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Clinical Reasoning: A 48-Year-Old Woman Presenting With Vertigo, Ptosis and Red Eyes

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Abstract

We describe acute vestibular syndrome in a 48-year-old woman with breast cancer who was finally found to have anti-Ma2-associated encephalitis. Even though the initial diagnosis was vestibular neuritis elsewhere, progression of symptoms and additional findings of bilateral ptosis and circumlimbal injections, vertical saccadic slowing, and impaired convergence led to a suspicion of a rostral midbrain lesion and final diagnosis. The patient's symptoms and ocular motor signs improved markedly after administration of intravenous methylprednisolone and oral tacrolimus. Our patient again stresses the importance of scrutinized ocular motor evaluation for detection of central lesions even in patients with the clinical features of unilateral peripheral vestibulopathy.

Section 1

A 48-year-old woman presented with spontaneous vertigo and nausea for two weeks. The patient was diagnosed with vestibular neuritis elsewhere, but her dizziness and imbalance worsened despite treatments. She reported a constant spinning sensation of her body irrespective of position changes. The patient also developed painful red eyes one week before presentation. Two years earlier, she had been diagnosed with invasive lobular carcinoma in her right breast and underwent modified radical mastectomy followed by adjuvant chemotherapy and tamoxifen. The patient was not placed on any immunosuppressive treatment, thereafter. She did not have headache, tinnitus, ear fullness, or hearing loss.

Examination showed circumlimbal injection and ptosis in both eyes (Figure 1) as well as spontaneous nystagmus beating rightward. Ductions and versions were full, but saccades seemed slow in vertical direction. Convergence was also impaired. Bedside head-impulse tests (HITs) were positive for the left horizontal canal (HC). The patient fell immediately on standing without support, yet was able to sit on her own (truncal ataxia grade

3). Slit lamp examination revealed uveitis and cells in the anterior chamber in the right eye.

Neurologic examination was otherwise normal.

Question for consideration:

1. Which findings stand against the diagnosis of vestibular neuritis?
2. What are some advanced vestibular function tests that can help determine central vs. peripheral involvement?

Section 2

Vestibular neuritis is characterized by acute spontaneous vertigo, nausea/vomiting, and unsteadiness due to unilateral vestibular deafferentation.¹ Patients exhibit spontaneous horizontal-torsional nystagmus beating away from the lesion side, positive HITs, ipsilesional canal paresis, and a tendency to fall toward the lesion side. The contralateral spontaneous nystagmus and positive HITs initially appeared to support the diagnosis of vestibular neuritis in our patient. However, severe truncal ataxia and worsening of symptoms over a two-week span are atypical for vestibular neuritis. Moreover, ptosis, vertical saccadic slowing and painful red eyes raised suspicion of a midbrain lesion, associated with systemic inflammation.

For these reasons, a thorough vestibular evaluation was conducted (Table). Video-oculography showed spontaneous nystagmus beating rightward and clockwise without visual fixation (Figure 2A). Horizontal saccades were hypometric and vertical saccades were slow (Figure 2B, Video 1). Video-HITs showed decreased gains of the vestibulo-ocular reflex (VOR) for the anterior and posterior canals on both sides as well as for the left HC (Figure 2C). Bithermal caloric tests showed a canal paresis of 76% in the left ear (sum of the peak slow-phase velocities = $17^{\circ}/s$). Torsional quick phases were abolished during head tilting to both sides and optokinetic stimulation (Video 2). Pure tone audiometry was normal.

Question for consideration:

1. How does the laboratory testing change your differential diagnosis?
2. What is the localization of the lesion based on these findings?
3. What are the possible etiologies causing these findings?
4. What are the next tests you would order?

Section 3

Bilaterally abnormal HITs of the vertical canals make the diagnosis of vestibular neuritis least likely. Rather, the combination of impaired torsional VOR and diminished torsional quick phases with vertical saccadic slowing, and impaired convergence suggest a rostral midbrain lesion predominantly involving the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and the interstitial nucleus of Cajal (INC). Bilateral ptosis in the absence of gaze palsy suggests an incomplete nuclear or infranuclear lesion of the oculomotor nerve. The contralateral spontaneous nystagmus and positive HITs indicates an asymmetric involvement of the direct VOR circuit from the primary vestibular afferent to the ocular motor nuclei.

