Clinical Pathologic Conference

A Rare Adult Cause of Dizziness

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A 55-year-old man was seen with progressively worsening dizziness over 10 months. The initial assessment with unremarkable laboratory and imaging studies suggested a peripheral vestibular disorder. He was then lost to follow-up but later was seen with worsening ataxia. Additional imaging studies showed subtle parenchymal lesions in the posterior fossa. The differential diagnoses included nutritional deficiencies, autoimmune disorders, systemic malignancies, and intracranial tumors. The final diagnosis was confirmed by a biopsy.

Laboratory and Imaging Studies

Laboratory results showed vitamin E and 25-hydroxyvitamin D₃ deficiencies, elevated C-reactive protein level, and an abnormal serum protein electrophoresis panel (Table). All other laboratory study results were unremarkable: complete blood cell count, comprehensive metabolic panel, thyroid function tests, vitamin A and B₁₂ levels, folate level, cardiac enzyme levels, coagulation studies, complement levels, prostate-specific antigen level, syphilis serology, human immunodeficiency virus serology, urine protein electrophoresis, and cerebral spinal fluid indices. A paraneoplastic antibody panel was not performed.

Neuroimaging Studies (Dr Oberle)

A second MRI (10 months after symptom onset) showed an interval increase in the previously ill-defined FLAIR hyperintense lesions in the right cerebellum (Figure 1C and D), with a slight local mass effect. In the right cerebellar hemisphere, there was an area of localized restricted diffusion on diffusion-weighted images that correlated with hypointensity on the apparent diffusion coefficient map (Figure 1E and F). These lesions appeared infiltrative and hypointense on T₁-weighted images, without enhancement (not shown). In addition, single-voxel magnetic resonance spectroscopy with the voxel placed over the abnormal FLAIR signal in the right cerebellar hemisphere demonstrated a markedly elevated choline to N-acetylaspartate peak ratio (Figure 1G and H). Magnetic resonance imaging of the entire spine with and without contrast did not show any abnormalities.

Clinical Discussion (Dr Shu)

This patient was seen with a late-onset, progressively worsening, right-sided appendicular and truncal ataxia over 10 months. Although the initial presentation pointed toward a peripheral vestibular lesion, a central cause was suggested by the severe position-independent vertigo, trunk and limb ataxia, sustained nystagmus, ataxic gait, and associated motor and sensory changes. These symptoms localized to
the right cerebellar hemisphere, vermis, and brainstem. In addition, the initial images suggested involvement of the right superior cerebellar hemisphere and right dentate nucleus (Figure 1A and B). Altogether, with cachexia in the setting of vitamin D and E deficiencies and elevated inflammatory markers, the differential diagnoses included nutritional deficiencies, autoimmune and inflammatory disorders, systemic malignancies with brain metastases, and primary intracranial neoplasms.

Nutritional deficiencies of vitamins B1, B12, or E can cause ataxia, and this patient was deficient in vitamin E. Classically, ataxia with vitamin E deficiency is an autosomal recessive disorder with an adolescent onset. It mimics Friedreich ataxia by progressive ataxia, proprioceptive loss, and areflexia. Also, head titubation, dystonia, retinitis pigmentosa, and cardiomyopathy are seen. Hemolysis develops because of the shortened life span of red blood cells. An observed mechanism is a missense mutation in the α-tocopherol transfer protein gene on chromosome 8q13, which impairs the incorporation of vitamin E into very low-density lipoprotein. Therefore, vitamin E cannot be properly distributed throughout the body to neutralize free radicals, which subsequently damage the cerebellum. Other causes of ataxia with vitamin E deficiency include fat malabsorption syndromes such as pancreatic insufficiency, cystic fibrosis, and short-bowel syndrome. Steatorrhea is a common symptom. This patient did have chronic calcific pancreatitis, but his late onset of symptoms and exclusive complaint of ataxia without any concomitant features commonly seen in ataxia with vitamin E deficiency suggest that vitamin E deficiency alone could not explain his entire presentation.

