Central Neurogenic Hyperventilation in A Conscious Patient with Chronic Brain Inflammation

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Abstract

Central neurogenic hyperventilation (CNH) is a rare and easily forgotten diagnosis. A 53-year-old male patient presented with dyspnea for the past 1 month. His consciousness was clear and had bilateral upward gazing palsy. The arterial blood gas analysis showed severe respiratory alkalosis. Brain magnetic resonance imaging revealed symmetric hyperintense lesions involving the midbrain and the area surrounding the fourth ventricle. A brain biopsy showed gliosis and chronic inflammation. CNH results from an uninhibited respiratory drive due to pons or medulla disorders, and a conscious patient can mislead the initial judgment of the physician. However, severe respiratory alkalosis and persistent nocturnal dyspnea should raise the clinical suspicion of CNH. Chronic brain inflammation with CNH has seldom been reported in the literature. This case provides another pathological possibility of CNH. (J Intern Med Taiwan 2013; 24: 328-333)

Key Words: Central neurogenic hyperventilation, Inflammation, Conscious

Introduction

Hyperventilation is defined as an increase in alveolar ventilation that results in excessive metabolic carbon dioxide expulsion. It may result in a decrease in arterial carbon dioxide tension to below the normal range. Many clinical conditions and diseases can lead to an excessive ventilatory drive, such as hypoxemia, pulmonary disorder, and metabolic disorder. Central neurogenic hyperventilation (CNH) is a rare respiratory syndrome which was first reported by Plum and Swanson in 1959.[1] It is defined as respiratory alkalosis induced by lesions in the central nervous system without cardiac, pulmonary or other organic disease. Herein, we present the case of a conscious patient with CNH.

Case presentation

This 53-year-old male patient visited our emergency room (ER) with the chief complaint of progressive dyspnea in the recent one month. He denied drinking, smoking, or having previously undergone gastrointestinal surgery. The rapid respiratory rate was persistent even when he slept.

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He worked in an industrial plastics factory and he had continued to work for the past month. He had visited a local clinic, however the symptoms had not improved at all. At our ER, his initial body temperature was 36.8°C, with a pulse rate of 100 beats per minute, respiratory rate of 36 breaths per minute and blood pressure of 121/85 mmHg. His consciousness was clear. A physical examination did not demonstrate any remarkable findings, including clear breathing sounds and regular heart rhythm. Neither audible cardiac murmurs nor leg edema were noted. The oxygen saturation was 99% in room air. A hemogram only revealed mild anemia, and the hemoglobin level was 13.0 g/dL. Biochemistry showed normal renal and liver function tests, and only mild hypokalemia was noted with a potassium level of 3.18 mmol/L. The initial chest radiograph showed neither significant lung lesions nor cardiomegaly. Electrocardiography showed a normal sinus rhythm. The B-type natriuretic peptide level was less than 5 pg/mL. Chest computed tomography revealed normal opacification of the pulmonary artery without evident filling defects and clear bilateral lung fields. Hyperventilation syndrome was initially suspected, however the symptom did not resolve after treatment for hyperventilation at the ER.

His respiratory rate was around 30 breaths per minute after hospitalization. Due to a normal cardiopulmonary function test, the hyperventilation was assumed to be caused by a neuropsychiatric disease such as generalized anxiety disorder. Thus alprazolam (0.5 mg) 1# tid was prescribed, however the patient became irritable. Alprazolam was thus discontinued and he subsequently calmed down. All of the series of arterial blood gas analysis showed persistent severe respiratory alkalosis and sufficient oxygen saturation (Table 1). After we excluded other etiologies of hyperventilation, CNH was highly suspected and a neurologist was consulted.

On neurological examination, the patient was alert and his language function was normal. His pupils were equal and reactive, however he had obvious upward vertical gaze palsy. No other brainstem signs existed. The muscle power of all four limbs was full with normal muscle tone, however deep tendon reflexes were brisk in all limbs. Plantar reflex showed a flexor response on both sides. His coordination system was relatively preserved. His neck was supple and there was no Kernig or Brudzinski's sign. Based on the neurological findings, we localized as a midbrain lesion.

Further brain magnetic resonance imaging was arranged which revealed far more extensive lesions: symmetric hyperintense FLAIR/T2 lesions involving bilateral periventricular white matter, frontotemporal regions, part of the basal ganglia, and midbrain (Fig. 1). The differential diagnosis from the neuroimaging findings included encephalitis, demyelinating disease, and infiltrative glioma. A cerebrospinal fluid study was within normal ranges, and the results of bacterial and viral detection tests were negative (Table 2). The level of folic acid and vitamin B12 were within normal ranges (folic acid: 7.23 ng/mL, vitamin B12: 692 pg/mL). Tracing back his history, there was no obvious evidence of malnutrition. Intoxication surveys including carbon monoxide and cocaine were all negative. Because the nature of the brain lesions was unknown, we suggested a brain biopsy. He was then transferred to another hospital for the biopsy and the final pathological report showed gliosis and chronic inflammation only. The patient did not come back to our hospital for further treatment. We could not contact with him or his family by the telephone. We are sorry that his outcome cannot be reported.