The excitatory burst neurons that generate vertical and torsional saccades reside in the riMLF, which project bilaterally to the ocular motor neurons of the elevator muscles, but ipsilaterally to those of the depressor muscles.¹ The riMLF lies dorsomedial to the rostral pole of the red nucleus and lateral to the periaqueductal gray matter, rostral to the INC (eFigure 1).¹ Experimental severance of the bilateral riMLF causes vertical saccadic slowing, and abolishes torsional quick phases during torsional VOR or optokinetic stimulation. The INC, which lies just beneath the riMLF, plays a key role in holding eccentric vertical gaze as well as in vertical and torsional VOR.² It projects ipsilaterally to the ocular motor neurons via

the posterior commissure. Inactivation of the bilateral INC causes reduced gain of the vertical and torsional VOR as well as vertical gaze-evoked or upbeat nystagmus.¹⁻³ Given the predominant impairment of vertical and torsional saccades, along with vertical and torsional VOR impairments, the riMLF and INC may have been damaged in our patient. Bilateral ptosis also indicates a partial involvement of the central caudal nucleus.

Several diseases involving the rostral midbrain present vertical supranuclear eye movement abnormalities.⁴ The subacute onset observed in our patient raises a suspicion of inflammatory, infectious, or demyelinating disease involving the rostral midbrain, such as anti-Ma2 associated encephalitis, viral rhombencephalitis, Creutzfeldt-Jakob disease, or Whipple disease. It could also be caused by neurodegenerative diseases such as progressive supranuclear ophthalmoplegia, Niemann-Pick type C, midbrain infarction, or even a pineal gland tumor compressing the rostral midbrain tectal plate.

The abovementioned information necessitated brain MRI and cerebrospinal fluid (CSF) analysis. Brain MRIs and angiography with gadolinium-enhancement were normal, and there were no discernible findings on fat suppression images of the orbit. CSF analysis showed pleocytosis of 114/mm³ (75% lymphocytes) and protein of 69 mg/dL. CSF cytology and venereal disease research laboratory tests were negative. The serum was positive for anti-Ma2 antibody, but negative for other paraneoplastic antibodies. The serum was also negative for autoimmune and viral markers. Breast ultrasonography, mammography, and CT with contrast for the chest, abdomen, and pelvis all yielded normal results. ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) did not reveal any evidence of metastasis or tumor relapse. The patient was administered 1 g per day of intravenous methylprednisolone for five consecutive days, followed by 1 g per day of tacrolimus for one month. The patient reported improvement of dizziness and was able to walk without support. The right-beating nystagmus and abnormal HITs improved markedly, and the patient's ptosis and uveitis resolved one

month later.

Question for consideration:

1. What is the diagnosis and prognosis?

Discussion

Our patient with anti-Ma2-associated encephalitis showed vertical saccadic slowing, abnormal HITs for the vertical semicircular canals, impaired torsional VOR, and disappearance of torsional quick phases along with anterior uveitis.

Ma1 and Ma2 are intracellular proteins expressed in the testis and brain, particularly in the limbic and brainstem region.⁵ Patients with anti-Ma2-associated encephalitis can therefore present with memory impairment, hypersomnolence, and ocular motor abnormalities.⁶ These symptoms are mostly associated with testicular tumors but sometimes with lung, breast, or ovarian cancers. Unlike other paraneoplastic syndromes that rapidly progress over six to eight weeks, anti-Ma2-associated encephalitis progresses slowly, thereby complicating the diagnosis.^{6,7} Although tacrolimus was chosen for treatment in consideration of our patient's economic status, rituximab, mycophenolate mofetil, and cyclophosphamide are more widely used for immunomodulation in paraneoplastic syndrome. In general, anti-Ma2-associated paraneoplastic syndrome is challenging to treat since neurologic deterioration can be observed in nearly half of all patients.⁶ Yet, a favorable outcome can be expected in patients aged younger than 45 years, those with limited involvement of the nervous system in the limbic, brainstem, and cerebellum, or those with favorable tumor response to treatment.⁶ Furthermore, since anti-Ma2-associated encephalitis is frequently accompanied by ocular motor abnormalities,^{4,6} analyses of ocular motor function can aid in early detection, leading to a favorable outcome. Likewise in our patient, vertical gaze paresis is the most prominent

ocular motor finding in anti-Ma2-associated encephalitis along with other ocular motor abnormalities such as ptosis, vertical ophthalmoplegia, opsoclonus, downbeat or upbeat nystagmus, and skew deviation.⁶⁻⁸

Acute unilateral peripheral vestibulopathy may initially have been presumed based on the horizontal nystagmus and abnormal HITs. However, red eyes may be an alarm for inflammation not confined to the vestibular afferents in our patient. Although the patient exhibit neurologic signs of unilateral peripheral vestibulopathy, other ocular motor findings should be fully sought especially among those with an atypical presentation.

