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## Toxic exposure in a clinical pathology laboratory as a potential occupational hazard causing small fibre neuropathy

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### Abstract

**Introduction:** Small fibre neuropathy (SFN) is a heterogeneous condition involving the thinly-myelinated A $\delta$  and unmyelinated C-fibres, characterised by pain and altered temperature sensation and perception. Toxins such as alcohol and chemotherapeutic agents are known causes of SFN, with research into other toxic aetiologies underway. Pathologists are routinely exposed to a variety of organic solvents, such as xylene, acetone and methanol, which potentially lead to the development of SFN. **Methods:** A retrospective review was performed performed a retrospective review of all pathologists who were treated at the SFN clinic in our hospital between January 2020 and May 2021. Their clinical presentation, disease course, treatment and outcomes were described. **Results:** Three patients with SFN were identified. These patients experienced somatic symptoms of SFN such as burning pain, paraesthesia and autonomic symptoms, including tachycardia and postural hypotension. Normal nerve conduction studies indicated intact large nerve fibres. Abnormal SFN tests, including quantitative sensory testing, quantitative sudomotor axonal testing, and tilt table testing, contributed to the diagnosis of SFN. Inflammatory and autoimmune markers were raised in two of the three pathologists. Toxicology screens performed later were negative, possibly indicating that blood solvent concentrations had decreased to undetectable levels over time. Administration of intravenous immunoglobulin (IVIg) resulted in an improvement in symptoms and functional outcomes. **Conclusion:** Chronic exposure to organic solvents in the routine job scope of pathologists may lead to the development of SFN. Awareness of this hazard is imperative in order to ensure occupational safety.

## 1. INTRODUCTION

Small fibre neuropathy (SFN) is a condition that involves the thinly-myelinated A $\delta$  and unmyelinated C-fibres, characterised by pain and altered temperature perception (Chan & Wilder-Smith, 2016). There are many aetiologies of SFN, including exposure to toxins. Although associations between common toxins such as alcohol and chemotherapeutic

agents (Chan & Wilder-Smith, 2016) and SFN have been well reported, a wide variety of other toxins that lead to SFN remains to be described (Dick, 2006). Research to discover other toxins that lead to SFN is well underway. The association between toxins such as xylene, n-hexane and methyl-n-butyl ketone has been established in recent years (Dick, 2006).

Pathologists are routinely exposed to a variety of organic solvents (Aquino et al., 2016). It is proposed that some may be toxic and prolonged exposure may lead to the development of SFN (Dick, 2006). Although this is a common occupational hazard for pathologists, little is known about the association of solvent exposure in pathology to the development of SFN (Aquino et al., 2016). We present a case series of 3 pathologists who developed SFN.

This case series explored the presentation, clinical course and outcomes of pathologists who developed SFN. The aim of this study is to provide preliminary insight into the role of solvent exposure in the pathology of SFN, and to draw attention to this potential occupational hazard.

## 2. METHODOLOGY

In this retrospective case series, a hospital-wide search of all pathologists who were treated in the SFN clinic between January 2020 and May 2021 at National University Hospital, Singapore was performed. All patients with a definite diagnosis of SFN after investigation were included. The clinical parameters and results from SFN diagnostic tests were reviewed and interpreted by a consultant neurologist specialising in SFN, while the autoimmune panels were reviewed in consultation with an experienced rheumatologist. Informed consent was obtained from all patients. Ethics approval was obtained from the NHG Domain Specific Review Board (Domain A, DSRB number 2015/00238).

## 3. RESULTS

Three pathologists who were diagnosed with SFN based on clinical symptoms and supportive diagnostic investigations were identified. Here, we describe their presentation, clinical course and outcomes were described. Notably, none of the pathologists described presented with other causes of neuropathy such as diabetes mellitus and chronic alcohol use.

### 3.1 Case 1

A 55 year-old female worked as a pathologist for 28 years. She presented with a one-year history of gradual onset of burning pain and numbness on the soles of her feet that tremendously impacted her quality of life.

