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Case report

Vertical diplopia and oscillopsia due to midbrain keyhole aqueduct syndrome associated with severe cough

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ABSTRACT

Purpose: Midline structural defects in the neural axis can give rise to neuro-ophthalmic symptoms. We report a rare case of keyhole aqueduct syndrome presenting after two years of severe cough due to gastroesophageal reflux disease.

Observations: A 58-year-old woman with a 2-year history of daily, severe cough presented to the neuro-ophthalmology clinic with progressive diplopia and oscillopsia. Examination revealed a 1–2 Hz down-beating nystagmus in primary gaze that worsened with left, right, and down gazes. Gaze evoked nystagmus and mild paresis were also seen with up gaze. There was an incomitant left hypertropia due to skew deviation that worsened with right and up gazes and improved with down gaze. She also had a right-sided ptosis and a 3 mm anisocoria not due to cranial nerve 3 paresis or Horner's syndrome. Brain magnetic resonance imaging showed a 1.5 mm × 11.7 mm × 6 mm midline cleft in the ventral midbrain communicating with the cerebral aqueduct, consistent with keyhole aqueduct syndrome. Her nystagmus and diplopia improved with oral acetazolamide treatment, at high doses of 2500–3000 mg per day.

Conclusions and importance: We report the first case of midbrain keyhole aqueduct syndrome with ocular motor and other neuro-ophthalmic manifestations associated with severe cough. Although her cough was effectively treated and intracranial pressure measurement was normal, her ophthalmic symptoms continued to progress, which is common in previous cases reported. Treatment with acetazolamide led to significant improvement, supporting the use of acetazolamide in this rare condition.

1. Introduction

Eye movement abnormality and vertical nystagmus can arise from midline brainstem abnormalities due to Chiari malformation and rarely, from keyhole aqueduct syndrome or mesencephalic cleft. These latter two conditions have been reported in adults who typically develop progressive diplopia, ocular motor abnormality such as vertical nystagmus and internuclear ophthalmoplegia, balance issues, facial weakness, and sensory abnormality.[1] The term keyhole aqueduct syndrome is initially coined in 1986 by de la Monte et al. in two patients who were incorrectly diagnosed with multiple sclerosis and developed progressive gait abnormality, slurred speech, ocular motor abnormality, and ataxia.[2] On autopsy, these two patients had a keyhole-shaped syrinx in the midbrain and upper pons with open communication with the cerebral aqueduct and fourth ventricle.[2] Cerebellar atrophy and gliosis were also present on imaging. Since then, there have only been 9 published cases[1–7] in the English literature on idiopathic keyhole aqueduct syndrome or mesencephalic cleft. Several theories hypothesize that the mesencephalic cleft may be related to the formation of a midbrain syrinx, cerebellar ischemia, trauma, a congenital anomaly, or a pre-existing abnormality in the upper part of the brainstem.[2,3,5] In these cases, damage to the medial longitudinal fasciculus and oculomotor subnuclei can cause ptosis, anisocoria, ophthalmoparesis, and gaze-evoked nystagmus, along with other eye movement abnormalities.[4,5]

2. Case report

A 58-year-old Caucasian woman presented to the neuro-ophthalmology clinic with a two-month history of diplopia, oscillopsia, right-sided ptosis, and headache. Her past medical history was significant for a two-year history of severe cough associated with vomiting, headaches, and a hairline fracture in her right 8th rib. At presentation, her cough was already improving following treatment with a proton-pump

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inhibitor, consistent with gastroesophageal reflux disease. She also had a history of depression, anxiety, right total knee replacement, and osteoarthritis, and her medications included pantoprazole, venlafaxine, aripiprazole, lamotrigine, and clonazepam. There was no family history of craniospinal developmental abnormality, and her mother had idiopathic Parkinson's disease.

