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Clinical and Neurophysiological Features of Sensory Neuronopathy

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Abstract: *Objective*: To improve the understanding of clinical and neurophysiological features of sensory neuronopathy and to achieve early diagnosis of the cause of sensory neuronopathy. *Methods*: This study retrospectively analyzed the clinical manifestations and neurophysiological features of 16 cases of sensory neuronopathy with a clear diagnosis. *Results*: The study subjects consisted of 6 males and 10 females, aged 42–71 years old, with a mean age of 55 years old. 10 cases were diagnosed with the sensation of walking on cotton, 4 cases complained of numbness and burning sensation in one or both hands, and 2 cases complained of weakness of the limbs. 4 cases had paraneoplastic sensory neuronopathy, 3 cases had autoimmune sensory neuronopathy, 2 cases had platinum-associated sensory neuronopathy, and 7 cases had idiopathic sensory neuronopathy. Sensory nerve action potentials were significantly reduced or lost in 16 patients, 12 cases were widespread in the limbs, and 4 cases were asymmetric. There was no obvious abnormality in motor nerve conduction. *Conclusion*: Sensory neuronopathies of various etiologies have common characteristic neurophysiological manifestations, and mastering the neurophysiological characteristics of sensory neuronopathies can lead to early identification of sensory neuronopathies.

Keywords: Sensory neuronopathy; Neurophysiology; Neoplastic sensory neuronopathy; Immunological sensory neuronopathy

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1. Introduction

Sensory neuron disease (SND) is a non-length-dependent peripheral nerve disease characterized by selective invasion of the dorsal root ganglion, with clinical manifestations of superficial and deep sensory deficits, reduced tendon reflexes, gait abnormalities, and may be accompanied by autonomic dysfunction, whose etiology is mainly due to a variety of factors including tumors, autoimmune diseases, drug intoxication, and infections, with unknown pathogenesis. The pathogenesis of SND is unknown. At present, the delayed diagnosis and misdiagnosis rate of SND is still very high. Since non-idiopathic SND is often associated with tumors or autoimmune diseases, early identification and early diagnosis of SND are of great significance. This paper summarised and analyzed the clinical data and neurophysiological characteristics of 16 cases of SND, to increase the alertness to SND and find the cause of the disease as early as possible.

2. Information and methodology

2.1. Clinical information

The clinical data of 16 SND patients with a clear clinical etiological diagnosis from January 2016 to October 2023 were collected from the hospital. Among them, 6 cases were male and 10 cases were female; the age was 42–71 years old, and the average age was 55 years old; subacute or chronic onset of disease with gradual progression. 4 cases suffered from tumors, 3 cases suffered from autoimmune diseases (2 cases of desiccation syndrome, 1 case of systemic lupus erythematosus), 2 patients were on platinum-based chemotherapeutic drugs, and the etiology of 7 cases was not clear. 2 patients had self-consciously limb weakness and inflexible movement; 4 patients had numbness of one side of the hand or both hands. The remaining 10 cases presented with varying degrees of walking on cotton, and unsteady gait, and one case was severe enough to require a wheelchair. Of which 7 cases initially had pain, numbness, or indescribable sensory abnormality in a single lower limb, an upper limb, and the face, which gradually progressed to the contralateral side or all four limbs. 2 female patients with cancer were undergoing platinum-based chemotherapy, 1 patient was accompanied by dizziness and palpitations, and 1 patient had self-consciousness of dry eyes and dry mouth. 16 patients had no special family history of toxicity, and 1 patient had no specific family history of toxicity. None of the 16 patients had any special family history, history of toxic exposure, history of drug overdose, or history of infection. Neurological examination of 16 patients showed pain and temperature sensation, hypesthesia, and weakened or disappeared tendon reflexes of the limbs; 5 patients showed sensory ataxia gait; 8 cases were positive for difficulty in standing with closed eyes, and other neurological examinations were negative.

2.2. Neurophysiological testing methods

All neurophysiological examinations were done by an experienced electrophysiologist using a Cadwell EMG instrument according to standard methods. The limb temperature was maintained above 35 °C. Motor nerve conduction was detected from the median, ulnar, tibial, and common peroneal nerves. Sensory nerve conduction was detected using the cis-recording method, measured from the median, ulnar, and peroneal nerves, respectively. F-wave and H-reflexes were obtained by stimulating the wrist of the median nerve and popliteal fossa of the tibial nerve in the upper limb, respectively. The electrophysiological parameters recorded included distal latency, motor conduction velocity, amplitude of compound muscle action potential (dCMAP), sensory nerve conduction velocity, sensory nerve action potential (SNAP), F-wave, and H-reflex latencies. Needle electromyography (EMG) was performed on the upper limbs, including the bunion and biceps muscles, and on the lower limbs, including the tibialis anterior, gastrocnemius, and intramuscular femoral muscles, to observe the spontaneous potentials and muscle MUP.

