Clinical Reasoning: Burning hands and feet

SECTION 1
A 25-year-old banker, a nonsmoker and non-drinker, presented with pain in the hands and feet for 4 weeks that progressed to involve shoulders and hips. Pain was associated with constipation, followed by diarrhea. He had no prior trauma, vaccinations, or infectious symptoms. Medical history was noncontributory; he was on no medication. He had consulted numerous doctors for the pain, who noted transient urinary hesitancy, tachycardia, and hypertension that required short duration treatment with antihypertensives. All symptoms except the pain resolved spontaneously. On examination, he was afebrile, alert, and oriented. Cranial nerves were intact; there was no ptosis, diplopia, or facial plegia. Four-limb power was Medical Research Council 5/5 proximally and 4/5 distally, limited by pain. Reflexes were just elicitable (1+); anal tone was intact. Cerebellar signs were absent. Gait was slow from bilateral sole pain. No joint deformities or skin abnormalities were seen. He often adopted a posture with both arms abducted and fingers extended, which alleviated pain. Sensory testing revealed hyperalgesia and brush allodynia over the hands and feet. Temperature, vibration, and proprioception were preserved.

Questions for consideration:
1. What differential diagnoses would you consider?
2. What investigations would you perform to confirm the diagnosis?
SECTION 2
Hyporeflexia and glove stocking sensory disturbance strongly suggest a length-dependent polyneuropathy. Allodynia and pain in the distal extremities in the absence of vibration, proprioception, and touch involvement point toward involvement of the nociceptive small sensory fibers, sparing large sensory fibers.

Question for consideration:
1. What preliminary investigations would you consider?
SECTION 3
The most apparent abnormality in the blood tests was hyponatremia. The syndrome of inappropriate antidiuretic hormone (SIADH) is diagnosed when urine osmolality and sodium are high in the presence of low serum osmolality and hyponatremia. In view of the subacute onset of dysesthesia and pain, hyporeflexia, and SIADH, a sensory variant of Guillain-Barré syndrome (GBS) should be considered.

Workup for other causes of subacute polyneuropathy included normal values for vitamin B₁₂, fasting glucose, and thyroid function, making nutritional and metabolic disorders improbable. Normal erythrocyte sedimentation rate (ESR), normal C-reactive protein, and absence of specific autoantibodies render autoimmune causes from systemic lupus erythematosus or Sjögren syndrome unlikely. Thorough history and a normal toxicology screen excluded neurotoxins such as metronidazole and solvents, which can cause small fiber neuropathy. Infectious causes from HIV and hepatitis B and C were excluded with negative serum antibodies and negative hepatitis B surface antigen. Additionally, in parts of the world where Lyme disease is endemic, serologic testing for *Borrelia burgdorferi*, an infectious cause of peripheral neuropathy, should be performed. A small proportion of sarcoidosis patients have associated peripheral neuropathy, and in populations where sarcoidosis is common, chest X-ray is performed to look for hilar adenopathy or parenchymal changes consistent with pulmonary sarcoidosis, and serum angiotensin converting enzyme levels checked. Chronic drinkers are prone to developing thiamine deficiency, which may present as a small fiber neuropathy, necessitating serum vitamin B₁ level assessment. For patients of ethnicities where celiac disease is common (North European and Australasian populations), antigliadin antibodies should be worked up.

Chest X-ray and CT of the thorax, abdomen, and pelvis were performed to exclude occult malignancies as a cause of paraneoplastic neuropathy, which all had normal results. Small-cell lung cancer is the commonest malignancy that can lead to sensory neuropathy, mainly of the large fiber type. Other associated neoplasias are multiple myeloma, monoclonal gammopathies, and lymphomas. Normal ESR, lactate dehydrogenase, and hematologic profile exclude these.

Contrasted MRI spine, brain, and brainstem to look for inflammatory and demyelinating lesions had normal results. Enlarged nerve roots, such as can occur in chronic sensory ganglionopathies, were absent.

**Question for consideration:**

1. What further investigations would you consider?
SECTION 4
To define the type of polyneuropathy, nerve conduction studies (NCS) of all 4 limbs were ordered and had normal results.

