Clinical Reasoning: A Dizzy Architect

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Abstract

There is an increasing body of evidence describing an association between anti–Kelch-like protein 11 (KLHL11) encephalitis and various tumors such as seminoma. However, when the diagnosis of neoplasia is uncertain and the clinical syndrome resembles those caused by other etiologies, the possibility of anti-KLHL11 encephalitis may not be obvious during early clinical evaluations. We present the case of a 68-year-old man with clinical features of anti-KLHL11 encephalitis, in whom no clear signs of an active neoplasia could be found. However, a burnt-out germ cell tumor was suspected. This case highlights the importance of having a high clinical suspicion for anti-KLHL11 encephalitis in patients who exhibit symptoms and signs, even in the absence of an active tumor.

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Section 1

A 68-year-old retired architect with an unremarkable medical and family history presented to his primary care provider with acute vertigo, nausea, and vomiting. There was no history of excessive alcohol consumption, illicit drug use, or exposure to toxins. He was a smoker (33py). A brain MRI showed nonspecific white matter disease (Figure 1A) but was otherwise normal. He was diagnosed with vestibular neuritis and was prescribed symptomatic treatment, which led to partial improvement.

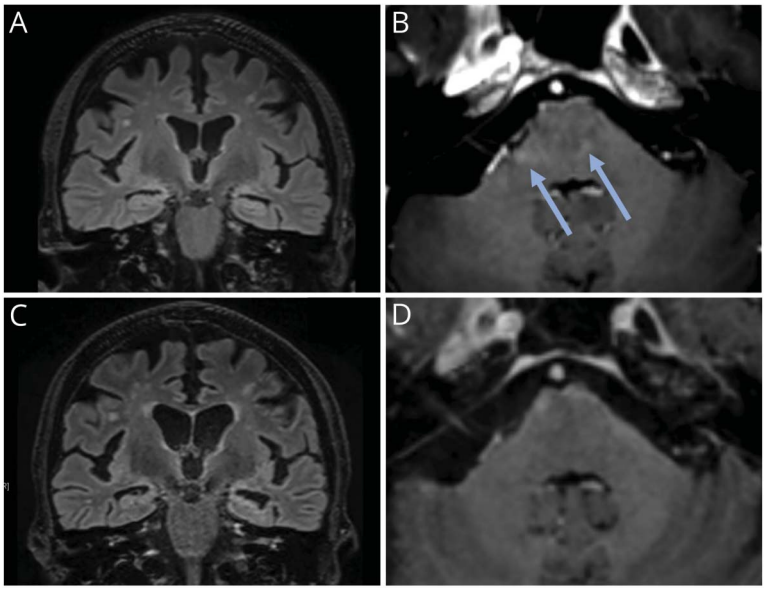
Over the next 5 months, he complained of fluctuating vertigo and nausea, fatigue, a 13-kg weight loss, and depression with anxiety. There were no headaches, diplopia, dysphagia, dysarthria, muscle weakness, troubles with coordination or sensation, diarrhea, vomiting, joint pain, fever, night sweats, or skin/mucosal changes.

In the 4 weeks before admission, he had progressive diplopia and difficulty walking. On examination, the patient was fully oriented, afebrile, and in a poor general state of health. Spontaneous grade I horizontal left-beating nystagmus, catch-up saccades during the head-impulse test to the right, and saccadic slowing to the right with limited range of motion were observed. Smooth pursuit eye movements and vestibulo-ocular reflex (VOR) to the right were preserved. Strength and sensation to light touch were normal. Pallesthesia was 4–5/8 on both malleoli. Reflexes were 1+ on the right and 2+ on the left. Slight ataxia was present in all extremities along with a slight unsteadiness while standing. Romberg sign was negative. Straight-line walking was impossible.

Question for Consideration:

1. What is the localization of the symptoms/signs?

Figure Brain MRI Scans



(A) Initial brain MRI (FLAIR, coronal view) showing nonspecific white matter hyperintensities. (B) Initial brain MRI (T1-MPR after IV gadolinium, axial view) showing patchy gadolinium enhancement in the pons involving the right lateral pontomedullary junction and paramedian structures (arrows). (C) Brain MRI after 6 months (FLAIR, coronal view) showing progressive atrophy and white matter disease. (D) Brain MRI after 6 months (T1-MPR after IV gadolinium, axial view) without gadolinium enhancement.

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Section 2

Left-beating spontaneous nystagmus and pathologic head-impulse test to the right are typically signs of a right-sided peripheral vestibulopathy, yet the fluctuating vertigo and nausea for 6 months and ocular motor disturbances make this unlikely. A lesion of the lateral pontomedullary junction involving the vestibular nerve root entry zone and the vestibular nuclei can mimic a lesion of the vestibular nerve. The saccadic gaze palsy with slowing to the right indicates a lesion of the right paramedian pontine reticular formation (PPRF). Ataxia of all limbs, stance, and gait are compatible with a pan-cerebellar dysfunction. In sum, all signs can be explained by a CNS disorder involving the right paramedian caudal pons, right lateral pontomedullary junction, and the cerebellum. The combination of cerebellar and pontomedullary dysfunction is defined as rhombencephalopathy.

