RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Clinical Reasoning: Multiple cranial neuropathies in a young man

John C. Probasco, MD
Ashley T. Munchel, MD
Justin C. McArthur, MBBS, MPH
Jaishri O. Blakeley, MD

Correspondence to Dr. Probasco: jprobas1@jhmi.edu

SECTION 1

A 19-year-old man with no significant medical history noted 3 weeks of right facial numbness and slurred speech. On examination, he had decreased sensation in the right middle and lower trigeminal nerve distributions, right tongue deviation, and bilateral facial weakness. A lumbar puncture yielded CSF with a lymphocytic predominant pleocytosis (50 leukocytes/mm^3, 95% lymphocytes), elevated protein (260 mg/dL), and normal glucose (49 mg/dL), without other evidence of inflammation or infection, while serum studies were normal. Brain MRI with gadolinium demonstrated a subcentimeter left frontal subcortical white matter lesion on fluid-attenuated inversion recovery images and a nonenhancing pineal cyst.

Question for consideration:

1. What is the differential diagnosis?

In an otherwise healthy young person, diagnostic considerations would include tumors, demyelinating conditions, infectious processes such as CNS borreliosis or fungal meningitis, and systemic inflammatory conditions including neurosarcoidosis. A nonenhancing pineal cyst raises concern for a germ cell tumor, pineal parenchymal tumor, and low-grade glioma.

GO TO SECTION 2

From the Department of Neurology (J.C.P., J.C.M., J.O.B.), Johns Hopkins University, Baltimore; Division of Pediatric Oncology (A.T.M.), Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore; and Pediatric Oncology Branch (A.T.M.), National Cancer Institute, Bethesda, MD.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

SECTION 2

Over 6 months, the patient developed right horizontal jerking nystagmus, bilateral hearing loss, dysarthria, and dysphagia. Two lumbar punctures demonstrated a persistent lymphocytic pleocytosis (37 leukocytes/mm^3, 87% lymphocytes, and 60 leukocytes/mm^3, 77% lymphocytes) with elevated protein (197 and 377 mg/dL) and elevated glucose (69 and 70 mg/dL) in the CSF with negative infectious studies and atypical lymphocytes on flow cytometrics. Serum studies were unremarkable.

Question for consideration:

1. What additional tests/studies should be considered?

Repeat brain MRI with gadolinium and detailed imaging of the midbrain, pons, and medulla; whole-body CT; CSF fungal cultures; CSF acid-fast bacilli stain and culture; 3 large volume (>30 mL) CSF collections for cytopathology; serum and CSF α-fetoprotein (αFP); and β-human chorionic gonadotropin (βHCG).

GO TO SECTION 3

SECTION 3

Repeat MRI of the brain with gadolinium demonstrated enhancement of cranial nerves V, VII, IX, X, XI, and the pineal gland cyst. Cervical and thoracic spinal MRI was normal. PET demonstrated hyperplastic marrow but no metastatic disease. He had been treated with a slow oral taper of prednisone, IV glucocorticoids, and IV immunoglobulin (IVIg).

On transfer to a tertiary facility, he endorsed dyspnea, weak cough, difficulty managing secretions, progressive weakness in the legs, diminished sensation in the left arm and leg, and 1 month of urinary incontinence and constipation. His medications on transfer were oral prednisone as well as antibiotics for an aspiration pneumonia, gastric ulcer prophylaxis, and symptom management for nausea and oral secretions. There were no notable medical conditions in his family history. He was a high school graduate with no significant substance use or travel history.

His neurologic examination was remarkable for visual sensation only for light and movement, fixed dilated pupils, downgaze in primary position, upward and lateral eye movement paresis, bilateral ptosis, diminished bilateral facial sensation, bilateral facial weakness, diminished hearing, poor soft palate elevation, weak cough, and absent gag reflex. His left leg was externally rotated with otherwise antigravity strength throughout the bilateral legs. He demonstrated resistance to movement which could be overcome throughout the bilateral arms. His reflexes were brisk throughout with plantar flexor responses bilaterally. He was well coordinated in all extremities except for slow and dysrhythmic left foot tap. Gait could not be assessed.

