Oaklander and colleagues (ANA, 2012a) reported on their findings that a substantial number of patients with fibromyalgia have small fiber neuropathy. They measured the intraepidermal nerve fiber densities (IENF) in punch skin biopsies from patients with fibromyalgia and found that 50% had IENF densities below the 5th percentile of normal controls. The IENF density in fibromyalgia patients averaged 24 +/- 0.1% of predicted norm vs. 64 +/- 0.07 % in controls. Autonomic function testing and the Utah Early Neuropathy Scale also pointed to neuropathic changes in many of the fibromyalgia patients. The authors conclude that substantial numbers of fibromyalgia patients meet rigorous diagnostic criteria for small fiber neuropathy, possibly explaining their pain.

Klein and colleagues (2012) reported that 50% of their patients with antibodies to voltage gated potassium channels (VGKC) had pain not attributable to other causes. In 72% it was accompanied by other neurological manifestations. The symptoms were previously attributed to fibromyalgia in 6% and psychogenic causes in 13%. Evidence of neuronal hyperexcitability including hyperhidrosis, hyperalgesia, or electromyographic excitability was 25 more common in pain patients. Thirteen of 16 patients reported pain relief with immunotherapy.
Lancaster and colleagues (2012) reported on their work with anti-Caspr2 autoantibodies. Caspr2 localizes with VGKC in the central and peripheral nervous system, and is the target of a subset of anti-VGKC complex antibodies which have been associated with acquired peripheral nerve excitability (Isaac syndrome), peripheral neuropathy, or encephalopathy. They showed that surface Caspr2 is only expressed on the surface of axons, and at the juxtanodes of myelinated fibers, which is where the autoantibodies probably exert their effect. This contrast with anti-NMDA receptor antibodies that bind to synapses.

**MONONEUROPATHY AND COMPLEX REGIONAL PAIN SYNDROME (CRPS)**

Oaklander and Ochoa (ANA, 2012b) described 5 patients with pain, hypoesthesia, allodynia and microvascular changes lateral and distal to the knee, that were diagnosed with complex regional pain syndrome type 1 (CRPS-1). All had remote history of knee surgery. Two had routine EMG and nerve conduction studies that were normal. Skin biopsy studies in one of the patients showed reduced epidermal nerve fiber density at the territory of the lateral cutaneous nerve of the calf (LCNC), with re-innervation correlating with resolution of the symptoms. CRPS can occur as a consequence of nerve injury or mononeuropathy that may be detectable by skin biopsy.

R.H. Coletti (AANEM 2012) reported that in patients with chronic sciatica, not associated with disc disease, treatment with chemodenervation, using 0.5% phenoxybenzamine with 2% lidocaine, resolved the sciatica in almost all patients. In patients with disc disease, the treatment often improved but not resolve the symptoms.

Kharkar and colleagues (2012) reviewed the results of skin biopsy studies in 43 patients with complex regional pain syndrome type I (CRPS-I). They found that 20% of their patients had evidence for denervation as detected by a reduction in the epidermal or sweat gland nerve fiber densities. They note that there is increasing evidence for involvement of small nerve fibers in CRPS-I, but that structural alterations may not be detectible in many patients as the changes may be functional, too mild to be detected by conventional measures, or occur at more proximal sites.

**NEUROPATHY AND METABOLIC SYNDROME**

Zhou and colleagues (2012) reviewed the charts of 194 subjects that had skin biopsies. Of these, 151 had mild, moderate, or severe length dependent small fiber neuropathy with no large fiber involvement, and 43 had normal skin biopsies. The prevalence of metabolic syndrome was higher in the neuropathy group (27.8%) than in the normal biopsy group (2.3%, p< 0.001), and was higher in the severe (38.1%) than in the moderate (26.0%) or mild (14.7%) neuropathy groups (p=0.04). They found that metabolic syndrome, age, hypertension, and obesity were independent risk factors for sensory small fiber neuropathy.

Singleton and colleagues (2012) reported on their studies in patients with metabolic syndrome. They measured the intraepidermal nerve fiber (IENF) density in skin punch biopsies to quantify nerve regeneration following axotomy with capsaicin. They found that patients with metabolic syndrome, with pre-diabetes or diabetes, had reduced regenerative capacity, but that following dietary counseling and exercise, nerve regeneration improved in parallel to improvement in basal metabolic index (BMI) and serum triglycerides.

**MYELINATED NERVE FIBERS IN NEUROPATHY SKIN BIOPSIES**

Doppler and Colleagues (2012) evaluated morphological abnormalities of myelinated fibers in skin biopsies from the proximal leg of patients with neuropathy. Dermal myelinated fibers and the number of nerve bundles with myelinated fibers was reduced in patients with polyneuropathy. Elongated nodes of Ranvier were detectable in demyelinating neuropathies only. The findings suggest that evaluation of the number and morphology of myelinated fibers in skin biopsies can confirm the diagnosis of neuropathy, help to distinguish between demyelinating and axonal neuropathy, and differentiate purely small fiber neuropathy from more generalized polyneuropathy.
SMALL FIBER NEUROPATHY – GENETICS

Hoeijmakers and colleagues (2012) reviewed their findings in patients with SCN9A-gene variants and small fiber neuropathy. They showed that the variants produced gain of function changes in sodium channel Na(V)1.7, which is preferentially expressed in small diameter peripheral axons, rendering the dorsal root ganglion neurons hyperexcitable. These channels could be targets for new therapies.

SMALL FIBER NEUROPATHY - DIAGNOSIS

Saperstein et al (2012) reported on their studies of the usefulness of skin biopsy in suspected small fiber neuropathy (SFN). Skin biopsy was abnormal in at least one site in 59% of patients. Patients with confirmed SFN were significantly more likely to have pain and were more than twice as likely to respond to standard neuropathic pain medications.

Kahn and Zou (2012) compared 63 patients with non-length dependent small fiber sensory neuropathy (SFSN) to 175 patients with length dependent SFSN. They found that non-length dependent SFSN was more common in women, presents at a younger age, and is more likely to be associated with immune mediated conditions than length dependent SFSN. Disease associations were identified in 26 or 63 (41.3%) patients with NLD-SFSN including diabetes or prediabetes in 10 (15.9%), connective tissue diseases in 6 (9.5%), thyroid dysfunction in 4 (6.3%), sarcoidosis in 3 (4.8%), vitamin B12 deficiency in 2 (3.2%), and paraproteinemia in 1 (1.6%).

Uncini and Yuki (2012) noted that Guillain-Barre syndrome can occur as an acute, monophasic, pure sensory polyneuropathy, that is characterized clinically by exclusive sensory symptoms and signs, that reach their nadir in a maximum of 6 weeks, without other causes for neuropathy. Based on their review of the literature and their own cases, they propose the following 3 main subtypes: acute sensory demyelinating polyneuropathy, acute sensory large fiber axonopathy-ganglionopathy, and acute sensory small fiber neuropathy-ganglionopathy.

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