Lumbar puncture showed normal opening pressure with a CSF leukocyte count of 5/μL, erythrocyte count of 789/μL, glucose 3.3 mmol/L (reference range [RR] 2.2–3.9 mmol/L), and protein of 2.3 g/L (RR 0.1–0.4 g/L). Gram stain and cytology were normal, further excluding infections. Despite a traumatic tap, the patient’s CSF studies showed albuminocytologic dissociation, which often occurs in inflammatory neuropathies, malignancies, or leptomeningeal metastases. The latter 2 are unlikely in view of normal imaging and CSF cytology.

Subacute glove and stocking sensory impairment with allodynia, hyporeflexia, and autonomic involvement in combination with normal NCS findings is strongly suggestive of a small fiber neuropathy. The presence of SIADH and albuminocytologic dissociation makes GBS the likely cause. SIADH and albuminocytologic dissociation occur in 50% and 80% of all patients with GBS, respectively.

Antiganglioside antibodies (anti-GM1, anti-GQ1b, anti-GD1a, anti-GD1b, and anti-GT1a) were negative, but the sensitivity and specificity of autoantibodies in small fiber GBS is unknown. In the first days of GBS, NCS may be normal. Initial changes include delayed, absent, or impersistent F and H reflexes, a result of proximal nerve root demyelination. In the first to second week, sural sparing occurs with the demyelinating form. With subsequent segmental demyelination, motor studies show prolonged distal latencies, conduction block, and temporal dispersion.1 Half of the patients will have changes by 2 weeks, and most by 3 weeks. Our patient presented 4 weeks after the onset of symptoms, a time by which changes in NCS should be detectable. Repeated NCS throughout the illness had normal results. A limitation of NCS is that it cannot detect damage to small nerve fibers, which were predominantly affected in this patient.

Question for consideration:
1. What further investigations can be done to help confirm the diagnosis of small fiber/autonomic involvement?
SECTION 5
Skin biopsy was performed and stained for protein gene product 9.5, which showed absence of intraepidermal nerve fibers, consistent with a small fiber neuropathy.

Although unstable blood pressure and heart rate and enteric symptoms had resolved prior to admission, we attempted to further investigate for limb sympathetic involvement. Stimulated skin wrinkling test with EMLA had normal results.

Figure  
Workup for the etiologic identification of small fiber neuropathy

Clinical features of small fiber neuropathy
- Positive sensory symptoms like: tingling, burning, prickling, shooting pain, or aching
- Worse at night and may interfere with sleep
- Alldynia, hyperesthesia and cramps
- May also have negative symptoms like numbness, tightness and coldness
- Distal and length dependent
- Autonomic symptoms – increased/decreased sweating, facial flushing, skin discoloration, dry eyes and mouth, changes in skin temperature, orthostatic hypotension or enteric symptoms
- Impaired thermal and pain sensitivity
- Normal muscle strength, proprioception and tendon reflexes

Check bloods according to clinical suspicion:
- Metabolic (DM, IFG, hypertriglyceridemia, hypothyroidism): HbA1C, FG, TFT
- Alcoholism / Nutritional Deficiencies: EtOH level, GGT, MCV, vit B1, vit B12
- Infectious (HIV, HBC, HBV, Lyme disease): CRP, HIV, Borrelia burgdorferi, HBV, HCV
- Autoimmune (Vasculitis, SLE, Sjögren’s yndrome, rheumatoid arthritis, connective tissue disease, celiac disease, sarcoidosis): ESR, ANA, anti-ENA, SLE panel, ANCA, anti-gliadin ab, RF, Serum ACEI, CXR
- Paraneoplastic (Small cell lung cancer, solid tumors, lymphoma, myeloma, monoclonal gammapathies): Tumor markers, LDH, myeloma screen, SPE, UPE, anti-Hu and anti-CV2/CRMP-5 antibodies
- Neurotoxins (Metronidazole, solvents): Urine + blood toxicology, screen and review drug history
- Hereditary (Fabry disease, Na, 1.7 and Na, 1.8 sodium channelopathies): Leukocyte alpha-galactosidase A and globotriaosylceramide (Gb3 or GL-3) levels, renal panel, urine protein, genetic testing for SCN9A, SCN10A
- Lumbar puncture if suspicious of inflammatory, autoimmune or paraneoplastic etiologies

