THERAPATH®
NEUROPATHOLOGY

NEUROPATHY DIGEST

WINTER 2014 VOL. IV

The following is a digest of select papers recently published in peer reviewed journals, that may be of interest to physicians that care for patients with small fiber neuropathy (SFN).

Neuropathy Digest is an online informational newsletter for physicians that care for patients with neuropathy, that is published and distributed by Therapath LLC.

For more information about small fiber neuropathy or Therapath's nerve and muscle pathology services, visit our website at www.therapath.com

QUALITY OF LIFE AND USEFULNESS OF SKIN BIOPSY IN SMALL FIBER NEUROPATHY

Bakkers et al examined a total of 265 patients diagnosed with small fiber neuropathy (SFN). They found that SFN was associated with a severe impairment in Quality of Life, with pain and autonomic symptoms explaining only a small portion of the findings.

Saperstein et al (2013) retrospectively reviewed the records of 145 patients with sensory symptoms or findings, and normal nerve conduction studies seen in a subspecialty neuromuscular private practice. They found that the skin biopsy was abnormal in at least one site in 59% of patients. Those with confirmed SFN were significantly more likely to have pain and were more than twice as likely to respond to standard neuropathic medications.

Boruchow et al (2013) examined the role of skin biopsy in the evaluation and management of patients with suspected SFN. Of 69 patients who underwent skin biopsy, 25 had pathological evidence of SFN, and 9 had borderline changes. A change in management of diagnosis occurred in 14 of 25 patients with definite SFN, 6 of 9 patients with borderline SFN, and 16 of 35 biopsy negative patients. They conclude that skin biopsy played a valuable role in the workup of these patients.

NON-LENGTH VS LENGTH DEPENDENT SMALL FIBER NEUROPATHY

Khan et al (2012) compared 63 patients with non length dependent SFN to 175 patients with length dependent SFN. They found that non-length dependent SFN was more common in women, presents at a younger age, and is more likely to be associated with immune mediated conditions.

NEUROPATHIC POSTURAL TACHYCARDIA SYNDROME (POTS), AND FATIGUE IN GULF WAR VETERANS ASSOCIATED WITH AUTONOMIC SMALL FIBER NEUROPATHY

Gibbons et al (2013) reported that 9 of 24 subjects with POTS had evidence for small fiber neuropathy. A subgroup of these patients had symptoms suggestive of gastrointestinal and genitourinary parasympathetic nervous system dysfunction. Li et al (2014) reported that of 16 patients with Gulf War veterans and post exertional fatigue, 6 had objective evidence for autonomic dysfunction, 2 of whom had small fiber neuropathy.

FIBROMYALGIA, COMPLEX REGIONAL PAIN SYNDROME (CRPS), AND UNEXPLAINED WIDESPREAD PAIN SYNDROME

Üceyler et al (2013) reported that in skin biopsies, total and regenerating intraepidermal nerve fibers at the lower leg and upper thigh were significantly reduced in patients with fibromyalgia syndrome compared with control subjects.

Oaklander et al (2013) reported that 41% of skin biopsies from subjects with fibromyalgia vs 3% of control subjects, were positive for small fiber neuropathy. They conclude that some patients diagnosed with fibromyalgia, have unrecognized small fiber neuropathy, a disease for which there is an objective test, and sometimes definite treatment.

Kharkar et al (2012) evaluated skin biopsies from 43 patients with Complex Regional Pain Syndrome –I. Abnormalities in epidermal or sweat gland nerve fiber density were found in 20% of the patients. Oaklander and Klein (2013) examined 41 consecutive patients under age 21 with unexplained widespread pain. Objective testing diagnosed definite SFN in 59%, probable SFN in 17% and possible SFN in 22%.

MUSCLE CRAMPS AND SFN

Lopate et al (2013) reported the results of skin biopsies in 12 patients with muscle cramps and no neuropathic complaints, eight of whom had normal small fiber sensation. Seven of the 12 patients had decreased intraepidermal nerve fiber density consistent with small fiber neuropathy.

SFN IN SUBCLINICAL HYPOTHYROIDISM

Magri et al (2013) reported that in 6 patients with hypothyroidism and SFN, 3 of whom had elevated TSH and normal T4, skin biopsy showed a significant increase in epidermal nerve fiber density after treatment with L-thyroxine.

SFN IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND SJOGREN'S SYNDROME

Oomatia et al (2013) reported that 123 of 2,097 patients with SLE (5.9%) had peripheral neuropathy with 82 of the 123 (66.7%) neuropathies attributable to SLE. Fourteen of the 82 (17.1) had small fiber neuropathy. SLE patients with SFN had neuropathic pain syndromes not consistent with a stocking-and-glove distribution, and had skin biopsies suggestive of dorsal root ganglia neuronal loss. This type of neuropathy is not currently included in the American College of Rheumatology neuropsyschiatric SLE case definitions. The authors suggest that a revision of the case definitions is warranted.

Sene et al (2013) analyzed the clinical immunological, and neurophysiologic features of primary Sjögren associated small fiber neuropathies in 40 consecutive patients. In comparison to patients without neuropathy, those with SFN were older, and had a distinctive immunologic profile hallmarked by a lower frequency of serum B-cell activation markers including anti-SSA/SSB antibodies, ANA, RF, or hypergammaglobulinemia.

