

# NEUROPATHY DIGEST

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The following is a digest of select publications related to Small Fiber Neuropathy that were published in peer review journals the past quarter of 2011. Neuropathy Digest is a quarterly informational newsletter that is published and distributed to physicians by Therapath LLC. For more information about small fiber neuropathy or Therapath's pathology services, visit our website at [www.therapath.com](http://www.therapath.com).

## **GENERAL CONSIDERATIONS; DIAGNOSIS AND TREATMENT**

### **Length vs Non-Length Dependent Small Fiber Neuropathy**

Gemignani et al reported on their findings in patients with non-length dependent small fiber neuropathy (SFN). Of 44 patients diagnosed with SFN, 11 had non-length dependent neuropathy. Of these, 2 had Sjögren's syndrome, 1 each had impaired glucose tolerance, rheumatoid arthritis, hepatitis C virus, or Crohn's disease, and 5 were idiopathic. Patients with distal small fiber neuropathy tended to be older, and approximately 50% had impaired glucose metabolism.

### **Sweat Gland Nerve Fiber Density (SGNFD) in Small Fiber Neuropathy**

At this year's meeting of the Peripheral Nerve Society, Hays et al, from Therapath, reported that in a study of 524 patients with suspected small fiber neuropathy, enumeration of Sweat Gland Nerve Fiber Density (SGNFD) in addition to Epidermal Nerve Fiber Density (ENFD) increased the diagnostic yield of punch skin biopsy by approximately 18%. The study suggests that determination of SGNFD could help make a diagnosis in patients with suspected small fiber neuropathy and normal ENFD.

### **Erythromelalgia and Small Fiber Neuropathy**

Erythromelalgia is characterized by burning pains and reddish discoloration in the extremities. Cook-Norris et al reviewed the records of 32 cases of childhood erythromelalgia evaluated at

the Mayo Clinic. Of the patients studied, 59% had evidence for small fiber neuropathy, none had large fiber neuropathy, and 22% had a first degree relative that was also affected. Physical activity was limited due to discomfort in 66%, and school attendance was adversely affected in 34% of the patients. Disease course was variable. The authors concluded that erythromelalgia is associated with substantial morbidity, that most patients have associated small fiber neuropathy. A safe treatment has not been determined.

### **Restless Genital Syndrome**

Restless genital syndrome is characterized by unwanted unpleasant genital sensations, restless legs, and overactive bladder, caused by small fiber neuropathy. In the past, it has only been reported in women with neuropathy of the dorsal clitoral nerve. Waldinger et al report of 2 men diagnosed with restless genital syndrome, associated with hypersensitivity in the territory of the pudental nerve. TENS application relieved the symptoms in one of the patients. The authors conclude that dorsal genital syndrome can be a manifestation of small fiber sensory neuropathy in both men and women.

### **Sjögren's Syndrome**

Approximately 40% of patients with primary Sjögren's syndrome experience chronic neuropathic pain with normal electrodiagnostic studies. Fauchais et al report that skin biopsies in Sjögren's patients with painful paresthesias and normal electrodiagnostic studies showed reduced ENFD in 13 of 14 consecutive patients. They conclude that the sensory symptoms in Sjögren's disease are caused by small fiber neuropathy.

### **IVIG in Sarcoid Neuropathy**

Small fiber neuropathy is sometimes associated with sarcoidosis. Parambil et al report that 3 patients with sarcoidosis and sensory and autonomic small fiber neuropathy significantly improved following response to therapy with intravenous immunoglobulins (IVIG). These observations indicate that sarcoid neuropathy may be caused by inflammatory mechanisms, and that controlled studies are needed to confirm the efficacy of IVIG in that condition.

## **CAUSES OF SMALL FIBER SENSORY OR AUTONOMIC NEUROPATHY**

### **Autoimmune Autonomic Neuropathy**

Manganelli et al report on their pathological studies of sural nerve and skin biopsies in a patient with autoimmune autonomic neuropathy and elevated ganglionic nicotinic acetylcholine receptor antibodies. Sural nerve and skin biopsy examination revealed somatic nerve and postganglionic autonomic damage. These findings help define the pathophysiology of autoimmune autonomic neuropathy.

### **Sodium Channel Mutations in Idiopathic Small Fiber Neuropathy**

Faber et al reported that 8 of 26 (25%) patients with idiopathic small fiber neuropathy, diagnosed by skin biopsy, had novel mutations in the sodium channel Na(V)1.7 gene SCN9A. Functional analysis showed that the mutation resulted in gain of function changes, or hyperexcitability in sensory ganglia. The study suggests that gain of function mutations in sodium channels may be a cause of painful small fiber neuropathy. Of interest is that mutations in sodium channel Na(V)1.7 have previously been associated with erythromelalgia or paroxysmal extreme pain disorder in several families.

### **Fabry Disease**

Burlina et al reported on the recommendations of an expert panel in Fabry disease, an X-linked inherited condition that is caused by alpha galactosidase A deficiency. The panel noted that Fabry disease can cause a small fiber neuropathy, with pain and autonomic symptoms, in both affected males and female carriers. Early diagnosis and enzyme replacement treatment can prevent progression and development of other complications such as cardiomyopathy or renal disease.

### **Bariatric Surgery**

Philippi et al report on 3 patients that developed small fiber neuropathy following bariatric surgery. All had prominent neuropathic pain, massive weight loss, and multiple nutritional deficiencies. The authors note that the spectrum of peripheral

neuropathies complicating bariatric surgery is wide, and includes small fiber neuropathy in addition to demyelinating and axonal neuropathies.

### Chronic Renal Disease

Chao et al reported on their investigation of neuropathy in patients with chronic kidney disease. Of their patients, 52.5% had limb paresthesias or autonomic symptoms, 67.5% had skin denervation, 37.5% had abnormal nerve conduction studies, and 72.5% had abnormalities on autonomic function testing. A reduction in ENFD was correlated with the duration of renal disease and autonomic dysfunction. The authors conclude that small fiber sensory and autonomic neuropathies constitute the major form of neuropathy in later stage chronic renal disease.

### Bortezomib Therapy

Bortezomib is a new chemotherapeutic agent used in the treatment of multiple myeloma. Giannoccaro and colleagues describe the involvement of autonomic skin nerve fibers in 3 patients with small fiber neuropathy induced by bortezomib treatment.

### Hypothyroid Disease

Magri et al reported on their studies of newly diagnosed patients with hypothyroid disease. They found that approximately 50% of patients had small fiber neuropathy, as evidenced by a length dependent reduction of ENFD, in comparison to normal controls. They conclude that subclinical small fiber neuropathy is common in patients with undiagnosed thyroid disease.

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