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Severe sensory ganglionopathy as a manifestation of mixed connective tissue disease

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ABSTRACT

Sensory ganglionopathies (SG) are a rare but distinct clinical subgroup of peripheral neuropathies characterized by damage to dorsal root ganglia. Typical manifestations include early gait and limb ataxia, widespread diminished or absent deep tendon reflexes accompanied by Romberg sign and pseudoathetoid movements.The diagnosis of SG is valuable since it may prompt towards early recognition of an underlying malignancy or autoimmune disorder. We report the case of a female diagnosed with mixed connective tissue disease (MCTD) along with severe SG. To our knowledge, such disease association has not been reported yet. The pathophysiology in cases linked to MCTD is unclear and asks for further studies. Moreover, the important degree of disability associated with this condition highlights the need for effective therapies' development.

Keywords: mixed connective tissue disease; dorsal root ganglia; sensory ganglionopathy; sensory neuronopathy

INTRODUCTION

Sensory ganglionopathies (SG) are a rare but distinct clinical subgroup of peripheral neuropathies characterized by damage to dorsal root ganglia (DRG) [1]. Degeneration of DRG sensory neurons and their projections leads to involvement of both short- and long-length axons. As a result, the clinical picture differs from the distal and symmetrical pattern of the more common axonal neuropathies. Typical manifestations include early gait and limb ataxia, widespread diminished or absent deep tendon reflexes accompanied by Romberg sign and pseudoathetoid movements [1,2]. The diagnosis of SG is valuable since it may prompt towards early recognition of an underlying malignancy or autoimmune disorder [3]. There is a well-recognised connection between Sjögren syndrome (SS) and SG but sporadic cases linked to systemic lupus erythematosus (SLE) or autoimmune hepatitis have also been described [1,2]. We report the case of a female diagnosed with mixed connective tissue disease (MCTD) along with severe SG. To our knowledge, such disease association has not been reported yet. Increased awareness is needed in the medical community in order to take into consideration the possible association of SG with MCTD.

CASE PRESENTATION

A 41-year-old female was admitted to the neurology department complaining of unsteady gait, loss of dexterity in the hands and intense burning sensation in all limbs. Her medical history included breast augmentation surgery with silicone implants six years before presentation. Additionally, a MCTD diagnosis was established three years afterwards

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when she presented for arthritis and Raynaud phenomenon. She also complained of paresthesia on the right side of the face which was interpreted as anxiety-related. The immunological workup at that time revealed high levels of ANA (1/1280; coarse speckled) and anti-U1RNP antibodies (63U/mL, negative < 5 U/mL). Despite treatment with methotrexate and hydroxychloroquine improving her rheumatological symptoms, her neurological complaints progressed. Over the course of three years, she developed paresthesia on both sides of the face and in the left upper arm, followed by coordination difficulties in the upper limbs, especially on the left side along with diffuse burning sensations in all limbs. Her gait became unsteady and she had frequent falls, especially in dim light. Her treatment was switched to methylprednisolone, azathioprine, and cyclosporine without any benefit.

At presentation in the neurological department, the clinical examination revealed a severe asymmetrical sensory ataxia (with positive Romberg test, aggravation of ataxia with eye closure, pseudoathetosis, abolished deep tendon reflexes) associated with decreased sensation for pain and temperature involving the proximal and distal parts of the upper and lower limbs.

Nerve conduction studies (NCS) showed reduced sensory nerve action potentials (SNAPs) in the lower limbs and absent SNAPs in the upper limbs, suggesting a non-length-dependent nerve damage (Table 1).

Moreover, motor conduction velocities as well as motor amplitudes were within limits. These results indicated a SG. According to the diagnostic criteria [4], our patient scored 12.7 points (maximum) which made the diagnosis of SG possible.

