Small-fiber Polyneuropathy
小纤维多发神经病

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http://NeuropathyCommons.org

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Symptoms and treatments 症状和治疗
Diagnostic tests for SFPN SFPN的诊断
Discovery that SFPN affects the young
发现SFPN影响年轻人
SFPN underlies some fibromyalgia cases
某些纤维肌痛患者
Current research 研究进展

Most "small fiber" diseases are still uncharacterized
多数“小纤维”疾病还没有确定特性

80% of peripheral axons are small-diameter fibers 80%外周神经元是小直径纤维

They innervate and modulate organs and tissues它们激活和调节器官和组织

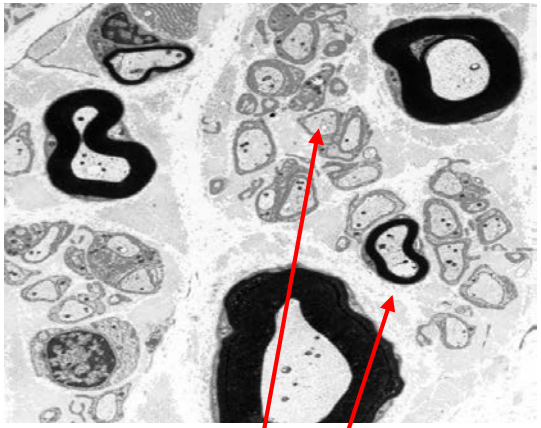
- skin, blood vessels, sweat glands, gut, bone, heart 皮肤、血管、汗腺、肠道、骨骼、心脏

They have multiple functions它们有多重功能

- Mediate sensations of pain and itch 调节痛感和痒感
- Mediate autonomic functions 调节自主神经功能
- Mediate responses to injury and illness 调节对损伤和疾病的反应
- Maintain tissue and body homeostasis 调节组织和身体协调

SFPN symptoms affect many organs and tissues SFPN症状影响许多器官和组织

- Patients see a different specialist for each symptom 患者会为每一种症状寻求不同专科医生诊治
- Underlying neuropathy remains unrecognized 还没有认识其神经病理



“小纤维是最常见的外周神经元类型“Small-fibers” are the most common type of PNS axon

- C-fibers C-纤维
- A-delta fibers A-delta纤维
- autonomic axons自主神经元

SFPN causes chronic widespread pain
SFPN引起慢性广泛疼痛

Small fibers mediate nociception, so widespread chronic pain is a common SFPN symptom

小纤维调节痛感，广泛慢性疼痛是一个常见症状

Length-dependent SFPN starts distally, spreads proximally

长度依赖性SFPN由远端开始，传播到近端

Distal axons are targeted 作用于外周轴突

S. W. Mitchell. On a rare vaso-motor neurosis of the extremities, and on the maladies with which it may be confounded. *Am J Med Sci*, 1878.

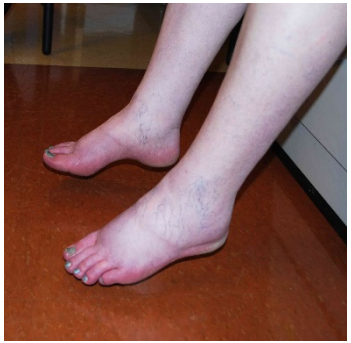
Non-length dependent SFPN starts patchy or proximally

非长度依赖性SFPN开始于小区域或近端

Neuronal cell bodies in trigeminal or spinal ganglia are targeted 作用于三叉神经节或脊神经节

"Erythromelalgia" phenotype

"红斑性肢痛"表现



A woman with red, burning feet and hands due to SFPN

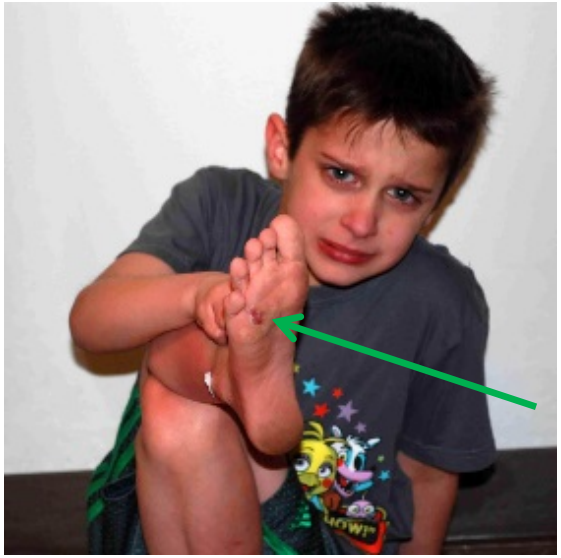
一位妇女由于SFPN导致的手脚发红、烧痛

This woman must carry a fan to cool her painful face. Her diagnosis is trigeminal ganglionitis from Sjögren's. Immunosuppression was effective.

该妇女必须携带风扇为疼痛的脸部降温。诊断是干燥综合征所致三叉神经痛，免疫抑制剂有效。

Reproduced from Oaklander AL, Immunotherapy prospects for painful small-fiber sensory neuropathies and ganglionopathies, *Neurotherapeutics*, 2015

Gene variants in voltage-gated sodium channels (Na_v) cause pain disorders
钠离子通道(Na_v)基因变异导致疼痛障碍



June 1 2016 WCVB evening news clip about Sebastian and his SFPN
2016年6月1日WCVB晚间新闻报道 Sebastian和他所患的SFPN
http://www.wcvb.com/health/doctors-finally-able-to-help-boy-suffering-with-chronic-pain-for-years/39849148

A boy with painful burning feet, itchy legs and painless foot ulcers. 男孩脚烧痛、腿痒、无痛性溃疡

Mother has same symptoms since age 7, 3-year old brother has foot pain. 母亲从7岁有同样症状、3岁弟弟有脚痛。

Mom's skin biopsy showed loss of skin innervation.母亲皮肤活检显示皮肤神经缺失

Mom's Na_v sequencing showed pathogenic G856D variant in Na_v 1.7 gene that encodes SCN9A.母亲钠序列显示编码SCN9A的Na_v 1.7基因有病理性G856D变异
Hoeijmakers et al., 2012; Houlden et al., 2012; Brouwer et al., 2014

His pain did not respond to other pain medications but mexiletine is very effective只有美西律有效，其他疼痛药物无效

SFPN SYMPTOM: Cardiovascular
SFPN症状：心血管系统

- Tachycardia is common, caused by loss of small-fiber innervation of the heart and hypotension 心动过速
- More than 50% of POTS (postural orthostasis tachycardia syndrome) is caused by SFPN 体位性心动过速综合征
  - Thieben, P. et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. *Mayo Clin.Proc. 82 (3):308-313, 2007.*
- Microvessels lose innervation and responsiveness微血管神经缺失
- Neurogenic cardiovasculopathy impairs circulation 循环损害
  - Effects on **muscles**: fatigue, exercise intolerance, shortness of breath,
  - Effects on **nerves**: dying back, impaired regeneration
  - Effects on **GI tract**: poor digestion, impaired nutrition

TABLE 2

The Grading of Orthostatic Intolerance

Grade
Normal orthostatic tolerance
Grade I
1. Orthostatic symptoms are infrequent, or only under conditions of increased orthostatic stress**
2. Able to stand >15 minutes on most occasions
3. The subject typically has unrestricted activities of daily living
Grade II
1. Orthostatic symptoms are frequent, developing at least once a week Orthostatic symptoms commonly develop with orthostatic stress
2. Able to stand >5 minutes on most occasions
3. Some limitation in activities of daily living is typical
Grade III
1. Orthostatic symptoms develop on most occasions, and are regularly unmasked by orthostatic stresses
2. Able to stand >1 minute on most occasions
3. Marked limitation in activities of daily living
Grade IV
1. Orthostatic symptoms are consistently present
2. Able to standing <1 minute on most occasions
3. Patient is seriously incapacitated, being bed- or wheel chair bound because of orthostatic intolerance
Syncope/presyncope is common if patient attempts to stand

