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CASE REPORTS

Diffuse midline glioma presenting with central sleep apnea and pulmonary hypertension in a 4-year-old patient: a case report

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Central sleep apnea is a rare disorder in the pediatric population with various initial presentations and is secondary to many underlying diseases. We report on a 4-year-old boy with episodes of syncope. He also had pulmonary hypertension and cardiomegaly. Polysomnography showed the finding for central sleep apnea with a high apnea-hypopnea index (up to 138.1 events/h). Brain magnetic resonance imaging showed an ill-defined area near the medulla oblongata and lower pons. The lesion from a brainstem biopsy confirmed the diagnosis of low-grade glioma. Conservative medical follow-up was suggested, and brain magnetic resonance imaging 6 months later showed no obvious tumor progression. To our best knowledge, this is the first case report that workup on the cause of syncope and pulmonary hypertension led to the final diagnosis of central sleep apnea and a brain neoplasm.

Keywords: syncope, loss of consciousness, apnea-hypopnea index, brainstem glioma, children

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INTRODUCTION

Central sleep apnea (CSA) is a rare disorder among children; however, it can be one presentation of severe underlying diseases, such as brain malignancies.[1] Here, we present a case of a 4-year-old boy who had episodes of syncope, and further echocardiography confirmed pulmonary hypertension. A comprehensive workup on the etiology of pulmonary hypertension demonstrated that CSA was the cause of pulmonary hypertension. Brain magnetic resonance imaging (MRI) showed that brain glioma was the cause of all of his clinical symptoms.

