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**Clinical Reasoning: A 43-Year-Old Man With Subacute Onset of Vision Disturbances, Jaw Spasms, Balance, and Sleep Difficulties**

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## Abstract

A brainstem syndrome is recognizable in patients presenting with a combination of visual disturbances, incoordination, gait problems, speech and swallowing difficulties and new onset sleep symptomatology. Brainstem disorders of subacute onset (onset and progression with accumulation of disabling deficits in 6-12 weeks) are generally of autoimmune, infectious, inflammatory or infiltrative neoplastic cause. An autoimmune or infectious brainstem disorder may be referred to as brainstem encephalitis or rhombencephalitis. We describe a patient with a paraneoplastic autoimmune rhombencephalitis, in whom diagnostic clues included: diverse visual and sleep symptoms, trismus and choking in the history; see-saw nystagmus, opsoclonus, dysarthria, jaw dystonia and episodic laryngospasm on examination; subtle but longitudinal and non-enhancing T2 MRI abnormalities in the brainstem and upper cervical cord, and oligoclonal bands in CSF. His movement disorder-specific neural IgG profile revealed ANNA-2 (anti-Ri) and KLHL-11-IgG. Both are biomarkers of paraneoplastic brainstem encephalitis, and KLCHL-11-IgG has been reported to accompany germ cell tumors, which was found in a solitary metastasis to the left inguinal lymph node in our patient, along with an atrophic left testis. Multidisciplinary treatment (autoimmune neurology, sleep medicine, ophthalmology, and psychiatry) led to significant clinical improvements. This case provides a framework for evaluation of patients with subacute onset brainstem syndromes, and the investigation and management of those with paraneoplastic and other autoimmune diseases.

## Section 1

A 43-year-old man, with prior left testicular torsion, presented with 2 weeks of imbalance, gait incoordination, double and blurred vision, and vertigo, and right lower extremity weakness. He denied confusion, disorientation, or associated memory issues. Observed eye movement abnormalities and ataxia upon initial evaluation, and elevated white cell count and protein in CSF, led to a Miller-Fisher syndrome diagnosis. He was treated with IVIg, accompanied by improvement in vertigo. Eight weeks later, diplopia and oscillopsia occurred, and he had jaw opening difficulties and clenching episodes (trismus), and hypersialorrhea. He required pureed diet, and subsequently gastrostomy tube for nutrition. He developed severe daytime hypersomnolence and sleep-related complex motor behaviors, with violent, thrashing limb movements, and screaming and shouting vocalizations. He was briefly hospitalized after a possible isolated seizure, though never confirmed (EEG did not reveal epileptiform discharges). Sixteen weeks into his illness, he developed choking episodes, nocturnal stridor and hypoxia. He was hospitalized again. He developed acute respiratory failure necessitating mechanical ventilation.

On examination, he had horizontal plane ophthalmoplegia (not overcome with vestibular ocular reflex), esotropia, jerk see-saw vertical nystagmus (**Video 1**) and superimposed opsoclonic bursts (**Video 2**). He had mixed flaccid-hyperkinetic dysarthria, and jaw closing dystonia (**Video 2**). He had oral-phase and pharyngeal dysphagia. He was wheelchair bound, only taking steps with a walker and maximum assistance. He had moderate upper extremity dysmetria (minimal in the lower extremities) and normal limb tone and strength. Jaw jerk and deep tendon reflexes were brisk, and sensory examination was normal. Hoffman and Babinski signs were negative. A left

inguinal mass was detected. Episodic shortness of breath accompanied by cyanosis (laryngospasm) was noted. Tracheostomy placement precluded polysomnographic studies.

Questions for considerations:

1. What is the significance of symptom onset and progression?
2. Where do the symptoms and signs localize to?
3. What is the differential diagnosis?
4. What tests would you perform?

## Section 2

The onset and progression, leading to significant disability within 6-12 weeks is consistent with a subacute disorder.<sup>1</sup> The age of onset and progression rate is atypical for hereditary disease and degenerative CNS diseases (except for Creutzfeldt-Jakob disease, where ataxia could be prominent and progress rapidly).

