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Paroxysmal sympathetic hyperactivity caused by neurosyphilis

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ABSTRACT

Background Paroxysmal sympathetic hyperactivity (PSH) is a condition characterised by dysregulation of the autonomic nervous system commonly associated with severe traumatic brain injury. Recently, non-traumatic causes, such as infections and autoimmune conditions, have also been reported as potential triggers.

Case presentation A 30-year-old man presented with convulsions following 5 days of soliloquy, insomnia and agitation. Neurosyphilis was diagnosed based on elevated non-treponemal and treponemal test findings in the serum and cerebrospinal fluid. Intravenous penicillin administration improved his alertness; however, by day 9, he experienced recurrent episodes of tachycardia, tachypnoea, hyperthermia, hypertension, limb stiffness and diaphoresis. The exclusion of sepsis, pulmonary embolism and malignant syndrome, combined with unremarkable interictal electroencephalogram findings and a high PSH Assessment Measure Score, led to a PSH diagnosis on day 40. Treatment with propranolol, gabapentin and clonidine resolved the episodes, and the patient regained independent ambulation.

Conclusions This is the first reported case of neurosyphilis accompanied by PSH. Although PSH is rare in central nervous system infections compared with traumatic brain injury, early recognition is crucial, as untreated cases can persist and result in severe complications.

INTRODUCTION

Paroxysmal sympathetic hyperactivity (PSH) is an excessive sympathetic activity disorder characterised by paroxysmal hyperthermia, tachycardia, hypertension, tachypnoea, excessive diaphoresis and motor posturing.[1] PSH is most commonly observed following brain trauma but can also be triggered by non-traumatic causes of acute brain disease, including anoxic–ischaemic coma after cardiac arrest and intracranial haemorrhage.[1] Recent reports have further suggested a potential involvement of central nervous system (CNS) infections[2 3] and autoimmune encephalitis[4–6] in the development of PSH. However, PSH associated with neurosyphilis has not been previously reported.

CASE PRESENTATION

A 30-year-old man presented to our hospital with convulsions lasting approximately 1 min. 5 days before admission, he exhibited agitation and confusion and engaged in nocturnal soliloquies accompanied by slurred speech. He had no history of growth or developmental problems during childhood, nor any relevant medical history, including mental disorders. He was not consuming prescription medications or illicit supplements. However, his frequent visits to brothels culminated in his divorce from his ex-wife.

On admission, the patient was agitated and could not be examined thoroughly without sedation. His vital signs were as follows: temperature, 38.1°C; blood pressure (BP), 138/71 mm Hg; pulse, regular 121 beats/min; respiratory rate, 22 breaths/min; and oxygen saturation, 98% while breathing ambient air. There was no evidence of a rash on any part of his body, including the penis. His Glasgow Coma Scale (GCS) Score was E4V1M5. Motor paralysis was not observed, and the patient exhibited no neck stiffness. Argyll-Robertson pupils, commonly associated with neurosyphilis, were absent.

Laboratory tests revealed an elevated white blood cell count (19.45×10^9 cells/L) and C reactive protein (0.76 mg/dL), normal thyroid function and elevated serum rapid plasma reagin (RPR) and *Treponema pallidum* latex agglutination (TPLA) values of 64.0 RPR units (RU; normal range: <1.0 RU) and 26160.0 TPLA units (TU; normal range: <10.0 TU), respectively. The patient tested negative for HIV antibodies and antigens. Cerebrospinal fluid (CSF) examination revealed pleocytosis (213 cells/μL, mononuclear cells: 85.9%). The IgG index was elevated (2.12), and oligoclonal bands (OCBs) were detected. PCR of the serum/CSF was negative for herpes simplex virus (HSV) 1, HSV2, varicella–zoster virus, Epstein-Barr virus, cytomegalovirus and enterovirus. MRI of the brain revealed a slightly high intensity in the medial temporal lobe bilaterally on fluid-attenuated inversion recovery (figure 1A).

The possibility of herpes simplex encephalitis or autoimmune limbic encephalitis could not be ruled out; therefore,

