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 inconstant 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3} Cerebellar atrophy and gliosis were also present on imaging. Since then, there have only been nine published cases\textsuperscript{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.\textsuperscript{2,5–7} In these cases, damage to the medial longitudinal fasciculus and oculomotor subnuclei can cause ptosis, anisocoria, ophtalmoparesis, and gaze-evoked nystagmus, along with other eye movement abnormalities.\textsuperscript{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 inhibitor.
in the parenchyma surrounding the cleft or in the brainstem. Spinal cortical white matter of both cerebral hemispheres, greater than typical gliosis or other midline structural abnormalities. Her neurological exam of the parasympathetic pupillary pathway on the left. the parasympathetic pupillary pathway with 0.1% pilocarpine showed drop test followed by a 1% phenylephrine drop test, both of which Horner’s syndrome was excluded by performing a 0.5% apraclonidine modative pupillary response in both eyes. She also had right ptosis. normal pupillary light response in the left eye, and brisk accom- dx.doi.org/10.1016/j.ajoc.2018.02.009. decreased in amplitude, and her left hypertropia worsened. with down gaze and ipsilateral head tilt. When supine, her nystagmus in primary gaze that worsened with right and up gazes and improved with down gaze and ipsilateral head tilt. When supine, her nystagmus in primary gaze worsened, with right gaze, and right hypertropia with left gaze). Her an- socoria 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 sig- nificant 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 gra- dually 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 wor- sening of her nystagmus and ocular alignment, confirming the benefit of acetazolamide. Repeat brain MRI six months later showed no struc- tural changes despite improvement of her symptoms. Although her nystagmus stabilized, her right eye ptosis did not improve with 2.5% phentolamine 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 syn- drome 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 syn- drome or mesencephalic cleft in the English literature, which are as- sociated with eye movement abnormality, ptosis, ataxia, and other neuro-ophthalmic issues.2,6 The most common ocular motor abnorm- alities 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 connec- tions to the interstitial nucleus of Cajal, leading to an upward drift and compensatory down-beating nystagmus.3 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 syn- drome.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 clefs show compression and edema of structures in and around the midbrain, suggesting a disruption of CSF flow can lead to formation of an alter- nate 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 pathway11 and causes an upward CSF wave that can potentially cause midline CSF pressure pulsations on the
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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References

1. Ahmad O, Reddel S, Lueck CJ. Midbrain cleft as a cause of chronic internuclear ophthalmoplegia, progressive ataxia, and facial weakness. J Neuro Ophthalmol. 2010;30:145–149.
2. de la Monte SM, Horowitz SA, Larocque AA, Richardson Jr EP. Keyhole aqueduct syndrome. Arch Neurol. 1986;43:926–929.
3. Lagreze WD, Warner JE, Zamani AA, Gouras GK, Koralnik IJ, Bienfang DC. Mesencephalic clefts with associated eye movement disorders. Arch Ophthalmol. 1996;114:429–432.
4. Samples JR, Howard Jr FM, Okazaki H. Syringomesencephalia. Report of a case. Arch Neurol. 1983;40:757–759.
5. Burgett RA, Kawasaki A. Mesencephalic clefts and eye movement disorders. Arch Ophthalmol. 1997;115:824.
6. Chen CM, Lin SH. Wall-eyed bilateral internuclear ophthalmoplegia from lesions at different levels in the brainstem. J Neuro Ophthalmol. 2007;27:9–15.
7. Fredericks EJ, Van Nuis C. Diverticulum of the rostral cerebral aqueduct with ocular dysfunctions. Arch Neurol. 1967;16:32–36.
8. Glasauer S, Hoshi M, Kempermann U, Eggert T, Buttner U. Three-dimensional eye position and slow phase velocity in humans with downbeat nystagmus. J Neurophysiol. 2003;89:338–354.
9. Williams B. Cerebrospinal fluid pressure changes in response to coughing. Brain. 1976;99:331–346.
10. Martin RA, Loth F. The influence of coughing on cerebrospinal fluid pressure in an in vitro syringomyelia model with spinal subarachnoid space stenosis. Cerebrospinal Fluid Res. 2009;6:17.
11. Bedford TH. The effect of increased intracranial venous pressure on the pressure of the cerebrospinal fluid. Brain. 1935;58:427–447.
12. Levine DN. The pathogenesis of syringomyelia associated with lesions at the foramen magnum: a critical review of existing theories and proposal of a new hypothesis. J Neurol Sci. 2004;220:3–21.
13. Supuran CT. Acetazolamide for the treatment of idiopathic intracranial hypertension. Expert Rev Neurother. 2015;15:851–856.
14. Rusbridge C, Greitz D, Iskandar BJ. Syringomyelia: current concepts in pathogenesis, diagnosis, and treatment. J Vet Intern Med. 2006;20:469–479.
15. Chalaupka FD. Therapeutic effectiveness of acetazolamide in hindbrain hernia headache. Neurol Sci. 2000;21:117–119.
16. Vaphiades MS, Braswell R. Resolution of Chiari I malformation following acetazolamide therapy. Semin Ophthalmol. 2007;22:9–11.