Low et al. J Cardiovasc Electrophys 2009

DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

Neuropathic POTS is treatable
神经病理性POTS可治

- Stand up slowly, particularly after meals or toilet use缓慢起立
- Add salt and fluids to raise BP 增加盐和液体摄入提供血压
- Regular exercise adds heart and skeletal muscle, capillaries and mitochondria 规律锻炼增加心肌和骨骼肌、毛细血管和线粒体
- Elevate head of bed with bricks提高床头
- Compression stockings, abdominal binders弹力袜、腹带
- Improve tissue oxygenation (no smoking, treat atherosclerosis) 提供组织氧含量
- Avoid hypoxia (flying, high altitude)避免缺氧（飞行、高地区）
- Medications include midodrine, fludrocortisone 药物
- Rarely, consider continuous IV saline hydration 极少情况考虑持续静脉输盐水

Top panels – normal control muscle

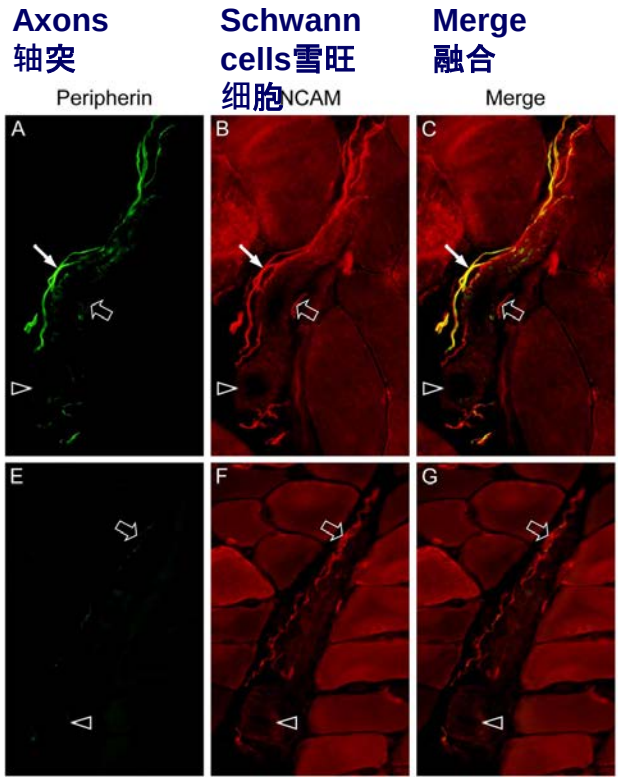
Bottom panels – muscle from SFPN patient

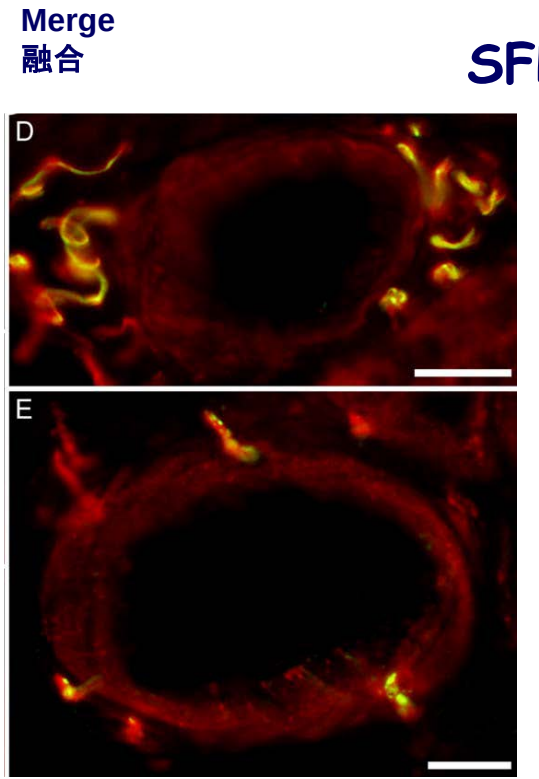
上：正常控制肌肉

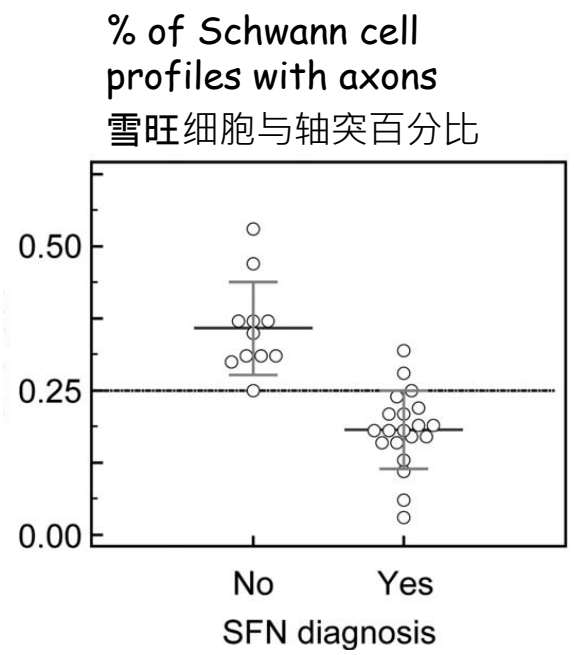
下：SFPN患者肌肉

SFPN causes denervation of blood vessels in muscles (exercise intolerance)

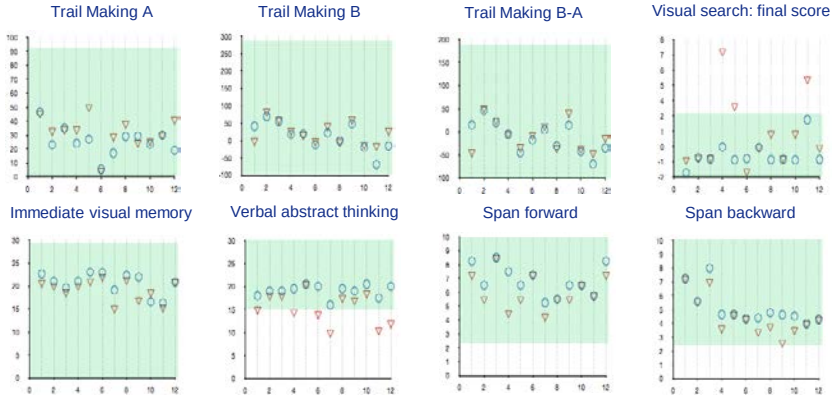
SFPN引起肌肉中血管神经缺失







from: Dori, Lopate, Keeling, Pestronk. Myovascular innervation: axon loss in small-fiber neuropathies. *Muscle Nerve, 2015*



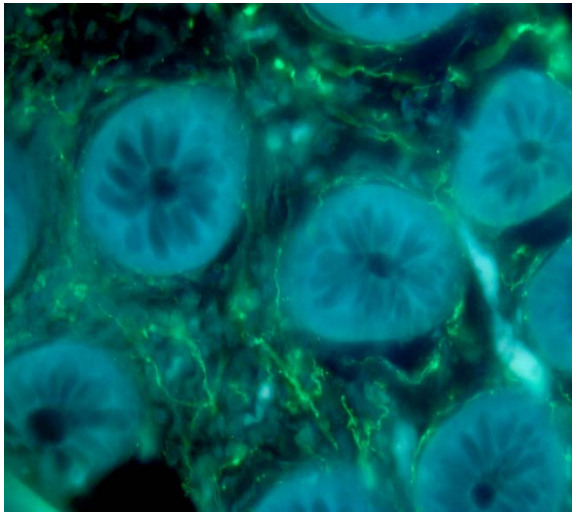
Standing worsens cognitive functions in patients with neurogenic orthostatic hypotension.
Poda et al., Neurological Sciences, 2012

