Paroxysmal Sympathetic Hyperactivity in a Child with Tuberculous Meningitis

A Case Study and Review of Related Literature

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ABSTRACT

A one-year old boy was admitted to hospital for lethargy and vomiting over three days. Neurological examination revealed abnormalities. Cerebrospinal fluid examination showed evidence of meningitis. A purified protein derivative (PPD) test, T-SPOT.TB and radiological examination indicated tuberculous meningitis. During treatment, the child developed hypertension, sinus tachycardia, tachypnoea, dystonia and high fever. These episodes improved after administration of propranolol, artane and clonazepam. Paroxysmal sympathetic hyperactivity is a rare manifestation of tuberculous meningitis. Early detection is very important as it can avoid diagnostic errors and overtreatment.

Keywords: Child, paroxysmal sympathetic hyperactivity, tuberculous meningitis

Hiperactividad Simpática Paroxística en un Niño con Meningitis Tuberculosa:

Un Estudio de Caso y Revisión de Literatura Relacionada

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RESUMEN

Un niño de un año de edad fue admitido al hospital de letargia y vómitos durante tres días. La examinación neurológica reveló anormalidades. Examinación del líquido cerebroespinal demostró evidencia de la meningitis. Una prueba de proteína purificada derivado (PPD), T-SPOT.TB y examen radiológico indican meningitis tuberculosa. Durante el tratamiento, el niño desarrolló hipertensión, taquicardia, taquipnea, distonía y fiebre alta. Estos episodios se mejoraron después de la administración de propranolol, artane y clonazepam. Hiperactividad simpática paroxística es una manifestación rara de la meningitis tuberculosa. La detección temprana es muy importante, ya que puede evitar sobretratamiento y errores de diagnóstico.

Palabras claves: Niño, hiperactividad simpática paroxística, la meningitis tuberculosa

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INTRODUCTION

Paroxysmal sympathetic hyperactivity (PSH) is often the result of acquired brain injury (ABI). It is a group of syndromes mainly featured with sympathetic hyperactivity. Brain trauma is found in most cases. Infection-induced cases are rare. It is not easy to identify early manifestations of this syndrome. Delayed treatment may lead to poor prognosis. Here, we report one PSH case as a result of tubercular meningitis that we treated, in the hope of improving clinical doctors' understanding of this disease.

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CASE REPORT

A one-year old boy was admitted to hospital for lethargy for three days, with intermittent vomiting. Three weeks before the attack, the boy was diagnosed with pneumonia for intermittent mild fever and cough. After administration of cephalosporin antibiotics for one week, cough was improved, but intermittent mild fever remained before this admission. There were no special accounts in his personal and family history and his family denied contact with infectious diseases. The vaccination history was normal.

Physical examination at admission showed the boy's temperature was 36.8 °C. The respiratory rate was 28 beats per minute (bpm), heart rate 140 bpm, blood pressure 86/60 mmHg, Glasgow coma scale (GCS) 8 points, full mucous membrane, no rash haemorrhagic spot, no large thyroid, no

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pharyngeal hyperaemia, no abnormalities in heart, lungs or abdomen, pupil equal and reactive to light, no sensitivity to light reflex, neck hyperactivity (+), increased muscle tone, normal patellar tendon reflex and positive Babinski sign on both sides. Laboratory examination: no abnormalities in blood, urine or stool routines, normal liver and kidney function and normal thyroid function. Results for cerebrospinal fluid examination are shown in Table 1: strong positive purified protein derivative (PPD) test and positive T-SPOT.TB. Enhanced head magnetic resonance imaging (MRI) showed hydrocephalus and multiple meningeal pathological reinforcements at skull base. Chest computed tomography (CT) indicated small nodular shadows in the left ligule.

Treatment process: After admission to our hospital, the child was diagnosed with tuberculous meningitis. Soon, we initiated a combined chemotherapy of isoniazide, rifampin, pyrazinamide and streptomycin and administered mannitol and dexamethasone, *etc*. But later, his conscious state continued to get worse. By the 3rd day after admission, GCS dropped to 4 points. The boy developed paroxysmal muscle tone, limb stiffness and trismus. Meanwhile, he ran a fever of more than 39 ˚C. The respiratory rate increased to 40–50 bpm, the heart rate to 180–190 bpm and systolic blood pressure to 110 mmHg. Mydriasis occurred for a few minutes each time, several times a day. The reason remained unclear. There was no obvious sweating during and after attack, nor was there any epilepsy wave after repeated electroencephalograms (EEGs) during the

Table 1: Results of cerebrospinal fluid examination

Admission (days)	Pressure (cmH_2O)	White blood cell ($/mm^3$)	Lymphocyte count ($/mm^3$)	Glucose (mg/dL)	Protein (mg/dL)	Chlorine (mmol/l)	Culture
1	240	30	18	18	117	113	Negative
5	108	54	40	28	84	114	Negative
10	280	26	16	33	63	113	Negative
20	220	10	6	50	47	123	Negative
30	180	2	2	48	60	122	Negative
45	180	4	4	53	54	123	Negative