On examination, her uncorrected visual acuity was 20/25 in the right eye and 20/30 in the left eye, and anterior and posterior segment exam were normal with a cup-to-disc (C/D) ratio of 0.2 in both eyes. Her ocular motor exam revealed 1–2 Hz down-beating nystagmus worse on horizontal and down gaze (measured on exam and using 60-Hz three-dimensional binocular infrared video oculography). On down gaze, she also had bilateral alternating dysconjugate gaze-evoked nystagmus (video 1). On up gaze, she had a mild gaze evoked nystagmus and paresis. There was no internuclear ophthalmoplegia or any other eye movement abnormalities. Assessment for ocular alignment showed a skew deviation with an incomitant left hypertropia (14 prism diopter) in primary gaze that worsened with right and up gazes and improved with down gaze and ipsilateral head tilt. When supine, her nystagmus increased in amplitude, and her left hypertropia worsened.

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Pupillary exam showed a 3 mm anisocoria in the dark (3.5 mm, right; 6.5 mm, left), reduced pupillary light response in the right eye, normal pupillary light response in the left eye, and brisk accommodative pupillary response in both eyes. She also had right ptosis. Horner's syndrome was excluded by performing a 0.5% apraclonidine drop test followed by a 1% phenylephrine drop test, both of which showed no change in her ptosis and pupillary responses. Assessment of the parasympathetic pupillary pathway with 0.1% pilocarpine showed hypersensitivity in the left pupil, consistent with a relative dysfunction of the parasympathetic pupillary pathway on the left.

Her systemic exam revealed normal vitals and no evidence of scoliosis or other midline structural abnormalities. Her neurological exam was unremarkable with a normal sensory and motor examination, no extrapyramidal findings, or any evidence of cerebellar ataxia (normal mental status, facial strength and sensation, truncal and extremity strength and sensation, low normal deep tendon reflexes). She had a normal base and was able to ambulate well. A brain magnetic resonance imaging (MRI) from another hospital completed three months ago was read as normal.

Extensive workup to rule out other causes of her nystagmus and diplopia was unrevealing, with normal blood count, metabolites, anti-acetylcholine antibody, and absence of paraneoplastic antibodies in the serum (NeoComplete paraneoplastic antibody profile) and cerebrospinal fluid (CSF) (ANNA-1 to 3, AGNA-1, PCA-1, PCA-2, PCA-Tr, amphipysin, CRMP-5). She had normal CSF assessments including intracranial pressure (17cm H20), cell count, protein, glucose, IgG/albumin index, and IgG profiling by electrophoresis. A high resolution brain MRI revealed a 1.5 mm wide, 11.7 mm long, and 6 mm tall fluid-filled cleft in the midline of the ventral midbrain, which involved the entire ventral tegmentum and communicated with the cerebral aqueduct, consistent with keyhole aqueduct syndrome (Fig. 1). There was also prominent T_2 hyperintense lesions in the periventricular and subcortical white matter of both cerebral hemispheres, greater than typical for age, and mild ventricular and sulcal prominence likely related to parenchymal volume loss (not shown). There was no evidence of edema in the parenchyma surrounding the cleft or in the brainstem. Spinal MRI showed no syrinx in the cervical and thoracic spine and revealed multilevel degeneration of the cervical spine (primarily C4-C5) with bilateral neuro-foraminal narrowing and moderate spinal canal stenosis. The initial MRI was reviewed, and in retrospect, revealed the same midline midbrain cleft seen in the second MRI though more difficult to see given thicker sections were obtained.

Over several months, her symptoms and nystagmus worsened, with a new alternating skew deviation (left hypertropia in primary gaze worse with right gaze, and right hypertropia with left gaze). Her anisocoria decreased by 1 mm in both eyes. Trials of 4-aminopyridine (up to 10 mg twice per day), gabapentin (up to 1800 mg per day), baclofen (up to 10 mg twice per day), and clonazepam (up to 0.5 mg twice per day) either did not improve her ocular motor symptoms or led to significant side effects. She was then started on the carbonic anhydrase inhibitor, acetazolamide (1000mg per day), which led to significant improvement of her symptoms and examination. Her dosage was gradually increased to 3000 mg per day because of further clinical improvement on higher dosage and absence of significant side effects. A trial of dose reduction from 2000 mg to 1500 mg per day led to worsening of her nystagmus and ocular alignment, confirming the benefit of acetazolamide. Repeat brain MRI six months later showed no structural changes despite improvement of her symptoms. Although her nystagmus stabilized, her right eye ptosis did not improve with 2.5% phenylephrine eye drops, oral pyridostigmine (up to 60 mg three times per day), prednisone (up to 60 mg per day), or acetazolamide, and was repaired with levator advancement.