Repeat brain MRI with gadolinium (figure 1A) and dedicated fast imaging employing steady-state acquisition series (figure 1B) demonstrated multiple areas of cranial nerve enhancement, including the bilateral oculomotor, trigeminal, abducens, facial, and spinal accessory nerves as well as enhancement of the pineal gland and soft tissue masses in the bilateral trigeminal caves. Spine MRI (figure 1, C and D) with gadolinium demonstrated multiple focal lesions within the spinal cord and central canal as well as a heterogeneously enhancing intradural, extramedullary thoracolumbar mass.

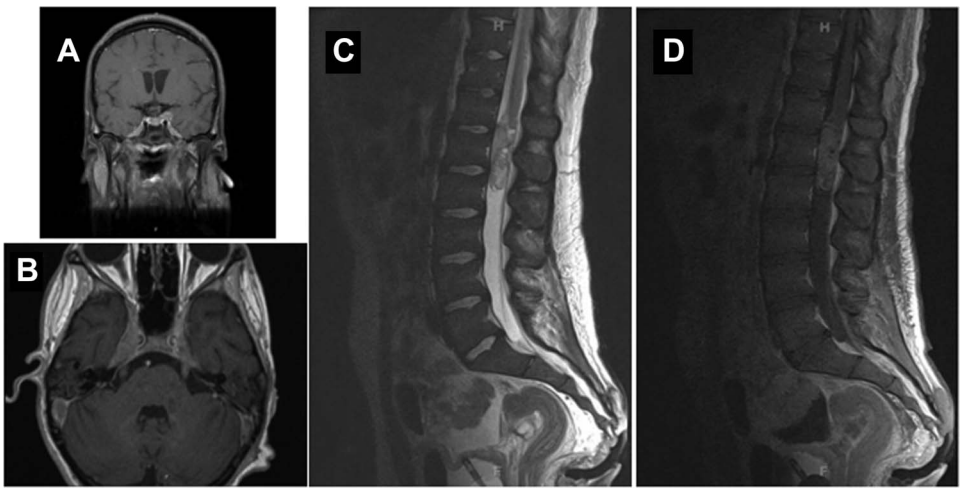
Question for consideration:

1. What is the differential diagnosis for an intradural, extramedullary spinal cord mass?

Primary tumor considerations include meningioma, schwannoma, neurofibroma, dermoid tumor, and lipoma. The differential also includes drop metastases of medulloblastoma, ependymoma, glioma, and germ cell tumor.

GO TO SECTION 4

Figure 1 Imaging



Repeat MRI with gadolinium of brain demonstrates symmetric enhancement of (A) bilateral trigeminal nerves within trigeminal cave. (B) Fast imaging employing steady-state acquisition series demonstrates enhancement within bilateral cavernous sinuses, bilateral jugular foramen, as well as facial and vestibulocochlear nerves. MRI of thoracolumbar spine (C) T2 and (D) T1 postgadolinium sequences demonstrate heterogeneously enhancing intradural, extramedullary thoracolumbar spinal mass.

SECTION 4

Bilateral first and second lumbar vertebrae laminectomies were performed with resection of the thoracolumbar mass. A lumbar puncture was performed to assay CSF levels of αFP βHCG for comparison to serum levels. βHCG levels were elevated in both serum (1,123 mIU/mL) and CSF (4,104 mIU/mL). αFP levels in the CSF (<1 ng/mL) and serum (7 ng/mL) were normal. The thoracolumbar mass contained multiple germ cell layers with differentiated tissue (figure 2, A–C). Several OCT-4 and c-kit positive germinoma cells with focal staining for αFP and βHCG were also noted (figure 2D).[1,2] Final pathologic and oncologic diagnosis was immature teratoma with germinoma cells.