SFPN affects the brain
(who knew?)
SFPN对脑的影响

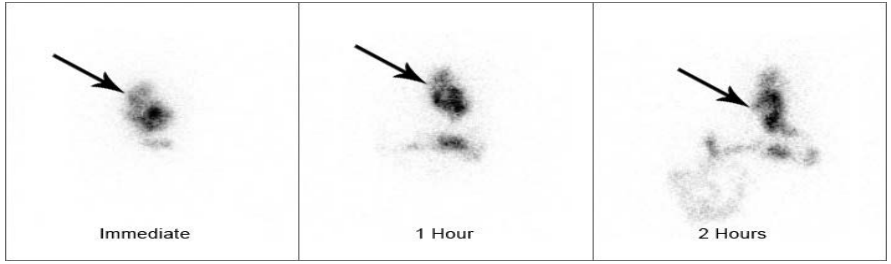
Neurogenic orthostatic hypotension (POTS) can cause temporary impairment of损害

- **immediate memory短时记忆**
- **working memory工作记忆**
- **sustained attention持续注意力**
- **visual search视觉**
- **abstract thinking抽象思维**

- Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans. Henrich et al. *Brain*, 2015
- Imaging signatures of altered brain responses in small-fiber neuropathy: reduced functional connectivity of the limbic system after peripheral nerve degeneration. Hsieh et al. *PAIN*, 2015
- Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome. Ocon et al. *Clin Sci (Lond)*, 2012



SFPN affects the GI tract
SFPN对消化道影响



Upper GI symptoms of SFPN:

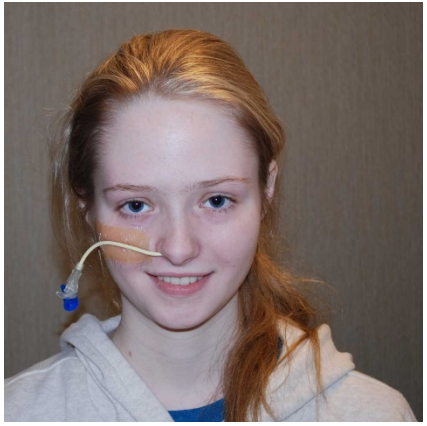
Nausea and vomiting after meals, reflux, esophageal erosions and strictures

上消化道:恶心、呕吐、反流、食道侵蚀与狭窄

Lower GI symptoms of SFPN:

Constipation, diarrhea, or both (irritable bowel)

下消化道:便秘、腹泻或肠易激



Tests for gastrointestinal symptoms of SFPN:

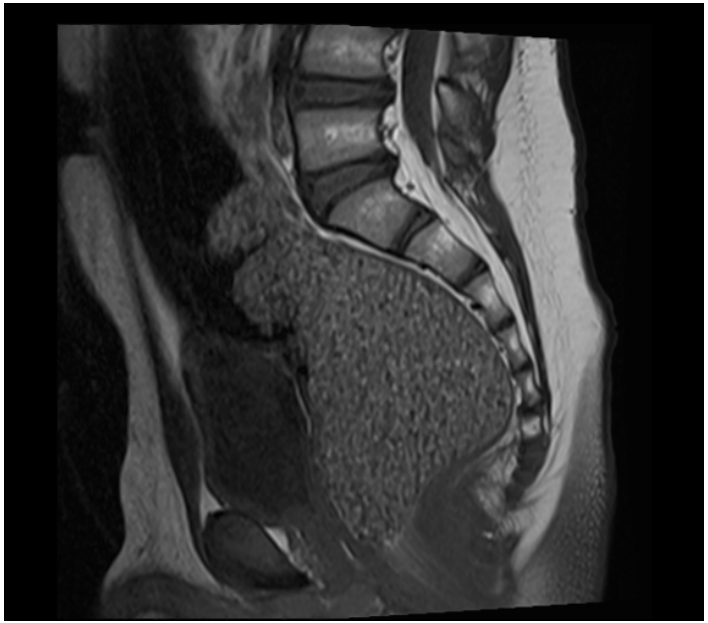
- Gastric-emptying scintigraphy (above) shows slow emptying of stomach (arrows)
- Sitz marker study to measure colon transit time

GI symptoms of SFPN can be treated:

Nausea, vomiting, anorexia, constipation, diarrhea

消化道症状可治

- High-fiber diet, small meals, elevate head-of-bed, don't lie down after meals 高纤维饮食、少餐、抬高床头、餐后勿躺下
- Over-the-counter and prescription nausea treatments can help 治疗恶心非处方或处方药物有帮助
- Alternative nausea treatments include marijuana, ginger 替代恶心治疗包括大麻、生姜
- Severe constipation may require disimpaction 严重便秘可采用去阻塞法
- Obstipation may require cecostomy catheter to flush colon from externally 严重便秘需要造口外部冲洗结肠



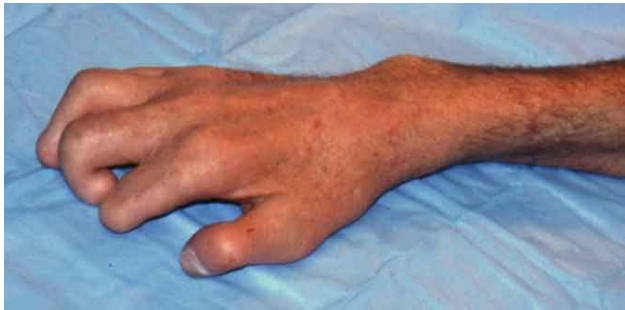
Spine MRI in boy with early-onset SFPN

SFPN affects the bones and joints
SFPN对骨和关节影像

- **Periosteum, cortical, trabecular bone and marrow are densely innervated by small-fibers**
  - *Offley et al. Capsaicin-sensitive sensory neurons contribute to the maintenance of trabecular bone integrity. J Bone Miner Res, 2005*
- **Nerve injuries are the major cause of fracture non-union in well-set fractures**
  - *Santavirta et al. Immunologic studies of non-united fractures. Acta Orthop Scand, 1992*
- **Innervation of bone marrow may influence immune system (not studied)**
- **SFPN contributes to distal osteopenia, Charcot joints, osteomyelitis, pathological fractures**
- **Patients with severe SFPN can have osteoporosis, bone deformities, pathological fractures, bone pain or painless fractures**

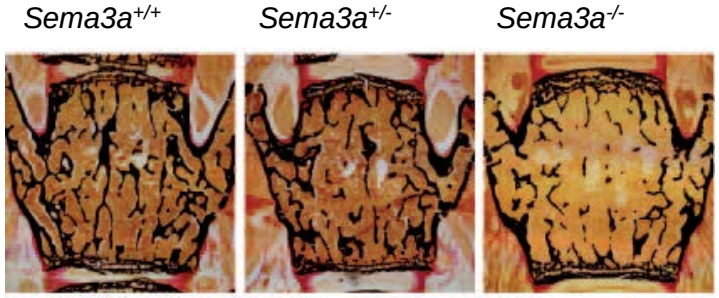
Spontaneous resorption of the fingers in HSAN-1

V. Fridman, A. L. Oaklander, W. S. David, E. A. Johnson, J. Pan, P. Novak, R. H. Brown, and F. S. Eichler. Natural history and biomarkers in Hereditary Sensory Neuropathy Type 1. Muscle Nerve 51:489-495, 2015.



