Article • Sudden-Onset Esotropia and Upbeat Nystagmus in an Adult with Wernicke's Encephalopathy: A Case Report

Margaret Burton, OD • VA Illiana Healthcare System • Danville, Illinois
Guadalupe Mejia, OD • VA Illiana Healthcare System • Danville, Illinois

Margaret Burton, OD
Danville, California
Optometrist, Boghossian Vision
Residency in ocular disease and primary care at the VA Illiana Healthcare System
2017: Illinois College of Optometry
2013: University of Michigan

ABSTRACT

Background: Wernicke's encephalopathy, a condition characterized by a triad of mental confusion, ophthalmoplegia, and gait ataxia, can be reversed if treatment is initiated promptly.

This case examines optometry's role in co-management when patients present with oculomotor manifestations of this condition.

Case Report: A 53-year-old Caucasian male diagnosed with Wernicke's encephalopathy was referred to the VA optometry clinic with symptoms of oscillopsia and diplopia. Examination revealed that his symptoms were caused by upbeat nystagmus and an acquired large-angle alternating esotropia. Over the course of several months, in conjunction with systemic treatment, the patient's ocular symptoms completely resolved. However, many of his systemic manifestations persisted.

Conclusions: This paper reviews literature discussing sudden-onset esotropia and nystagmus in cerebellar disease and defines optometry's role in treatment.

Keywords: acquired esotropia, diplopia, oscillopsia, Wernicke's encephalopathy

Introduction

First described in 1881 by Carl Wernicke, Wernicke's encephalopathy is a severe, potentially life-threatening condition caused by a thiamine deficiency. The classic presentation includes a triad of mental confusion, ophthalmoplegia, and gait ataxia.[1] Based on post-mortem studies, Wernicke's encephalopathy has an incidence of up to 2.8% in the general population.[1] This number increases by up to 12.5% when known alcoholics are considered.[2] However, because modern post-mortem studies are rare, Wernicke's encephalopathy often goes unrecognized. In the same post-mortem studies used to determine the incidence, only 20% of cases were diagnosed antemortem.[1]

Because the diet is the only source of thiamine, Wernicke's encephalopathy can be caused by any condition that causes poor nutrition.[3] For example, alcoholics are at a high risk of malnutrition and contracting Wernicke's encephalopathy because they are prone to self-neglect, they imbibe primarily low-vitamin or mineral-rich alcoholic beverages, and the alcoholic's liver has a low capacity to store vitamins.

Although classically regarded as a problem limited to alcoholics, up to 23% of Wernicke's encephalopathy cases occur in non-alcoholics, none of which were diagnosed antemortem.[4] Indeed, a study reviewed several case reports and found an association between recent bariatric surgery and a diagnosis of Wernicke's encephalopathy presenting four to twelve weeks later.[5] Other studies of similar surgeries found that during the two- to eight-month post-operative period, patients who lost more than seven kilograms per month were at a higher risk of developing Wernicke's encephalopathy.[6] Additionally, those with prolonged malnutrition due to frequent vomiting, poor dietary compliance, or limited intake are at an increased risk.[5,6] Wernicke's encephalopathy is more common in males than females.[6]

Poor nutrition, namely lack of the vital vitamin thiamine, is the causative agent in the pathogenesis of Wernicke's encephalopathy. Thiamine is a key co-factor for enzymes essential to energy metabolism. Without thiamine, there is decreased activity in these enzymes, which eventually leads to cytotoxic

and vasogenic edema in astrocytes and neurons and a breakdown of the blood-brain barrier. After about two weeks, these changes lead to neuronal necrosis and irreversible structural lesions in certain highly susceptible regions of the brain.[3,6] At this point, symptoms include mental status changes, oculomotor abnormalities, gait ataxia, stupor or coma, hypotension, hypothermia, cardiovascular signs, and peripheral neuropathies.[6]

Diagnosis can be aided by lab testing and imaging; however, the gold standard is clinical evaluation.[7] The most readily available lab test is serum thiamine, but it can be unreliable. More specific tests include erythrocyte thiamine transketolase (ETKA) and high-performance liquid chromatography (HPLC).[7,8] Unfortunately, these tests are not often available in the emergency setting. Magnetic resonance imaging (MRI) greatly supports the diagnosis and allows for monitoring of treatment efficacy.[9] Imaging studies will often show acute diencephalic and periventricular lesions, diffusion abnormalities surrounding the aqueduct and third ventricle and within the medial thalamus, dorsal medulla, tectal plate, and mammillary bodies.[9,10] However, with a sensitivity of only 53%, lack of findings does not eliminate a diagnosis.[9] Instead, diagnosis is confirmed by response to treatment.