Table 2A: Paroxysmal sympathetic hyperactivity assessment measure (PSH-AM), clinical feature scale (CFS, #)

	0	1	2	3
Heart rate	< 100	100–119	120–139	≥ 140
Respiration	< 18	18–23	24–29	≥ 30
Systolic pressure	< 140	140–159	160–179	≥ 180
Temperature (˚C)	< 37	37–37.9	38–38.9	≥ 39.0
Sweating#	No obvious sweat	Wet skin	Beads of sweat	Profuse sweating
Posture at attack	No changes in muscular tone	Slightly increased muscular tone, flexible limbs	Increased muscular tone, hard to flex limbs	Rigid and inflexible limbs

CFS subtotal___

2B: Diagnosis likelihood tool (DLT)

Items	Scores
Clinical features occur simultaneously	1
Sudden attack	1
Painless stimuli	1
Clinical features occur for 3 consecutive days	1
Clinical features persist for over 2 weeks following brain injury	1
Clinical features persist after differential diagnosis and switching therapy	1
Number of attacks in a day ≥ 2	1
Lack of parasympathetic neural symptoms during attack	1
No other explanations in clinical features	1
The primary disease is acquired brain injury	1

(Score 1 point for each feature present) DLT subtotal_____

2C: Score for PSH-AM

PSH diagnostic likelihood	Unlikely	Likely	Very likely
Total score (CFS+DLT)	< 8	8–16	> 17

attacks. Relevant laboratory examination did not suggest exacerbated secondary infections or neural system infection.

The 16th day after admission, considering PSH, we added propranolol, artane and clonazepam and kept his limbs in a functional position. Later, the frequency and extent of the above attacks were reduced and his temperature was around 38 °C. The heart rate, respiration and systolic rate, respiration and systolic blood pressure were lower than before. The muscle tone decreased and the attack time was shortened to one to three times per day, accompanied by intermittent hiccups, tears and yawning. The 30th day after admission, head imaging re-examination suggested hydrocephalus. His GCS rose to 7 points. After implanting an Ommaya reservoir to reduce hydrocephalus, PSH attacks gradually disappeared and the boy's temperature returned to normal. After anti-tuberculosis treatment for three months, the boy's GCS rose to 9 points. We started hyperbaric oxygen therapy (HBOT) and rehabilitation soon after.

DISCUSSION

Paroxysmal sympathetic hyperactivity is a group of clinical syndromes following ABI featured with paroxysmal dysphoria, high fever, sweat, high blood pressure, tachycardia, tachypnoea and myodystonia. In terms of nomenclature, PSH has no fewer than 31 names (1), such as decerebrate rigidity and vegetative signs, fever of central origin, hyperpyrexia associated with sustained muscle contractions, hypothalamic storing, paroxysmal sympathetic storms/diencephalic seizures and hypothalamic-midbrain dysregulatory syndrome. Some names were abandoned after only appearing in the literature several times. In 2004, Blackman recommended using the term "paroxysmal autonomic instability with dystonia" (PAID) to describe a series of abnormal syndromes in PSH, accompanied by hypermyotonia or abnormal posture (2). As terms were not unified, by 2014, nine PSH diagnostic criteria had come out in succession (3). These criteria included descriptions about temperature, heart rate, respiration, blood, sweat, posture or dystonia, as well as definition of disease background, such as brain injury severity, cognitive function, frequency and time of attacks.

In 2014, Baguley *et al* (4) defined the concept, naming and diagnostic criteria of PSH, on the basis of previous data and presented a paroxysmal sympathetic hyperactivity assessment measure (PSH-AM). The assessment included two parts: one for clinical feature scale (CFS), which reflected the symptoms and sympathetic hyperactivity severity, and the other for diagnosis likelihood tool (DLT). All indicators of CFS and DLT had corresponding scores. Added together, they constituted a final score of PSH-AM. The possibility of PSH was judged from the final score, as shown in Table 2. It is noteworthy that not every case has all clinical symptoms in the indicators and it is not significant to rule out any clinical symptoms.

Paroxysmal sympathetic hyperactivity assessment measure provided a simple and feasible diagnosis solution for clinical doctors and facilitated the early detection of PSH. Although PSH-AM was an adult criterion, after excluding differences of respiration, heart rate and blood pressure and referring to this criterion, in this case, CFS was 14 points, DLT was 9 points and the final score of PSH-AM was 23. It was "very likely" to be PSH. Even by previous diagnostic criteria (5), this case could still be diagnosed as PSH. It is worth noting that regardless of the primary disease of PSH, a high PSH-AM score is often associated with longer intensive care. Thus, more positive interventions were needed. In this case, the intensive care time was more than one month. After adopting Ommaya reservoir implantation, HBOT and other interventions, they were of predictive significance for diagnosis and management to support PSH- AM.

In ABI-induced PSH, traumatic brain injury (TBI) is the main cause. Anoxia, subarachnoid haemorrhage, hydrocephalus, tumour and infection due to various factors are causes too (6–8). For PSH associated with tuberculous meningitis, we retrieved two cases reported recently, *ie* a 69-year old male was reported by Dutch scholars in 2010 (9) and a one-year old female was reported by Indian scholars in 2011 (10). The diagnostic processes were similar to this case. The PSH attacks and conscious level were synchronous, with poor prognosis.

