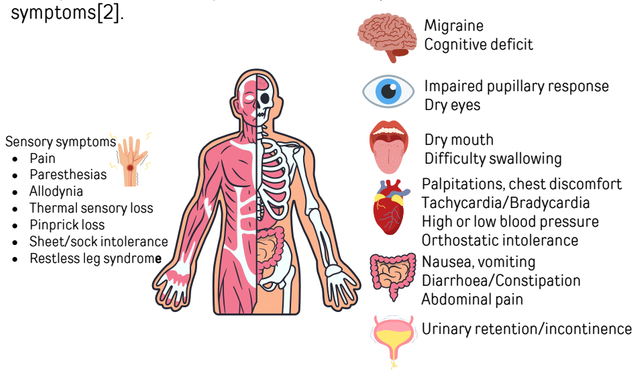
Case Reports of Teenage Onset Prolonged Debilitating Dysautonomia and Small Fiber Neuropathy: Pitfalls and Challenges

Jia Wei Audrey Lee[1], Xinying Velda Han[1,2], Lawrence Chao Ping Wang[1,2]

1.National University Hospital, Singapore
2.Yong Loo Lin School of Medicine, National University of Singapore, Singapore

INTRODUCTION

Small fiber neuropathy (SFN) is a type of peripheral neuropathy that affects the small unmyelinated or thinly myelinated C nerve fibers and A delta fibers present in skin, peripheral nerves, and organs[1]. Their role is to innervate skin sensations and help control autonomic function. As such, patients with SFN present with sensory and autonomic symptoms[2].



SFN has consensus case definitions and common etiologies described but no uniform diagnostic criteria has been established[3]. SFN is also poorly recognized in children despite previous case reports and series[2, 4]. Lack of an awareness of this condition hampers patient care.

In Juvenile onset SFN, as part of the debilitating dysautonomia, the most prevalent neurological symptoms are pain, fatigue, headache, dizziness, sleep difficulties. Gastrointestinal symptoms of nausea, abdominal pain, diarrhea/constipation, and gastroparesis can be debilitating. Natural course can be slowly progressive over time. It can impair physical and mental well-being, education, and family finances.

OBJECTIVES

We present two severe cases to better illustrate the spectrum of presentations of SFN and possible associations with underlying medical conditions of hypermobility and dysimmunity.

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METHODS AND PATIENTS

We report two patients with skin-biopsy proven SFN with debilitating dysautonomia who have undergone extensive work up and trial of multiple immunotherapeutic agents for management of SFN.

Case 1: Non-length dependent SFN

19-year-old overweight female whose symptoms started at 15 years of age with severe migraine headaches after hand foot mouth viral infection. She developed complex regional pain syndrome after surgical repair of left knee meniscal tear, and multisystemic debilitating dysautonomia during the hospitalisation.

Symptoms of dysautonomia:
- Dry eyes, dry mouth
- Orthostatic intolerance
- Neurogenic bladder on intermittent self-catheterisation
- Nausea, diarrhoea alternating with constipation
- Feed intolerance requiring nasojejunal (NJ) tube feeding

Sensory symptoms:
- Complex regional pain syndrome
- Severe migraine headache

Others:
Hypermobile Ehler-Danlos syndrome (hEDS), Allergic rhinitis, Non-specific skin rashes, Multiple drug allergies

Physical examination:
- High Body Mass Index (BMI)
- Hypermobility
- Piezogenic papules over ankles
- Red fingertips and toes
- Neurological examination notable for sensory loss gradient in distal lower extremities to pinprick and mild hand tremors.

Case 2: Length-dependent SFN

19-year-old underweight female whose symptoms started at 17 years of age with positional headache, vertigo, ataxia, nausea, vomiting, loss of appetite, gastroparesis, weight loss. These symptoms increased in severity following Human Papillomavirus and COVID vaccine and episodes viral infections

Symptoms of dysautonomia:
- Orthostatic intolerance
- Syncope
- Severe prolonged gastrointestinal dysmotility including NJ tube intolerance requiring TPN

Sensory symptoms:
- Migraine headaches

Others:
- Hypermobile Ehler-Danlos syndrome, Neurogenic median arcuate ligament syndrome , Skin rashes, Hypersensitivity to medications eg steroid, opioids

Physical examination:
- Low BMI
- Baseline low systolic blood pressure in 80-90s
- Pallor
- Cold hands and feet and hypermobility
- Neurological examination notable for distal sensory loss gradient up to lower leg bilaterally to sharp object.