Nerve conduction studies (NCS) were unremarkable, indicating absence of large fibre pathology. To investigate pathology in the small fibres, SFN investigations were carried out including Quantitative Sudomotor Axon Reflex Test (QSART) which measures the function of nerves that control sweating, stimulated skin wrinkling test (SSW) which measures the ability of skin to form wrinkles, Quantitative Sensory Testing (QST) which measures the ability to perceive heat and the Tilt Table Test (TTT) which measures postural hypotension. Results of the QSART and SSW were abnormal. Skin biopsy was also carried out for histopathological confirmation of SFN. It showed a reversal of the intra-epidermal nerve fibre density (IENFD) ratio at the distal leg compared to the distal thigh, characteristic of SFN (Khoshnoodi et al., 2016). A raised serum titre of anti-nuclear antibodies (ANA) and erythrocyte sedimentation rate (ESR) was found suggestive of an inflammatory or autoimmune component. A 2gm/kg course of intravenous immunoglobulin (IVIg) was administered. Pregabalin and Amitriptyline were continued at the same doses that she had previously been on for neuropathic pain.

Pain, numbness, functional mobility and quality of life improved markedly after IVIg. Subsequent follow up over 18 months with the rheumatologist did not reveal any new systemic autoimmunity. The patient resigned as a hospital resident pathologist 12

months after discharge, following which her symptoms resolved, and she has weaned off all neuropathic pain medications.

Toxicology tests were not performed as Patient 1 was the first in the series of pathologists who sought medical advice for SFN, and suspicion of toxic exposure was low upon consultation.

### 3.1 Case 2

A 42 year-old female patient worked as a pathologist for 15 years. She presented with gradual onset of paraesthesia of both lower limbs. This was associated with fasciculations in both calves. NCS was normal. Needle electromyography showed benign fasciculations.

SFN investigations revealed abnormal results for the QSART and SSW. Skin biopsy was positive for SFN, indicated by an IENFD <5<sup>th</sup> percentile, corrected for age and gender (Lauria et al., 2010). Blood tests revealed raised ANA and raised ANCA, suggesting a possible inflammatory component. Lumbar puncture was performed, and cerebrospinal fluid (CSF) showed an elevated white blood cell count of 28/uL, which was lymphocyte-predominant. CSF tests for meningitis, encephalitis and tuberculosis were negative. Computed tomography (CT) of the thorax, abdomen and pelvis was negative for malignancy. Toxicology screens were performed to investigate diethylene glycol, ethylene glycol and propylene glycol, acetone, benzene, ethanol, isopropanol, methanol, toluene and xylenes, but were negative. Heavy metal screen for lead, arsenic, cadmium and mercury was also negative.

Owing to the presumed inflammatory cascade triggered by the toxins, a trial of a 2gm/kg course of intravenous immunoglobulin was administered over five days. No side effects were experienced, and she reported an improvement in paraesthesia. Rheumatology follow-up did not meet the requirements for systemic autoimmune disease. She remained as a pathologist. Measures were taken to improve the ventilation in the laboratory and her symptoms resolved apart from intermittent fasciculations at one-year follow-up.

### 3.3 Case 3

A 47 year-old female worked as a pathologist for 19 years. She had no significant past medical history and presented with gradual onset of burning pain and paraesthesia over her hands, feet, body and face over one week. She also experienced autonomic symptoms, including palpitations and postural giddiness.

NCS was normal. SFN investigations revealed abnormal results for the QSART and QST. A borderline ANA and normal ESR were found. Skin biopsy revealed an IENFD count at the 30<sup>th</sup> percentile for age and gender, which is considered negative for SFN (Lauria et al., 2010). A toxicology screen was performed to investigate acetone, benzene, ethanol, isopropanol, and methanol, toluene, xylenes, ethanol, isopropanol and methanol, which was negative.

The diagnosis of SFN was made definite based on the abnormal QST, normal NCS and classical presentation (Tesfaye et al., 2010). Due to the short time course from presentation to skin biopsy, it is possible that the full damage to the small nerve fibres had not been fully reflected in the skin biopsy. IVIg was not administered due to unconvincing evidence of an ongoing inflammatory or autoimmune aetiology. She reported static to slight worsening of symptoms subsequently. She was prescribed Gabapentin 100 mg BD for her pain and paraesthesia. She continued her job as a pathologist. Measures were taken to improve the ventilation in the laboratory and her symptoms improved by 15% at 1-year follow-up.

