Conversion of upbeat to downbeat nystagmus in Wernicke encephalopathy

Jorge C. Kattah, MD, Ali Saber Tehrani, Sascha du Lac, PhD, David E. Newman-Toker, MD, PhD, and David S. Zee, MD

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Correspondence

Dr. Kattah
kattahj@uicomp.uic.edu

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Abstract

Objective

To explain (1) why an initial upbeat nystagmus (UBN) converts to a permanent downbeat nystagmus (DBN) in Wernicke encephalopathy (WE) and (2) why convergence and certain vestibular provocative maneuvers may transiently switch UBN to DBN.

Methods

Following a literature review and study of our 2 patients, we develop hypotheses for the unusual patterns of vertical nystagmus in WE.

Results

Our overarching hypothesis is that there is a selective vulnerability and a selective recovery from thiamine deficiency of neurons within brainstem gaze-holding networks. Furthermore, since the circuits affected in WE are commonly paraventricular, especially medially, just under the floor of the fourth ventricle where lie structures important for control of vertical gaze, we suggest the patterns of involvement in WE also reflect a breakdown in vulnerable areas of the blood–brain barrier. Many of the initial deficits of our patients improved over time, but their DBN did not. Irreversible changes in paramedian tract neurons, which project to the cerebellar flocculus, may be the cause. Here we suggest that conversion of UBN to permanent DBN points to thiamine deficiency and may argue for a chronic, nonprogressive DBN/truncal ataxia syndrome. Finally, we posit that the transient switch of UBN to DBN reflects abnormal processing of otolith information about linear acceleration, and often points to a diagnosis of WE.

Conclusion

Recognizing the unusual patterns of transient switching and then permanent conversion of UBN to DBN in WE is vital since long-term disability from WE may be prevented by timely, parenteral high-dose thiamine.

From the Department of Neurology (J.C.K., A.S.T.), University of Illinois College of Medicine; Illinois Neurologic Institute (J.C.K., A.S.T.), Peoria; Departments of Otolaryngology–Head and Neck Surgery (S.d.L., D.E.N.-T., D.S.Z.), Neuroscience (S.d.L., D.E.N.-T., D.S.Z.), and Neurology (S.d.L., D.E.N.-T., D.S.Z.), and Division of Neuro-Visual & Vestibular Disorders (D.E.N.-T.), Johns Hopkins University, Baltimore, MD.

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Glossary

BBB = blood–brain barrier; DBN = downbeat nystagmus; GAD = glutamic acid decarboxylase; INC = interstitial nucleus of Cajal; PDHE α = pyruvate dehydrogenase E1 α ; PTN = paramedian tract neurons; TPP = thiamine pyrophosphate; UBN = upbeat nystagmus; VOR = vestibulo-ocular reflex; WE = Wernicke encephalopathy.

We describe 2 patients with Wernicke encephalopathy (WE) who we followed for 6 and 7 years. They showed a conversion from an initial upbeat nystagmus (UBN) to a later, permanent downbeat nystagmus (DBN). They also showed on initial examinations a transient switch from UBN to DBN induced by provocative maneuvers such as convergence, head shaking, skull vibration, positional changes, or changes in eye position. We summarize details of the eye movement findings in our 2 patients in videos 1 and 2. An additional 11 patients from previous reports (table 1)^{1–10} exhibited an initial spontaneous UBN, 8 of them in

the context of WE and 3 with other causes but with transient switch or permanent conversion from UBN to DBN. In the entire group of 13 patients, 7 patients had either transient switch of UBN to DBN or variable suppression of UBN on their initial examination (table 1).^{1–10} Over time, UBN resolved completely in 2 patients and partially in 1; it was unchanged at 37 days and 10 weeks in 2 patients (short follow-up period) and converted to permanent DBN in 8 patients. However, data were not available to document when conversion to permanent DBN occurred. The conversion from UBN to permanent DBN was recognized

Table 1 Chronological review of previous reports of upbeat nystagmus (UBN) in acute and chronic brainstem disorders due to Wernicke encephalopathy and other etiologies