He was subsequently transferred to the pediatric oncology service and completed the first 2 courses of induction chemotherapy with carboplatin, etoposide, and ifosfamide prior to transfer to his local medical facility. At time of transfer, his serum βHCG was markedly reduced (15 mIU/mL). At his local medical facility, he completed induction and consolidation chemotherapy. In time, he regained his hearing to a conversational volume, and the ability to partially open his eyes, speak with partial occlusion of his tracheotomy site, and walk with assistance. After 18 weeks of chemotherapy and a prolonged inpatient course, he died due to cardiac arrest.

DISCUSSION Multiple cranial neuropathies are common in neurology, with etiologies ranging from the relatively benign and treatable to malignant and life-threatening (table 1).[3–5] This presentation still poses a formidable diagnostic challenge, as cranial nerves can be disrupted at any site along their course from the brainstem to the superficial soft tissues.[3] The differential diagnosis is extensive, with the patient's age, immunocompetence, and tempo of progression all key considerations for clinical evaluation (table 2). The basic evaluation includes assessment for evidence for metabolic derangements suggestive of systemic processes. Our understanding of the etiologies for multiple cranial neuropathies has been limited to case reports and case series.[4] In the largest series, cancer accounted for 30% of cases.[5]

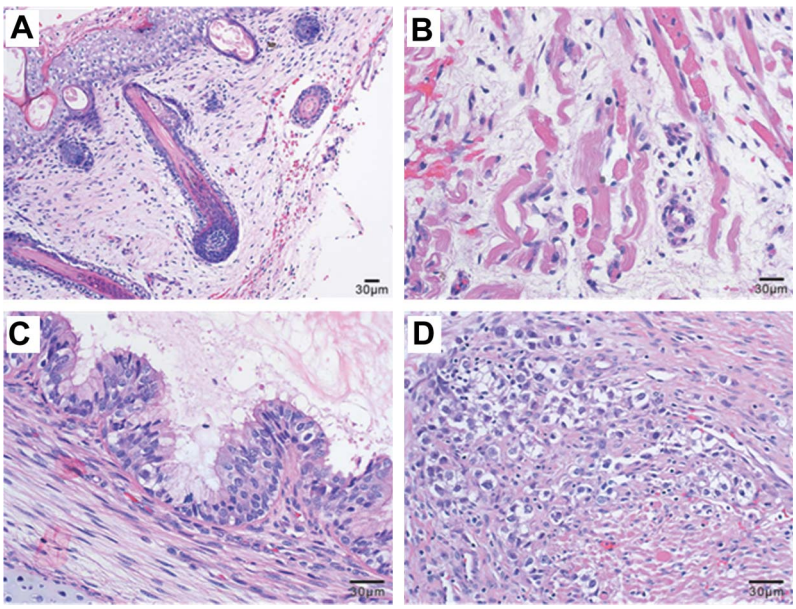
CNS germ cell tumors (GCT) are rare primary brain tumors, accounting for 0.6%–3% of all brain tumors, with an incidence of 0.16 per 100,000 person-years among pediatric patients 0–19 years of age.[6,7] Typically, CNS GCT present in the second decade of life.[7,8] GCT are broadly classified as germinomatous (composed solely of germinoma cells) or non-germinomatous (NGGCT). This distinction is clinically relevant as germinomas, like gonadal GCT, are highly curable with 5-year survival rates greater than 90%.[7–9] In contrast, NGGCT portend a worse prognosis, with survival of 30%–40% with radiation alone. The addition of platinum-based chemotherapy regimens and surgical resection has boosted survival rates in NGGCT to 90% at a mean of 96 months.[9]

Thought to originate from primitive embryonal cells, GCT are divided histologically by their resemblance to primordial germ cells (germinoma), embryonic differentiated cells (teratoma), yolk sac endodermal cells (yolk sac tumor), blastocytes (choriocariocarcinoma), or embryonal pluripotent stem cells (embryonal carcinoma).[7,8] Mixed GCT are composed of various histologic types, with the most malignant component determining overall prognosis.[9]