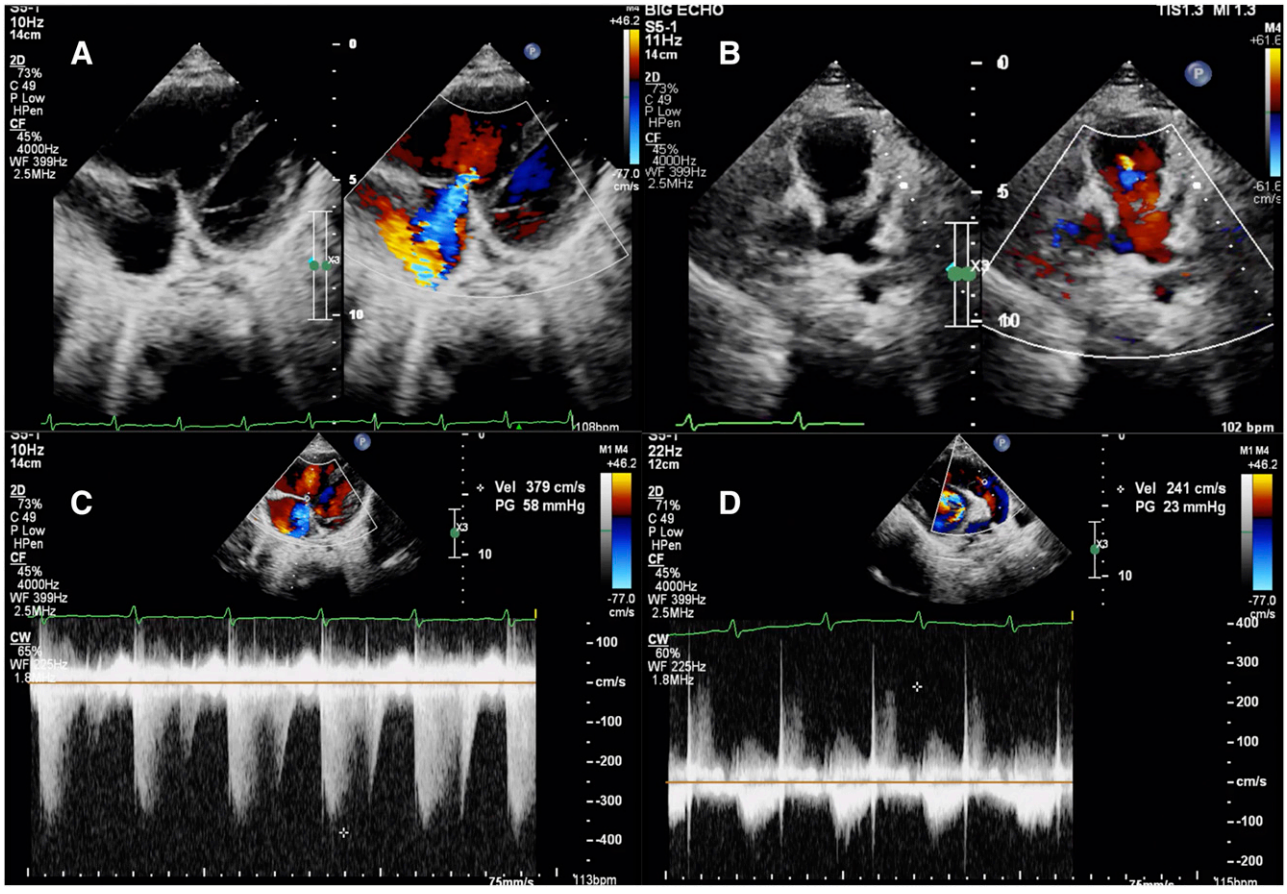
REPORT OF CASE

The presented patient is a boy aged 4 years and 4 months old (26 kg, >99th percentile) with frequent episodes of syncope during the past 6 months. He had history of febrile seizure at 1 year and 6 months and asthma without regular medication control. According to his mother, the febrile seizure presented with 4-limb convulsions and upward gaze of both eyes. The seizure duration was 1–2 minutes. The seizure stopped by itself in 1–2 minutes without the use of any medication.

The patient had the first syncopal episode at the age of 3 years and 10 months, which started with sudden onset of loss of consciousness, lip cyanosis, and a pale face, then followed by clenched fists, upward gaze of both eyes, and trismus. He did not show an obvious convulsion at that time. Mouth-to-mouth ventilation was performed by his father, and the boy gradually awakened 1 minute later with clear consciousness. He developed another 2 similar episodes of syncope 2 weeks before admission. Both episodes occurred when he got excited and presented with a sudden onset of loss of consciousness, lip cyanosis, and a pale face. He did not have any concurrent convulsion. He did not have any previous problems of falling asleep or obvious daytime sleepiness. But, according to his mother, he often sat up during sleep at night approximately 2–3 times per week with closed eyes and unclear consciousness, and then he lay down, falling asleep about 30 seconds later. Sometimes he complained of headache when he sat up, but then he fell asleep a few seconds later. No obvious snoring was noticed during sleep. He usually went to sleep at 21:00–23:00 hours and woke up around 7:00 hours.

The patient's electroencephalography and 24-hour Holter electrocardiography showed negative findings. His chest X-ray films showed the finding of cardiomegaly, with a cardiothoracic ratio of 0.62. Echocardiography showed fair left-ventricular systolic function with an *m*-mode ejection fraction of 78.5%, mild to moderate tricuspid regurgitation with a pressure gradient of 51 mmHg, and mild pulmonary regurgitation with a pressure gradient of 23 mmHg (**Figure 1**). All these findings indicated elevated systolic pressure of the right ventricle and pulmonary hypertension. Electrocardiographically gated computed tomography also revealed the finding of distended pulmonary trunk, bi-atrial enlargement, and right-ventricle hypertrophy, suggesting pulmonary hypertension. Further workup on the cause for pulmonary hypertension using polysomnography (PSG) demonstrated central hypoventilation because his apnea-hypopnea index was high (up to 835 events/h; normal range: <5 events/h), and the frequencies of central apnea and obstructive

Figure 1—Echocardiography.



Echocardiography showed mild to moderate tricuspid regurgitation **(A)** and mild pulmonary regurgitation **(B)**. The pressure gradient of tricuspid regurgitation was measured as 58 mmHg **(C)**. The pulmonary regurgitation pressure gradient was measured as 23 mmHg **(D)**. CF = color flow Doppler, CW = continuous wave Doppler, Hpen = penetration preferred, PG = pressure gradient, Vel = velocity, WF = wall filter.