3. Discussion

We report a rare case of isolated midbrain keyhole aqueduct syndrome that manifested with down-beating nystagmus, skew deviation, balance issues, and headache, which improved with acetazolamide treatment. There are only 9 reported cases of keyhole aqueduct syndrome or mesencephalic cleft in the English literature, which are associated with eye movement abnormality, ptosis, ataxia, and other neuro-ophthalmic issues.[1–7] The most common ocular motor abnormalities in patients with keyhole aqueduct syndrome include vertical and rotatory nystagmus, ocular misalignment, internuclear ophthalmoplegia, and convergence insufficiency syndrome.[1–5]

In our patient, the keyhole aqueduct may affect the structure of the brainstem including the midbrain, which contains the vertical gaze center. Down-beating nystagmus can be due to dysfunction of connections to the interstitial nucleus of Cajal, leading to an upward drift and compensatory down-beating nystagmus.[8] The skew deviation can result from disruption of the vestibular input in the medial longitudinal fasciculus without causing an internuclear ophthalmoplegia, which is frequently seen in other cases of keyhole aqueduct syndrome.[1] Her brain MRI also showed significant cerebral white matter disease around the lateral ventricle, which may lead to misdiagnosis of multiple sclerosis, described in previous reports of keyhole aqueduct syndrome.[2,6]

The formation of keyhole aqueduct syndrome may be similar to the pathogenesis of syringomyelia, a fluid-filled cavity in the spinal cord. Clinical manifestations of keyhole aqueduct syndrome may be related to a local disturbance of CSF outflow, which contributes to the delayed onset, clinical manifestation at different ages, and slow progression over years.[3,5] Histopathological studies of other cases of midbrain clefts show compression and edema of structures in and around the midbrain, suggesting a disruption of CSF flow can lead to formation of an alternate route through a midbrain cleft, which in our case, connects the fourth ventricle to the cerebral aqueduct.[2,4] The formation of midbrain syrinx from trauma or increased intracranial pressure is extremely rare.

A case of keyhole aqueduct syndrome associated with severe cough has not previously been reported. Although mechanistically interesting, we do not know how the severe cough contributed to her symptoms. Because Valsalva maneuvers such as coughing can cause spikes in intracranial pressure, this raises the interesting hypothesis that spikes in intracranial pressure may precipitate neuro-ophthalmic manifestations or even cause structural damage to the brainstem over time.[9,10] During coughing and other maneuvers that increase intracranial pressure, there is a surge of blood into the epidural venous plexus from the abdominal and thoracic cavities, which squeezes the dura. The venous pulsation is easily transmitted into the CSF pathway[11] and causes an upward CSF wave that can potentially cause midline CSF pressure pulsations on the