GCT are classically found in the pineal gland but can present anywhere within the CNS. Tumor location governs presenting symptomatology. Patients with pineal lesions often present with obstructive hydrocephalus and Parinaud syndrome (paralysis of upgaze, pupillary light-near dissociation and convergence-retraction nystagmus).[9]

Differentiating between germinomas and NGGCT directly influences treatment choices. While there are potentially subtle differences in germinomas and NGGCT on MRI, imaging alone is not sufficient to differentiate between the two.[7,8] Biopsy is necessary to confirm the diagnosis unless tumor markers are pathognomonic. βHCG and αFP should be checked in both serum and CSF if GCT is on the differential. While germinomas can secrete low levels of βHCG and αFP, βHCG levels greater than 50 IU/L and αFP levels >10 ng/dL in the CSF confirms a diagnosis of NGGCT without the need for biopsy, and markedly

Figure 2 Histopathology



Hematoxylin & eosin–stained histopathologic samples from intradural extramedullary thoracolumbar mass demonstrate multiple germ cell layers including (A) keratinized skin with hair follicles, (B) smooth muscle, (C) bronchiolar tissue, and (D) germinoma cells with striated muscle.

Table 1 Differential diagnosis of etiologies of multiple cranial neuropathies[3–5]

Cancer	Vascular	Infection	Systemic disease
Schwannoma	*Infarction*	*Bacterial*	*Inflammatory diseases*
Meningioma	Associated with meningitis	Borreliosis (Lyme)	Sarcoidosis/neurosarcoidosis
Metastases	Associated with trauma	*Mycobacterium* tuberculosis	Behçet disease
Lymphoma	Associated with surgical complication	Pseudomonas	Amyloidosis
Pontine glioma	Mixed connective tissue disease	Mycoplasma	Tolosa-Hunt syndrome
Nasopharyngeal carcinoma	Syphilis	Syphilis	Melkersson-Rosenthal syndrome
Pituitary adenoma	Diabetes mellitus	Botulism	Histocytosis
Chordoma	Carotid artery dissection	Diphtheria	
Leukemia	Jugular venous thrombosis	Listeria	*Vasculitis*
Epidermoid			Wegener granulomatosis
Glomus tumor	*Hemorrhage*	*Fungal*	Lymphomatoid granulomatosis
	Hypertension	Cryptococcosis	Polyarteritis nodosa
Miscellaneous cancer	Arteriovenous malformations	Histoplasmosis	Temporal arteritis
Plasmacytoma	Angiomas	Coccidiomycosis	
Neuroectodermal	Aneurysm	Blastomycosis	*Connective tissue disease*
Fibrosarcoma	Carotid-cavernous fistula	Mucormycosis	Rheumatoid arthritis
Rhabdomyosarcoma		Aspergillosis	Sjögren disease
Cholesteatoma	*Trauma*	Candida	Systemic lupus erythematosus
Chondroma	Blunt closed head injury		Scleroderma
Myeloma	Penetrating injury	*Viruses*	
Ependymoma		Herpes zoster	*Bone disease*
Craniopharyngioma	Surgical complication	Epstein-Barr	Osteopetrosis
Hemangioblastoma		Cytomegalovirus	Paget disease
Ewing tumor	*Demyelinating disease*	HIV 1 & 2	Hyperostosis cranialis interna
Endolymphatic sac tumor	Multiple sclerosis	Mononucleosis related	Fibrous dysplasia
Germinoma	Guillain-Barré syndrome	Hepatitis related	
	Miller Fisher syndrome		*Other neurologic disorders*
Leptomeningeal cancer	Chronic demyelinating inflammatory polyneuropathy	*Parasites*	Idiopathic intracranial hypertension
Lung		Chagas disease	Chiari malformation
Breast	*Toxic exposure*	Cysticercosis	Wernicke encephalopathy
Gastric	Radiation necrosis		Idiopathic pachymeningitis
Unknown primary	Chemotherapy toxicity	*Associated with AIDS*	Idiopathic cranial polyneuropathy
Lymphoma		Lymphoma	Myasthenia gravis
Leukemia	Functional/nonorganic disease	Cryptococcus	Oculopharyngeal muscular dystrophy
Sarcoma		Histoplasmosis	Fascioscapulohumeral muscular dystrophy
Myeloma		Herpes zoster	Mitochondrial disorders
Epidermoid inflammation		Cytomegalovirus	Congenital syndromes (e.g., Moebius)