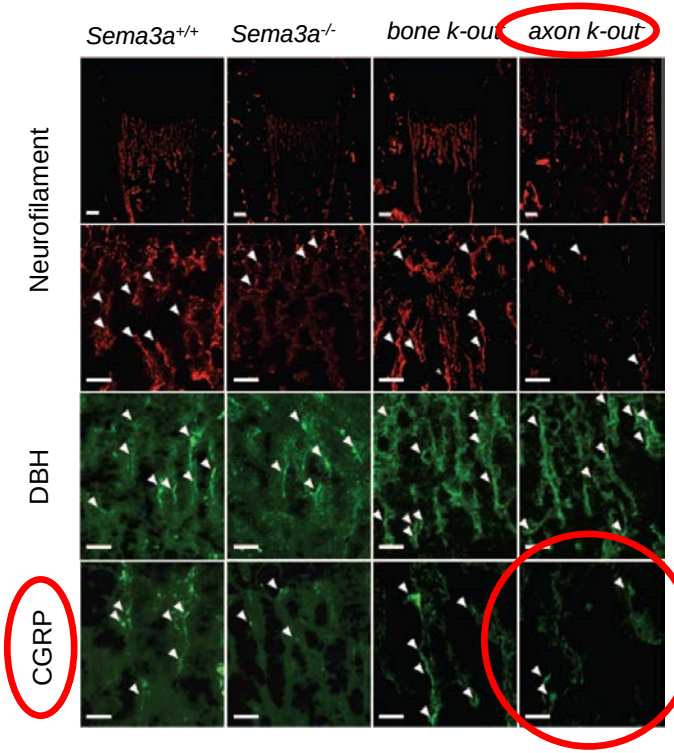
Semaphorin 3a in "somatic" small-fibers mediates bone density
"体"小纤维中Semaphorin 3a调节骨密度

- Sema3a is expressed in axons and bone
- Osteoblast knock-out of Sema3a in does not reduce bone mass
- Neuronal knock-out of Sema3a ($Sema3a_{synapsin}^{-/-}$ or $Sema3a_{nestin}^{-/-}$) causes severe total-body low bone mass.
- Knock-out Sema3a reduces density of CGRP+ and TRPV1+, but not DBH+ bone innervation, implicating somatic and not sympathetic axons



Histological analysis of bone mass in 3 month-old mice

Fukuda,T. et al. Sema3A regulates bone-mass accrual through sensory innervations. Nature, 2013



Tibial bone immunolabeled for neuronal markers

Survey of SFPN patient-reported symptoms shows more symptoms than we knew

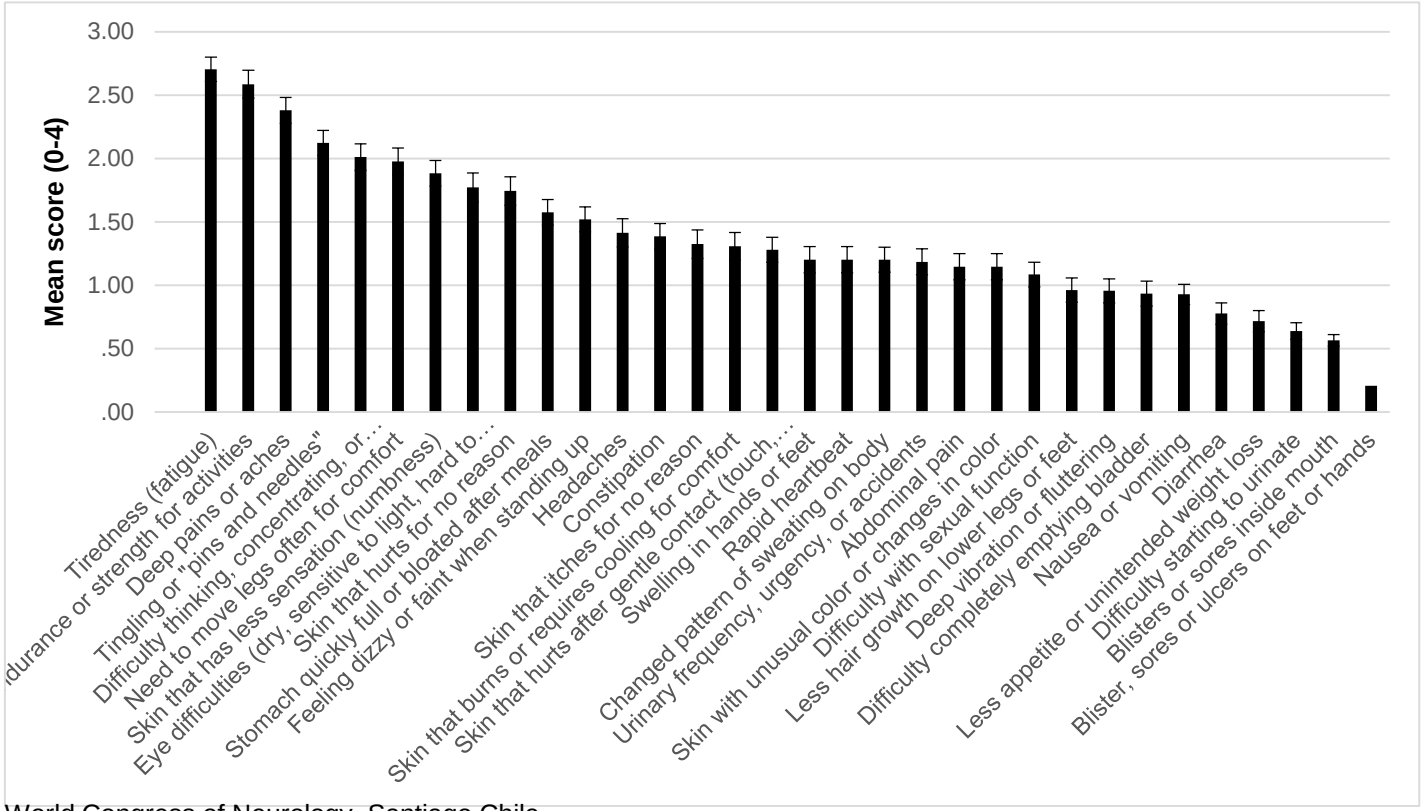
对患者调查显示SFPN症状超过我们已知的数量

SFPN symptom survey developed at MGH, currently being validated

Study subjects:
"gold-standard" patients with objective confirmation of SFPN by biopsy or autonomic function testing

179 patients participated among 470 contacted

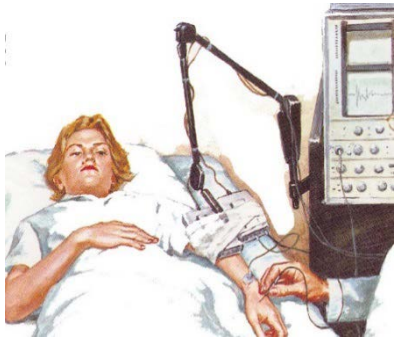
73.2% female
92.2% were Caucasian
46.6 ± 15.6 y mean age



Treister et al., presented at the 2015 World Congress of Neurology, Santiago Chile


Symptoms, mechanisms, treatments
Objective diagnostic testing客观诊断性检查
Discovery that SFPN affects the young
SFPN underlies some fibromyalgia cases
Current research

Objective confirmation of SFPN is difficult
客观确诊SFPN是困难的



Neuro exam has low sensitivity神经检查低敏感性

- No muscle weakness, atrophy, fasciculations
- Reflexes typically preserved
- Large-fiber sensations (vibration, joint position, touch) typically OK
- Small-fiber functions (pin, thermal, sweating) not entirely lost at onset

EMG/NCS does not detect SFPN肌电图无法探测SFPN

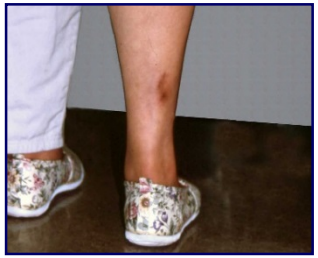
Electromyography only studies motor axons and muscle

Surface nerve conduction studies only large myelinated sensory and motor axons

Quantitative sensory testing (QST)量化感觉检测(QST)

NOT an objective test; relies on patient report of perception

R. Freeman, et al. Quantitative sensory testing cannot differentiate simulated sensory loss from sensory neuropathy. *Neurology, 2003.*



外科神经活检Surgical nerve biopsy

Used to be the "gold standard"

Still useful in rare selected patients

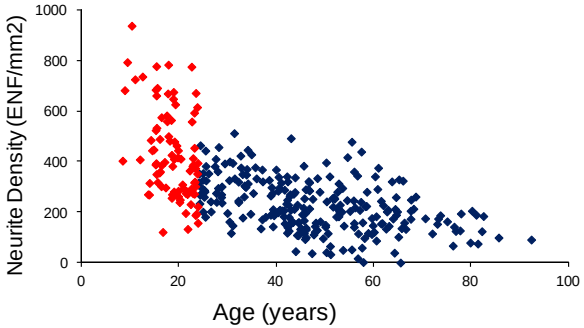
BUT, invasive, expensive, not widely available, leaves numb and sometimes painful area