Case or cases	Transient UBN/DBN switch in acute phase	Permanent DBN in follow-up examination, chronic phase	Etiology lesion localization
Cox et al. ¹	UBN with transient switch to DBN on convergence	No: UBN unchanged 37 days after initial examination	WE: unknown
Fisher et al. ^{2,a}	UBN suppressed with OKN stimulation	No: UBN unchanged until patient died within 10 weeks from initial examination	WE: autopsy with gliosis in brainstem nuclei surrounding the aqueduct and IVth ventricle
Furman and Becker ³	Possible transient switch to DBN with convergence	No: UBN resolved 7 months after initial examination	WE: CT scan cerebral and cerebellar atrophy
Rousseaux et al. ⁴	UBN in primary gaze; UBN suppression or switch to DBN not described	Yes: DBN present 2.5 months after initial examination and present for 3 years; UBN still on upgaze	Hematoma in medial medulla
Kattah and Dagi ⁵	UBN suppressed with head tilt right; switch to DBN with hanging head position	No: UBN resolved 6 months after initial examination	Unilateral brachium conjunctivum hemorrhage
Sakuma et al. ⁶	Primary position UBN; increased in downgaze	Yes: DBN present in follow-up	WE: normal CT scan
Kastrup et al. ⁷	Case 1 UBN suppressed in up and lateral gaze at months 2, 5, 8	Yes: DBN present at 12 and 18 months after initial examination; partially suppressed with baclofen; UBN returned at month 20 after discontinuing baclofen	WE: no lesion noted, had vermis atrophy
Suzuki et al. ⁸	UBN switch to DBN in downgaze	Yes: DBN present 8 months after initial examination; partially suppressed with clonazepam	WE: no lesion noted
Shin et al. ¹⁰	UBN switch to DBN in upgaze	No: Trace UBN 5 months after initial examination	WE: increased FLAIR signal in middle cerebellar peduncles + thalami
Abouaf et al. ⁹	Case 1: UBN suppressed by supine/prone positions; case 2: UBN decreased in downgaze	Yes: case 1: DBN 1 year after initial examination; no: case 2: UBN improved 6 months after initial examination	WE: in case 2, increased FLAIR signal in mammillary bodies, medial thalami, and midbrain
Doherty et al. ³⁷	Autoimmune encephalitis	Yes: DBN present 2 months after initial examination; on immunosuppression	Unknown
Current patients	Case 1: UBN switch to DBN with convergence and skull vibration; case 2: UBN switch to DBN with head shaking and convergence	Yes: case 1: DBN present 4 months after initial examination, unchanged for 7 years; yes: case 2: DBN present 2 months after initial examination, unchanged for 6 years	WE: case 1: periventricular signal changes in pontomesencephalic gray and medulla

Abbreviations: DBN = downbeat nystagmus; FLAIR = fluid-attenuated inversion recovery; OKN = optokinetic nystagmus; WE = Wernicke encephalopathy.

^a This patient with WE with UBN, suppressed by OKN stimulation, died 10 weeks after the initial examination and had gliosis and neuronal loss in midbrain and pons.

as early as 2 months in one of our patients (table 2) or as late as 1 year.⁹ The longest DBN duration in follow-up is in our patients, 6 and 7 years. In addition, 2 previously reported patients with chronic DBN probably had a prior episode of thiamine deficiency.^{11,12} The frequent association with WE in our patients and the literature suggests that thiamine deficiency affects neurons involved in the control of vertical eye movements.

Why a UBN/DBN conversion in WE?