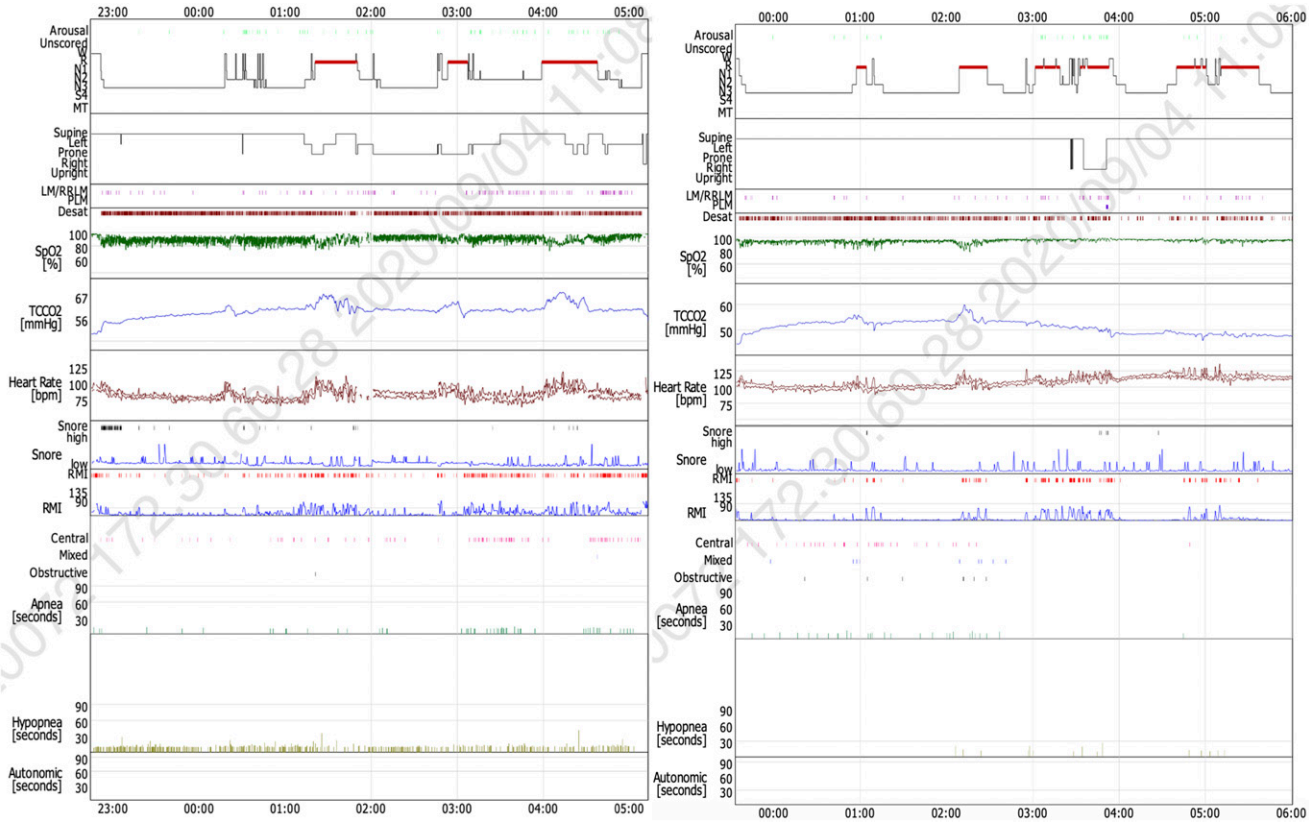
apnea were 14.7 times and 0.2 times per hour, respectively. In addition, the obstructive apnea occurred only 1 time in 6 hours (0.2 times/hour), and central apnea was as high in frequency at 89 times in 6 hours (14.7 times/hour). Detailed physical/neurological examination, laboratory/imaging, and PSG findings are available in the **supplemental material**.

The patient's hypopnea was 774 times (123.1 events/h) in frequency during the examination. Biphasic positive airway pressure (BPAP) support was recommended during sleep. The setting of BPAP was as follows: spontaneous/timed mode, inspiratory positive airway pressure = 11 cmH_2O, expiratory positive airway pressure = 7 cmH_2O, rate = 18 counts per minutes, maximum time the driver spends in inspiratory positive airway pressure = 1.5 seconds, minimum time the driver spends in inspiratory positive airway pressure, and rise time = 200 milliseconds. We repeated polysomnography 7 days later after the use of BPAP and PSG showed that his apnea-hypopnea index was reduced from 835 (138.1 events/h) to 84 (13.6 events/h) after the use of BPAP. **Figure 2, left panel**, shows the summary graphics of the initial PSG, demonstrating frequent desaturation and hypopnea episodes during sleep. As shown in **Figure 2, right panel**, 7 days after the use of BPAP, repeated PSG revealed a remarkable decrease in desaturation and hypopnea episodes. Complete PSG reports can be found in the **supplemental material**.

We also performed mutation analysis on the paired-like homeobox 2b gene for congenital central hypoventilation syndrome but did not detect any missense mutation. Neurological examination revealed no focal neurological deficit. Brain MRI revealed an ill-defined area of faintly increased signal intensity on T2WI near the medulla oblongata and lower pons, suggesting the diagnosis of brainstem glioma. Brainstem biopsy was performed, and pathology of the tumor biopsy specimen displayed a desmoplastic lesion with a low-grade glial component and some choroid plexus–like structures. With preserved H3K27me3 nuclear staining in this lesion, we excluded the diagnosis of diffuse midline glioma. Based on the diagnosis of low-grade glioma, we recommended a conservative management—that is, medical follow-up of the brain tumor. In addition, the patient had BPAP support during sleeping because of sleep apnea and associated pulmonary hypertension. He did not show any syncope episode again after the use of BPAP during a 14-month follow-up.

The tumor showed a slow progression and enlargement to 5 mm in diameter at a 6-month follow-up. No new neurological sign was found at the last neurology clinic visit.

Figure 2—Polysomnography results before and after BPAP.