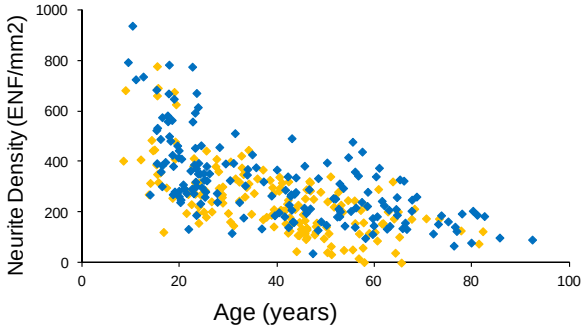
Can't be repeated to monitor disease progression or response to treatment

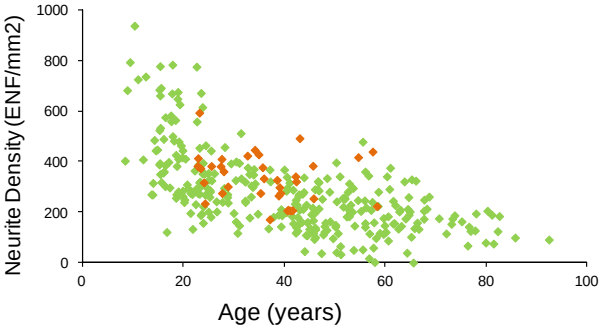
Best test for SFPN: Distal-leg skin biopsy
对SFPN最好的检测方法：远端腿部皮肤活检

- 2-3 mm diameter skin punches removed from lower leg using local anesthesia
- Biopsies can be performed locally, put in Zamboni fixative, mailed to pathology lab
- Skin biopsies are immunolabeled against PGP9.5, a pan-axonal marker, to allow causing of epidermal nerve fibers (ENF) using light microscopy
- **Virtually all epidermal nerve fibers are small fibers**实际上，所有表皮神经纤维都是小纤维。
  - Simone, *et al. J Neurosci* 18 (21):8947-8959, 1998
- Biopsies can be removed in distant medical offices and mailed to a lab for analysis
- Endorsed by American Academy of Neurology and European Federation of Neurological Societies for SFPN diagnosis
  - England, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the AAN, AANEM, and AAPMR. Neurology, 2008
  - Lauria, et al. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol. 12 (10):747-758, 2005.
- **SFPN is diagnosed if patient's ENF density is ≤ 5th centile of predicted**
- **如果患者ENF密度≤预测的5%，可以诊断SFPN。**
  - Predicted value is calculated from biopsying many normal volunteers (population sample)
  - Accurate diagnosis of SFPN depends on having accurate norms

MGH has skin biopsy norms from 392 screened normal volunteers as young as age 7
MGH有从最小7岁的392例患者皮肤活检标准







There are age effects

People under age 24 y (red; n = 102) have more ENF than older subjects (blue; n = 285)

421 vs. 226 ENF/mm^2; p<0.001

There are sex effects

Females (blue; n=196) have more ENF than males (yellow; n=196)

309 vs. 247 ENF/mm2; p<0.001

There are race effects

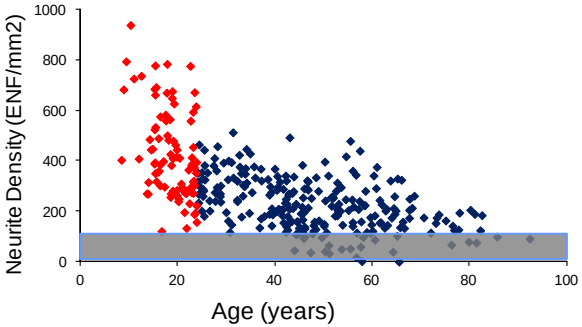
Asians (orange; n=36) have more ENF than age-matched non-Asians (green; n=189)

330 vs. 239/mm^2; p<0.001

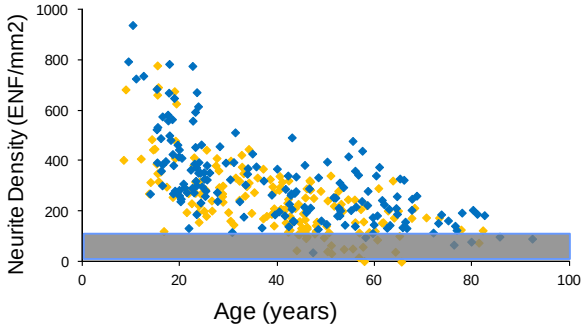
Klein, Downs, Oaklander
Presented at 45th annual meeting of Society for Neuroscience
Chicago IL, October 21 2015.

MGH's multivariate regression normative model improves accuracy of skin-biopsy diagnosis

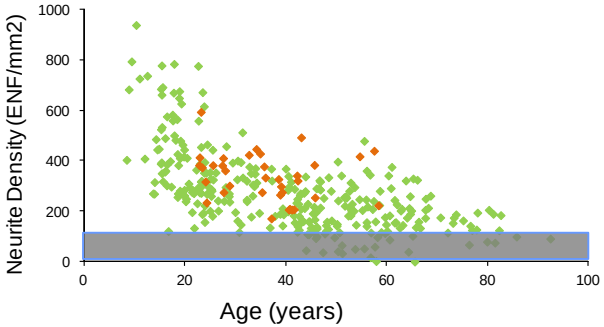
MGH多变量正态回归模型促进皮肤活检诊断的准确性



There are age differences



There are sex differences



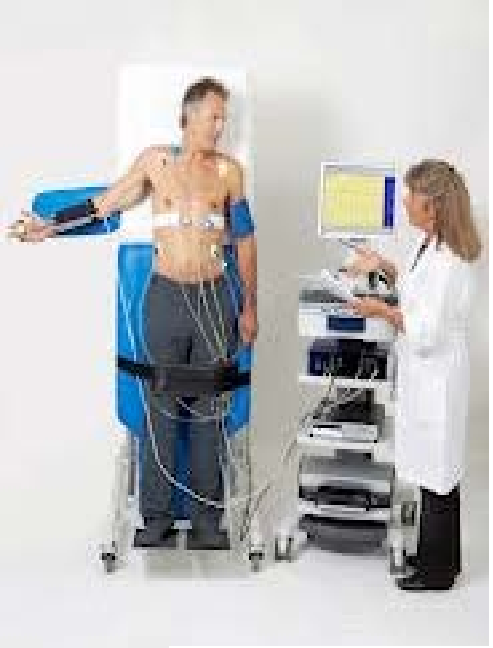
There are ethnic differences

Most diagnostic laboratories use a single threshold "cutoff" (76 ENF/mm^2) to assess normality of submitted biopsies.

We developed a multivariate regression to calculate an age-, sex-, race-specific predicted norms for each individual biopsy.

Among all 105 biopsies from patients under 40 that MGH diagnosed with SFPN in 2012-2013, applying the single threshold "cutoff" (76 ENF/mm^2) would only detect SFPN in 26 (*75% false negative diagnosis*).