Judgment criteria for abnormal electrophysiological results: Nerve conduction electrophysiological parameters exceeding the mean ± 2 SD of normal reference values were defined as abnormal. The presence of denervation potentials, such as fibrillation potentials and positive sharp waves in the EMG of the detected muscles suggests nerve damage.

3. Results

Sensory nerve abnormalities were found in all 16 patients, with 12 cases showing widespread and symmetrical changes in the limbs and 4 cases showing asymmetrical changes. The sensory nerve action potential (SNAP) examined in 10 patients was markedly reduced or disappeared, with the wave amplitude as low as 1.2–3.4 μV, all sensory nerves in 6 patients had disappeared, some sensory nerves in 5 patients showed mild slowing down of their conduction speeds, and the rest of the sensory nerves showed normal conduction speeds. There

was no obvious abnormality in all motor nerve conduction. There was no abnormality in the distal latency of sensory and motor nerve conduction. There was no obvious neurogenic or myogenic damage in the needle pole electromyography. The H-reflex disappeared in all cases, and there was no abnormality in the F-wave.

4. Discussion

Sensory neuron disease (SND) is a specific subgroup of peripheral nervous system disorders caused by the degeneration of T-shaped sensory neurons in the dorsal root ganglion (DRG), resulting in simultaneous damage to both the peripheral and central synapses of sensory nerves, and the distribution of sensory deficits in a non-length-dependent fashion, which is different from that of the typical sensory nerve axonal degeneration [1]. The clinical features of SND depend on the size of the neuron affected by the root ganglion and its rate of progression. It tends to have an asymmetric onset but gradually becomes symmetric in the middle and late stages of the disease. Involvement of large DRG neurons leads to sensory ataxia and reduced tendon reflexes, which in the early stages of the disease are mainly manifested by unsteady gait and the feeling of stepping on cotton. In the later stages of the disease, the patient is unable to sit or stand, and this is the main reason for the disability of SND. Impaired proprioception of the upper limbs leads to the clumsiness of hand movements and pseudo-embolic dyskinesia of the fingers [2]. If the small DRG neurons are involved, the patient will experience pain, burning sensations, and hypalgesia, while lesions that involve the root ganglion will cause pain, burn, and hypalgesia. If the lesion involves the autonomic nervous system, tonic pupils, postural hypotension, gastrointestinal symptoms, and sexual dysfunction can occur [3–4]. In this paper, most of the patients initially showed asymmetric deep and superficial sensory deficits of different degrees but gradually progressed to symmetric. 10 patients gradually appeared to walk unsteadily, and one case was so serious that he needed to sit in a wheelchair. However, two patients complained of limb movement weakness and inflexibility, which may be due to the impaired proprioceptive afferents leading to imprecise and uncoordinated limb movements showing pseudo-muscular weakness [5]. One patient was accompanied by postural dizziness, palpitations, autonomic nervous system hypodynamia, and dysesthesias, while one patient was accompanied by postural dizziness and palpitations. However, two patients complained of limb movement weakness and inflexibility, probably due to imprecise limb movement coordination caused by proprioceptive afferent impairment.

The causes of SND are complex and unknown, and about 50% of the cases have no obvious cause, which is called idiopathic SND. SND can also be caused by tumors, autoimmune diseases, drug toxicity, infections, genetics, and so on, which is called non-idiopathic SND. The clinical diagnosis of SND is based on the new quantitative diagnostic criteria based on clinical and neurophysiological data proposed by Camdessanché et al. in 2009. The diagnosis is confirmed by dorsal root ganglion biopsy, which is an invasive operation with certain risks and is therefore not recommended at present [6]. The clinical and neurophysiological manifestations of SND are the key to early recognition of SND. However, the delayed diagnosis and misdiagnosis rate of SND is still very high, which may be related to the lack of limb movement disorder in the early stage of SND, which has not attracted the attention of clinicians, who then neglected the neurophysiological examination, or due to the lack of understanding of the disease by neurophysiologists and clinicians, which has led to their misinterpretation of the suspected clinical symptoms and abnormal neurophysiological findings. In a retrospective study, the mean time to diagnosis of non-paraneoplastic SND was 5.4 ± 5.3 years, with a mean misdiagnosis rate of 3.4 ± 1.5 years, and shorter diagnostic delays for onset before the age of 40 years compared with onset after the age of 40 years. The clinical features of paraneoplastic SND are homogeneous and stereotypical, whereas non-paraneoplastic SND has a high degree of diversity in clinical presentation, with some patients presenting predominantly with symptoms of small fiber damage while others present predominantly with symptoms of large nerve fiber damage [7]. The

course of the disease is highly variable, ranging from an acute progression to a chronic progression, factors that further increase the likelihood of misdiagnosis and diagnostic delays in non-paraneoplastic SND [8].