While the gait and balance difficulties, and extremity weakness do not localize well, the bilateral horizontal gaze palsies with opsoclonus, jerk see-saw nystagmus, laryngospasm, jaw dystonia, dysarthria, dysphagia and probable REM sleep behavior disorder assist in brainstem syndromic localization. Jerk see-saw nystagmus localizes to either medulla or mesodiencephalon, whereas pendular see-saw nystagmus localizes to the brainstem-mesodiencephalic junction.<sup>2</sup> A possible seizure suggested CNS multifocality, though this event could have represented hyperekplexia or generalized dystonic posturing with brainstem localization. While subacute peripheral nervous system disorders such as myasthenia gravis, Lambert-Eaton syndrome, and Miller-Fisher syndrome were considered, they were excluded because of CNS signs present, and absence of



fatigable weakness, autonomic and neuropathic signs. A brainstem disorder was the appropriate localizing syndrome. Differential diagnostic considerations for subacute onset brainstem disorders include toxic, infectious, neoplastic, inflammatory, and autoimmune causes (**Table**). Opsoclonus (with or without myoclonus) is rarely encountered beyond immune-mediated etiologies.<sup>3</sup>

A comprehensive evaluation including blood tests, MRI imaging, CSF analysis, and EEG was undertaken. General tests (CBC with differential, electrolytes, fasting glucose, C-reactive protein, liver function tests, urinalysis, chest x-ray) were all normal. Second-line blood tests were also normal (vitamin B12, methylmalonic acid, folate, antinuclear antibody with connective tissue diseases cascade, ANCA vasculitis panel and celiac disease serology). Discrete, longitudinally-extensive T2 hyperintensities in the pontine and medullary tegmentum, extending into the cervical cord (**Figure**), without mass effect, without enhancement has been reported in paraneoplastic disorders.<sup>3</sup> Typical features of demyelinating disease and CLIPPERS (pontine perivascular enhancement) were absent.<sup>4</sup> CSF studies revealed 37 white blood cells/mL (normal, <5/mL, 92%), lymphocyte-predominant, protein of 59 (normal, £35 mg/dL), normal glucose, normal IgG index and synthesis rate, and 4 CSF-exclusive oligoclonal bands (normal, <2). An elevated white cell count could also be encountered in infectious meningoencephalitis, but CSF-exclusive oligoclonal bands (or elevated CSF kappa free light chains) are indicative of CNS inflammation.<sup>5</sup> In addition, gram stain, aerobic and anaerobic cultures, and cytology were negative. CSF tests for herpes viruses, Lyme disease and listeria were also negative. EEG exhibited diffuse, generalized nonspecific slowing. Left groin ultrasound revealed atrophic testis and enlarged lymph node. CT whole-body did not reveal malignancy.

Questions for considerations:

1. What additional testing would you obtain to determine the diagnosis?

### Section 3

The subacute onset, syndromic features and inflammatory CSF, made the term rhombencephalitis appropriate. The presence of opsoclonus, the groin mass, the ‘tractopathy’ MRI findings, and CSF-exclusive oligoclonal bands made an autoimmune paraneoplastic cause most likely. A profile of neural antibodies pertinent to paraneoplastic and other autoimmune movement disorders was requested in serum (**Table**), revealing antineuronal nuclear antibody type-2 (ANNA-2, or anti-Ri) and kelch-like protein 11 (KLCHL11)-IgG. An excisional biopsy of the left inguinal lymph node revealed neoplastic components (**Figure, A-D**). Marked SALL4 reactivity was observed by immunohistochemistry, consistent with germ cell tumor. Marked NOVA1 (Ri, but not KLCHL-11) immunoreactivity was noted in the nuclei. PET-CT showed no evidence of retroperitoneal involvement. The patient underwent orchiectomy of the left testis (without additional chemotherapy). Pathology revealed a fibrotic testis surrounded by atrophic and sclerotic seminiferous tubules, without malignancy. Serial follow-up body imaging by FDG PET-CT over 1 year (and planned for 2 more) did not reveal cancer recurrence. Immune treatment (IV methylprednisolone 1g weekly for 12 weeks, and cyclophosphamide 1g/m<sup>2</sup> monthly for 6 months) was followed by near resolution of nystagmus and opsoclonus. Mobility gradually improved to the patient walking with a gait belt after 6 months follow-up, with further rehabilitation planned. The esotropia was treated with a 25-prism diopter (base out) Fresnel prism, but the patient continued to have significant horizontal gaze palsies. Jaw dystonia only marginally improved with a combination of botulinum toxin therapy, clonazepam and tizanidine, and ongoing gastrostomy feeding support was required. The patient received non-invasive positive-pressure ventilation with bilevel positive airway pressure for sleep-disordered breathing.

The patient's probable REM sleep behavior disorder improved with nighttime clonazepam, and daytime sleepiness improved with methylphenidate.