To explain the initial UBN, we draw on past clinical pathologic and imaging studies that point to lesions in nuclei (intercalatus and Roller) in the caudal medulla in the perihypoglossal region as a cause of UBN, though lesions in more rostral circuits have also been implicated.^{13–16} Projections to the cerebellum from these regions may also contribute to the development of UBN (figure 1). Key to our formulation for the conversion of UBN to permanent DBN is a pivotal role of the paramedian tract neurons (PTN) and the sites in the cerebellum to which they project (figure 1). PTN receive input from the interstitial nucleus of Cajal (INC) and the vestibular nuclei,¹⁷ and convey excitation to the flocculus and possibly to other portions of the vestibulocerebellum. The flocculus, in turn, projects back to the brainstem and inhibits the vestibular nuclei that mediate upward slow phases (anterior semicircular canal-vestibulo-ocular pathways)¹⁸ (figure 1). As expected, lesions of the cerebellar flocculus cause DBN, at least in part by disinhibition of the vestibular nuclei that normally mediate upward slow phases.¹⁸ In addition, experimental lesions of PTN also cause DBN.¹⁹ Presumably, the mechanism is the loss of the excitatory input from the PTN to the flocculus, producing relative hypofunction of the flocculus. Again, DBN emerges because of a disinhibition of the vestibular nuclei that normally mediate

upward slow phases.¹⁸ We note these circuits not only influence the balance between up and down vestibulo-ocular pathways but also the up and down vertical gaze-holding networks (neural integrators).^{20,21} An inherent compensatory upward bias in these circuits has been hypothesized to counteract an inherent downward bias from the pull of gravity on the globe.¹³ We suggest here that with some focal structural lesions as well as with WE, this balance is disturbed, leading to a preponderance of a downward slow-phase bias and a consequent UBN.²²

Another facet of this concept is that PTN provide feedback to the flocculus so that it can use error signals to adaptively correct for any abnormal downward biases that arise in patients with focal brainstem lesions associated with UBN.^{14,16} In fact, the UBN in patients with focal structural lesions in the brainstem usually subsides relatively quickly without residual DBN.^{13,15} Presumably, an intact flocculus aids recovery from UBN in these cases by rebalancing in central vestibular and gaze-holding pathways. In contrast, patients with a primary DBN usually recover little.²¹ Their DBN probably persists because most structural lesions that create DBN affect cerebellar circuits directly, eliminating the ability to adapt to or recover from DBN.

In contrast, we suggest that diffuse metabolic disruptions within the brainstem, such as with WE, initially cause prominent UBN by impairing vulnerable neurons in circuits that normally produce an upward slow-phase bias. These would include the caudal perihypoglossal nuclei (figure 1) (or possibly rostrally in the INC in the midbrain).^{2,5} As these affected neurons recover, the pathologic downward slow-phase bias (and UBN) lessens. However, we further hypothesize that PTN are more vulnerable to thiamine deficiency and do not

Table 2 Clinical and eye movement abnormalities in the acute phase and follow-up in 2 patients with Wernicke encephalopathy with conversion from initial upbeat nystagmus (UBN) to chronic downbeat nystagmus (DBN)

Patient	Age, y	Timing between symptom onset and first examination	Nystagmus characteristics on presentation	Nystagmus characteristics on follow-up	Video head impulse test, gain (normal gain 0.7 to 1.0)	Initial MRI
1	60 ^a	1 mo	UBN in primary gaze; transiently suppressed by convergence and vertex vibration with subtle DBN present during stimulation and UBN return after stimulation ended	DBN in primary gaze increasing in lateral gaze and in prone position	RL: 0.34 (±0.05) ^b LL: 0.39 (±0.02) LA: 0.80 (±0.10) RP: 0.17 (±0.12) RA: 0.15 (±0.17) LP: 0.20 (±0.16)	Increased FLAIR in medial thalami, mammillary bodies, periaqueductal midbrain, caudal pons medulla
2	45 ^a	~12 h	UBN in primary gaze suppressed by convergence and head shaking with subtle DBN present during stimulation and UBN return after stimulation ended	DBN only in lateral gaze and downgaze; UBN still in upgaze; UBN in supine right and left ear down position; DBN in prone position	RL: 0.75 (±0.10) ^b LL: 0.83 (±0.05) LA: 0.73 (±0.13) RP: 0.75 (±0.18) RA: 0.65 (±0.18) LP: 0.82 (±0.09)	Increased FLAIR signal, mammillary body

Abbreviations: aVOR = angular vestibulo-ocular reflex; FLAIR = fluid-attenuated inversion recovery; LA = left anterior; LL = left lateral; LP = left posterior; RA = right anterior; RL = right lateral; RP = right posterior.
^a Both patients were alcohol-dependent and neither had ophthalmoplegia during their first examination.
^b We obtained quantitative aVOR gain with video head impulses in 2016. The manual horizontal aVOR gain was bilaterally abnormal during the initial presentation in both patients. The manual and quantitative video head impulse test gain improved only in patient 2.