Paraneoplastic cerebellar degeneration, classically associated with anti-Hu, anti-Yo, or voltage-gated calcium channel antibodies, involves an immune-mediated attack against onconeural antigens in the setting of a systemic malignancy. This results in cerebellar degeneration, patchy demyelination, microglial proliferation, and perivascular lymphocytic infiltration. This disease must be considered in patients with adult-onset vertigo, subacute progressive nystagmus, and asymmetrical ataxia of gait and limbs. Cerebellar T2 hyperintensity can occasionally be seen as a result of reactive gliosis, though imaging in paraneoplastic cerebellar degeneration is usually normal. The MRI in this case did show T2 prolongation in the right cerebellum (Figure 1C and D). Paraneoplastic cerebellar degeneration associated with small cell lung cancer or lymphoma would be the main considerations and the former is favored in this smoker who had weight loss and abnormal chest CT findings. Other paraneoplastic antibodies that can be associated with paraneoplastic cerebellar degeneration and small cell lung cancer are anti-CV2 and anti-PCA2. In this case, no paraneoplastic antibody results were available.

Another possible inflammatory entity is neurosarcoïdosis. A clinically protean disease, sarcoidosis is a granulomatous disease mediated by CD4+ helper T subtype 1 cells and mononuclear phagocytes. The presence of hilar adenopathy would support a unifying diagnosis of sarcoidosis. Moreover, cerebral granulomas could evade the detection of MRI, so the absence of well-defined enhancing lesions on the imaging does not exclude sarcoidosis. Lesions usually localize to the seventh cranial nerve, hypothalamus, meninges, spinal cord, peripheral nerves, and muscle. In contrast, progressive cerebellar ataxia is an extremely rare manifestation in neurosarcoïdosis.
Multiple sclerosis, an inflammatory demyelinating process characterized by neurologic symptoms disseminated in space and time, can include prominent cerebellar complaints; therefore, it must be considered. The findings on the patient's single-voxel and multivoxel magnetic resonance spectroscopy suggested either tumefactive demyelination or a neoplastic process. The depressed N-acetylaspartate peak indicating loss of neuronal tissue and elevated choline peak representing cell membrane turnover were consistent with tumefactive multiple sclerosis (Figure 1G and H). When there are multiple large lesions greater than 2 cm, edema and ring enhancement are often observed. The severity of the clinical presentation varies among patients even when brain lesions appear similar. An acute demyelinating process, however, is less likely in this case because his MRI never demonstrated contrast-enhancing lesions and the cerebral spinal fluid indices did not suggest inflammation.

The slowly progressive course and restricted diffusion of the cerebellar lesions (Figure 1E and F) suggest a neoplastic process. The patient's smoking history, weight loss, and abnormal chest CT further increased the suspicion of a systemic malignancy. Cancers that commonly metastasize to the brain include lung, melanoma, breast, kidney, and gastrointestinal tumors. Small cell lung cancer can present with isolated or miliary brain metastases and is more commonly observed in supratentorial locations. In contrast, pelvic can present with isolated or miliary brain metastases and is more commonly observed in supratentorial locations. In contrast, pelvic

### Table. Abnormal Laboratory Results

<table>
<thead>
<tr>
<th>Laboratory Results</th>
<th>Abnormal Values</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E, μg/mL</td>
<td>3</td>
<td>5.5-17</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D₃, ng/mL</td>
<td>9.2</td>
<td>30.0-74.0</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>4.5</td>
<td>0-0.3</td>
</tr>
<tr>
<td>Serum protein electrophoresis panel</td>
<td>Elevated α₂ globulin and β-globulin, polyclonal increase in γ-globulin, but no M protein</td>
<td></td>
</tr>
</tbody>
</table>

SI conversion factors: To convert vitamin E to micromoles per liter, multiply by 23.22; 25-hydroxyvitamin D₃ to nanomoles per liter, multiply by 2.496; and C-reactive protein to nanomoles per liter, multiply by 9.524.

Medulloblastomas, which invariably arise in the posterior fossa, must be considered. Prevalence is about 1 in 200,000, accounting for 6% to 8% of all central nervous system tumors. Predominantly encountered in children, medulloblastomas account for only 0.4% to 1% of adult primary brain neoplasms, with the affected adults usually between the ages of 20 and 40 years. In one of the largest clinical series of 532 cases, more than 75% were well-circumscribed tumors in the vermis that could disseminate through cerebral spinal fluid spaces. Involvement of lateral cerebellar hemispheres is less frequent and usually seen in adults. Truncal ataxia and spasticity present in patients with midline tumors, while limb ataxia and dysdiadochokinesia are associated with lateral tumors. Headache and sixth nerve palsy are also common manifestations. Disabling symptoms usually develop within 3 months. Computed tomography lesions almost always show hyperattenuation and homogenous enhancement. In 2 reviews of 420 and 233 patients, 89% showed CT hypodensity and 97% demonstrated enhancement, respectively.

