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A Case Report of Recurrent Guillain-Barré Syndrome with Orthostatic Hypotension Syncope as the First Symptom

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Abstract: Guillain-Barré syndrome (GBS) is an immune-mediated peripheral neuropathy with acute or subacute onset of flaccid paralysis of the limbs with symmetrical hypesthesia and autonomic nerve involvement [1]. The clinical manifestations of autonomic nerve damage are complex and varied, which may involve extensive or limited autonomic function damage, including abnormalities of the skin, pupil, urinary tract, gastrointestinal tract, cardiovascular system, body temperature, lacrimal and salivary glands, and sexual function, etc. [2], and some patients may even have autonomic nerve damage as the only symptom, which is a variant of GBS and is prone to misdiagnosis or underdiagnosis. Recurrence of GBS is rare, and the manifestations of recurrence are often similar to those of the first symptoms [3], but the patient admitted to our hospital had syncope as the main clinical manifestation of recurrence, which was completely different from that of the first incidence, and syncope is not a common and typical clinical manifestation of GBS, so misdiagnosis is highly likely.

Keywords: Orthostatic hypotension; Syncope; Guillain-Barré syndrome

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1. Case presentation

1.1. Medical history

The patient was a 53-year-old male, who was admitted to the hospital on 11 December 2023 with "transient loss of consciousness for 5 hours." The patient had a sudden loss of consciousness while standing up 5 hours before admission, and fell to the ground without any limb twitching or urinary incontinence, and his consciousness cleared after about 1 minute. His medical history included Guillain-Barré syndrome (GBS) diagnosed a year ago, leaving a slight facial paralysis on the right side; history of hypertension for 10 years; no history of diabetes mellitus or coronary artery disease; denied a history of thyroid disease; denied a history of drug abuse and exposure to toxins. There was no family history of hereditary disease.

The patient had been diagnosed with GBS a year ago, which was mainly characterized by bilateral peripheral facial paralysis, loss of muscle strength in the limbs, decreased tendon reflexes, and protein-cell

separation of the cerebrospinal fluid, which improved with the administration of gamma globulin.

1.2. Neurological physical examination

The patient was conscious, spoke fluently, answered questions, and moved his eyes freely bilaterally without nystagmus. Bilateral pupils were equal in size and round, with sensitive light reflexes. The right nasolabial sulcus was shallow, the tongue and the uvula were centered, and the soft palate was lifted powerfully bilaterally. Bilateral pharyngeal reflexes were symmetrical, head-turning and shoulder shrugging were powerful, limb muscle tone was normal, distal muscle strength of upper limbs was grade 4, tendon reflexes of limbs were weakened, there was no superficial and deep sensory hyperalgesia, and pathological reflexes were negative bilaterally. The bilateral finger-nose test and heel-knee-shin test were still accurate.

1.3. Ancillary examinations

Based on the results of the routine blood test, routine urine test, routine stool test, and routine coagulation test, blood glucose + blood lipids + liver function + kidney function + homocysteine + glycated hemoglobin test were all normal; tumor markers, HIV antibody test, anti-syphilis spirochete specific antibody test, hepatitis B antigen and antibody, hepatitis C antibody test, and anti-nuclear antibody spectrum test were normal.

Cerebrospinal fluid analysis: Cerebrospinal fluid was colorless and clear; Pandy's reaction was negative; total cell count was 6 x 10^6/L and protein was 0.43 g/L; cerebrospinal fluid stained negatively for Gram stain, Ziehl–Neelsen stain, and Indian ink stain.

Upright tilt test: Hypotension in the upright position with $\Delta HR/\Delta BP < 0.5$ beats/min/mmHg suggests a neurogenic cause.