Discussion

Among many etiologies of hyperventilation, CNH is a so rare that easily forgotten diagnosis. The consciousness of the patient with CNH is often influenced by brain disorders. The fact that our

patient was able to work as usual and continue with his daily activities while he sought medical help is extremely rare, and made the initial diagnostic approach in the ER difficult. The arterial blood gas analysis revealed longstanding respiratory alkalosis with metabolic compensation. The white blood cell count of 6 /μl was only slightly increased, and would only have been significant had it been over 10 /μl. Mildly elevated WBC counts with lymphocyte predominance in cerebrospinal fluid analysis can appear with demyelinating processes, tumor, stroke, or rarely, parameningeal irritation (such as extensive sinusitis infiltrating the meninges). According to the symmetric lesions and no obvious parameningeal irritation focus in the neuroimaging findings, a demyelinating process seemed most likely. Since this patient had a prolonged clinical course, a bacterial central nervous system infection was unlikely, so his pH and lactate levels were not measured.

The mechanism causing CNH is still poorly understood, and three have been proposed. First, and also the most traditional theory, was proposed by Plum and Swanson in 1959.[1] They suggested that there are three main respiratory centers in the brainstem: medullary center, pontine apneustic center, and pontine pneumotaxic center.[2] The medullary respiratory center mainly controls breathing impulses, while the other two pontine

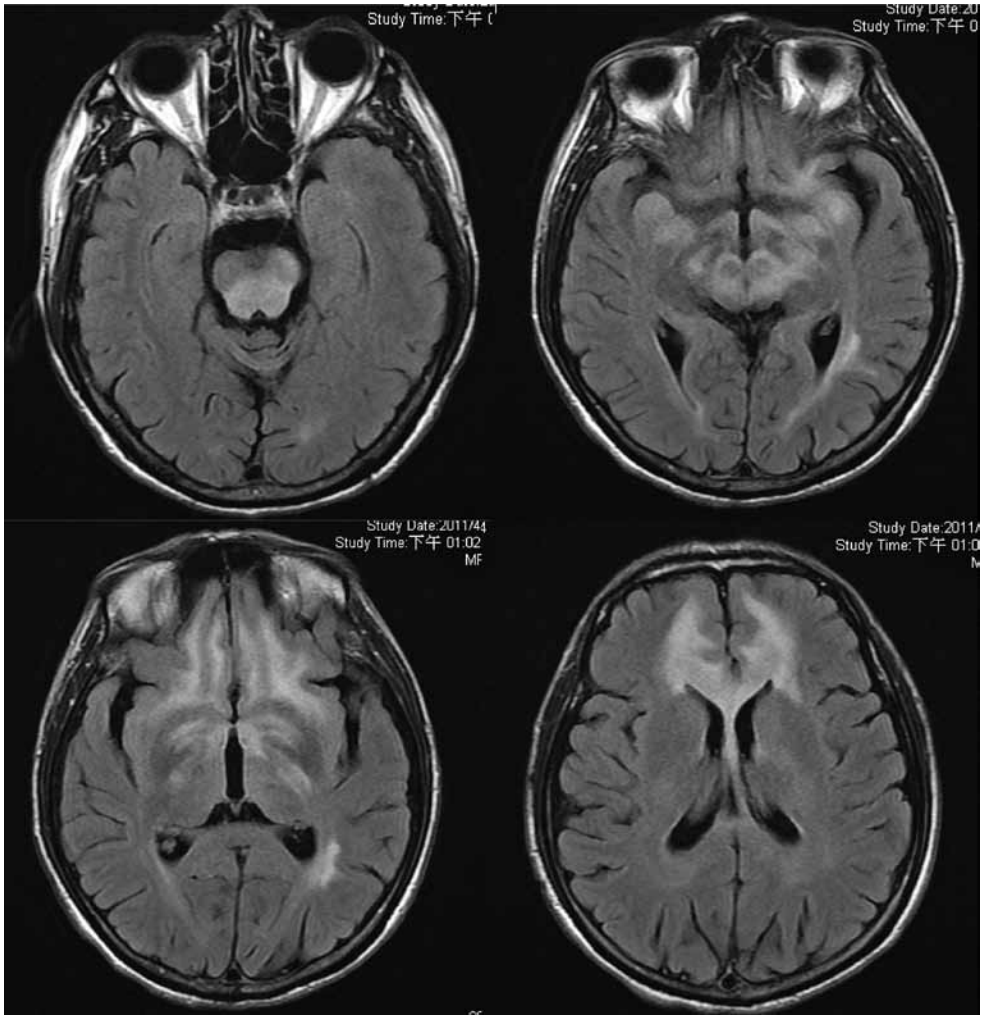

Fig. 1. The FLAIR images of brain magnetic resonance imaging showed symmetric subcortical hyperintensity in bilateral frontotemporal and basal ganglia, dorsal pontine, and midbrain.

centers adjust respiratory rhythm. Infiltrative lesions, such as in our patient, damage the pons which may result in a disconnection syndrome of the above system.[3] The second hypothesis is that local lactate production in the central nervous system can stimulate medullary chemoreceptors.[4] The third theory, which is based on an animal model by Takahashi et al., also advocates that chemical stimulation may lead to CNH.[4] The authors found that a glutamate injection into lateral parabrachial neurons in the pons led to an increase in respiratory rate.