Treatment typically includes intravenous thiamine for two to five days, followed by long-term oral thiamine (Figure 1). Fortunately, thiamine is very safe, inexpensive, and effective.[6,7] Prompt diagnosis and treatment are essential because up to 20% of cases result in death. Even with treatment, 60% of cases result in permanent horizontal nystagmus, 60% with remaining ataxia, and 80% with deficits in learning and memory. Between 56 and 84% develop Korsakoff's syndrome, a permanent condition causing severe memory impairment.[11]

Case Presentation

A 53-year-old Caucasian male with a recent diagnosis of Wernicke's encephalopathy was referred to the VA optometry clinic from the hospital with symptoms of constant oscillopsia and intermittent diplopia. The patient was not alert or oriented and was in and out of consciousness during this exam, so the case history was provided by a nurse. The patient's medical history prior to his diagnosis of Wernicke's encephalopathy included alcoholism, deep vein thrombosis, generalized anxiety, and gastrointestinal reflux disease. His conditions were medically managed with enoxaparin, haloperidol, and valproic acid.

Initial exam findings included uncorrected visual acuity of 20/80, right eye and left eye. After checking acuity, the patient fell asleep, and the exam was continued the following day. At this follow-up, the patient was able to describe constant movement in both eyes and in all fields of gaze at distance and near. The diplopia was described as intermittent, and

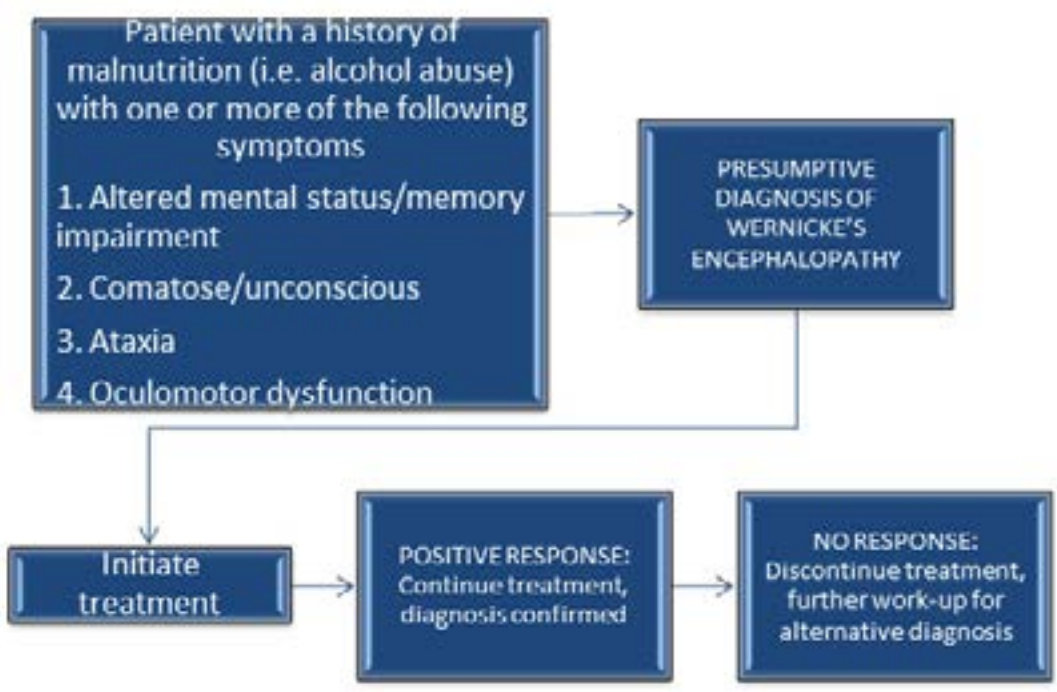

Figure 1. *Recommended treatment protocol for Wernicke's encephalopathy*[6,7]

he reported that closing one eye helped. He believed it was horizontal but was not sure if it was present at distance, near, or both.