Summary graph of the initial polysomnography revealed frequent desaturation and hypopnea episodes during sleeping (**left panel**). After the use of BPAP for 7 days, repeated polysomnography revealed significant decrease of desaturation and hypopnea episodes (**right panel**). BPAP = biphasic positive airway pressure. LM/RRLM = leg movement/respiratory-related leg movement, MT = monitoring time, PLM = periodic leg movement, RMI = respiratory mechanic instability.

DISCUSSION

CSA is a rare disorder in the pediatric population. The prevalence of CSA is between 4% and 6% among children, using a cutoff of >5 events/h. CSA can be caused by systemic conditions, including heart, airway, genetic, endocrine, and neurological conditions.[2] Brain neoplasm is a rare cause of CSA and was only reported in a case review of 14 children with brain neoplasms.[1]

Central nervous system tumors are the second most common neoplasm and the most common solid-organ tumor among the pediatric population, whereas gliomas account for the majority of solid tumors of the brain parenchyma.[3] Gliomas arising from the brainstem represent approximately 10–20% of all central nervous system tumors in children.[4] The clinical symptoms and signs of children with brainstem glioma vary depending on the location of lesion (midbrain, pons, and oblongata), and the most common symptoms at presentation are nausea and vomiting (45.7%), motor weakness (45.7%), and headache (31.4%).[5] The presentations of sleep disorders caused by neoplasms of the central nervous system depend on the area of the brain that has been invaded. In a case series of 14 children, Rosen et al[1] described that children with hypothalamic/pituitary region involvement develop excessive daytime sleepiness regardless of whether the damage was the result of the tumor, surgery, hydrocephalus, or radiation. On the other hand, respiratory insufficiency during wake and/or sleep was noted in 2 children whose tumors involved the medulla. A similar finding was also noted in our patient whose neoplasm was located at the medulla and with the PSG finding of respiratory insufficiency.

Surgical resection is not recommended for children with diffuse brainstem glioma due to the high morbidity and mortality rates. Radiotherapy is the mainstay of treatment. However, the long-term survival rate is still poor. The 2-year survival rate was less than 10% (6.7–7.1%).[6] Therefore, after careful explanation to his family about the possibility of a poor outcome, they decided on conservative follow-up rather than aggressive radiotherapy.

In our patient, we thought his syncope was most likely due to pulmonary hypertension, which was secondary to CSA. Syncope occurred in 31% of children with pulmonary hypertension in a registry study.[7] On the other hand, sleep-disordered breathing, especially obstructive sleep apnea, is a potential cause of pulmonary hypertension.[8] Unlike obstructive sleep apnea, only a few studies were reported to show the prevalence of CSA in patients with pulmonary hypertension. In only 1 study, Bin-Hasan et al[9] described a case of periodic breathing in a child with

idiopathic pulmonary arterial hypertension and the pulmonary hypertension resolved after the child was treated for her periodic breathing. Therefore, we suggest that the cause of pulmonary hypertension in our patient is secondary to CSA, caused by a diffuse medulla glioma.

Pulmonary hypertension is a rare disease among the pediatric population. The European Pediatric Pulmonary Vascular Disease Network published an updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension in 2019, suggesting that electrocardiography, lung function tests, chest X-ray, and cardiopulmonary exercise tests are ideal initial examinations for evaluating children with suspected pulmonary hypertension. Furthermore, the European Pediatric Pulmonary Vascular Disease Network also suggests that PSG should be performed in the patients with pulmonary hypertension at risk for sleep-disordered breathing, especially in those with trisomy 21, systemic disease, a small upper airway, or those with significant daytime sleepiness.[8] Another multicenter cohort study showed that chest radiograph and electrocardiography are good screening tools for pediatric pulmonary hypertension. Additional examinations such as a Holter monitor, 6-minute-walk test, PSG, cardiopulmonary exercise test, pulmonary function test, lung perfusion scintigraphy, chest MRI/computed tomography, and lung biopsy should be used in selected patients.[10] Applying the above to our patient, we used PSG for etiologic survey of pulmonary hypertension based on the rationale of his obesity (body weight >99th percentile) and the suspicion of obstructive sleep apnea. The results of PSG produced important clues and showed CSA. Later, we performed examinations including MRI and surgical biopsy. With the experience on the current patient, we suggest that workup on the cause of pulmonary hypertension in children should include those tests (eg, PSG) on sleep apnea.

CONCLUSIONS

CSA is a rare disease in the pediatric population, and it can present as syncope and as a result of many underlying diseases. Detailed history taking and comprehensive workup should be done to rule out any potential causes. Brain MRI is an effective tool for detecting underlying lesions causing CSA and should be arranged in children with the diagnosis of CSA.

ABBREVIATIONS

BPAP, biphasic positive airway pressure
CSA, central sleep apnea
MRI, magnetic resonance imaging
PSG, polysomnography

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at National Taiwan University Hospital and Medical College, National Taiwan University, Taipei, Taiwan. The authors report no conflicts of interest.