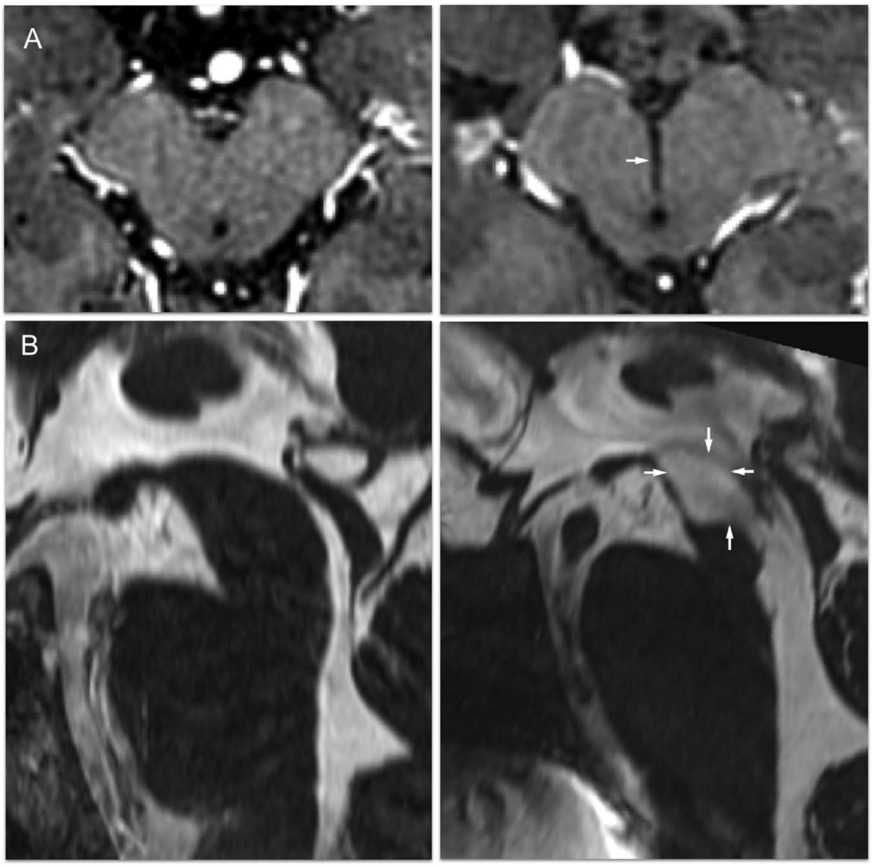

Fig. 1. Brain magnetic resonance imaging demonstrating a 1.5 mm wide by 11.7 mm long by 6 mm tall keyhole aqueduct. **A.** Images from axial T_1–weighted spoiled gradient-recall (SPGR) sequence with gadolinium enhancement of a 55-year-old control (left) and a 58-year-old female with keyhole aqueduct syndrome (right arrow). Images are 1 mm thick. **B.** Images of sagittal T_2–weighted fast imaging employing steady-state acquisition (FIESTA) sequence from 58-year-old control (left) and patient (right arrows). Images are 0.8 mm thick.

cerebral aqueduct and around brainstem. Healthy controls can typically absorb the abrupt CSF pressure waves after coughing without inducing tissue damage, but patients with syringomyelia or spinal stenosis may have increased CSF pressure gradients and altered fluid dynamics leading to anatomical, compliance, or pressure abnormalities that can exacerbate the effect of coughing, straining, and other maneuvers that impact CSF flow.[10,12]

There has been no previously reported effective treatment for keyhole aqueduct syndrome or mesencephalic cleft. Our patient's improvement on high dose acetazolamide provided support for consideration of this medication in other patients with keyhole aqueduct syndrome and mesencephalic cleft and suggested that manipulation of CSF synthesis or dynamics can ameliorate symptoms of keyhole aqueduct syndrome. Acetazolamide, a carbonic anhydrase inhibitor that decreases CSF production and secretion, can help improve symptoms of intracranial hypertension,[13] syringomyelia,[14] hindbrain herniation headache,[15] and Chiari malformation.[16] Furthermore, a majority of patients with keyhole aqueduct syndrome exhibit a progressive clinical course, although some have a static course.[1] In one patient with a slit-like lesion in the paramedian midbrain, the lesion decreased in size and the patient's eye movement abnormality improved over four months with no reported medication.[6] It will be interesting to see whether acetazolamide can impact the progression of disease, especially given some patients progress over years, with severe debilitation of their activities of daily living.[1]

Limitations to our study include the inherent limitation of a single case report, inability to confirm contribution of coughing to a disturbance in CSF dynamics, and lack of prior imaging.

4. Conclusion

The etiology of keyhole aqueduct syndrome is controversial, and our case suggests severe coughing and spikes in intracranial pressure may be associated with its formation. Brain MRI should be performed in patients with abnormal ocular motor behavior, especially in the setting of coughing or possible spikes in intracranial pressure because these symptoms can be associated with significant brainstem lesions. Our patient's eye movement abnormality and symptoms also improved with high dose acetazolamide therapy, suggesting manipulation of CSF flow plays an important role in treating these patients.

Patient consent

Informed written consent was obtained from patient for publication of personal and medical record details.

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Conflicts of interest

None. The following authors have no financial disclosures: AJO, BAL, YJL.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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