elevated levels are associated with more aggressive tumors with worse prognosis.[7–10] When positive, tumor markers also serve as a sensitive method to monitor therapy response. If a GCT is confirmed, complete craniospinal imaging is recommended as 10%–30% of patients, predominantly NGGCT, have spinal drop metastases or leptomeningeal spread.[7–10] The patient presented here developed multiple cranial neuropathies from leptomeningeal spread along his cranial nerves and drop metastasis.

We present the case of a young man in his second decade with progressive multiple cranial neuropathies. CSF lymphocytic pleocytosis and elevated protein were persistent features of his evaluation with no other evidence of infectious, hematologic, or rheumatologic conditions. He had no response to antibiotic,

Table 2 Basic evaluation with additional considerations for evaluation of patients with multiple cranial nerve palsies

Basic initial neurologic imaging:	Additional neurologic imaging to consider:	
CT of head without contrast	Cavernous sinus syndrome: MRI brain with gadolinium with dedicated series of orbits, CT sinuses/orbits	
Brain MRI with and without gadolinium	Cerebellopontine syndrome: MRI brain with gadolinium with FIESTA dedicated series of the cerebellopontine angle and brainstem	
	Jugular foramen syndrome: MRA and MRV brain and neck, CTA	
	Leptomeningeal disease: Total spine MRI with gadolinium	
	Ischemic/hemorrhagic stroke: GRE/SWI series, MRA or CTA brain and neck, cerebral angiogram	
Basic CSF assessment:	**Additional CSF assessments to consider:**	
Cell count and differential	Immunocompromise:	Chronic meningitis:
Glucose and protein	Fungal culture	Fungal culture
Bacterial culture	Acid-fast bacilli stain and culture	Acid-fast bacilli stain and culture
Viral PCR: Herpes simplex, VZV	Viral PCR: CMV, EBV	Viral PCR: CMV, EBV
Venereal disease reference laboratory	*Mycobacterium* PCR	Lyme IgG and PCR
Oligoclonal bands	Cryptococcal antigen	*Mycobacterium* PCR
IgG index (with matched serum IgG)	Histoplasma antigen	Fungal antibodies: *Aspergillosis, Blastomycosis, Candida, Coccidiomycosis*
	Fungal antibodies: *Aspergillosis, Blastomycosis, Candida, Coccidiomycosis*	Flow cytometry
	Flow cytometry	Cytopathology (3 large volume collections)
	Cytopathology (3 large volume collections)	
		Adolescent/young adult:
		α-Fetoprotein
		β-Human chorionic gonadotropin
Basic blood studies:	**Additional blood studies to consider:**	
Complete blood cell count with differential	Autoimmune/vasculitis:	Infectious:
Chemistry panel	Antinuclear antibody	Lyme antibody
Hepatic panel	Anti-DNA antibody	Hepatitis A, B, and C antibodies
Erythrocyte sedimentation rate	Antineutrophilic cytoplasmic antibodies	Mononucleosis antibody
C-reactive protein	Anti-Ro/La antibody	Cryptococcal antigen
HIV antibody	Urine and serum peptide electrophoresis with immunofixation	Fluorescent treponemal antibody
Thiamine	Rheumatoid factor	Adolescent/young adult:
	Acetylcholine receptor antibody	α-Fetoprotein
		β-Human chorionic gonadotropin
Basic general imaging and procedures:	**Additional imaging and procedures to consider:**	
Chest radiograph	Abdominal and pelvic/testicular ultrasound	
CT chest, abdomen, and pelvis	PET	
	Biopsy of relevant tissue (e.g., lymph nodes, bone marrow, meninges)	