2. Discussion

Guillain-Barré syndrome (GBS), also known as acute inflammatory demyelinating polyradiculoneuropathy, is an autoimmune disease characterized by demyelination of peripheral nerves and nerve roots and inflammatory reactions of lymphocytes and macrophages around small blood vessels. GBS has an acute onset, with symptoms peaking at about two weeks, and includes the following subtypes: acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, acute motor-sensory axonal neuropathy, Miller Fisher syndrome, acute sensory neuropathy, and acute pan-autonomic neuropathy. GBS is rare in the subtype with autonomic involvement and is characterized by the following clinical features: (1) Antecedent events, where patients often have upper respiratory tract infections and gastrointestinal symptoms. (2) Acute onset, rapid progression of the disease, mostly reaches the peak in 1–2 weeks, with a small number of subacute onset. (3) First clinical manifestations include dizziness, palpitations, postural hypotension, dry eyes and mouth, heat intolerance, and less sweating; and nausea, vomiting, urinary retention, diarrhea, abdominal distension, constipation, and intestinal paralysis in severe cases. (4) The patient does not have or is accompanied by slight limb weakness, partial distal hyperalgesia, and loss of tendon reflexes. (5) Cerebrospinal fluid shows protein-cell separation. (6) Electrophysiological examination shows generally normal nerve conduction and electromyography. (7) Abnormalities are seen in autonomic examinations such as skin sympathetic response and R-R variability.

For many years, autonomic nerve damage in GBS patients has been underappreciated, yet it is widespread along with motor and sensory nerve damage. GBS patients present with autonomic nerve impairment, which may occur early in the disease, at its peak, or even during the recovery period, and can be life-threatening in severe cases. Some studies have reported that about 20% of patients with Guillain-Barré syndrome have

symptoms of autonomic impairment, and this percentage can reach 66–75% in patients with tetraplegia. It is particularly common in young people [4]. The reason for this is currently believed to be the presence of lymphocytic infiltration in the ganglia of the autonomic nerves, the hypothalamus, and the brainstem, which destroys the ganglion cells within the wall, causing inflammation and edema in the autonomic ganglia, leading to lysis of nerve cells. At the same time, autoantibodies to gangliosides, such as anti-GM1 antibodies, may be present, all of which ultimately cause dysregulation of the excitatory disorders of the sympathetic and parasympathetic nervous systems, leading to sympathetic and parasympathetic hyper- or hypofunction [5]. When autonomic damage is highlighted by symptoms such as syncope, gastrointestinal dyskinesia, dysuria, dyspareunia, and dyshidrosis, it is easy to misdiagnose it as cardiovascular, gastrointestinal, or urological disorders and delay treatment, and it is even easier to misdiagnose it when autonomic damage is the first or the only symptom in some patients with GBS.

Anandan *et al.* [6] studied the occurrence of autonomic dysfunction in patients with GBS and found that the most common manifestations of autonomic dysfunction were: diarrhea/constipation (15.5%), hyponatremia (14.9%), syndrome of abnormal secretion of antidiuretic hormone (SIADH) (4.8%), bradycardia (4.7%), and urinary retention (3.9%). The probability of reversible cardiomyopathy, syncope, tachycardia, and Horner syndrome was higher in patients with GBS compared to controls ($P < 0.0001$). In a study by Gupta *et al.* [7], it was found that 54.2% of 96 patients developed cardiovascular complications including ECG changes, hypertension, unstable hypertension, tachycardia, bradycardia, and arrhythmia rates, and other cardiovascular complications including elevated BNP precursors, elevated troponin T levels, acute coronary syndromes, heart failure, and abnormal 2D echoes. According to a retrospective study [8], approximately 30% of patients with GBS experience adverse cardiovascular events, and GBS patients with less cranial nerve damage are more likely to experience adverse cardiovascular events. A study on GBS mortality showed [9] that up to 67% of patient deaths occurred during the neurological recovery phase of GBS due to cardiovascular and respiratory complications, which shows that autonomic dysfunction in GBS deserves attention. Zhang *et al.* [10] reported a case of a patient with GBS who had orthostatic hypotension as the first symptom, and the patient developed limb weakness and numbness only subsequently, which improved after the administration of intravenous immunoglobulin (IVIG). Tan *et al.* [11] studied the recovery of cardiovascular autonomic dysfunction in patients with GBS and found that autonomic dysfunction in GBS gradually improved along with the recovery of locomotor dysfunction. Sakakibara *et al.* [12] reported a case of GBS patients with nerve axonal injury, in which the patient presented mainly with limb weakness and urinary retention; however, when limb strength was gradually restored, the urinary retention remained unimproved. Urodynamics showed that the cause of urinary retention was not bladder paralysis but urethral sphincter dysfunction.