The combination of ocular inflammation and vestibulopathy may also raise a suspicion of Cogan syndrome; an inflammatory disorder due to autoantibodies against the cornea and inner ear. However, red eyes are ascribed to non-syphilitic interstitial keratitis in Cogan syndrome. Moreover, our patient did not have hearing loss, which is characteristic of Cogan syndrome.⁹ Let alone the central ocular motor signs from midbrain dysfunction, our patient implicates that detection of the subtle signs of systemic inflammation is important in patients presenting with acute/subacute vestibular syndrome.^{9, 10}

Our patient showed no evidence of recurrence of breast cancer. Indeed, recurrence of tumor can follow paraneoplastic syndrome.¹¹ This may be ascribed to limited diagnostic yield of conventional screening tests. Since the smallest breast tumor detectable by mammography measures 2.1 mm,¹² and sensitivity of FDG-PET in detecting breast tumors less than 2 cm in size is less than 50%,¹³ a recurrence may have been missed. Given that the average tumor volume doubling time of breast cancer is 280 days,¹⁴ a repeated screening with breast MRI and mammography every 6 months at least for 4 years is recommended for our patient.¹⁵

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References

1. Leigh RJ, Zee DS. The Neurology of Eye Movements, 5th ed. New York: Oxford University Press; 2015.
2. Helmchen C, Rambold H, Fuhry L, Büttner U. Deficits in vertical and torsional eye movements after uni- and bilateral muscimol inactivation of the interstitial nucleus of Cajal of the alert monkey. *Exp Brain Res* 1998;119:436–452.
3. Bhidayasiri R, Plant GT, Leigh RJ. A hypothetical scheme for the brainstem control of vertical gaze. *Neurology* 2000;54:1985–1993.
4. Lloyd-Smith Sequeira A, Rizzo J-R, Rucker JC. Clinical approach to supranuclear brainstem saccadic gaze palsies. *Front Neurol* 2017;8:429.
5. Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J. Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. *Ann Neurol* 2001;50:339–348.
6. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 2004;127:1831–1844.
7. Castle J, Sakonju A, Dalmau J, Newman-Toker DE. Anti-Ma2-associated encephalitis with normal FDG-PET: a case of pseudo-Whipple's disease. *Nat Clin Pract Neurol* 2006;2:566–572.
8. Garcia-Reitboeck P, Thompson G, Johns P, Al Wahab Y, Omer S, Griffin C. Upbeat nystagmus in anti-Ma2 encephalitis. *Pract Neurol* 2014;14:36–38.
9. Lee SU, Kim JS, Hyon JY, et al. Pearls & Oysters: Cogan syndrome: A potentially grave disorder of audiovestibulopathy with many faces. *Neurology* 2019;93:39–41.
10. Russo FY, Ralli M, De Seta D, et al. Autoimmune vertigo: an update on vestibular disorders associated with autoimmune mechanisms. *Immunol Res* 2018;66:675–685.
11. Graus F, Delattre J, Antoine J, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135–1140.
12. Spratt JS, Greenberg RA, Heuser LS. Geometry, growth rates, and duration of cancer

and carcinoma in situ of the breast before detection by screening. *Cancer Res* 1986;46:970–974.

13. Avril N, Rose C, Schelling M, et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. *J Clin Oncol* 2000;18:3495–3502.
14. Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. *J Surg Oncol* 1997;65:284–297.
15. Titulaer M, Soffiatti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol* 2011;18:19–e13.