Kawagashira et al (2012) reported on their histopathological findings of two autopsy cases of neuropathy associated with primary Sjögren's syndrome, one with the ataxic form and one with the painful form. In the painful form, there was a prominent reduction of small neuropathy, while in the ataxic form, large neurons were predominately lost. Prominent CD8+ T-lymphocyte infiltration was present in the DRGs, sympathetic ganglion, epineurial and perineurial space throughout the peripheral nerve trunks.

METABOLIC SYNDROME AND SFN

Zhou et al (2011) reviewed the records of patients in their database that underwent skin biopsy, to compare those with reduced nerve fiber density to those with normal densities. They found that the incidence of metabolic syndrome was higher in those with SFN (27.8% to 2.3%), and correlated with the severity of the neuropathy.

SODIUM CHANNEL MUTATIONS IN SFN

Faber et al (2012) reported that 8 of 28 patients with idiopathic small fiber neuropathy were found to carry gain of function mutations in the SCN9A gene encoding voltage gated sodium channel Na(V)1.7, that rendered dorsal root ganglion neurons hyperexcitable.

Hoeijmakers et al (2012) described a family with small fiber neuropathy, pain, dysautonomia, and small hands and feet associated with a novel Na(V)1.7 mutation (G856D; c.2567G>A), that rendered dorsal root ganglia hyperexcitable.

Han et al (2013) reported 2 patients with painful small fiber neuropathy that had a novel sodium channel Na(V)1.8/G1662S substitution, that rendered dorsal root ganglia hyperexcitable. These observations indicate that mutations in Na(V)1.8 can contribute to the pathophysiology of painful peripheral neuropathy.

REFERENCES

Bakkers M, Faber CG, Hoeijmakers JG, Lauria G, Merkies IS. Small fibers, large impact: Quality of life in small fiber neuropathy. Muscle Nerve 2013; May 28.

Boruchow SA, Gibbons CH. Utility of skin biopsy in management of small fiber neuropathy. Muscle Nerve 2013; 48: 877-82.

Han C, Vasylyev D, Macala LJ, et al. The G1662S NaV1.8 mutation in small fibre neuropathy: impaired inactivation underlying DRG neuron hyperexcitability. J Neurol Neurosurg Psych 2013; Sept 4.

Hoeijmakers JG, han C, Merkies IS, et al. Small nerve fibres, small hands, and small feet: a new syndrome of pain, dysautonomia and acromesomelia in a kindred with a novel NaV1.7 mutation. Brain 2012; 135: 345-58.

Faber CG, Hoejimakers JG, Ahn HS, et al. Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol 2012; 71: 26-39.

Gibbons CH, Bonyhay I, Benson A, Wang N, Freeman R. Structural and functional small fiber abnormalities in the Neuropathic Postural Tachycardia Synrome. PLOS ONE 2013; 8 (issue 12) e84716

Kahn S, Zhou L. Characterization of non-length dependent small fiber sensory neuropathy. Muscle Nerve 2012; 45: 86-91.

Kawagashira Y, Koike H, Fujioka Y, et al. Differential, size-dependent sensory neuron involvement in the painful and ataxic forms of primary Sjögren's syndrome-associated neuropathy. J Neurol Sci 2012; 319: 139-46.

Kharkar S, Venkatesh YS, Grothusen JR, Rojas L, Schwrtzman RJ. Skin biopsy in complex regional pain syndrome: case series and literature review. Pain Physician 2012; 15: 255-66

Li M, Xu C, Yao W, et al. Self-reported post-exertional fatigue in Gulf War veterans: role of autonomic testing. Frontiers in Neuroscience 2014; 7: article 269, 1-7.

Lopate G, Streif E, Harms M, Weihl C, Pestronk A. Cramps and small fiber neuropathy. Muscle Nerve 2013; 48: 252-5.

Magri F, Buonocore M, Camera A, et al. Improvement of intra-epidermal nerve fibre density in hypothyroidism after L-thyroxine therapy. Clinical Endocrinology 2013; 78: 152-154.

Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small fiber polyneuropathy underlies some illness currently labeled as fibromyalgia. Pain 2013; 154: 2310-6.

Oaklander AL, Klein MM. Evidence of small fiber polyneuropathy in unexplained, juvenile onset ,widespread pain syndrome. Pediatrics 2013; 131 (4): e1091-100.

Oomatia A, Fang H, Petri M, Birnbaum J. Peripheral neuropathies in systemic lupus erythematosus (SLE): clinical features, disease associations, and immunological characteristics evaluated over a 25 year study period. Arthritis Rheum 2013; Dec 10.

Saperstein DS, Levine TD, Levine M, Hank N. usefulness of skin biopsies in the evalaluation and management of patients with suspected small fiber neuropathy. Int J Neurosci 2013; 123: 38-41.

Sene D, Cacoub P, Authier FJ, et al. Sjögren syndrome-associated small fiber neuropathy: characterization from a prospective series of 40 cases. Medicine 2013; Aug 26.

Üceyler N, Zeller D, Kahn A-K, et al. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013; 136: 1857-67.

Zhou L, Li J, Ontaneda D, Sperling J. Metabolic syndrome in small fiber sensory neuropathy. J Clin Neuromusc Dis 2011; 12: 235-43.