When a patient's conscious state significantly worsened, PSH was easily mistaken for epileptic seizure, but EEG showed no changes of epileptic characteristics. Therefore, the early literature used the term "diencephalic epilepsy" but abandoned it later (11). Besides, PSH also needed to be distinguished from malignant syndromes, loss of autonomic spinal neural reflex, sepsis, hyperthyroidism, central high fever and withdrawal syndromes, *etc* (12, 13).

Typical clinical manifestations of PSH attacks included autonomic neural and motor symptoms. Apart from the foregoing manifestation of PSH, autonomic neural symptoms may have paroxysmal parasympathetic hyperactivity (PPH) as well, such as low heart rate, slow respiration, low blood pressure, Cheyne-Stokes breathing, hypothermia, corestenoma, hiccups, tears and yawning. Therefore, autonomic neural symptoms can be divided into two types: pure PSH and mixed PPH and PSH. In 2010, Perkes *et al* (14) found by analysing the literature that although this disease may have changes in parasympathetic neural activities, over 77.9% of cases were represented as PSH. Traumatic brain injury-related PSH was often represented as pure PSH, while non-TBI-related PSH may be represented as PPH. Our case did not have obvious sweating during attacks, but hiccups, tears and yawning, similar to the foregoing analysis. Both the sympathetic hyperactivity and motor symptoms of PSH were repetitive and intermittent. They often appeared simultaneously or alone. It was often difficult to identify a single symptom, so diagnosis could be differentiated. Innocuous stimuli, such as sputum suction, change of position, turnover, passive limb motion, *etc* may be induced. We could not identify the causes of some attacks and thus the difficulty of diagnosis was increased (15).

The purpose of PSH management is to control clinical symptoms. Although there are many drugs, they cannot rectify abnormal symptoms thoroughly. Most treatment experience came from small sample studies or individual experiences. Random, double-blind and studies or individual experiences. Random, double-blind and controlled large sample studies were inadequate. It was generally believed that morphine was the most effective drug to end attacks, but sometimes we needed to increase its dosage. Other medications included dopamine receptor agonists (*eg* bromocriptine), non-selective beta-blockers (*eg* propranolol), α2-adrenergic receptor agonists (clonidine), benzodiazepines, muscle relaxants, dopamine (*eg* levodopa), GABA drugs (*eg* gabapentin and baclofen), *etc*. In most cases, they needed to be taken together (12, 14, 16, 17). Small sample studies suggested that HBOT can serve as an auxiliary means of medication (18). This can improve the aerobic metabolism of injured brain tissues at a mitochondrial level and improve the prognosis of ABI patients. As for this case, due to the presence of tuberculous meningitis, we chose to administer HBOT after controlling the primary disease. To reduce unnecessary stimuli and give bath, doing turnover, endotracheal intubation, sputum suction and other medical care softly and gently can reduce PSH attacks. As PSH was recurrent, the body was at a high metabolic state during attacks and a patient's nutritional requirements were often higher than average people. Special attention should be paid to the patient's heat, water and mineral intake (18). For some patients with abnormal postures, it was necessary to keep functional positions and prevent heterotopic ossification (19, 20).

Paroxysmal sympathetic hyperactivity originated from an intermittent increase or disorder of sympathetic neurotransmitters. But the exact pathological mechanism remains unclear. Paroxysmal sympathetic hyperactivity attacks have no clear correlation with brain injury severity. At present, widely accepted theories are disconnection theories and the excitatory:inhibitory ratio (EIR) model (14, 21, 22). Disconnection theories suggest that PSH followed the release of one or more excitatory centres from higher centre control. The EIR model suggests that PSH derived from sympathetic and parasympathetic disconnection and/or imbalance and resulted in sympathetic hyperactivity. It further divided PSH attacks into three stages, *ie* the hidden, typical and remittent stage. At the hidden stage, as the symptoms were not typical, it was difficult to make a diagnosis. At the typical stage, characteristic PSH syndromes appeared. At the remittent stage, with the improvement of neurological functions, attacks were gradually alleviated, but dystonia and joint spasm were the same. In this case, the EIR model can readily explain the attack process and therapeutic response of the child.

Paroxysmal sympathetic hyperactivity may cause secondary brain injury, prolong hospitalization time and cause heavy medical burden. Hyperventilation and high blood pressure during attacks may result in brain tissue anoxia, exacerbated cerebral oedema and intracranial hypertension. Sustained sympathetic hyperactivity can lead to haemodynamic changes and even neurogenic pulmonary oedema. Increased metabolism may result in weight loss, poor nutrition and water, electrolyte and acid-base balance disorder. Dystonia and abnormal posture may increase the risk of heterotopic ossification. Since it is difficult to distinguish PSH attacks from sepsis or infection, antibiotics abuse is apt to occur. Therefore, early diagnosis and timely treatment are of great significance.

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