The characteristics of CNH are respiratory alkalosis with a decrease in arterial carbon dioxide tension ($PaCO_2$) and normal arterial oxygen tension (PaO_2) without evidence of pulmonary or cardiac abnormalities. CNH may occur following stroke,[5] multiple sclerosis,[4] or brain tumors.[6] Tumor or inflammatory cytokine infiltration in the respiratory center may stimulate a tachypnea response.[6] Brain neoplasms, and especially primary central nervous system lymphoma, is the most common cause of CNH.[7,8] From the histological findings, our patient had a chronic immunological response to unknown stimuli. Chemical irritants in his work environment may have played a role. We proposed this final diagnosis and conclusion by carefully excluding other etiologies after the neuroimaging diagnosis. Symmetric periventricular lesions on magnetic resonance imaging are usually caused by demyelination. The other two possible diagnoses were a central nervous system infection and tumor, however these lesions are not usually so symmetric. The clinical course and magnetic resonance imaging finding did not support the diagnosis of multiple sclerosis or paraneoplastic syndrome. We therefore surveyed for uncommon demyelination diseases such as Wernicke's encephalopathy, and toxic and drug related encephalopathy. After these surveys and even a brain biopsy, only a toxin could explain the whole picture. We suspected that this

Table 1. The series of the arterial blood gas analysis

	1st day	4th day	5th day	6th day (sleep)
PH	7.637	7.637	7.638	7.638
PCO_2	8.2	5.7	8.1	11.8
PO_2	126.7	157.5	154.4	116.7
HCO_3	8.6	5.9	8.5	12.4
BE	-7.3	-9.5	-7.4	-4.3
O_2Sat	99.1	99.4	99.4	99

Table 2. The results of cerebrospinal fluid examination

CSF item	result	reference	unit
Appearance	Colorless/clear		
Protein: Pandy	Negative	(-)	
Glucose (CSF)	63	50~80	mg/dl
Total Protein (C)	75.2		mg/dL
Cell count: RBC	0		/μl
Cell count: WBC	6	0~5	/μl
WBC DC Poly/Lym/Mono	0/5/1 (only count:6)		
Indian Ink Stain	Not Found	(-)	
HSV PCR (polymerase chain reaction)	Not detected	(-)	
Immuno-Electrophoresis	No paraprotein	(-)	
Cryptococcus Antigen	negative	(-)	

patient had chronic central nervous system inflammation due to chronic exposure to plastic elements, as the final biopsy report from the other hospital showed only gliosis and chronic inflammation. Unfortunately, we did not try steroid therapy, since central nervous system lymphoma is known to respond dramatically to steroids. We regard this as a limitation to this case report.

There are very few reports about the relationship between chronic brain inflammation and CNH, and this case provides further evidence of this relationship. Because of the insidious course and unusual presentation, it is a challange for physicians to make correct diagnosis at the ER. However, CNH should be added to the differential diagnosis of hyperventilation, particularly in the patients with severe respiratory alkalosis. Clinical alertness and careful neurological examinations, especially detail neuro-ophthalmic exam, may help to detect occult brain lesions.

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慢性大腦發炎誘發之中樞神經性換氣過度

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摘　要

內科急診常會遇見過度換氣症候群的病患，其發生的病因很多，中樞神經性病變因罕見而不易列於起始的鑑別診斷中。於我們所報告的這位53歲男性病患，當他因呼吸會喘求診時，意識清楚且尚能工作。他的理學檢查顯示呼吸聲音清澈且心跳規則無雜音，動脈血分析報告顯示極度呼吸性鹼中毒 PH: 7.637, $PaCO_2$: 8.2 mmHg, PaO_2:126.7 mmHg, HCO_3^-:8.6 mmol/L, BE: -7.3 mmol/L and O_2Sat: 99.1%. 胸部電腦斷層檢查未發現明顯病兆。神經學檢查發現其眼睛向上看有困難，腦部核磁共振檢查顯示有大腦病變，經腦部切片檢查顯示其有慢性發炎狀態。在處理過度換氣症候群的病患，對於極度呼吸性鹼中毒又有代謝性代償時，適當的神經學檢查將有助於發現潛在的中樞性病兆。