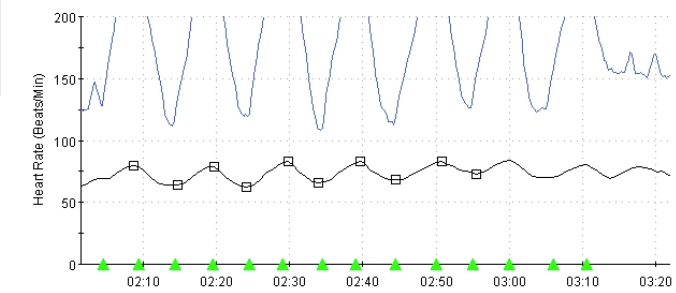
Composite autonomic function testing (AFT) also endorsed for SFPN diagnosis and done at MGH
复合自主功能检测(AFT)



Autonomic functions controlled by small fibers 小纤维控制的自主功能

1. Heart-rate response to deep breathing
2. Heart-rate and blood-pressure responses during Valsalva maneuver
3. Heart-rate and blood-pressure responses to tilt
4. Sudomotor response (sweat production)

AFT is noninvasive and repeatable, but expensive, not widely available, not totally specific for SFPN



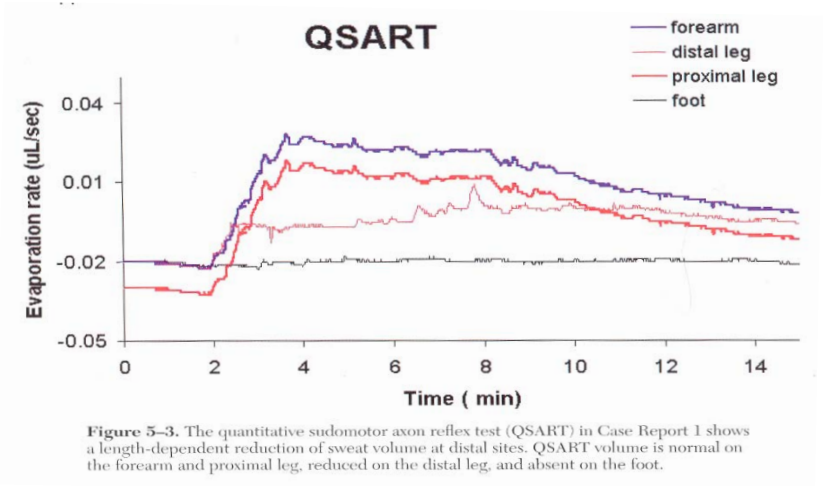


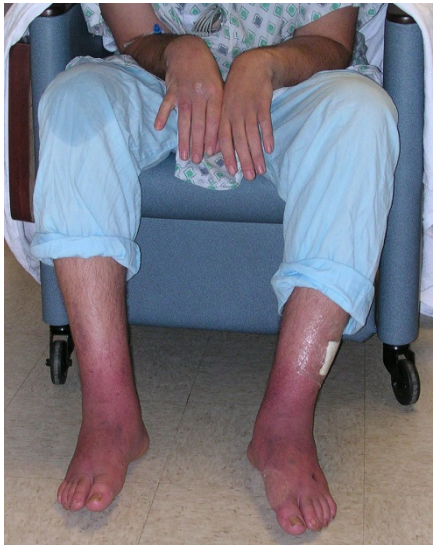
Figure 5–3. The quantitative sudomotor axon reflex test (QSART) in Case Report 1 shows a length-dependent reduction of sweat volume at distal sites. QSART volume is normal on the forearm and proximal leg, reduced on the distal leg, and absent on the foot.

J. D. England, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology* 72, 2009.


Symptoms, mechanisms, treatments
Diagnostic tests
Discovery that SFPN affects the young
发现SFPN影响年轻人
SFPN underlies some fibromyalgia cases
Current research

SFPN was considered very rare in young people until our index patient
一直认为SFPN在年轻人中很稀少

- Few children have the medical problems that cause polyneuropathy很少儿童有引起多发神经病的医学问题
- Very rare mendelian genetic polyneuropathies present in infants/toddlers 婴儿/小儿遗传学多发神经病很稀少
  - Familial dysautonomia/Riley-Day/HSAN III
  - Sodium channel NaV mutations



Paticoff et al. Defining a treatable cause of erythromelalgia: acute adolescent autoimmune small-fiber axonopathy. Anesth Analg, 2007

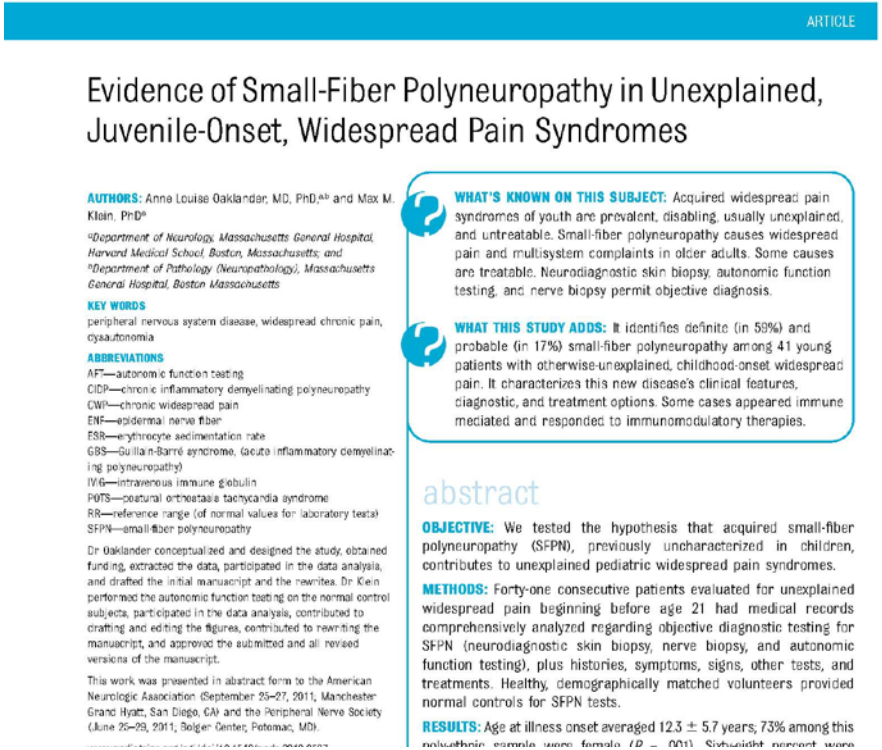
A healthy college student developed sudden burning pain in his hands and feet, tachycardia, nausea.

Skin biopsy showed SFPN, blood testing did not identify a cause.

Corticosteroid treatment gave rapid pain relief and eventual cure.

No recurrences in a decade off all pain medications

We analyzed records of 41 consecutive patients with chronic widespread pain that began before age 21
连续分析了41例21岁前发生慢性广泛性疼痛的病历



ARTICLE

Evidence of Small-Fiber Polyneuropathy in Unexplained, Juvenile-Onset, Widespread Pain Syndromes

AUTHORS: Anne Louise Oaklander, MD, PhD,[a,b] and Max M. Klein, PhD[a]

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KEY WORDS
peripheral nervous system disease, widespread chronic pain, dysautonomia

ABBREVIATIONS
AFT—autonomic function testing
CIDP—chronic inflammatory demyelinating polyneuropathy
CWP—chronic widespread pain
ENF—epidermal nerve fiber
ESR—erythrocyte sedimentation rate
GBS—Guillain-Barré syndrome, (acute inflammatory demyelinating polyneuropathy)
IVIG—intravenous immune globulin
POTS—postural orthostatic tachycardia syndrome
RR—reference range (of normal values for laboratory tests)
SFPN—small-fiber polyneuropathy

Dr Oaklander conceptualized and designed the study, obtained funding, extracted the data, participated in the data analysis, and drafted the initial manuscript and the rewritea. Dr Klein performed the autonomic function testing on the normal control subjects, participated in the data analysis, contributed to drafting and editing the figures, contributed to rewriting the manuscript, and approved the submitted and all revised versions of the manuscript.

This work was presented in abstract form to the American Neurologic Association (September 25–27, 2011, Manchester Grand Hyatt, San Diego, CA) and the Peripheral Nerve Society (June 25–29, 2011, Bolger Center, Potomac, MD).

WHAT'S KNOWN ON THIS SUBJECT: Acquired widespread pain syndromes of youth are prevalent, disabling, usually unexplained, and untreatable. Small-fiber polyneuropathy causes widespread pain and multisystem complaints in older adults. Some causes are treatable. Neurodiagnostic skin biopsy, autonomic function testing, and nerve biopsy permit objective diagnosis.