A comprehensive workup was performed in order to exclude the following etiologies: 1) autoimmune- mediated disorders (anti-dsDNA, anti-SSA, anti-SSB, cryoglobulins, anti-Scl70, ANCA, ASMA-normal; Schirmer test- within limits; duodenal biopsy excluded celiac disease); 2) paraneoplastic (antineuronal antibodies -negative, CT of the thorax, abdomen and pelvis- no abnormalities); 3) toxic (vitamin B6 level within normal limits, no history of platinum salts exposure); 4) nutritional (vitamin B12 and E levels within normal limits); 5) infections (HIV, VDRL - negative). In addition, brain and spinal cord MRI as well as lumbar puncture were unremarkable. A sural nerve biopsy was performed which described wallerian degeneration without regeneration clusters, alongside no signs of inflammation (Figure 1). Other etiologies such as mitochondrial disorders, Friedreich's ataxia, spinocerebellar ataxia, cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) were considered unlikely due to absence of other neurological signs over the course of three years as well as relative rapid symptom progression. As a result, SG was interpreted as being secondary to the MCTD.

Eventually, the patient was prescribed treatment for the neuropathic pain along with methotrexate for MCTD. While there was no improvement with gabapentin, pregabalin, amitriptyline or duloxetine, a minor favorable response to venlafaxine and carbamazepine was noted. Evaluation after one year showed mild disease progression as related to her symptoms and NCS parameters.

DISCUSSION

The association between SG and immune mediated disorders was first described in SS, but other cases linked to autoimmune hepatitis, rheumatoid arthritis, and SLE have been reported as well [1,2]. Whereas sensory polyneuropathies have previously been described in association with MCTD [5], SG has not been reported yet. While the etiopathogenesis behind all these cases remains unclear, some studies provide possible mechanisms. Evidence suggests that sensory ganglia may be susceptible to autoimmune attacks due to a loose blood-nerve barrier formed by fenestrated capillaries [1]. Therefore, some diseases such as SS seem to have a predominantly cellular immune response with infiltration of

TABLE 1. Sensory nerve conduction studies

Nerve; Site	Onset Latency (ms)	Peak Latency (ms)	Amplitude (mV)	Segment	Distance (mm)	Conduction Velocity (m/s)
Superficial peroneal L; Ankle	1.6	2.2	16	Dorsum of foot-Ankle	70	44
Sural R; Lower leg	3.2	4.0	4	Ankle-Lower leg	130	41
Sural L; Lower leg	2.7	3.5	5	Ankle-Lower leg	120	44
Median R; Wrist	NO	NO	NO	Digit II -Wrist	105	NO
Median R; Mid palm	NO	NO	NO	Wrist-Mid palm	80	NO
Ulnar R; Wrist	NO	NO	NO	Digit V-Wrist	100	NO
Median L;Wrist	2.5	3.2	6	Digit II -Wrist	105	42
Ulnar L; Wrist	2.0	3.1	3	Digit V-Wrist	100	50
Radial R; Forearm	NO	NO	NO	Anatomical snuff box Forearm	120	NO
Lateral antebrachial cutaneous.R; Elbow	NO	NO	NO	Forearm-Elbow	100	NO