The patient's uncorrected acuity was 20/400 in the right eye and 20/200 in the left eye at this visit. Pinhole acuity and near acuity were attempted, but the patient did not understand either test. Refraction was difficult but resulted in +1.25-0.50x105 in the right eye with an acuity of 20/80 and +1.25-0.75x075 in the left eye with an acuity of 20/80. The reduction in entering acuity was attributed to a lack of understanding of the test, especially considering that the corrected acuity was similar to the previous day. Pupils were equal, round, and reactive to light without an afferent pupillary defect, and confrontation visual fields were full to finger count in each eye. Extraocular muscle testing revealed an upbeat nystagmus in all fields of gaze with a relative null point in downgaze. Anterior segment exam with slit lamp showed normal lids and lashes, white and quiet conjunctiva, clear corneas, flat and even irises, and an open Von Herrick angle without anterior chamber cell or flare. There were grade 1 nuclear sclerotic cataracts in both eyes. There was no proptosis or ptosis of either eye. Dilated fundus exam revealed a 0.30 cup-to-disc ratio in both eyes with pink and healthy rim tissue, a flat and even macula in both eyes, normal vasculature, and flat and unremarkable peripheral retinas in both eyes. Intraocular pressure was 16 mmHg in the right eye and 16 mmHg in the left eye measured with Goldmann tonometry. Binocular vision assessment, including cover test, revealed orthophoric posture both distance and near.

Glasses were prescribed for full-time wear, and follow-up was scheduled for one month to repeat oculomotor testing with hope for improved patient participation in the exam. During that time, the patient remained admitted to the hospital and was treated with intravenous thiamine infusions and magnesium.

At the one-month follow-up visit, he continued to report persistent symptoms of constant oscillopsia and intermittent diplopia. His best-corrected vision had improved to 20/60 OD and OS with his glasses. Additionally, his mental status had improved but was still impaired. However, he did not have any memory of our first appointment. Oculomotor testing revealed stable upbeat nystagmus and orthophoric cover test at distance with a mild esophoria at near. Maddox rod testing at near revealed an 8 prism diopter esophoria. All other testing and exam findings, including an anterior and posterior segment exam, were within normal limits and stable. At this point, the patient was referred to a neuro-ophthalmologist and scheduled for a one-month follow-up to repeat testing and monitor for stability.

At the second follow-up, the corrected vision had improved to 20/25 right eye and left eye. The patient reported improvement in his oscillopsia but now had constant diplopia. Exam findings revealed a persistent upbeat nystagmus in all fields of gaze. The cover test revealed a 25 prism diopter intermittent (90% tropia, 10% phoria) alternating (left eye equal to right eye) esotropia at distance and 20 prism diopter intermittent (90% tropia, 10% phoria) alternating (left eye equal to right eye) esotropia at near. This defect was equal in all fields of gaze. All other testing and exam findings were within normal limits and stable. At this time, the patient was diagnosed with an acquired esotropia, and a 25 prism diopter Fresnel prism and a 20 prism diopter Fresnel prism were ordered. He was provided with an eye patch to use until the prism arrived in the clinic and was educated to return if symptoms worsened.

Fortunately, when the patient returned one month later, he had a complete resolution of all symptoms. Best-corrected visual acuity improved further to 20/25+ right eye and left eye. Oculomotor testing revealed a low-frequency, low-amplitude upbeat nystagmus, orthophoric posture at distance, and an 8 prism diopter esophoria at near. Although the patient's visual symptoms had improved dramatically, this did not parallel the course of his systemic manifestations.

At his last optometry visit, the patient was wheelchair-bound, when previously he was able to ambulate with minimal assistance. Additionally, he did not remember any of his previous appointments. His diagnosis was updated to Wernicke-Korsakoff syndrome with gait ataxia. Korsakoff syndrome is defined as a memory disorder with anterograde, retrograde amnesia and confabulation, caused by significant and permanent cerebellar damage from Wernicke's encephalopathy.[10] His long-term treatment plan was to continue taking multivitamins, thiamine, and folic acid supplementation, and he was to be discharged to a long-term rehab and care center. The patient's ocular findings were discussed with his nursing staff present at the exam, and it was decided that his esophoria at near would not be addressed since he was asymptomatic and his daily living activities did not include near work.

The patient saw a neuro-ophthalmologist one month later. At that time, the patient maintained 20/25 acuity right eye and left eye. New findings of horizontal nystagmus in left and right gaze, downbeat nystagmus on downgaze, and upbeat nystagmus on up gaze were also observed. Binocular vision testing revealed a 4 prism diopter esophoria at near and impaired vergence eye movements. The patient reported that he was still doing well and did not have any reoccurring symptoms.