Table

Table. Summary and explanation of key ocular motor findings in the patient

Vestibular and ocular motor tests	How-to-do / purpose of the test	Normal findings	Positive findings in our patient	Interpretation (*)
Ocular alignment and movement	Measurement of the ocular alignment and of angles of strabismus with alternate cover test using a prism bar	Orthophoria with normal duction and version	Exotropia of 6 prism diopters No skew deviation Impaired convergence	Impaired convergence pathway (supraoculomotor area in the rostral midbrain)
Spontaneous nystagmus	Recording of spontaneous nystagmus while fixating on a target and in darkness	No nystagmus	Right and clockwise nystagmus without visual fixation	Impaired VOR for the left semicircular canals
Saccades	Shifting one's gaze between two separated targets while not moving the head / Assessment of the patient's ability to accurately move	Normal saccadic initiation (latency), gain, velocity	Vertical saccadic slowing, hypometria	Impaired saccadic generation (superior colliculus or riMLF)

	the eyes from one designated point to another in a single, quick movement			
Video HITs	Staring at an earth-fixed target during head impulses along the alignment of the semicircular canals / Evaluation of the high-frequency VOR	Normal gains and no covert or overt saccades	Reduced gain of the VOR for left HC and vertical canals in absence of corrective saccades	Impaired VOR in the left, impaired VOR for the ACs and PCs on both sides (INC)
Bithermal caloric tests	Eliciting a convection current of the endolymph using cold and warm water (or air) in each ear / Evaluation of the low-frequency VOR	Canal paresis < 25% Directional preponderance < 30%	canal paresis of 76% in the left ear	Impaired VOR in the left horizontal canal
Rotatory chair tests	Sinusoidal angular rotation and acceleration or	Normal VOR gain, symmetry, phase, time	Decreased gain of the VOR, counter-	Impaired VOR in the left

	deceleration of the	constants,	clockwise	
	body in the yaw	normal tilt	asymmetry,	
	plane / Evaluation	suppression	and phase lead	
	of mid-frequency		during	
	VOR		sinusoidal	
			harmonic	
			acceleration	
Optokinetic	Placing a moving	Nystagmus with	Abolished	Decreased gain of
nystagmus	optokinetic drum	slow phases in	vertical and	vertical and
	or visual patterns	the direction of	torsional quick	torsional VOR;
	on a monitor in	the pattern	phases of the	impaired torsional,
	front of the	movement	optokinetic	vertical reflexive
	patient's visual		nystagmus	saccade generation
	field / Evaluation			(riMLF)
	of the reflexive			
	saccades			

- 1 *Most plausible neural substrates responsible for the abnormal eye movements in our patient
- 2 [†the upper poles of the eyes beating to the patient's right shoulder.
- 3 AC = anterior canal, HITs = head-impulse tests, INC = interstitial nucleus of Cajal, PC =
- 4 posterior canal, riMLF = rostral interstitial nucleus of medial longitudinal fasciculus, VOR =
- 5 vestibulo-ocular reflex

Figure Legends

Figure 1. The patient shows circumlimbal injection and ptosis in both eyes, more prominent in the right (validated bulbar redness scale 90 in the right and 50 in the left eye). Please note the irregular-shaped pupil around the lower pupillary margin in the right eye from posterior synechiae (yellow arrow).

Figure 2. Neurotologic findings of the patient. **A.** Video-oculography (SLVNG, SLMED, Seoul, Republic of Korea) shows right-beating spontaneous nystagmus without visual fixation. The torsional trace is removed due to severe noise. **B.** Saccades are slow in vertical directions. **C.** Video head-impulse tests show decreased gains of the vestibulo-ocular reflex (VOR) for the anterior (ACs, normal gain = 0.75 – 1.29) and posterior canals (PCs, normal gain = 0.77 – 1.13) on both sides as well as for the left horizontal canal (HC, normal gain = 0.88 – 1.27). Note the absence of corrective saccades despite the decrease of VOR gain for the vertical semicircular canals. Upward deflection indicates rightward or upward eye motion in figures A and B.

H = horizontal position of the left eye, INC = the interstitial nucleus of Cajal, riMLF = rostral interstitial nucleus of the medial longitudinal fasciculus, V = vertical position of the left eye.

Video legends

Video 1. Video-oculography shows prominent saccadic slowing in vertical directions. For comparison, vertical saccades in a healthy subject are also presented. The horizontal saccades are hypometric but exhibit mostly normal saccadic velocity in our patient. Please note the irregular lower pupillary margin due to the posterior synechiae from anterior uveitis involving the right eye.

Video 2. The torsional VOR is impaired along with diminished torsional quick phases during head tilt to either side and torsional optokinetic stimulation.

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