## **Discussion**

Paraneoplastic rhombencephalitis should be considered in patients with subacute onset of gait, coordination, visual, speech and swallowing difficulties.<sup>1</sup> Broadly, brainstem encephalitis may be ataxia-predominant (with accompanying vertigo and other visual symptoms) or may mimic atypical neurodegenerative parkinsonism with prominence of supranuclear gaze palsy, postural instability and falls. Though infectious causes (such as listeriosis), neoplasia and other inflammatory disorders (such as sarcoidosis) can present subacutely, brain imaging would generally demonstrate mass effect, basilar leptomeningeal or parenchymal enhancement. Other major categories can largely be excluded by their onset, hyperacute (stroke or hemorrhage) or insidious (such primary brain tumor or progressive supranuclear palsy).

In addition to subacute onset and progression, clues to autoimmunity include opsoclonus (jaw closing dystonia and laryngospasm, reported with ANNA-2, IgLON5 and KLCHL-11 antibodies).<sup>6-8</sup> A locked jaw is also sometimes encountered in progressive encephalomyelitis with rigidity and myoclonus (usually glycine receptor antibody positive).<sup>9</sup> Sleep disorders and episodic laryngospasm are common in brainstem encephalitis and should be sought out and treated. Incipient symptoms of sleep disordered breathing may be a harbinger of nocturnal respiratory arrest, particularly in Ma2 and IgLON5 autoimmunity.<sup>10,11</sup> Early hearing loss is encountered in 40% of KLCHL-11 patients.<sup>8</sup> Ataxia, vertigo, hearing loss, and tinnitus are more common with KLHL11 encephalitis than with Ma2 encephalitis. DPPX encephalitis may present with diarrhea and weight loss.<sup>12</sup> Type 1 diabetes or thyroid disease, and stiff-person phenomena

autoimmunity may preexist or coexist in GAD65 autoimmunity.<sup>13</sup> Some patients with paraneoplastic neurological disorders may have multifocal presentations and different phenotypes can be encountered with most autoantibodies (such as IgLON5 autoimmunity which may present with chorea, ataxia, or parkinsonian brainstem syndrome).<sup>7</sup>

A neural IgG profile assists in confirming an autoimmune diagnosis, but also assists in predicting cancer type in patients with a paraneoplastic cause. Typical accompaniments for ANNA-2 are breast adenocarcinoma or lung small cell carcinoma, and for KLCHL-11 seminoma (testicular or extra-testicular) and germ cell testicular neoplasms (as in our patient). KLHL-11 is less abundant than Ri protein, perhaps explaining the lack of tumor staining. Though the autoantibody diagnosis was made in serum, neurological phenotype-specific autoantibody evaluations in both serum and CSF are generally recommended.<sup>1</sup> The patient was at risk for testicular neoplasia given the atrophic testis.<sup>14</sup>

Neural IgG profiles also inform treatment decisions and prognosis derived from prior clinical experience. For instance, DPPX-IgG potentially has pathogenic effects upon binding to the extracellular domain of DPPX potassium channel subunit.<sup>15</sup> Improvements in neurological symptoms may occur upon receiving antibody-depleting plasma exchange and rituximab.<sup>1</sup> On the other hand, KLCHL-11 and Ri proteins are nuclear proteins, and not accessible to effects of IgGs. Rather, these IgGs appear to be biomarkers of CD8+ cytotoxic T cell-mediated pathophysiology and may be more amenable to cancer treatment and T cell suppression with chemotherapy, corticosteroids and cyclophosphamide.<sup>1,6,8</sup>

In summary, subacute onset of eye movement abnormalities and postural instability should prompt consideration of brainstem encephalitis, particularly when accompanied by one or more

of dysarthria, dysphagia, sleep disorders, trismus and laryngospasm. Neural antibody testing profiles can assist in autoimmune neurological and cancer diagnosis.