Discussion

We report a case of Wernicke's encephalopathy with a rare finding of acquired esotropia. The pathogenesis of acquired esotropia is controversial. In a case series by Wong et al.,[12] seven patients with symptomatic diplopia and concomitant cerebellar disease were examined. Amongst these seven patients, diplopia secondary to esotropia was commonly the first expression of an underlying problem. In all cases, the patients had an esotropia worse at distance, showed no slowing of abducting saccades, and had full range of motion of both eyes. Additionally, each patient's binocular system was within normal limits, thereby decreasing the likelihood of diplopia caused by a decompensated congenital esotropia.

Two major theories have garnered more acceptance than the rest. The first, and most likely, is that cerebellar esotropia is caused by an excess in convergence tone.[12] This theory is supported by research that shows the important role the cerebellar vermis plays in vergence eye movements.[13,14] Lesions to this area could produce excessive convergence tone. In Wernicke's encephalopathy, lesions arise throughout the brainstem and cerebellum, and our patient had long-term cerebellar atrophy.[10] This theory has been tested in animal and human studies. In one study including patients with cerebellar strokes, researchers found that those in which the vermis was involved showed difficulty with slow vergence eye movements and an impairment in divergence. The pursuit conjugate system remained intact, implying that the vermis plays an important role in vergence control.[13] Likewise, in a study on patients with cerebellar degeneration, all subjects had an esodeviation.[14] Additionally, in a primate study, animals that underwent ablation to the vermis showed an esodeviation following the procedure.[15] Another possibility is that these patients can suffer a lateral rectus paresis. However, in our case, there were no clinical findings to support this hypothesis. In the same case series, all patients were successfully treated with prism, botulinum toxin, or surgical intervention.[12]

These cerebellar acute-onset esotropias do not behave in the same way as a typical esotropia and are much more volatile.[12] Careful evaluation and monitoring is crucial. Additionally, it is important to speak with the patient's other providers to evaluate their overall clinical picture when making decisions. Based on current limited research, it is reasonable to assume that using prism on these patients will improve their symptoms. In this case, the patient's esotropia resolved without treatment. Most importantly, when an acute-onset esotropia presents, especially in the presence of other cerebellar symptoms, Wernicke's encephalopathy must be a differential diagnosis since prompt treatment is essential.

In addition to the rare finding of acquired esotropia, this patient also had the classic finding of nystagmus. Most patients with upbeat nystagmus from cerebellar disease are asymptomatic, as it is unusual for the amplitude of the nystagmus to be large enough to cause oscillopsia.[16] As such, treatment is usually not indicated. Upbeat nystagmus is typically associated with diffuse damage to the brainstem, namely the medulla. Other common structural and non-structural causes include multiple sclerosis, meningitis, encephalitis, stroke, Pelizaeus-Merzbacher disease, and nicotine intoxication.[16] Nystagmus develops secondary to a disruption of the vestibular signals or to the neural integrator. For example, with upbeat nystagmus, if the vestibular input fibers from the anterior semicircular canals are disrupted before the vestibular nucleus, the eyes will slowly drift down, causing the quick corrective upbeat. Damage to the mesencephalic interstitial nucleus of Cajal, the vertical gaze neural integrator, can also lead to nystagmus by disrupting the ability to maintain eccentric fixation. Without the neural integrator, there is no signal to agonist extraocular muscles to surmount the drive pulling the eyes back to the central position. As a result, nystagmus will develop, with its fast element in the direction of gaze and its slow element, with no inhibitory signal, drifting back to primary gaze.[17] The most important aspect of treating nystagmus is determining the underlying cause. As acquired nystagmus is overwhelmingly due to brainstem pathology, further evaluation is imperative and potentially lifesaving. For the majority of patients diagnosed with Wernicke's encephalopathy, their nystagmus will resolve after treatment is initiated. However, this is not always the case. Our patient had persistent nystagmus months after his diagnosis.

Interestingly though, his presentation changed to be gaze-dependent, with the fast phase in the direction of fixation. This indicates a disruption in the horizontal and vertical neural integrators.[17] Fortunately, due to the low amplitude of this persistent nystagmus, he remained asymptomatic. Proposed treatments for oscillopsia vary greatly from optical to more invasive options. Several limited studies have shown modest success with fitting gas permeable lenses, with the goal of obtaining retinal image stabilization. However, most of these studies have focused on congenital nystagmus. Additionally, success is narrowed by several parameters, including type of nystagmus, underlying acuity, presence of a null point, and visual acuity.[18,19] Another avenue with some promise is using botulinum toxin; however, this treatment also comes with significant risks and the potential for unwanted side effects, including diplopia.[19]

Conclusions

This paper reviews literature discussing sudden-onset esotropia and nystagmus in cerebellar disease and defines optometry's role in treatment. These patients suffer deficits in their mental, psychological, and motor function, in addition to their visual findings. Proper education and open discussion between providers is crucial for recovery. For example, a patient's physical therapy efforts may be limited by significant visual symptoms such as oscillopsia and diplopia. Furthermore, these patients may have difficulty advocating for themselves due to their mental capacity or speech impairments. Optometrists are in a unique position to educate others on these rare visual symptoms and provide insight into how such symptoms could affect other areas of recovery.