Magnetic resonance imaging lesions show T2 hypointensity and T1 isointensity or hypointensity and almost always enhance with a heterogeneous pattern. Cysts, calcification, or hemorrhage can also be seen. In a review of 9 adult patients, 8 showed enhancement on the MRI. Although our patient was well beyond age 40 years, had other symptoms in addition to cerebellar signs, did not demonstrate a well-demarcated enhancing mass on either CT or MRI, and did not have a hypodense lesion on CT, medulloblastoma remains in the differential diagnosis based on the location of the lesion and the suspicion for a neoplasm.

### Neuropathological Discussion (Drs Hatanpaa and Herrdon)

A stereotactic biopsy of the lesion showed multiple fragments of the cerebellar cortex containing neoplastic cells beneath the arachnoid and pia mater and in Virchow-Robin spaces (Figure 2A). These cells showed a clear to vacuolated cytoplasm and rounded nuclei with stippled chromatin (Figure 2B). The tumor cells were immunoreactive for a neuronal marker, microtubule-associated protein 2. No immunoreactivity was seen in those stained with antibodies to cytokeratin (CAM 5.2), glial fibrillary acidic protein, hematolymphoid marker CD45, thyroid transcription factor 1, and epithelial membrane antigen. These findings were consistent with medulloblastoma, classic type.

### Clinical Outcome

The patient received craniospinal radiotherapy and 4 concurrent sessions of weekly vincristine sulfate but refused further chemotherapy because of significant fatigue and dysphagia. At the most
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Figure 2. Histopathological Findings From Biopsy of the Right Cerebellum

A. Neoplastic cells invaded the subarachnoid, subpial, and Virchow-Robin spaces (hematoxylin-eosin, original magnification ×100; size bar = 100 μm). B. These cells showed a clear to vacuolated cytoplasm and rounded nuclei with stippled chromatin (hematoxylin-eosin, original magnification ×400; size bar = 50 μm).

recent follow-up 2 years after the treatment, he complained of continued vertigo and ataxia but was overall independent with activities of daily living. His examination demonstrated mild intention tremor and dysmetria of the right upper extremity. Another repeated MRI showed a small ill-defined enhancing area along the posterior lateral margin of the prior biopsy site in the right cerebellum. Magnetic resonance imaging of the spine did not show any evidence of drop metastasis.

Conclusions

There are several histological subtypes of medulloblastoma and the most common is the classic subtype, characterized by dense sheets of cells with hyperchromatic round to oval nuclei and increased mitoses and apoptoses. They are believed to originate in the ventricular zone of the developing cerebellum. In contrast, the second main subtype, the desmoplastic variant, has a predilection for adults and has reticulin-free nodules called pale islands surrounded by dense reticulin collagen fibers; these tend to express markers of granule cell lineage and show heterogeneous MRI signal intensities in the lateral cerebellar hemisphere.6,12-14

The correlation of the lateral involvement in older patients may be due to migration of precursor cells away from the midline over time. The typically better prognosis in adults with the desmoplastic variant is likely correlated with its higher degree of cellular differentiation and richer involvement of nodules that are of low cellularity with nuclear uniformity.

Maximal resection, craniospinal radiation, and chemotherapy play a pivotal role in treating pediatric medulloblastomas, but there is no universally established protocol for adults. Current research on the inhibitors of the sonic hedgehog signaling pathway will likely provide new therapeutic targets.6,15

This was an illuminating case because medulloblastoma is unusual beyond age 40 years. Moreover, the initially nonspecific vestibular symptoms, progressive clinical involvement of the brainstem, atypical imaging features, and a classic histology in the lateral hemisphere in an adult were altogether rare. Although the differential diagnoses were appropriately broad, the time course of the clinical progression and imaging features of restricted diffusion, increased perfusion, and elevated choline to N-acetylaspartate peak ratio suggested an intracranial neoplastic process. Ultimately, a biopsy and histopathological diagnosis were imperative.

ARTICLE INFORMATION

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REFERENCES