**Table.** Differential diagnosis of acquired brainstem syndromes

<b>Category</b>
<p>Ischemic stroke</p> <p>Hemorrhage</p> <p>Primary brain neoplasm</p> <p>Lymphoma</p> <p>Carcinomatosis</p>
<p><i>Autoimmune rhombencephalitis (alternate name, and associated cancer where applicable) *</i></p> <p>ANNA-2 (anti-Ri; small cell carcinoma, breast adenocarcinoma)</p> <p>DPPX (Occasional B cell neoplasias)</p> <p>IgLON5</p> <p>GAD65</p> <p>GQ1B (Bickerstaff encephalitis)</p> <p>KLCHL-11 (Testicular seminoma)</p> <p>Ma2 (Testicular germinoma)</p> <p>MOG</p> <p>PCA-1 (anti-Yo; breast &amp; gynecologic adenocarcinomas)</p> <p>PCA-Tr (anti-DNER; lymphoma)</p>
<p><i>Other autoimmune or inflammatory rhombencephalitis categories</i></p> <p>figMultiple sclerosis</p> <p>Sarcoidosis</p> <p>CLIPPERS</p> <p>Behcet disease</p> <p>Systemic lupus erythematosus</p> <p>Vasculitis (multiple cranial neuropathies)</p>

*Infectious rhombencephalitis*

Listeria

Herpes viruses (HSV, VZV, EBV, CMV)

Tuberculosis

*Other brainstem disorders*

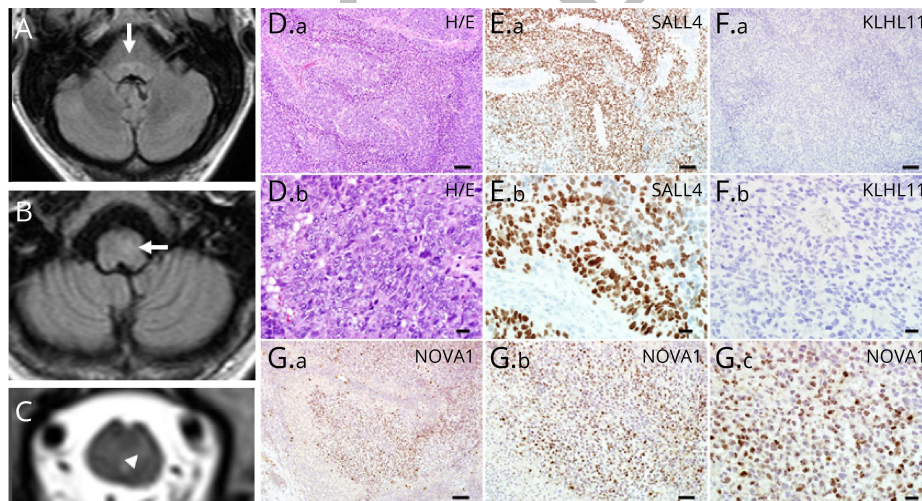
Degenerative 'Parkinsonism-plus' syndromes (e.g. progressive supranuclear palsy)

Metronidazole toxicity

\*Brainstem syndromes considered characteristic. Brainstem disorders also described in the context of paraneoplastic or other autoimmune encephalomyeloneuropathies accompanying the following IgG antibodies: ANNA-1 (anti-Hu), PCA-2 (MAP1B-IgG), amphiphysin, ANNA-3, AGNA, CRMP-5, glycine receptor.

**Figure.** Radiologic and tumor histopathologic findings.

MRI brain (T2 FLAIR) and cervical cord (T2) reveal T2 hyperintensity in pontine (A) and medullary tegmentum (B), arrows, which extended to the upper cervical cord (C). (D.a) The left inguinal lymph node biopsy from a 43-years-old male patient with testicular mass shows metastatic neoplastic components (hematoxylin and eosin stain). The tumor cells present variable morphologies. Most of the tumor cells show a large nucleus with prominent nucleoli (D.b, enlarged view of D.a). (E.a) Immunohistochemistry shows marked SALL4 immunoreactivity in the tumor cells which is consistent with germ cell tumor (enlarged view in E.b). (F.a) The tumor cells show no KLHL11 immunoreactivity (enlarged view in F.b). (G.a) Tumor cells demonstrate marked NOVA1 immunoreactivities in the nuclei (enlarged views in G.b and G.c). Scale bars: 100  $\mu$ m (D.a, E.a, F.a, G.a), 50  $\mu$ m (G.b), 20  $\mu$ m (D.b, E.b, F.b, G.c).



**Video 1.** Jerk see-saw nystagmus, observed when the patient was in ICU early on in his illness. Cyclically, and with a jerky appearance, one eye rises and intorts, as the other falls and extorts, followed by reversal of the same movements.

**Video 2.** Three sequential video segments demonstrating bursts of opsoclonus, dysarthria and jaw closing dystonia and trismus.

WNL-2022-200908\_vid1 --<http://links.lww.com/WNL/C172>

WNL-2022-200908\_vid2 --<http://links.lww.com/WNL/C173>

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