This case study, which highlights the rare finding of acquired esotropia in Wernicke's encephalopathy, also demonstrates the importance of optometrists evaluating for cerebellar disease when patients present with acute-onset esotropia. This case reviewed two of the ocular manifestations of Wernicke's encephalopathy; however, these are just two of many. Other documented neuro-ophthalmic manifestations include ophthalmoparesis, other forms of nystagmus, vestibular dysfunction, deficits in saccades and pursuits, pupillary dysfunction, and rarely, vision loss associated with papilledema or at the level of the cortex. It is imperative that Wernicke's encephalopathy and other cerebellar conditions are considered in the differential diagnosis of oculomotor disorders, particularly because the prognosis of Wernicke's encephalopathy changes drastically based on when treatment is initiated. It is essential that these patients are frequently monitored by an optometrist due to rapidly changing and unstable binocular vision findings.

References

1. Harper C, Fornes P, Duyckaerts C, Lecomte D, Hauw JJ. An international perspective on the prevalence of the Wernicke-Korsakoff syndrome. Metab Brain Dis 1995;10(1):17-24.
2. Martin PR, Singleton CK, Hiller-Sturmhofel S. The role of thiamine deficiency in alcoholic brain disease. Alcohol Res Health 2003;27(2):134-42.
3. Torvik A, Lindboe CF, Rogde S. Brain lesions in alcoholics: A neuropathological study with clinical correlations. J Neurol Sci 1982;56:233-8.
4. Lindboe CF, Loberg EM. Wernicke's encephalopathy in non-alcoholics: An autopsy study. J Neurol Sci 1989;90:125-9.
5. Singh S, Kumar A. Wernicke encephalopathy after obesity surgery: A systematic review. Neurology 2007;68(11):807-11.
6. Sechi G, Serra A. Wernicke's encephalopathy: New clinical settings and recent advances in diagnosis and management. Lancet Neurol 2007;6:442-55.
7. Galvin R, Bråthen G, Ivashynka A, et al. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol 2010;17:1408-18.
8. Talwar D, Davidson H, Cooney J, et al. Vitamin B1 status assessed by direct measurement of thiamin pyrophosphate in erythrocytes or whole blood by HPLC: Comparison with erythrocyte transketolase activation assay. Clin Chem 2000;46:704-10.
9. Antunez E, Estruch R, Cardenal C, et al. Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. AJR Am J Roentgenol 1998;171:1131-7.
10. Manzo G, De Gennaro A, Cozzolino A, et al. MR imaging findings in alcoholic and nonalcoholic acute Wernicke's encephalopathy: A review. Biomed Res Int 2014:503596.
11. Kopelman MD, Thomson AD, Guerrini I, Marshall EJ. The Korsakoff syndrome: Clinical aspects, psychology and treatment. Alcohol Alcohol 2009;44:148-54.
12. Wong SH, Patel L, Plant GT. Acquired esotropia in cerebellar disease: A case series illustrating misdiagnosis as isolated lateral rectus paresis and progression over time. Neuroophthalmol 2015;39(2):59-63.
13. Sander T, Sprenger A, Neumann G, Machner B, et al. Vergence deficits in patients with cerebellar lesions. Brain 2009;132:103-15.
14. Versino M, Hurko O, Zee DS. Disorders of binocular control of eye movements in patients with cerebellar dysfunction. Brain 1996;119:1933-50.
15. Takagi M, Tamargo R, Zee DS. Effects of lesions of the oculomotor vermis on eye movements in primate: Binocular control. Prog Brain Res 2003;142:19-33.
16. Beh SC, Frohman TC, Frohman EM. Neuro-ophthalmic manifestations of cerebellar disease. Neurol Clin 2014;32(4):1009-80.
17. Burde RM, Savino PJ, Trobe JD. Ocular oscillations. In: Burde RM, Savino PJ, Trobe JD, eds. Clinical Decisions in Neuro-Ophthalmology. St. Louis MO: Mosby, 2002:220-43.
18. Rushton D, Cox N. A new optical treatment for oscillopsia. J Neurol Neurosurg Psychiatry 1987;50:411-5.