During the first days of hospitalization, the patient complained of progressive diplopia and gait disturbance. Clinical signs progressed: saccades to the right became increasingly slow until, 6 days after admission, volitional saccades to the right were impossible. Saccades to the left became slowed as well, as did vertical saccades. Convergence remained intact, as did reflexive (smooth pursuit, VOR) conjugated eye movements except for muscle weakness in the right lateral rectus. Upward gaze was limited, speech became scanning, and gait increasingly broad based with need for a walker-rollator. Reflexes on the left side became exaggerated. In addition, perioocular myorhythmia and limb fasciculations appeared. Slight behavioral disinhibition, memory deficits, and a positive applause sign were noted.

Questions for Consideration:

1. What structures are involved explaining the progressive ocular motor disturbance?
2. What is the differential diagnosis?
3. Which investigations would you perform?

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Section 3

The progressive ocular motor signs are due to increasing dysfunction of both PPRFs, mostly the caudal parts and more on the right, and the abducens nerve fascicle innervating the right lateral rectus muscle. Altogether, the clinical syndrome is that of a subacute-progressive rhombencephalopathy with additional frontotemporal (disinhibition and memory deficits) and peripheral nervous system (myorhythmia and fasciculations) symptoms/signs. The initial fluctuating symptoms followed by rapid progression over several weeks, widespread nervous system involvement, and normal MRI at symptom onset make an ischemic, toxic, neurodegenerative, genetic, or mechanical cause unlikely. Likely pathogenetic causes are autoimmune-inflammatory, infectious, or metabolic.

The clinical picture here fits well into that of inflammation (i.e., rhombencephalitis), be there external pathogens (i.e., infectious/parainfectious), neoplasia (neoplastic or paraneoplastic), or idiopathic causes (i.e., rheumatologic diseases). A paraneoplastic disorder seemed possible, for example, associated with Ma-2/Ta, Yo, Hu, GAD, or CRMP5/CV2

Table Investigations

	Result	Normal value
Serum		
ANA, ANCA, and ENA-Screen	Negative	Negative
GQ1b Abs	Negative	Negative
Onconeural Abs (Hu, Ri, and Yo)	Negative	Negative
Paraneoplastic/autoimmune encephalitis Abs ([a])	Negative	Negative
HIV, HBV, HCV, *Treponema*, and *Borrelia* serology	Negative	Negative
Alpha-fetoprotein (AFP) (ng/mL)	16.1	<8.1
Thiamine (nmol/L)	120	67–200
***T. whipplei* PCR**	Negative	Negative
CSF		
Cell count (/μl)	4	<5
Protein (g/L)	1.018	<0.45
Glucose (mmol/L)	4.2	<3.9
Lactate (mmol/L)	2.2	<2.1
Oligoclonal IgG	Positive, >5 unmatched bands	Negative
***T. whipplei* PCR**	Negative	Negative
Protein 14-3-3 and RT-QuiC	Negative	Negative
HSV-1-, HSV-2-, and VZV-PCR	Negative	Negative
Electrophysiology	No signs of large fiber neuropathy	
CT scan		
Thorax, abdomen, and pelvis	Unremarkable	
Endoscopy		
Gastro-/colonoscopy and cystoscopy	Unremarkable	
Ultrasonography		
Thyroid gland	Unremarkable	
Testis	Left testis hypoechogenic, less vascularized. No mass lesion	
Caloric testing	Right areflexia, left normal	

[a] Amphiphysin, CRMP5/CV2, Ma-1/-2, GAD65, NMDA, GABA-B1, CASPR2, LGI1, AMPA-1/2, ANNA-3, PCA-2, TR, ZIC4, DPPX, ER1, Neurofascin (NF 155 and 186), AT1A3, mGluR-1 and -5, Neurexin, Neurochondrin, RhoGTPase-activating protein 26, Contactin 1, Dopaminreceptor2, Flotillin-1/2, GABA-A-R, GluRD2, Homer 3, and KCNA2.

antibodies. The rather long course and lack of infectious symptoms before neurologic symptoms argued against a parainfectious pathogenesis, yet a GQ1b antibody–associated disorder seemed possible. CNS tuberculosis seemed unlikely due to lack of immunosuppression, night sweats, fever, or chronic cough. An infection with *Tropheryma whipplei* (Whipple disease) can lead to myorhythmia, psychiatric symptoms, and gaze disturbances, but intestinal symptoms and fever are typically present. Myocloni, fasciculations, and cerebellar and pyramidal symptoms also evoke prion disease, but there was no evidence of dementia. Neuro-Behçet syndrome was considered unlikely due to the lack of oral or genital ulcers, as was progressive multifocal leukoencephalopathy because there was no immunosuppression whatsoever. Of course, thiamine deficiency should always be considered (and treated!) in patients with neuro-ophthalmic disorders and ataxia. The initial brain MRI performed 6 months before hospitalization was reanalyzed, and a patchy Gadolinium enhancement of the pontomedullary junction was noted (Figure, B, arrows).