Skin biopsy for PGP 9.5 staining for IENFD

Other small fiber tests:
- Stimulated skin wrinkling with water/EMLA
- Quantitative sensory testing (QST)
- Quantitative sudomotor axonal reflex testing (QSART)
- Microneurography

Suspicious for malignancy
- PET/CT whole body

Clinical features suggestive of amyloidosis
- Skin/nerve/fat pad biopsy for congo red staining

If all blood tests negative, consider small fiber sensory Guillain-Barré syndrome or chronic inflammatory sensory polyneuritis

The patient was treated with IV immunoglobulin (IVIg) 2 G/kg over 5 days and symptomatically with gabapentin. At follow-up 6 weeks later, symptoms, as assessed by the Visual Analogue Scale pain scale, had improved by more than 80%.

**DISCUSSION** This case illustrates an approach to acute-onset small fiber neuropathy (figure). Small fibers are unmyelinated C fibers, which are involved in thermal perception, nociception, and a number of autonomic and enteric functions. Hence in patients with small fiber neuropathies, in addition to presenting with burning dysesthesias or pain, which may be spontaneous or sensory induced, they may also present with autonomic and enteric features of constipation, diarrhea, urinary frequency, blood pressure changes, and postural dizziness.

Multiple diagnostic tests are available to confirm the diagnosis of small fiber neuropathies. Skin biopsy with estimation of intraepidermal nerve fiber density is a commonly accepted gold standard in the diagnosis of small fiber neuropathies and has a high sensitivity (>80%). The skin wrinkling test is simple with reasonable sensitivity (up to 80%). However, it only tests the sympathetic portion of small fiber neuropathy and in this case there were no clinical clues suggesting persistent sympathetic involvement.

Other tests include quantitative sensory testing, which assesses psychophysical thresholds for cold and warm sensations with a diagnostic efficiency of around 50%. Sympathetic skin response is commonly used to diagnose small fiber neuropathy but has varying sensitivity and reproducibility due to complex central and peripheral pathways. Quantitative sudomotor axon reflex test is an alternative diagnostic tool but test and pretest reliability have been found to be moderate. Finally, microneurography is an invasive test, which by placing recording microelectrodes within nerve fascicles, enables multiple small fibers to be recorded simultaneously.

The diagnosis of the underlying cause of subacute monophasic small fiber neuropathy depends on the identification of likely underlying causes. When appropriate testing fails to identify the possible etiologies, an autoimmune cause similar to small fiber neuropathy can be considered. A recent approach for GBS diagnosis is the Brighton Criteria, which stratifies patients into 4 levels of diagnostic accuracy, depending on core clinical symptoms and signs of bilateral and flaccid limb weakness, a monophasic course and time between onset and nadir (12 hours–28 days), and decreased or absent deep tendon reflexes, in the absence of any alternative diagnosis for weakness. CSF, neurophysiology, and autoantibodies are supportive. Most diagnostic criteria for GBS emphasize the motor nerves and criteria for sensory GBS are less readily established. Small-fiber GBS, which is also known as a form of sensory GBS, is a controversial diagnosis, but needs consideration where weakness is minimal and nerve conduction tests are normal, in the presence of monophasic signs and symptoms of small fiber involvement.

Saifudheen et al. found that 48% of patients with GBS had associated SIADH, which was also found to be a poor prognostic predictor. The pathogenesis of SIADH in GBS has not been fully understood but has been postulated to be due to osmotic resetting and enhanced renal tubular sensitivity to antidiuretic hormone.

Treatment of small fiber GBS is the same as other forms of GBS, and includes immunomodulatory therapy with IVIg or plasma exchange. Symptomatic treatment of neuropathic pain can be considered with GABA agonists, opioids, and nonsteroidal anti-inflammatory agents.

This case illustrates a patient with an acute small fiber neuropathy and highlights the role of blood tests, neurophysiology, lumbar puncture, and skin biopsy in its diagnosis. The most likely etiology is sensory GBS. According to the proposed classification for sensory GBS, our patient has an acute sensory small fiber neuropathy-ganglionopathy.

**AUTHOR CONTRIBUTIONS**

Amanda Chee Yun Chan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, statistical analysis. Einar P. Wilder-Smith: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

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