Abbreviations: CMV = cytomegalovirus; CTA = CT angiography; EBV = Epstein-Barr virus; FIESTA = fast imaging employing steady-state acquisition; GRE = gradient echo; IgG = immunoglobulin G; MRA = magnetic resonance angiography; MRV = magnetic resonance venography; SWI = susceptibility weighted imaging; VZV = varicella-zoster virus.

steroid, or IVIg therapy. Noted enhancement of the leptomeninges, a midline intracranial structure (pineal gland), and intracranial soft tissue masses were consistent with a GCT. The final diagnosis of NGGCT was made on pathologic examination of an intradural, extramedullary drop metastasis. Comparison of αFP and βHCG in the CSF and blood were also diagnostic. This case emphasizes the utility of assays for αFP and βHCG in

the CSF and blood when evaluating an otherwise healthy young person with multiple cranial neuropathies after a basic evaluation fails to present a clear diagnosis.

AUTHOR CONTRIBUTIONS

Dr. Probasco was involved in drafting/revising the manuscript for content, study concept and design, and analysis/interpretation of data. Dr. Munchel was involved in revising the manuscript for content. Dr. McArthur was involved in revising the manuscript for content. Dr. Blakeley was involved in revising the manuscript for content, study concept and design, and analysis/interpretation of data.

ACKNOWLEDGMENT

The authors thank Dr. Peter Burger and Mr. Norm Baker for preparation of the histopathology images and the patient's family for their help in the preparation of this manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

J. Probasco and A. Munchel report no disclosures. J. McArthur serves on a scientific advisory board for Relevare Services; is an author on patents re: Device for thermal stimulation of small neural fibers and Immunophilin ligand and treatment of antiretroviral toxic neuropathy; and receives research support from Biogen Idec, Pfizer Inc., the National Multiple Sclerosis Society, the Foundation for Peripheral Neuropathy, and grant 5P30MH075673 from the National Institute of Mental Health. J. Blakeley receives research support from GlaxoSmithKline, the National Cancer Institute, and the Cancer Therapy Evaluation Program. She has served as an unpaid consultant to Novartis. Go to Neurology.org for full disclosures.

Received March 19, 2012. Accepted in final form September 26, 2012.

REFERENCES

1. Nakamura H, Takeshima H, Makino K, Kuratsu J. C-kit expression in germinoma: an immunohistochemistry-based study. J Neurooncol 2005;75:163–167.
2. Hattab EM, Tu PH, Wilson JD, Cheng L. OCT4 immunohistochemistry is superior to placental alkaline phosphatase (PLAP) in the diagnosis of central nervous system germinoma. Am J Surg Pathol 2005;29:368–371.
3. Beal MF. Multiple cranial-nerve palsies: a diagnostic challenge. N Engl J Med 1990;322:461–463.
4. Carroll CG, Campbell WW. Multiple cranial neuropathies. Semin Neurol 2009;29:53–65.
5. Keane JR. Multiple cranial nerve palsies: analysis of 979 cases. Arch Neurol 2005;62:1714–1717.
6. Surawicz S, McCarthy BJ, Kupelian V, et al. Descriptive epidemiology of primary brain and CNS tumors: results from the Central Brain Tumor Registry of the United States, 1990-1994. Neuro Oncol 1999;1:14–25.
7. Matsutani M. Clinical management of primary central nervous system germ cell tumors. Semin Oncol 2004;31:676–683.
8. Fujimaki T. Central nervous system germ cell tumors: classification, clinical features, and treatment with a historical overview. J Child Neurol 2009;24:1439–1445.
9. Blakeley JO, Grossman SA. Management of pineal region tumors. Curr Treat Options Oncol 2006;7:505–516.
10. Keene D, Johnston D, Strother D, et al. Epidemiological survey of central nervous system germ cell tumors in Canadian children. J Neurooncol 2007;82:289–295.