GBS is widely regarded as a monophasic, self-limiting disease, and the recurrence rate of GBS and its variants is low. According to the literature, 2% to 6.8% of patients may experience recurrence, which is known as recurrent Guillain-Barre syndrome (RGBS) [1]. Mossberg *et al.* proposed that the following criteria should be met to diagnose RGBS: (1) at least two or more episodes, all of which meet the diagnosis of GBS, except chronic inflammatory demyelinating polyneuropathy (CIDP); (2) significant improvement of symptoms after treatment for each episode; and (3) at least 2 months between episodes [13,14]. Recurrent GBS should be distinguished from acute exacerbations of CIDP, which has little history of infection, is insidious, and progresses slowly, usually peaking at 6 weeks after the onset of the disease, with a certain degree of neurological deficits and a persistent increase in CSF protein during the intervals. In patients with CIDP, the symptoms of weakness may develop from distal to proximal, with little involvement of the trunk, respiratory muscles, and cerebral nerves, and in some patients, the atrophic muscles and the cerebral nerves are rarely involved. However, in recurrent GBS, the proximal muscle weakness is more severe than the distal one, the cervical muscles and even

the respiratory muscles may be involved, and the CSF protein may drop to normal during the recovery period.

The longest interval between recurrences of RGBS seen reported so far is 43 years, and the average is about 7 years. Most patients have one recurrence, while a few patients may have four to five recurrences, with a maximum of seven [15]. Although the time between recurrences varies, there is no significant correlation between disease duration and prognosis, and there is no obvious pattern, but the shorter the interval between recurrences, the more severe the functional deficit at the time of recurrence, which may also be due to the incomplete restoration of the site of the previous myelin sheath damage. Another retrospective study [14] found that RGBS had a shorter duration of illness than GBS patients with a monophasic course, probably because the trigger of upper respiratory tract infection was not as strong in RGBS.

The main clinical manifestations of RGBS are symmetrical numbness and weakness in the distal extremities, and purely motor or sensory and motor impairment types are common. Kuitwaard *et al.* [3] compared 32 cases of recurrent Guillain-Barré syndrome with 476 patients who did not have recurrences and found that there were a total of 81 episodes in the 32 patients with RGBS. Some of the patients had clinical symptoms similar to those of subsequent episodes of the first episode of GBS or its variant Miller Fisher syndrome (MFS). Although the neurological symptoms of the relapses were usually similar to those of the first attack, the severity of the symptoms varied. Patients with relapses (mean age 34.2 years) were younger and had more common MFS (P = 0.049) or milder symptoms (P = 0.011) than non-relapsing patients (mean age 46.9 years; P = 0.001). Basta *et al.* [16] examined the clinical characteristics of 13 patients with RGBS, all of whom had two episodes of the disease, and the most common subtype of GBS in the episodes was acute inflammatory demyelinating polyradiculoneuropathy. Approximately 23% of patients developed a variant during the second GBS episode, but disease severity was similar between the two episodes. Ishii *et al.* [17] studied recurrent GBS, MFS, and brainstem encephalitis, and showed that two out of 55 patients (4%) with GBS, four out of 34 patients (12%) with MFS, and two out of 8 patients (25%) with brainstem encephalitis had recurrences. Patients with recurrent MFS tended to be younger at the time of their first episode than patients with non-recurrent MFS (median age 22 and 37 years, respectively), and patients with recurrence had milder signs and symptoms during recurrence than during the first episode. Notturno *et al.* [18] retrospectively studied 236 patients with GBS and 73 patients with MFS, of which seven patients with recurrent GBS and one patient with recurrent MFS, and found that the frequency of recurrence of acute inflammatory demyelinating polyneuropathy in patients with recurrent GBS was higher than that of axonal injury type of GBS. Luan *et al.* [19] reported a case of recurrent GBS, the patient's first episode was 13 years ago, with acute axonal injury, and this time the recurrence was GT1a, GD1a, and cerebral thiolipids seropositive GBS variant i.e. pharyngeal-cervical-brachial GBS. A retrospective study in China found that high levels of serum thyrotropin were an independent risk factor for recurrence in patients with GBS [20].