## 4. DISCUSSION

Toxic exposure is a known cause of SFN, and its association with a variety of toxins such as alcohol and chemotherapeutic agents has been well reported in the literature (Chan & Wilder-Smith, 2016). Emerging evidence suggests that exposure to volatile organic solvents may also cause SFN (Dick, 2006). This case series discussed the presentation

and management of three pathologists who developed SFN, likely due to toxic exposure to volatile organic solvents in their work.

All the pathologists reported in this case series worked in the same hospital and laboratory. When the first pathologist developed symptoms of SFN, despite a thorough and algorithmic evaluation for underlying causes of SFN, a toxic aetiology of SFN was not originally suspected. ANA, anti-ENA, ANCA and ESR are frequently nonspecific and can be raised in inflammatory, autoimmune or infectious processes (Sato et al., 2009). Initial serology pointed to an autoimmune or ongoing inflammatory process. Hence treatment with intravenous immunoglobulin (IVIg), which has been found to be effective for idiopathic or autoimmune SFN, was initiated. Suspicions arose for a toxic aetiology when the second pathologist from the same institution developed SFN symptoms. The development of SFN symptoms in the third pathologist further raised suspicions as there were a total of 10 pathologists in the same institution diagnosed with SFN in a similar timeframe, which amounted to a prevalence of 30%, far outweighing the prevalence of peripheral neuropathy or SFN. The prevalence of peripheral neuropathy is quoted at 15% in the adult population over 40 years of age (Valentine, 2020), and the minimum prevalence of small fiber neuropathy is 0.1315% (Bitzi et al., 2021). Neurotoxicants have been shown to target signalling between the main components of the peripheral nerve, leading to multi-pronged inflammatory cascades, and finally to active programmed degenerative pathways (Valentine, 2020). The high prevalence of SFN in the same work setting lends credibility to the hypothesis that occupational exposure to toxins could lead to SFN.

During their work, pathologists were routinely exposed to volatile organic solvents such as xylene, toluene, acetone, and methanol to prepare pathology specimens.<sup>3</sup> During the COVID-19 pandemic, the doors and windows of the laboratory and offices were closed as part of infection control measures, leading to suboptimal ventilation. Pathologists were stationed primarily in the laboratory for upwards of 8 hours daily and directly contacted the specimens. Unofficial measurements of solvents and toxic chemicals in the air of the pathology lab revealed high levels of hazardous chemicals. This raises suspicion of a toxic aetiology of SFN (Ridgway et al., 2003). Currently, there is limited literature on the association between volatile organic solvents and SFN. As this is a potential occupational hazard for pathologists and other technicians involved in the preparation of pathology specimens (Berthold et al., 1983), more work needs to be done in this area to establish appropriate safety guidelines (Aquino et al., 2016). Toxicology tests were later performed for two of the pathologists as part of the investigations for the aetiology of SFN, but revealed negative results. Arrangement of rare toxicology tests require time, which possibly allows blood solvent concentration to decrease to undetectable levels. This highlights the importance of early toxicology screens in cases that are suspicious of toxic exposure.

Elimination of inciting substances is the mainstay of managing toxic neuropathy, but elimination alone does not stop the damage. "Coasting" occurs when clinical signs continue to progress for weeks to months following cessation of exposure (Valentine, 2020). During this period, patients who suffer from worsening symptoms may benefit from interim anti-inflammatory treatment or risk further damage to the nerves. Immunomodulatory treatment is an emerging treatment modality for idiopathic SFN, and quantitative improvement has been shown in autonomic function tests (Liu et al., 2018). Although the mechanism of IVIg therapy for SFN is not well understood<sup>12,13</sup>, higher doses of IVIg have been shown to inhibit inflammation and are efficacious in systemic inflammatory diseases (Tjon et al., 2015). Epigenetic mechanisms have been found to modify neuropathic pain (Ueda & Uchida, 2015), and epigenetic gene silencing underlies C-fibre dysfunction (Uchida et al., 2010). Whether toxicity or epigenetics precipitated an immunological attack to the small nerve fibres or an inflammatory cascade has yet to be investigated.

## 5. CONCLUSIONS

This case series highlights the possibility that chronic exposure to organic solvents in the routine job scope of pathologists may predispose them to the development of SFN.

Further studies are warranted to explore this association given the significant occupational health ramifications, and could additionally help clarify the efficacy of IVIg and other therapeutic targets.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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