Aquaporin-4 autoimmunity masquerading as a brainstem tumor

Case report

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Brainstem glioma is a highly devastating disease, and any mass-like lesion in the brainstem can raise suspicion of this diagnosis. However, other inflammatory, demyelinating, or degenerative diseases can mimic brainstem glioma in clinical presentation and imaging features. Therefore, diagnosis based solely on imaging is often insufficient for brainstem lesions and may lead to incorrect diagnosis and treatment.

This case report is the first description of central nervous system aquaporin-4 (AQP4) autoimmunity confined mainly to the brainstem. It demonstrates the wide spectrum of neuroinflammatory diseases in children and highlights the utility of surgical biopsy for suspicious brainstem lesions with atypical imaging features for glioma.

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Key Words • aquaporin-4 antibody • neuromyelitis optica • oncology • brainstem glioma

The brainstem is one of the most complex structures in the human body. Tumors in the brainstem cause serious neurological problems that usually progress over time. Glioma is the most common brainstem tumor, and the majority of brainstem glioma cases are diffuse intrinsic pontine glioma (DIPG) cases, which have a grim prognosis. Dorsally exophytic gliomas and focal intrinsic brainstem gliomas are localized tumors that can often be resected. Cervicomedullary gliomas are uncommon tumors that develop within the dorsal medulla oblongata and extend to the cervical spinal cord. These focal entities are usually benign in nature, but their treatment is challenging because of the brainstem’s intricate structure.

Each category of brainstem glioma displays certain characteristic radiological features on MRI, and MRI is therefore sufficient for many diagnoses. Moreover, many clinicians are reluctant to perform biopsies for tumorous brainstem lesions given the high diagnostic accuracy of MRI and the possibility of surgical complications. The medical community permits omitting a surgical biopsy for most patients with suspected DIPG because of patients’ almost invariably short life expectancy. Dorsally exophytic gliomas and cervicomedullary gliomas usually require a surgical biopsy or resection for treatment, but they are sometimes observed on serial MR images if the symptoms are not progressive. However, some unusual brainstem tumors can mimic brainstem gliomas, and even nontumorous diseases can exhibit radiological features similar to brainstem gliomas. Therefore, radiological diagnosis cannot be considered definitive, and a proactive surgical

Abbreviations used in this paper: AQP4 = aquaporin-4; AQP4Ab = anti-aquaporin-4 antibody; DIPG = diffuse intrinsic pontine glioma; IgG = immunoglobulin G; MET = L-[methyl-11C]methionine; NMO = neuromyelitis optica; NMOSD = NMO-spectrum disorder.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
biopsy can provide accurate diagnosis and prevent unnecessary treatment targeting.29

Neuromyelitis optica (NMO) is an autoimmune inflammatory disease primarily affecting the spinal cord and optic nerves.3 The identification of a highly specific autoantibody in the sera of patients and its associated target antigen (aquaporin-4 [AQP4]) have greatly changed the concept of the disease.30 In this regard, the term NMO-spectrum disorder (NMOSD) was introduced to include spatially limited forms of NMO with seropositivity for anti-AQP4 antibody (AQP4Ab).2 Moreover, the involvement of the cerebrum, especially in childhood NMO, radically expanded the anatomical territory of the disease.17 The exact diagnostic criteria and full spectrum of NMO-like diseases remain highly controversial, but AQP4Ab-seropositive disease with a lesion confined mainly to the brainstem has not previously been reported.

Case Report

History and Presentation. A 5-year-old boy was referred to our hospital with a presumed diagnosis of brainstem glioma. His chief symptoms were diplopia, drooling, and dysphagia. He had also experienced intermittent headache and dizziness for several months. Two months earlier, his parents noticed mild facial asymmetry, and he gradually developed overt right-sided facial palsy and drooling. He had also developed diplopia and dysphagia 1 month prior to examination.

Examination. Upon neurological examination, the boy was alert and cooperative. Right abducent nerve palsy and peripheral-type facial palsy were noted. He had no uvula or tongue deviation, but he failed to take enough food due to dysphagia. No weakness or sensory loss of limb or trunk was observed. Deep tendon reflexes of the 4 extremities were normal.