Figure 1 Block diagram illustrating the key structures involved in maintaining vertical eye position

Conceptual scheme for control of vertical gaze by brainstem and cerebellar structures. We emphasize the interactions between the cerebellum and brainstem circuits. Ventral tegmental tract (VTT) and medial longitudinal fasciculus (MLF) mediate connections between the caudal and rostral brainstem. In Wernicke encephalopathy, we propose that neurons in the PHC (nucleus intercalatus and nucleus of Roller) and in the PTN are both affected, with the net imbalance initially producing a downward bias and upbeat nystagmus (UBN). As neurons in the PHC nuclei recover, but those in the paramedian tract nuclei do not, an upward bias predominates and the nystagmus eventually shifts to a permanent downbeat nystagmus (DBN). Without input from the PTN neurons, the flocculus remains in a functionally lesioned state, leading to a release of the vestibular nuclei that generates upward slow phases, producing a DBN. In the PHC box, we hypothesize that the net effect of the PHC projection to the flocculus is inhibitory (dashed line).

recover, leaving the flocculus, deprived of excitation from PTN, in a perpetually “lesioned,” hypofunctioning state (figure 1). This would lessen inhibition from the flocculus on the vestibular nuclei that normally produce upward slow phases, and in turn, result in an enduring upward slow-phase bias and a permanent DBN. Furthermore, the loss of inputs from the PTN might also impair the ability of the flocculus to rebalance brainstem circuits adaptively. In other words, these patients with WE eventually behave like patients with permanent downbeat nystagmus due to degenerative lesions of the flocculus. In many patients with DBN, no cause is identified. However, 2 patients previously reported with chronic DBN probably had prior thiamine deficiency.^{11,12} Here we suggest that both the conversion of an initial UBN to a permanent DBN, as well as a stimulus-induced transient switching from UBN to DBN on a single examination, not only frequently point to thiamine deficiency but moreover can be a precursor of a chronic, nonprogressive DBN/truncal ataxia syndrome.

Selective vulnerability in WE and pathologic localization

In thiamine deficiency, there is pathologic and radiographic evidence of diffuse, symmetric involvement of vulnerable diencephalic and brainstem neurons with sparing of other nuclei, similar to the MRI findings in patient 1^{23–26} (figure 2).

There are many possible reasons for selective vulnerability of neurons in WE; we mention a few, primarily to emphasize that the peculiar pattern of ocular motor abnormalities in WE might help clarify the underlying biological basis of damage and recovery in these circuits. One early and important consequence of thiamine pyrophosphate (TPP) deficiency is decreased synthesis of α -ketoglutarate dehydrogenase within neuronal mitochondria; as a result, there is excessive accumulation of glutamate. Glutamate excitotoxicity can cause glial and neural lesions in WE.^{27,28} Glutamic acid decarboxylase (GAD) protects brain tissue from glutamate neurotoxicity. However, with high serum glutamate concentration, GAD is saturated and excess systemic glutamate can travel through gaps in a normal or altered blood–brain barrier (BBB).²⁹ Consequently, glutamate excitotoxicity can particularly involve structures that are near to where the BBB is more fragile, for example, near the area postrema in the dorsal medulla or other circumventricular locations.³⁰ Indeed, this localization coincides with the distribution of lesions in WE, and with contrast enhancement on MRI.²⁴