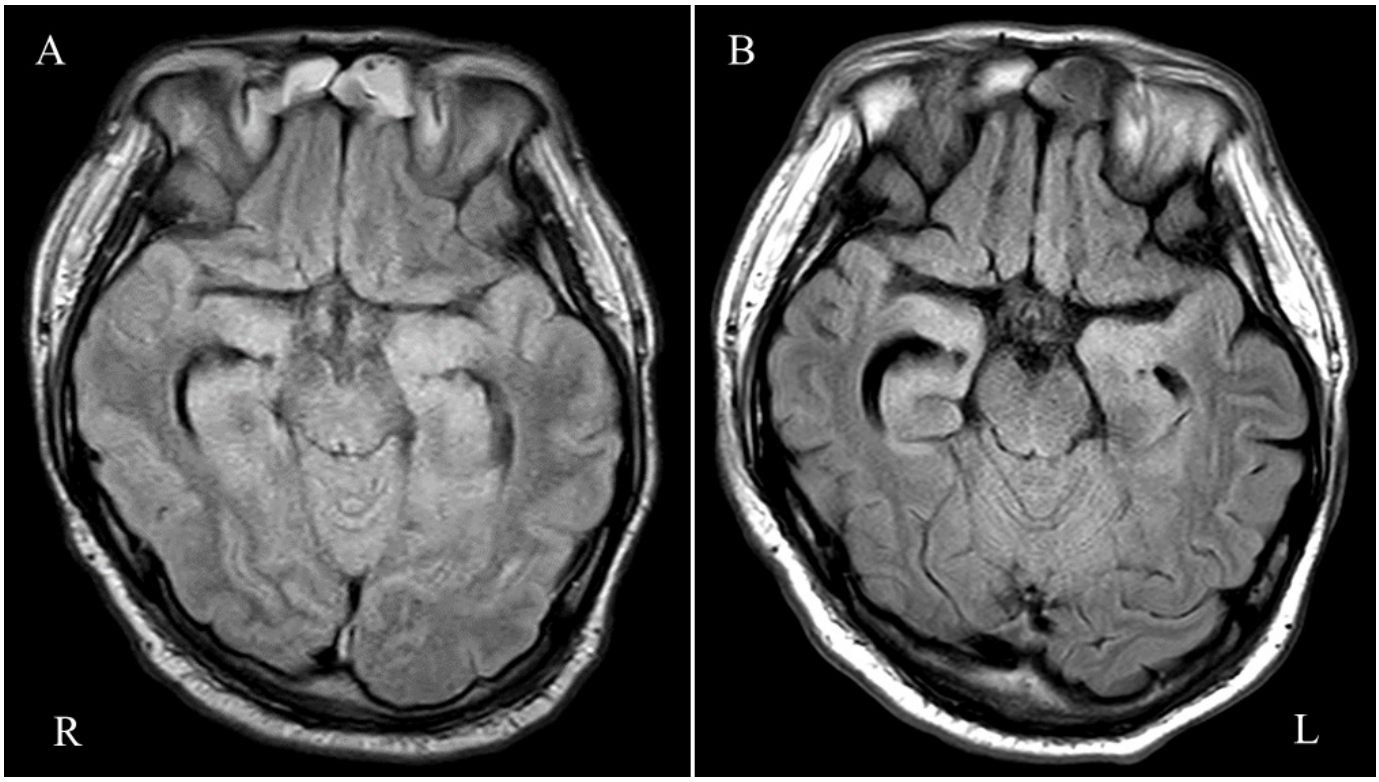

Figure 1 Time course of brain FLAIR-MRI results. MRI of the brain on day 3 showing a slightly high signal intensity bilaterally in the medial temporal lobes (A). Atrophy of the medial temporal lobe was conspicuous on day 57 after the identification of neurosyphilis concurrent with PSH (B). FLAIR, fluid-attenuated inversion recovery; PSH, paroxysmal sympathetic hyperactivity.

intravenous administration of acyclovir (1500 mg/day) and methylprednisolone pulse therapy (1000 mg/day) was initiated. After confirming the positive results of RPR (13.6 RU) and TPLA (5880.0 TU) in the CSF on day 3, a definitive diagnosis of neurosyphilis was made, and intravenous penicillin (24 000 units/day) was initiated. His confusion gradually improved, and he became communicative on day 5. His GCS Score at this stage was E4V4M6, and he began eating orally. Despite the decrease in the number of cells and RPR/TPLA value in the CSF over time, he started to experience repetitive attacks of hyperthermia (38–40°C), tachycardia (120–140 beats/min), tachypnoea (24–29 breaths/min), high BP (systolic BP: 180–200 mm Hg), drenching diaphoresis and limb stiffness, with tremors starting on day 9. He exhibited rigidity in all four limbs and the trunk, along with a resting tremor, predominantly affecting the right upper limb (online supplemental video 1). These attacks are typically evoked by subtle stimuli, such as calling one's name or light touch, but can be provoked naturally without any stimuli. Once these symptoms had started, they lasted for approximately 2–6 hours, occurring four to five times a day. The attacks never happened while sleeping, and the patient could follow simple instructions during the attacks. His episodic spells, led to significant functional decline, with an inability to eat, speak or walk, ultimately causing muscle disuse, rendering him bedridden.