The patient’s brain MR images revealed diffuse thickening and high signal abnormalities from the dorsalpons and medulla oblongata down to the cervical spinal cord. There was strong focal Gd enhancement in the dorsal medulla oblongata and upper cervical cord (C1–2). Bilateral optic nerves showed no specific abnormal findings (Figs. 1A–C). We preformed FDG-PET and [methyl-11C]methionine (MET) PET scanning to verify that the lesion indicated a tumorous condition. High metabolic uptakes were observed in the Gd-enhanced lesion in the medulla oblongata on both FDG-PET and MET PET scans (Fig. 1D and E). Whole-spine MRI revealed that there was no separate lesion below the medulla oblongata/high cervical cord lesion (Fig. 1F). The focially enhancing lesion on MRI was similar to a cervicomедullary glioma; however, the diffuse high-signal abnormalities in the brainstem and cervical cord were too widespread to be a cervicomедullary glioma or focal intrinsic glioma. They suggested a more malignant entity, and this hypothesis was reinforced by the PET scan results. Curiously, the basis pontis was spared from the diffuse signal abnormality, which was inconsistent with a malignant diffuse brainstem glioma.

Biopsy Operation. The imaging diagnosis was uncertain but most resembled an atypical cervicomедullary glioma. We recommended a surgical biopsy to the parents, and they consented. The fourth ventricle and brainstem were accessed through a midline suboccipital craniotomy and telovelar approach. A reddish mass protruded from the dorsal surface of the medulla oblongata (Fig. 2A). Diffuse gliomas do not violate the floor of the fourth ventricle, and the reddish color and ragged surface were incompatible with a dorsally exophytic or cervicomедullary glioma. We reasoned that the lesion could be another tumor entity or even a nontumorous disease. We decided to limit the operation to biopsy because of the profound diagnostic uncertainty. After electrical stimulation to identify the vagal and hypoglossal trigones, pieces of the mass were biopsied. No postsurgical complications occurred. Pathological examination of the biopsy tissue revealed many lymphoplasmacytoma cells, suggesting an active inflammatory lesion (Fig. 2B).

Diagnosis and Postoperative Course. The possibility of a brain tumor was excluded, and we searched for other clues for inflammatory diseases. There was no pleocytosis in the CSF, but the protein titer was elevated (129 mg/dl), and the immunoglobulin G (IgG) index was 0.65 (serum IgG 1188 mg/dl, CSF IgG 14.4 mg/dl, serum albumin 4.0 g/dl, CSF albumin 74.4 mg/dl). No CSF oligoclonal bands were detected. Tests for serum antinuclear antibody, antistreptolysin O, rheumatoid factor, and anti–double-stranded DNA were all negative. Ophthalmological examinations revealed mild optic disc swelling in the right eye, but visual acuity, pupillary response, visual field, and color vision tests revealed no abnormal findings. We performed an enzyme-linked immunosorbent assay7 for AQP4Ab using the patient’s serum and CSF, and both tests were positive. Based on these findings, the patient was diagnosed with CNS AQP4 autoimmunity and was started on methylprednisolone pulse therapy (30 mg/kg for 5 days). The patient’s neurological symptoms and facial palsy improved, but he developed headache and posterior neck pain 2 months after the surgical biopsy. Follow-up MRI showed no change of the lesion’s extent, but the patient had developed ventriculomegaly, suggesting hydrocephalus. His symptoms were alleviated by an endoscopic third ventriculostomy. Because of the extent of the unchanged lesion, the patient received 6 cycles of plasmapheresis. Unfortunately, after plasmapheresis, he developed aspiration pneumonia that progressed to respiratory arrest, and he fell into a vegetative state 3 months after the diagnosis.