WHAT THIS STUDY ADDS: It identifies definite (in 59%) and probable (in 17%) small-fiber polyneuropathy among 41 young patients with otherwise-unexplained, childhood-onset widespread pain. It characterizes this new disease's clinical features, diagnostic, and treatment options. Some cases appeared immune mediated and responded to immunomodulatory therapies.

abstract

OBJECTIVE: We tested the hypothesis that acquired small-fiber polyneuropathy (SFPN), previously uncharacterized in children, contributes to unexplained pediatric widespread pain syndromes.

METHODS: Forty-one consecutive patients evaluated for unexplained widespread pain beginning before age 21 had medical records comprehensively analyzed regarding objective diagnostic testing for SFPN (neurodiagnostic skin biopsy, nerve biopsy, and autonomic function testing), plus histories, symptoms, signs, other tests, and treatments. Healthy, demographically matched volunteers provided normal controls for SFPN tests.

RESULTS: Age at illness onset averaged 12.3 ± 5.7 years; 73% among this polysthnic sample were female (P = .001). Sixty-eight percent were

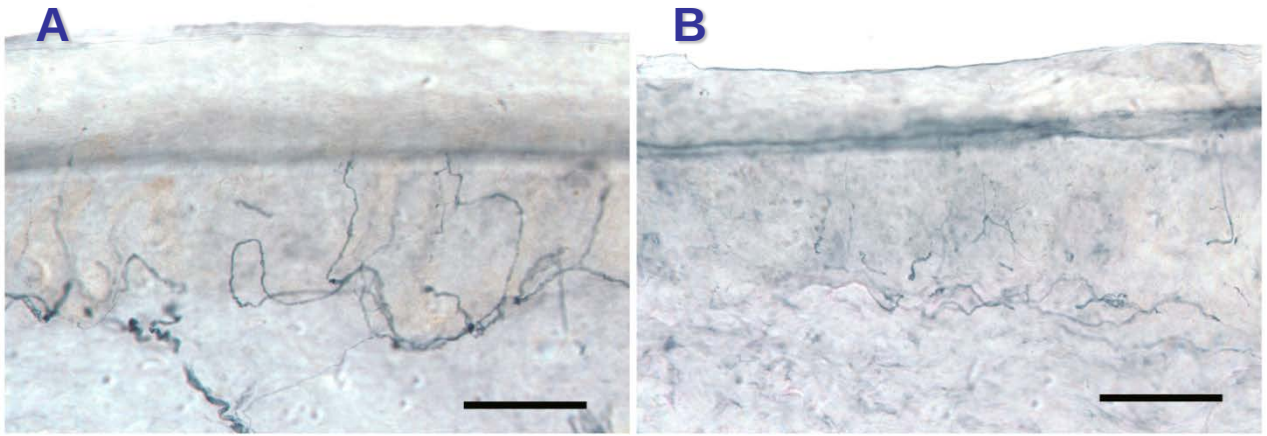
- Many called "juvenile fibromyalgia"被称作"年轻纤维肌痛"
- 73% were female
- 68% were disabled from school or work
- 76% had onset of pain in legs or feet
- 98% had non-pain complaints
  - 90% had cardiovascular symptoms (POTS, sinus tachycardia)
  - 82% had GI complaints (belly pain, nausea, vomiting, constipation, incontinence)
  - 63% had abnormal sweating
  - 34% had urological dysfunction
- 63% had chronic severe headaches

Oaklander & Klein, Pediatrics 2013

Results of objective tests for SFPN结果

59% of patients had objective confirmation of SFPN 59%患者确定SFPN

- 30% (11/37) of skin biopsies were diagnostic for SFPN 30%皮肤活检诊断确定
- 53% (18/34) of Autonomic Function Tests (AFT) were diagnostic for SFPN 53%AFT诊断确定
- 100% (2/2) of nerve/muscle biopsies were diagnostic for SFPN 100%神经/肌肉活检诊断确定



Oaklander & Klein, Pediatrics 2013

Normal 18-year old white male has 675 axons/mm2

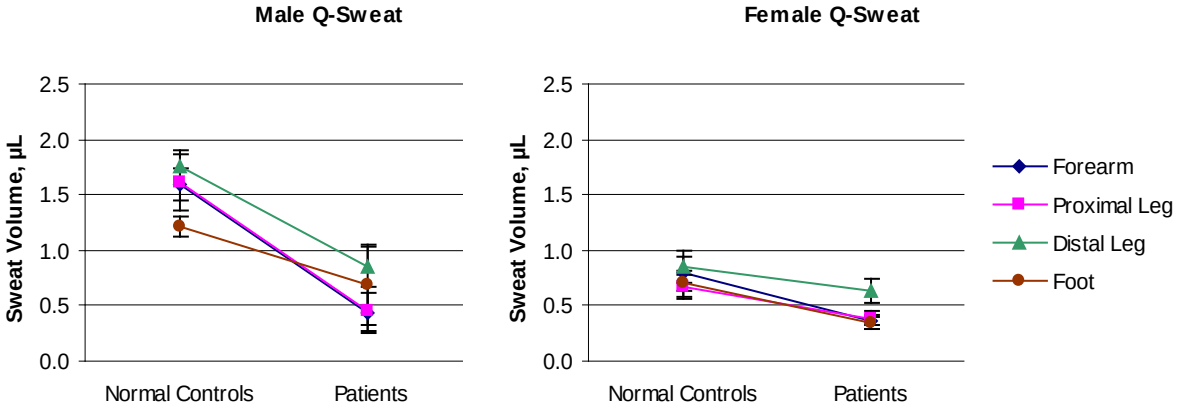
18-year old white male with chronic widespread pain has 155 axons/mm2

Autonomic Function Testing detected SFPN in 53%
AFT可检测53%SFPN

There are no normative data from children, so we recruited and studied demographically matched normal young control subjects

- **27%** of the young patients vs. **3%** of the controls had low heart-rate variability with respiration
- **42%** of the young patients vs. **0%** of the controls had abnormal cardiovascular response to Valsalva
- **75%** of the young patients vs. **18%** of the controls had abnormal heart-rate and/or BP during tilt-table
- **82%** of the young patients vs. **34%** of the controls had reduced sweating, often length-dependent

Oaklander & Klein, Pediatrics 2013



What causes "early-onset SFPN"?
引起SFPN“早期发作”的原因？

0% of patients had family history of neuropathy

0% of patients had history of major psychiatric illness

34% of patients had history of autoimmune illness:

- 6 autoimmune thyroiditis
- 2 systemic (juvenile Sjögren's, juvenile SICCA)
- 2 Henoch-Schönlein purpura
- 1 each brachial plexitis, type-I diabetes, post-viral arthritis, immune thrombocytopenic purpura, Crohn's, and trochleitis, one Hashimoto's encephalopathy

Oaklander & Klein, Pediatrics 2013

Noncontributory laboratory tests in early-onset SFPN

Cerebrospinal fluid tests	All tests were normal in 11 patients
Blood tests:	Complete blood count, electrolytes including glucose, renal, liver, and thyroid function, hemoglobin A1c, lipids, vitamins, immunoglobulins, serum protein immunofixation.
Urine tests:	Heavy metals, protein immunofixation, porphyrins, amino and organic acids.
Infectious tests:	Hepatitis C, syphilis, HIV, deer-associated zoonotic infections including Lyme, babesiosis, and human monocytic ehrlichiosis.
Immune tests:	Rheumatoid factor antibody, Sjögren's autoantibodies, lupus autoantibodies, anti-neutrophil cytoplasmic antibodies, total complement.
Genetic tests	(only occasionally performed): All genetic neuropathy tests including Charcot-Marie-Tooth, Fabry, transthyretin, hereditary neuropathy with liability to pressure palsy, also familial hemiplegic migraine, cystic fibrosis.