However, regardless of differences in etiology and clinical presentation, the manifestations of neurophysiological abnormalities in patients with SND are highly consistent. Therefore, initiating neurophysiological examination immediately when a patient complains of sensory deficits, regardless of the nature, degree, or location, may greatly reduce the delayed diagnosis of SND, and in turn, provide patients with a more timely etiological screening. The neurophysiological manifestation of SND is mainly a widespread decrease in the amplitude of the sensory nerve action potentials of the extremities (SNAP). Even in patients with asymmetric or patchy clinical presentations, this abnormality is non-length-dependent and should be regarded as a marker of ganglionic lesions. Somatosensory evoked potentials (SEP) and magnetic resonance imaging (MRI) of the neck provide evidence of damage to central sensory pathways, with a positive waveform undetectable by SEP in the majority of patients with a T2 high signal in the posterior cord of the spinal cord on cervical spine MRI. There were no abnormalities of the SND motor nerves distal to the latencies, conduction velocities, or motor-evoked wave amplitudes. All the patients in this paper were consistent with the neurophysiological and imaging features of SND. Despite the specificity of the neurophysiological manifestations of SND, it is still incorrectly interpreted as a general sensory nerve injury and is routinely treated with methylcobalamin and so on. SND is mainly differentiated from diseases that cause sensory nerve axonal injury. Sensory nerve axonal injury also shows a decrease in SNAP, but the lower limbs are heavier than the upper limbs, with length-dependent characteristics, which may be accompanied by a slowing down of sensory nerve conduction velocity. If the spinal cord is involved, the abnormal signals are not only confined to the posterior cords, but also the lateral cords, such as subacute combined degeneration, which has severe clinical distal symptoms, and the patient's age fluctuates over a wide range. Possible common causes of sensory axonal injury include tumors, intoxication (such as alcohol, drugs, and others), metabolic diseases (such as diabetes mellitus), and neurological hereditary degenerative disorders, which often involve motor nerves as well. In terms of pathophysiology, the basement membrane of the trophoblastic vessels in the dorsal root ganglion is loosely connected with large gaps, so inflammatory cells, toxins, and antibodies can easily enter the dorsal root ganglion through the lax blood-nerve barrier, hence the dorsal root ganglion is easily and selectively involved, and the length of the axon does not affect the progression of the disease. Sensory neuropathies are mostly caused by nutrient metabolism disorders or poisoning, so that the synthesis of proteins and other substances by the cell body is impaired or the axoplasmic transport is blocked, so that the most distal axon cannot get the necessary nutrients, and therefore their lesions often develop from the most distal to the proximal end of the axon. Acute sensory and autonomic neuropathy (ASANN), in which the lesions are located in the neuronal cells of the dorsal roots and autonomic ganglia, is a rare and severe peripheral neuropathy that is immunologically related and progresses rapidly, presenting as a loss of sensation in a non-length-dependent distribution in addition to autonomic failure including urinary, cardiovascular and gastrointestinal dysfunction [9]. The typical clinical symptom of SND is sensory ataxia, which is why it needs to be differentiated from other ataxic neuropathies, such as MFS, hereditary neuropathies, and toxicity and infection-associated neuropathies. Ataxic neuropathy is a broad and heterogeneous disease, with sensory ataxia as the main symptom or the first symptom, which may affect the dorsal root nerves, dorsal root ganglia, nerve trunks, distal nerve endings, or all of them, but is often accompanied by motor deficits, and therefore its clinical manifestations and electrophysiological characteristics are different. It can be classified into acute, subacute, and chronic according to the mode of onset of the disease [10]. Therefore, in combination with the history of the disease, specific clinical manifestations, and neurophysiological differences, Cameron's disease can be classified as an ataxic neuropathy, a neurological

disorder. Therefore, they can be differentiated by history, specific clinical manifestations, neurophysiological differences, and Camdessanché score.