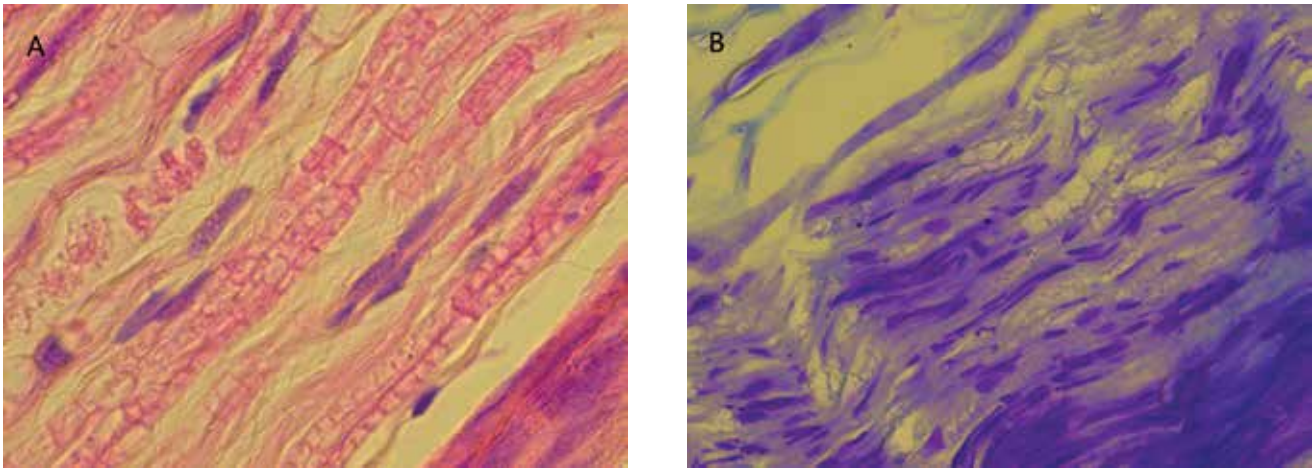

FIGURE 1. Sural nerve biopsy

A (400x, haematoxylin and eosin stain); B (400x, Luxol Fast Blue stain) show degeneration and vacuolization of the myelin sheath in the majority of axons. No signs of inflammation are noted

DRG with T lymphocytes, mostly cytotoxic [2]. In contrast, SG has been associated with anti-fibroblast growth factor receptor 3 (anti-FGFR3) antibodies, suggesting the involvement of humoral immune response as well [6]. Moreover, almost a third of the patients with different types of anti-FGFR3-associated polyneuropathies have other autoimmune diseases (including MCTD) [6]. Nonetheless, the involvement of these diverse pathogenetic mechanisms in SG remains to be established.

As a clinical observation, this patient had silicone implants. A novel entity called autoimmune syndrome induced by adjuvants (ASIA) has been described with silicone being one of the listed adjuvants [7]. ASIA has been associated with many autoimmune disorders (including MCTD) and neurological manifestations [7], yet there is still insufficient data in order to attribute the development of this conditions to specific adjuvants.

CONCLUSION

We presented the case of an adult female diagnosed with severe SG associated with MCTD. The pathophysiology in cases linked to MCTD is unclear and asks for further studies. Moreover, the important degree of disability associated with this condition highlights the need for effective therapies' development.

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REFERENCES

1. Sghirlanzoni A, Pareyson D, Lauria G. Sensory neuron diseases. *Lancet Neurol.* 2005;4(6):349-361.
2. Griffin JW, Cornblath DR, Alexander E, et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. *Ann Neurol.* 1990; 27: 304–15.
3. Camdessanché JP, Jousserand G, Franques J, Pouget J, Delmont E, Créange A, Kuntzer T, Maisonobe T, Abba K, Antoine JC; French CIDP study group. A clinical pattern-based etiological diagnostic strategy for sensory neuronopathies: a French collaborative study. *J Peripher Nerv Syst.* 2012 Sep;17(3):331-40
4. Camdessanché JP, Jousserand G, Ferraud K, Vial C, Petiot P, Honnorat J, Antoine JC. The pattern and diagnostic criteria of sensory neuronopathy: a case-control study. *Brain.* 2009 Jul;132(Pt7):1723-33
5. Bennett RM, Bong DM, Spargo BH. Neuropsychiatric problems in mixed connective tissue disease. *Am J Med.* 1978;65(6):955-962.
6. Kovvuru S, Cardenas YC, Huttner A, Nowak RJ, Roy B. Clinical characteristics of fibroblast growth factor receptor 3 antibody-related polyneuropathy: a retrospective study. *Eur J Neurol.* 2020;27(7):1310-1318.
7. Watad A, Bragazzi NL, McGonagle D, et al. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) demonstrates distinct autoimmune and autoinflammatory disease associations according to the adjuvant subtype: Insights from an analysis of 500 cases. *Clin Immunol.* 2019;2 03:1-8