Another consideration, which might explain some phenotypic variability of WE, is the genetic heterogeneity of the cofactors, enzymes, and transporters that are involved in the generation of active TPP from free thiamine by the enzyme thiamine pyrophosphokinase.^{28,31–33} Another source of selective vulnerability may relate to deficient metabolism of acetylcholine,³⁴ which is expressed in perihypoglossal neurons that

project to the flocculus.³⁵ Cholinergic neurons are particularly sensitive to neurodegeneration in experimental WE.³³ Interestingly, in support of an effect of changes in cholinergic activity in WE is the fact that nicotine, which has a cholinergic effect, induces in normal individuals a UBN that is modulated by head position, much as in our patients.³⁶

Chronic alcohol consumption causes additional alterations in thiamine metabolism³¹; absorption and transport of thiamine are impaired, leading to decreased production of TPP. TPP is a pyruvate dehydrogenase E1 α (PDHE α) cofactor in the oxidative phosphorylation cycle. TPP deficiency causes decreased PDHE α activity with loss of cellular energy utilization and neuronal injury. In addition, phosphorylation of PDHE α (PDHE kinase), which is the inactive form of this enzyme, further decreases PDHE α bioavailability. In experimental animal models of thiamine deficiency, the administration of acetyl-L carnitine along with thiamine replacement may accelerate return of neuronal function. It follows that giving acetyl-L carnitine to humans with WE might potentially improve outcome.³¹

While we cannot pinpoint the biochemical reasons for selective vulnerability of neurons in WE, it seems plausible to propose that PTN neurons, which we suspect are the culprit in the conversion of UDB to permanent DBN, may be selectively vulnerable to thiamine deficiency. Their midline location near the area postrema, where the BBB is fragile, may contribute to this vulnerability.

Similar ideas apply to a previous reported patient with a conversion of UBN to permanent DBN associated with an autoimmune encephalitis and immune-mediated channelopathy. In this case, immunosuppression presumably selectively restored function (or ameliorated impairments) in upward bias neurons more than PTN neurons.³⁷

Our hypothesis for conversion to a permanent DBN may apply even if the initial UBN relates to dysfunction of the INC which, along with the perihypoglossal nuclei,^{2,10,38} is another key area for processing information for vertical gaze-holding

and the vertical vestibulo-ocular reflex (VOR).³⁹ INC also projects to PTN neurons.¹⁷ In patient 1, neuroimaging obtained during his acute encephalopathy (figure 2) showed increased signal in the periaqueductal gray, the pons near the fourth ventricle, and the dorsal medulla (the region of the nucleus of Roller and the nucleus intercalatus). Although lesions in any of these nuclei might cause UBN,^{2,38,40} the pattern of eye movements in our patients, including their horizontal gaze-evoked nystagmus and hypoactive horizontal VOR, favored localization in the lower brainstem where the PTN and perihypoglossal nuclei cluster close to the floor of the 4th ventricle.

Finally, a word about why UBN switched to DBN with convergence, positional changes, mastoid vibration, head shaking, or changes in eye position. One explanation is that lesions in WE interfere with processing of linear acceleration information for otolith-ocular reflexes such as the response to translation of the head. Such responses normally can change direction depending on the direction of the line of sight (e.g., looking up or down while moving forward), and they are also markedly affected by viewing distance,⁴¹ possibly via mechanisms involving the flocculus.⁴² Moreover, spontaneous vertical nystagmus of otolith origin is elicited even in healthy people.^{43,44} In WE, the unusual transient changes in vertical nystagmus with vestibular stimuli could result from involvement of some of the medially located vestibular nucleus neurons that have been implicated in otolith processing via their connections with nodulus.⁴⁵

Caveats and further experiments

We propose that the unusual conversion of UBN to permanent DBN in WE occurred because replenishing thiamine selectively restored the function of neurons in the perihypoglossal complex (intercalatus and roller) that when lesioned produce UBN, but was unable to restore function in PTN that when lesioned produce DBN. We emphasize our hypothesis does not hinge on the original mechanism underlying the appearance of UBN after brainstem lesions. The key idea is that the neurons within the cell