When the diagnosis of SND is confirmed based on clinical and neurophysiological evidence, the next step should be to immediately initiate etiological screening. Acquired sensory neuronopathies include different diseases characterized by the degeneration of sensory neurons in the dorsal root ganglia. Pathology of SND secondary to tumors, HIV infection, dry syndrome, undifferentiated connective disease, and rare idiopathic SND show dorsal root ganglion degeneration associated with an inflammatory T-cell response, suggesting that dorsal root ganglion lesions are mainly caused by cell-mediated immune responses. In addition, sensory neuron cytosol has been shown to be a target of cisplatin toxicity. However, vitamin B6 toxicity or anti-dioxy antibody involvement in sensory neurons has only been observed in animal models. Various pure small-fibre neuropathies may also be associated with sensory ganglionopathy but this has not been confirmed [11]. The most common tumor associated with SND is small cell lung cancer and many patients have anti-Hu antibodies, as well as prostate, breast, pancreatic, neuroendocrine, bladder, and ovarian cancers. Typical neuropathy is detected 3–8 months before the cancer is detected. Sensory neuronopathy is also stabilized or improved when treatment of the underlying tumor is effective, so it is significant to make an early diagnosis of SND and to actively search for the underlying tumor [12]. Four of the patients in this paper had tumors in which SND was considered to be associated. Although a proportion of SND is considered to be idiopathic, a study by Tholance Yannick et al. found that antibodies to the intracellular region of the anti-fibroblast growth factor receptor 3 (FGFR3) are predominantly recognized to affect dorsal root ganglia [13]. Sensory neuronopathies often present as complications of autoimmune diseases in the peripheral nerves, such as dry syndrome, systemic lupus erythematosus, and autoimmune hepatitis, and three of the patients in this article were diagnosed with autoimmune-associated SND. Platinum-induced peripheral neurotoxicity is a common side effect of platinum-based chemotherapeutic agents, including acute neurotoxicity confined to oxaliplatin, as well as chronic, non-length-dependent sensory neuronopathies, and the motor and autonomic signs and symptoms are uncommon, the latter occurring with the duration of chemotherapy and drug accumulation [14]. In this paper, patients with breast and ovarian cancer treated with carboplatin chemotherapy developed pain and numbness in the hands and unsteady walking five months and one year after treatment, respectively. Vitamin B6 overdose can lead to periapical ganglion damage with a dose-dependent effect. Viral infections can also cause SND, most commonly HIV, but also EBV, varicella-zoster virus, measles, and human T-cell lymphotropic virus type 1.

The diagnosis of sensory neuron disease is mainly based on clinical and neurophysiological manifestations. The clinical manifestations are mainly asymmetric limbs, facial sensory deficits, and walking instability. When the neurophysiological examination results show that the widespread sensory nerves SNAP is significantly reduced, it should be suspected to be SND. Since SND is associated with tumors, autoimmune diseases, platinum-based chemotherapeutic agents, drug toxicity, infections, and so on, therefore, should be combined with the history of the patient to further screen for the cause. Further screening for the etiology, such as when a tumor is suspected, complete thoracic, abdominal, and pelvic imaging, tumor markers, anti-Hu antibodies, and even PET-CT should be performed. The pathology should be further clarified after the discovery of the tumor. If no tumor is found, the patient is recommended to be rechecked once every 4–6 months. If autoimmune correlation is considered to be more important, testing of ANA, anti-SSA/SSB antibodies, anti-dsDNA antibodies, and lip or Salivary gland biopsy should be performed. If the patient is on chemotherapy for a tumor, whether platinum-based chemotherapy drugs are used should be asked. If there is a history of vitamin B6 medication, the blood vitamin B6 level should be tested. When suspected of viral infection, the antibodies to HIV and EBV should be tested. In secondary sensory neuronopathies, it is often difficult to distinguish between chemotherapy-

induced and paraneoplastic. In chemotherapy-induced sensory ganglionopathy, laboratory tests (including paraneoplastic antibodies and autoimmune) and cerebrospinal fluid are usually normal. Whereas in paraneoplastic ganglionopathy, the cerebrospinal fluid may show increases in proteins and cells. Cerebrospinal fluid (CSF) analysis shows elevated protein and increased cell counts, sometimes with oligoclonal bands, in patients with paraneoplastic SN. Knowledge of the neurophysiological features of SND is key to achieving early recognition of SND, while knowledge of the pathogenesis and etiology of SND is fundamental to achieving early diagnosis.

Disclosure statement

The authors declare no conflict of interest.

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