The pathogenesis and exact etiology of GBS are unclear, but it is currently thought to be related to autoimmune reactions, with most patients having a history of fatigue, viral infections, or vaccinations prior to the onset of the disease, and cerebrospinal fluid (CSF) protein cytolysis is an immunological feature of GBS [21,22]. Classically, CSF protein cytolysis is defined as a markedly elevated CSF protein (usually more than 1.0 g/L) with a normal or mildly elevated CSF leukocyte count [23]. CSF protein cytology is not specific for GBS, but can also be seen in spinal cord tumors, etc. CSF protein cytology is more evident on the 16th–30th day of GBS, and a single lumbar puncture within a few days of the onset of the disease does not have a high rate of positivity for CSF protein cytology [24]. The basic clinical neurophysiological manifestations of recurrent GBS in the relapse phase are consistent with classical GBS manifestations, mainly multiple motor nerve damage; multifocal conduction block, maximal motor velocity (MCV) and/or sensory conduction velocity (SCV) slowing, prolonged distal latency, and decreased wave amplitude; F-wave abnormality manifested by a prolonged latency, and the disappearance or decreased occurrence of the F-wave; and EMG abnormality manifested by the

appearance of spontaneous potentials, prolonged time frame, and maximal exertion of the simplex phase.

Regarding the treatment of GBS, it is currently believed that IVIG therapy and plasma exchange have significant efficacy, and their mechanism of action is still unclear, while glucocorticoids are controversial in the treatment of this disease, and the majority of scholars believe that glucocorticoids do not significantly accelerate the recovery of GBS or affect the long-term outcome and that even the long-term use of glucocorticoids in high doses may cause blood glucose abnormality, gastrointestinal tract ulcers, hypokalemia, hypocalcemia and a range of adverse effects.

Orthostatic hypotension is one of the most common manifestations of autonomic dysfunction and is often misdiagnosed as cardiovascular disease when the patient has syncope as a prominent symptom. In this case, the patient had an acute onset of illness, with syncope as the first symptom, no other signs of autonomic nerve damage, no sensory impairment, and there was no obvious infectious trigger before the onset of illness, and no protein-cell separation phenomenon in the lumbar puncture, so the diagnosis of GBS was ignored at the initial stage of diagnosis. However, the patient had Guillain-Barré syndrome one year before, and the patient induced a syncopal aura during the upright tilt test certificate, $\Delta HR/\Delta BP < 0.5$ times/min/mmHg, suggesting neurogenic orthostatic hypotension, coupled with the patient's bilateral distal upper limb muscle strength decreased slightly, and the tendon reflexes of the limbs were weakened, so the diagnosis of GBS was made. Therefore, when the patient presents with limited autonomic dysfunction and is not accompanied by the typical clinical manifestations of GBS, the possibility of atypical GBS should be considered to avoid missed diagnosis.

In this case, the patient's recurrent clinical manifestations were mild, with only neurogenic orthostatic hypotension as an important manifestation, and there was no worsening of clinical symptoms compared with the initial onset of the disease, probably because the patient did not have any obvious infectious triggers for this onset of the disease. Recurrent Guillain-Barré syndrome is often regarded as a special type of GBS, and the clinical manifestations are similar to those of the first attack, but in this patient, the first attack one year ago was mainly manifested by muscle weakness and paralysis caused by cranial nerve and spinal nerve injuries, while the recurrence this time was mainly manifested by autonomic dysfunction, and the clinical manifestations of the two attacks were different.

3. Conclusion

In summary, when the patient has autonomic dysfunction as the main clinical manifestation, which is not accompanied by muscle weakness of cranial and/or spinal nerve innervation, hypesthesia of set-like sensation in the endings of the limbs, decreased or disappeared tendon reflexes, and separation of protein cells in the cerebrospinal fluid, it is important to not neglect the diagnosis of the GBS variant, in order to prevent misdiagnosis and missed diagnosis. In addition, the clinical manifestations of GBS recurrence may be different from those of the first attack, and the severity of the disease does not show any aggravation.

Disclosure statement

The authors declare no conflict of interest.

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