Involuntary body movements caused artefacts that hindered accurate EEG assessment, and repeated interictal EEGs were normal. Despite treatment with therapeutic doses of intravenous levetiracetam (2000 mg/day), lacosamide (200 mg/day) and continuous intravenous midazolam administration (4 mg/h), the abnormal episodic attacks did not abate. Serum autoantibodies, including those against amphiphysin, Hu, Yo, Ri, CV2, voltage-gated potassium channel, voltage-gated calcium channel, ganglionic acetylcholine and N-methyl-D-aspartate receptors (NMDAR), were all negative (anti-glutamic acid decarboxylase 65, anti-γ-aminobutyric acid-B receptor and glycine receptor were not measured). There were no findings indicative of sepsis, thyrotoxic crisis, pheochromocytoma, neuroleptic malignant syndrome or pulmonary embolism. All differential diagnoses were ruled out, and a high PSH Assessment Measure Score of 26 points (online supplemental table 1),[1] ultimately led to the diagnosis of PSH.

On day 40, we initiated treatment with gabapentin (2400 mg/day), bromocriptine (15 mg/day), propranolol (30 mg/day) and clonidine (225 µg/day). The patient's attacks improved dramatically, and he started eating and walking again on day 52. MRI of the brain on day 57 revealed atrophy in the medial temporal lobe, in the region where a faint high-intensity signal was observed in the previous scan, confirming remarkable limbic damage due to neurosyphilis (figure 1B).

The patient was finally discharged on day 101 to stay with his parents (online supplemental figure 1).

DISCUSSION AND CONCLUSIONS

To the best of our knowledge, this is the first report of PSH triggered by neurosyphilis. Unfortunately, the diagnosis and initiation of specific treatment for our patient was delayed by approximately 1 month from symptom onset. It should, therefore, be emphasised that symptom improvement cannot be achieved without specific treatment based on an accurate diagnosis.

PSH is a neurological disorder characterised by sudden episodic surges in sympathetic nervous system activity.[1] These surges can lead to rapid heart rate, increased respiratory rate, hypertension, fever, excessive sweating and posturing, which are commonly observed in patients with severe brain injuries. The excitatory–inhibitory ratio model is a recent theoretical framework used to explain the imbalance between excitatory and inhibitory neural activity in PSH. PSH is characterised by an excessive release of excitatory neurotransmitters, such as norepinephrine and glutamate, and a reduced release of inhibitory neurotransmitters, such as γ-aminobutyric acid. This leads to an increased excitatory–inhibitory ratio, meaning that the excitatory signals outweigh the inhibitory signals in the affected neural circuits. Approximately 80% of reported PSH cases develop following head trauma, with hypoxia (10%) being the second most frequent cause.[1] Reportedly, 3.6% of patients with severe non-traumatic brain injury develop PSH.[1]

Neurosyphilis is an infectious disease of the CNS caused by *T. pallidum*, which presents with variable and often non-specific symptoms. Given the diversity of its symptoms, it is known as a 'great imitator'.[7] With the recent global syphilis epidemic, several cases of autoimmune limbic encephalitis associated with neurosyphilis have been reported. In some cases of neurosyphilis, the detection of specific antibodies such as anti-NMDAR,[8] anti-leucine-rich glioma-inactivated 1,[9] anti-aquaporin 4,[8] anti-glutamic acid decarboxylase 65,[8] anti-contactin-associated protein 2,[10] anti-γ-aminobutyric acid-B receptor[11] and anti-myelin oligodendrocyte glycoprotein[12] has been reported. Cases of neurosyphilis complicated by autoimmune encephalitis, when autoantibodies remained undetected even after thorough investigation, have been further reported.[13] The presence of OCBs in our patient's CSF is consistent with the known inflammatory response in neurosyphilis.[14] This inflammatory process may disrupt normal sympathetic regulation, potentially leading to the onset of PSH.

In recent years, there have been sporadic reports of PSH resulting from autoimmune encephalitis, including anti-NMDAR encephalitis,[4] progressive encephalomyelitis with rigidity and myoclonus[6] and acute disseminated encephalomyelitis,[5] as well as neuroinfectious diseases, such as tuberculous meningitis[2] and COVID-19.[3] Although the exact causal relationship between these infectious or autoimmune encephalitis conditions and PSH remains unclear, a relatively high complication rate (9.1%–50%) of PSH has been reported in anti-NMDAR encephalitis.[4] By attacking NMDAR, encephalitis disrupts the sympathetic circuit, producing clinical manifestations of autonomic instability.[4]

In conclusion, clinicians should recognise that PSH may be attributable to CNS diseases beyond head trauma, including neurosyphilis. In such cases, it is crucial to expedite diagnosis and treatment.

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