INVESTIGATIONS

Neurological investigations and Autonomic Function Testing:
Both cases had showing reduced sweat response in all four limbs consistent with sudomotor dysfunction on Quantitative Sudomotor Axon Reflex Test (QSART) and normal electromyography (EMG) and nerve conduction study (NCS). Tilt Table Test showed neurogenic orthostatic hypotension in case 1 and was normal in case 2. Magnetic Resonance Imaging (MRI) of Brain for both were normal.

Autoimmune investigations:
(ANA, anti-dsDNA, C3, C4, Anti-β2-glycoprotein IgG/IgM, Anti-cardiolipin IgG/IgM, Anti-Ro, Anti-La, Anti-RNP/Sm, Anti-Jo1, Anti-SCI 70, Autoimmune dysautonomia evaluation (Mayo Clinic), Anti-TPO, Anti-Tg, Washington University Sensory Neuropathy Panel)
- Both cases had borderline high levels of GAD65 antibodies (0.04nmol/L)
- Case 1 had fluctuating ANA from <1:80 – 1:640
- Case 2 had high anti-TPO, anti-TG with intermittent low complement C3, normal C4 level. Case 2 also developed weakly positive Anti Plexin D IgG on serial Wash U Sensory neuropathy panel

Gastrointestinal investigations
- ·Oesophago-Gastro-Duodenoscopy and colonoscopy: gastritis in case 1 and colitis in case 2.
- ·Gastro-intestinal transit study showed lower colonic portion dysmotility for case 1 and very slow clearance of sitz marker in the lower intestinal tract for case 2
- ·Gastric emptying study were normal for both.
- ·Hydrogen breath test was abnormal in case 1 and normal in case2

Genetic testing
- Whole genome sequencing for case 1 and whole exome sequencing for case 2 did not find a clear cause of SFN..

IMMUNOTHERAPY AND OUTCOMES

Both cases received intravenous immunoglobulin (IVIG) 2g/kg/month at least 3 months. There was modest improvement of some symptoms temporarily and seemed to stabilize their disease flareups. Both patients experienced side effects of headaches, aseptic meningitis and fatigue from IVIG that can be mitigated with premedication, lower dose, slower infusion rate, and choice of IVIG formulation. Compass 31 scores before and after IVIG went from 71 to 69 in Case 1 and from 70 to 66 in Case 2 (Fig 1). Modest improved scores were not sustainable with symptom flareups more often off IVIG.

Intravenous Rituximab (CD20 antibody) in addition to IVIG showed initial significant clinical improvement in case 1 but was discontinued after a bout of septic shock. Case 2 developed severe lower abdominal pain 1 week after commencing treatment with intravenous rituximab off IVIG.

Pulse steroid therapy was not well-tolerated in case 1 due to weight gain and in case 2 due to breathlessness and chest pain.

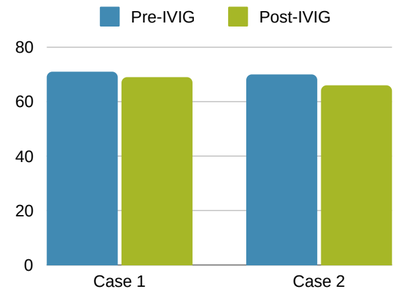

Figure 1: COMPASS 31 scores pre- and post-IVIG

CONCLUSIONS

1. SFN is an under recognized disease in the paediatric population. Early diagnosis is challenging as we only have normative data for QSART and nerve biopsy for children more than 16 years of age.
2. The multisystemic presentations of SFN co-occurring with hypermobility, hypersensitivity to medications, and evidence of dysimmunity can negatively impact daily functioning and activities of daily living. Education and multidisciplinary supportive care for patient and family to address the biopsychosocial issues are vital and essential for their physical and mental health.
3. Treatment is predominantly supportive with emerging evidence for use of immunotherapy to help stabilize the clinical course and maintain function, along with physical and occupational therapy, and psychological support.
4. Small fiber neuropathy is often found in patients with hEDS [5].
5. There is a need to better define and understand the medical causes and underlying pathophysiology of juvenile onset SFN and co- occurring hypermobility and dysimmunity in order to provide evidence-based recommendations for diagnostic pathway and treatment recommendation.