In conclusion, an autoimmune encephalitis seemed most likely. Considering the weight loss, which was ongoing during hospitalization culminating in 15 kg within 6 months, a paraneoplastic pathogenesis was probable. The results of the diagnostic tests are shown in the Table.

Questions for Consideration:

1. How do you interpret the results? What other tests would you order?
2. Would you treat the patient? How?

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Section 4

Compared with the initial MRI 6 months earlier, the actual brain MRI showed generalized cortical-subcortical atrophy (Figure, C) without DWI abnormalities or gadolinium enhancement (Figure, D). The white matter lesions were slightly progressive. CSF was inflammatory without signs of infection: Protein content was increased (with normal cell count), and >5 unmatched oligoclonal IgG bands (OCBs) were present. The presence of OCBs suggests inflammation (e.g., autoimmune) within the CSF. An extensive search for onconeural and autoimmune encephalitis antibodies revealed no positive results. Parainfectious and systemic antibodies were negative. No tumor could be found, yet sonography of the left testis showed hypoechogenicity and a reduced vascularization. Alpha-fetoprotein (AFP) was slightly elevated. A left orchiectomy was performed. Histologic examination of the entire left testis revealed fibrotic testicular tissue with no evidence of neoplasia. After orchiectomy, AFP returned to normal.

IV methylprednisolone 1000 mg daily for 3 days was begun due to a high level of suspicion for an inflammatory autoimmune etiology. The steroid treatment brought no significant clinical improvement.

Questions for Consideration:

1. Would you change the treatment?
2. What investigations would you perform?

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Section 5

Because of the lack of clinical improvement and suspicion of an autoimmune inflammatory etiology, he received IV immunoglobulins (IVIGs) 0.4 g/kg daily for 5 days, followed by a long-term tapered regimen of oral prednisolone. A slight improvement in ocular motility and gait was observed. Body FDG-PET-CT showed no signs of neoplasia.

We interpreted the histologic testicular findings as a burnt-out germ cell tumor and had Kelch-like protein 11 (KLHL11) antibodies in serum and CSF analyzed, which turned out positive (titer in serum 1:160,000, in CSF 1:16,000). The diagnosis of a KLHL11 antibody–associated paraneoplastic encephalitis (predominantly rhombencephalitis) was made.

The patient was discharged to a rehabilitation clinic. Five months after discharge, he developed spontaneous skin hematomas. An acquired hemophilia was diagnosed, and therapy with cyclophosphamide, plasmapheresis, and IVIG was initiated, followed by long-term immunosuppression with rituximab. Prednisolone was tapered over 10 months. In the 1.5 years after diagnosis, gait and eye motility improved: the patient is now able to walk with bilateral walking aids without risk of falling. He gained 8 kg and reported significant improvement in mood. Unfortunately, cognition deteriorated significantly resulting in a mild dementia, so the patient moved to a nursing home.

Discussion

KLHL11 antibody–associated paraneoplastic encephalitis associated with (regressed) germ cell tumor was first described in 2019[1]; KLHL11 antibodies appear to be one of the most common neurologic paraneoplastic antibodies with a prevalence of 1.4/100,000.[1-3] KLHL11 is an intracellular protein playing a role in ubiquitination. Histopathologic studies of patients with seminoma and KLHL11 antibody encephalitis showed T-cell lymphocytic infiltrates within seminoma tissue, suggesting T-cell activation by an onconeuronal antigen.[2]

The most common neurologic syndrome in KLHL11 antibody encephalitis is rhombencephalitis alone or in combination with limbic encephalitis.[1,2] However, limbic encephalitis may rarely occur alone. Half of affected patients have vertigo and a third hearing loss and tinnitus.[2] Other clinical manifestations include seizures, neuropsychiatric symptoms such as anxiety and panic attacks, trigeminal neuropathy, fasciculations, and dementia. Patients without active neoplasia seem to have a worse prognosis.[2] Whether hemophilia is associated with KLHL11 antibody encephalitis remains unclear.

The diagnostic challenge of this case resides in the absence of known autoimmune encephalitis antibodies and the presence of only subtle clues of testicular cancer, despite a comprehensive workup. Nevertheless, an inflammatory pathophysiology was suspected early. This case highlights the importance of thorough clinical reasoning in determining the neurologic syndrome, likely pathogenesis, and early treatment regimen, even in the absence of unequivocal pathogenetic evidence. In conclusion, subacute rhombencephalopathy with testicular fibrosis should prompt the search for anti-KLHL11 antibodies.

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Niklaus Meier, MD	Department of Neurology, Thun Hospital, Thun, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation

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