Discussion

Brainstem glioma is one of the most common pediatric brain tumors arising in the posterior fossa.13 DIPG accounts for the majority of brainstem gliomas; only a small portion are focal tumors, such as dorsally exophytic glioma or cervicomедullary glioma. However, not all nontumorous lesions in the brainstem are gliomas. Ogihara and Morota10 described the surgical biopsy results of intrinsic brainstem lesions with atypical MRI findings suggestive of DIPG in 7 patients. Although 4 patients had diffuse gliomas, 2 had primitive neuroectodermal tumors, and 1 was...
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diagnosed with pilocytic astrocytoma. Even other tumors can closely mimic dorsally exophytic glioma on clinical presentation and imaging findings.

Many nontumorous diseases involve the brainstem and sometimes mimic brainstem gliomas. These reported diseases include cavernous angiomata and some rare diseases, such as Alexander disease and neuro-Sweet disease. Their imaging features, exact lesion location, and clinical course are usually atypical for brainstem gliomas and prompt surgical biopsies and other ancillary tests. Neuromyelitis optica is classically known as a disease that characteristically involves only the optic nerve and spinal cord. Although brainstem involvement has been occasionally reported in patients with NMO in the course of the disease, no patient has presented with primary brainstem abnormalities. Pittcock et al described the case of a 38-year-old patient with an NMO lesion that extended from the cervical cord to the lower brainstem. There was also a striking report of an NMO patient who was misdiagnosed with DIPG and received radiation therapy, even though the patient had a history of acute myelitis and documented optic atrophy in one eye.

Neuromyelitis optica is far less common in children; pediatric patients constitute approximately 5% of AQP4Ab-seropositive cases. However, it is known that atypical features, such as cerebral involvement, are more common in pediatric NMO. The presence of AQP4Ab is currently regarded as a relatively specific marker of NMO, but AQP4Ab seropositivity alone is not pathognomonic for the disease. Recently, the spectrum of NMO has been extended to the restricted forms of NMO, such as recurrent isolated optic neuritis (so-called NMOSD). Assays for serum AQP4Ab also contributed to this concept of NMOSD. However, there are still patients who have peculiar clinical and imaging features and AQP4Ab seropositivity but in whom the diagnostic criteria for NMO or NMOSD are not met. Although our patient showed mild optic disc swelling in the right eye and lengthy cervical spinal cord involvement that extended from the brainstem, we concluded that his functional deficit was not evident enough to be diagnosed as optic neuritis and myelitis. Thus, we preferred CNS AQP4 autoimmunity to NMO or NMOSD as the best description of the present case.

Images obtained in our patient showed a strong enhancement of the dorsal medulla oblongata and upper cervical cord, which is characteristic of cervicomедullary gliomas, but signal abnormalities on T1/T2-weighted images in the present case far exceeded the usual extent of...
cervicomedullary gliomas. We next considered the possibility of diffuse glioma, but this diagnosis was not appropriate given the sparing of the basis pontis (commonly affected in DIPG) and the involvement of the fourth ventricular floor (upper medulla oblongata). Our suspicion of a brain tumor was reinforced by the high metabolic uptakes of FDG and MET on PET, which generally indicate a tumorous condition. However, MET metabolic uptake was limited to the enhancing area in the dorsal medulla oblongata, whereas it is more widespread in diffuse glial tumors with an enhancing portion. High glucose and MET uptake can occur in nontumorous diseases characterized by blood-brain barrier disruption or active inflammatory processes. High MET uptake has also been reported in large tumefactive multiple sclerosis plaques. Therefore, it is necessary to conduct surgical biopsies for any suspicious brainstem lesions with atypical imaging features or when the diagnosis is uncertain for any reason. Some experts may argue that the AQP4Ab test should have been performed before surgical biopsy. However, there is growing evidence for the coexistence of AQP4Ab with cancer, which could be regarded as a paraneoplastic manifestation. In this clinical context, both AQP4Ab testing and surgical biopsy were required to arrive at the correct diagnosis and treatment.

The risks of respiratory failure are high for NMO, especially when the disease involves the cervical cord. Pitocek et al. reported a 75% mortality rate in NMO patients who required mechanical ventilation for respiratory failure. Early institution of plasmapheresis is recommended for high-risk patients, but the prognosis is still grim, as demonstrated in the current case.

Disclosure

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