1 and 2). These are known as "covert" corrective saccades since they occur before the head comes to rest, rather than afterwards, and are therefore hidden to the naked-eye interpretation of the head impulse VOR response. Panels G and H show no corrective saccades because VOR gains have completely normalized post treatment (panel I).

Our series includes a rare case of a patient with Wernicke encephalopathy with an acute, 48-hour presentation closely mimicking vestibular neuritis or posterior fossa stroke.[14] Early recognition is critical given that hypoglycemia and hypovolemia can also produce dizziness, vertigo, and ataxia.[15] Patients seen in emergency departments may be erroneously treated with a glucose infusion or bolus, risking dangerous exacerbation of the underlying thiamine depletion.[16]

VOR testing is rarely performed in routine emergency practice. The head impulse test of VOR function revealed bilateral h-VOR failure in all 5 cases, presumably from direct involvement of the vestibular nuclei in the brainstem. This was true even in the case with an acute vertigo presentation; since vertigo is usually seen in patients with asymmetric vestibular lesions, we might speculate that this lesion began unilaterally and evolved to an asymmetric, bilateral lesion. Most bilateral vestibular failure is slowly progressive over months to years, including that

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seen in the cerebellar ataxia, neuropathy, and vestibular areflexia (CANVAS) syndrome.[17,18] Acute bilateral vestibular failure, particularly without hearing loss, is rarely seen except in gentamicin and related aminoglycoside ototoxicity.[19] Gentamicin damages vestibular hair cells and usually impairs the VOR in all 3 dimensions.[20] Thus, loss of bilateral h-VOR function with spared v-VOR function could be a fairly specific predictor of Wernicke in patients presenting with acute vestibular symptoms, particularly those who lack recent exposure to antibiotics. Furthermore, bilateral, horizontal, gaze-evoked, direction-changing nystagmus should not accompany gentamicin toxicity, while this finding is routinely present in Wernicke (83%, 192/232).[1] Further prospective study of these clinical signs is needed.

In one case where VOR abnormalities at the bedside were more difficult to detect clinically (case 4, video 3), use of a commercially available video-oculography device to measure the head impulse VOR helped identify the sign (figure). Rapid improvement of the VOR following parenteral thiamine, seen in 2 of our patients, may be a useful marker to gauge therapeutic effect and should be studied further. Quantification of VOR responses might assist in determining adequacy of thiamine repletion.

Oscillopsia likely resulted from nystagmus, bilateral VOR failure, or a combination of the two. The truncal ataxia found in our cases is likely the result of bilateral central vestibular failure in the brainstem, given the absence of a proprioceptive deficit or limb ataxia. A contribution from midline cerebellar dysfunction (due to Wernicke or alcohol cerebellopathy in cases 1 and 2) could also have been present.

Previous authors have suggested that the vestibulopathy and gaze-holding failure found in Wernicke disease is due to direct damage to the medial vestibular nuclei and nearby nucleus prepositus hypoglossi in the medulla.[8] The bilaterally impaired h-VOR and bilateral gaze-holding nystagmus and the lack of overt signs of cerebellar dysfunction seen in our patients support this assertion. In particular, true gaze-holding failure cannot result from isolated peripheral vestibular dysfunction.[2] Acute injury to the peripheral vestibular system produces unidirectional nystagmus that may increase with gaze in the direction of the fast phase, but should not change direction with gaze in the opposite direction[14] (also see table footnote). Nevertheless, we are unaware of any neuropathologic studies of the vestibular labyrinth or nerve in Wernicke patients. Accordingly, we cannot exclude the possibility of combined central and peripheral lesions in our patients, as seen in the slowly progressive neurodegenerative syndrome known as CANVAS.[18]

Based on the aforementioned clinical features, we believe that our patients had bilateral brainstem lesions, most likely in the dorsal medulla and pons in the region of the medial vestibular nuclei. However, only 1 of 5 patients' images (case 3) showed subtle increased signal changes involving the typical periventricular and periaqueductal locations of the dorsomedial brainstem and diencephalon—notably not located in the region of the vestibular nuclei. Hemispheric white matter hyperintensities in case 5 were probably incidental, but did not aid diagnosis given the high prevalence of leukoaraiosis in patients with acute dizziness.[21] Lack of radiologic evidence for brainstem lesions in the vestibular nuclei or 8th nerve fascicle in all 5 cases presumably indicates Wernicke neuropathology is subradiographic in these earlier/milder vestibular presentations.

Four of 5 patients recovered without neurologic sequelae, so this vestibular presentation of Wernicke may be reversible with prompt treatment. The rapid improvement probably reflects an early stage of thiamine deficiency, with normalization of neuronal metabolism after high-dose parenteral replacement. From the one case with quantitative measures, the rapid improvement within minutes was partial, rather than complete (figure). A partial response could be sufficient to help normalize the appearance of the clinical head impulse, so without quantitative recordings in the other patients who had dramatic improvement clinically (e.g., case 3, video 2), we cannot be sure that the immediate, dramatic improvement was complete. The failure of oral replacement in one patient to produce a clear benefit and the subsequent success of parenteral therapy suggests that, even in these milder (nonencephalopathic) cases, immediate IV repletion should probably be the first course of action. The benefit of high-dose IV thiamine in this clinical setting is probably both therapeutic and diagnostic, given that, absent encephalopathy, the diagnosis might remain uncertain pending delayed return of thiamine levels. This diagnostic role of IV therapy is particularly relevant given that MRI may be normal or nondiagnostic in these patients.

The frequent co-occurrence of folate deficiency without B_{12} deficiency or anemia in our series is interesting but of unclear significance. Folate deficiency can contribute to thiamine deficiency by reducing intestinal absorption.[22] Whether folate deficiency was partly responsible for the clinical phenotype (e.g., optic neuropathy[23] in case 1) is unknown, because optic neuropathy has been reported as a consequence of thiamine deficiency absent folate deficiency.[24] Measuring folate levels and insuring adequate repletion may be important diagnostic and therapeutic steps in this clinical context.

Based on these findings and discussion, patients with thiamine deficiency may present with predominantly vestibular symptoms and signs without encephalopathy. Head impulse VOR responses in these patients could be an important bedside marker for diagnosis, response to therapy, or prognosis. A pattern of bilateral vestibular failure (especially dissociated h-VOR loss) plus bilateral, horizontal, gaze-evoked, direction-changing nystagmus may be a helpful sign to identify Wernicke syndrome in patients with acute dizziness, vertigo, or ataxia. Further prospective study of these signs in larger patient samples is warranted. Frontline providers evaluating patients with acute vestibular syndrome or acute ataxia should consider the diagnosis of thiamine deficiency; in cases with a high index of suspicion for malnutrition, empiric parenteral thiamine may be indicated.

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