Figure 2 Axial MRI of the brain, patient 1

A) Bilateral symmetric increased diffusion-weighted image signal in the region of the perihypoglossal nuclei (arrow). (B, C) Increased fluid-attenuated inversion recovery sequence signal (arrows). Observe increased periventricular signal at the pontomesencephalic junction. Similar increased periaqueductal and diencephalic signal was present (not shown).

groups of the PTN, which project to and excite the cerebellar flocculus, are irreversibly damaged. Consequently, their permanent loss is the principal cause of permanent DBN in WE. The characteristic paraventricular localization of the lesions of WE may relate to their proximity to midline areas where the BBB is porous, e.g., the area postrema. Indeed, the dissociation of vestibular responses, with horizontal affected more than vertical, corresponds to the medial location of vestibular nuclei that subserve the horizontal VOR.^{25,30} Perfusion and contrast-enhanced MRI could be used to further evaluate changes in the BBB.⁴⁶ While we have emphasized the role of specific brainstem structures in the genesis of the UBN/DBN conversion, we acknowledge there could be damage to other structures in the brainstem including the vestibular nuclei and the INC.

There also could be damage to the cerebellum itself, related to acute thiamine deficiency, or more likely to a preexisting alcoholic or nutritional cerebellar degeneration.²³ Experimental lesions of the flocculus/paraflocculus^{18,21} and the nodulus cause DBN.⁴⁷ Functional MRI studies in DBN have shown hypometabolism of the flocculus.⁴⁸ MRI anatomical studies also implicate the tonsil (paraflocculus) in vertical gaze-holding humans.⁴⁹ In thiamine deficiency, at autopsy, there can be severe loss of Purkinje cells and granule cell changes in the cerebellar flocculus with milder neuronal loss in the nodulus.^{23,50} While the MRI in patient 1 did not show cerebellar abnormalities, a loss of function cannot be excluded. Although a primary cerebellar locus could account for the eventual emergence of a permanent downbeat nystagmus, the hypothesis of selective recovery in the brainstem remains viable since the flocculus would still be functionally deafferented.

As a final point, we never examined the patients during the actual conversion (when there was no spontaneous vertical nystagmus) from UBN to permanent DBN. Documenting this conversion, and correlating with changes in anatomical or biochemical MRI, could reveal more about the time course of the patterns of recovery of different cell groups from thiamine deficiency.

Author contributions

Jorge C. Kattah evaluated and followed the 2 patients, wrote the first manuscript draft and several iterations, proposed that brainstem structures responsible for UBN generation responded better to treatment with thiamine than those responsible for DBN and suggested that PMT neurons provide vertical eye position feedback to the flocculus, and approved the final version. Ali S. Tehrani edited videos, figures, and diagram; reviewed all manuscript iterations; and approved the final version. Sascha du Lac edited figures, diagrams, and the manuscript and approved the final manuscript version. David Newman-Toker participated in informal discussion about the cases and reviewed, edited, and approved the final manuscript version. David S. Zee generated the main study hypothesis proposing permanent dysfunction of neurons in the cell groups of paramedian tracts as the primary lesion responsible for development of persistent downbeat nystagmus and

developed the theoretical sequential interaction of the brainstem and cerebellum, key to the understanding of the clinical findings; edited the manuscript; provided the critical research literature that applied to our observations and hypothesis; and approved the final version of the manuscript.

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Disclosure

J. Kattah reports that Otometrics Corporation loaned research equipment in 2012; this equipment is no longer in use. He received honorarium as consultant for Questcor Laboratory. A. Tehrani and S. du Lac report no disclosures relevant to the manuscript. D. Newman-Toker reports that he evaluates media and legal cases and conducts funded research related to dizziness and stroke diagnosis. He has been leased research equipment from 2 commercial companies (Otometrics and Interacoustics). D. Zee reports that he received honoraria for lecturing in educational courses sponsored by Micromedical Technologies and by Sun Pharma and royalties from Oxford University Press. Go to Neurology.org/N for full disclosures.

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