Oaklander & Klein, Pediatrics 2013

Blood tests for causes of SFPN: The only consistent abnormalities were immune
SFPN原因血液化验

Elevated ESR (≥ 15 mm/hr)	37%
ANA (≥ 1:80 dilution)	45%
Low complement 3 (< 85 mg/dl)	21%
Low complement 4 (< 20 mg/dl)	46%
One or more of the above abnormalities	**89%**

Oaklander & Klein, Pediatrics 2013

Immunotherapy improved 12/15 (80%)
免疫治疗改善80%病例

- We only treated patients who were not recovering and who met rigorous criteria 仅治疗没有接受过治疗和复合标准的患者
  - Objectively confirmed SFPN (by skin biopsy or autonomic function testing)
  - History and/or lab tests consistent with dysimmune causes
  - Tests for other cause of neuropathy all negative
  - Disabling symptoms that are not improving on their own
- Corticosteroids were effective in 67% (10/15) 可的松有效67%
  - Patients in hospital given IV methylprednisolone 1 g/day x 3-5 days
  - Short-tem prednisone 1 mg/kg/day x 4 weeks only followed by 4 week taper
- Immunoglobulin (IVIG) was effective in 63% (5/8) 免疫球蛋白有效63%

Oaklander & Klein, Pediatrics 2013

Immunotherapy produced objective recovery during immunomodulation – AFT
免疫治疗可改善客观检查的各项指标

- All repeat AFT (6/6) documented improvement after immunomodulation
- 2/2 repeat AFT in non-immunomodulated patients showed no improvement
- Two patients had AFT 3 times; both had progressive improvement of tilt-table and sweating responses and heart-rate variability (13.6 → 14.0 → 19.1 beats/min; 4.0 → 9.2 → 14.7 beats/min). A low Valsalva ratio normalized (1.42 → 1.76 → 2.27)
- A patient treated with corticosteroids then IVIG during 10 months had normalization of heart-rate variability (13.6, 14.3, 19.1 beats/min), Valsalva ratio (1.42, 1.76, 2.27), and responses to tilt.

Oaklander & Klein, Pediatrics 2013

Some older adults with many years of unexplained chronic pain appear to have early-onset SFPN
某些患有多年无法解释的慢性疼痛成年人有SFPN早期发作

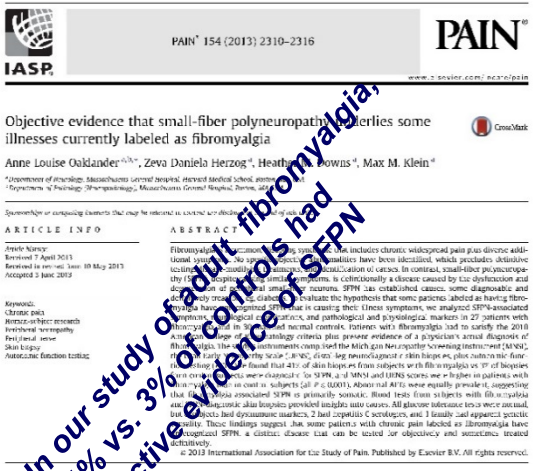
- Some cases develop in older adults during their 30's and 40's.
  - Dabby, Acute steroid responsive small-fiber sensory neuropathy: a new entity? *J PNS*, 2006
- Some cases develop in youth but persist undiagnosed for decades
  - DoD grant GW140169 funds us to develop ways to diagnose SFPN present for 25 years
- Preliminary evidence from clinic suggests that some patients still respond to immunotherapy even decades after onset of SFPN


Symptoms, mechanisms, treatments
Diagnostic tests
Discovery that SFPN affects the young
SFPN underlies some fibromyalgia cases
某些纤维肌痛患者是SFPN
Current research

Fibromyalgia affects 1-5% of population; 75% are female

We prospectively tested the hypothesis that SFPN underlies some cases of fibromyalgia

- We measured the prevalence of SFPN in adults with fibromyalgia
- Inclusion required meeting American College of Rheumatology 2010 diagnostic criteria for FMS plus physician's notes documenting fibromyalgia diagnosis
- Informed by power analysis, we studied 27 fibromyalgia patients, 30 matched controls
- Outcomes:
  - **Symptoms** were measured by Michigan Neuropathy Screening Instrument (MNSI)
  - **Signs** were measured by the Utah Early Neuropathy Scale (UENS)
  - **Pathology** was measured by PGP9.5-immunolabeled distal-leg skin biopsy
  - **Pathophysiology** was measured by autonomic function testing (AFT)
- **Results: 41% of fibromyalgia subjects vs. 3% of controls had skin biopsies diagnostic for SFPN; symptoms and signs of SPPN found in fibromyalgia patients but not controls**



PAIN® 154 (2013) 2310–2316

PAIN®

Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia

Anne Louise Oaklander, Zeva Daniela Herzog, Heather L. Downs, Max M. Klein

ARTICLE INFO

ABSTRACT

In our study of adult fibromyalgia, 41% vs. 3% of controls had objective evidence of SFPN

ARTICLE

Evidence of Small-Fiber Polyneuropathy in Unexplained, Juvenile-Onset, Widespread Pain Syndromes

In our study of juvenile fibromyalgia, 59% had objective evidence of SFPN

Every research study found objective evidence of SFPN in fibromyalgia

各项研究发现纤维肌痛是SFPN的证据

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de Tommaso, et al. **Update on laser-evoked potential findings in fibromyalgia patients in light of clinical and skin biopsy features.** J Neurol, 2014.

Kosmidis, et al. **Reduction of intraepidermal nerve fiber density (IENFD) in the skin biopsies of patients with fibromyalgia: A controlled study.** J.Neurol Sci, 2014.

Ramirez, et al. **Small fiber neuropathy in women with fibromyalgia. An in vivo assessment using corneal confocal bio-microscopy.** Sem Arthritis Rheumat, 2015

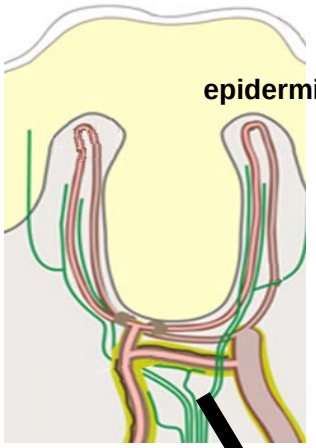
Doppler et al. **Reduced dermal nerve fiber diameter in skin biopsies of patients with fibromyalgia.** Pain, 2015

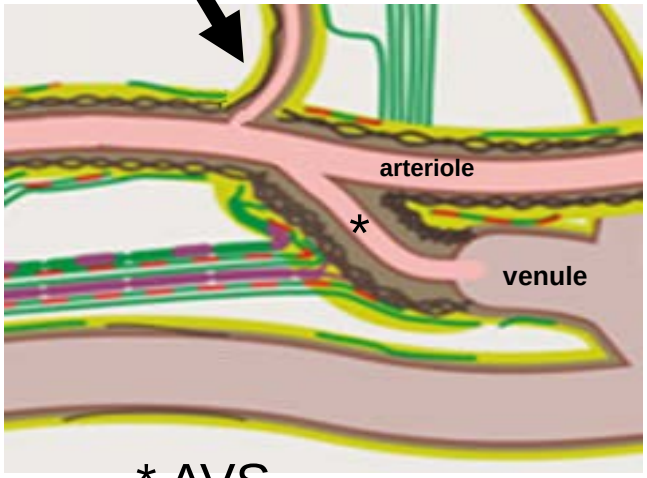
Fibromyalgia patients have myovascular denervation like SFPN patients

同SFPN患者一样，纤维肌痛患者有肌肉血管神经缺失

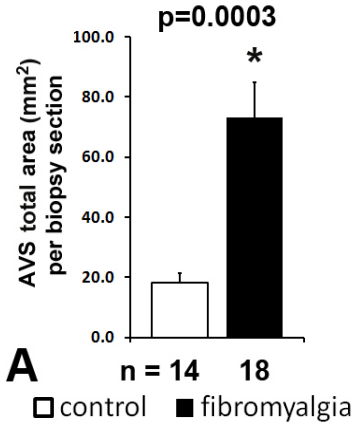
- Albrecht et al., Pain Medicine, 2013

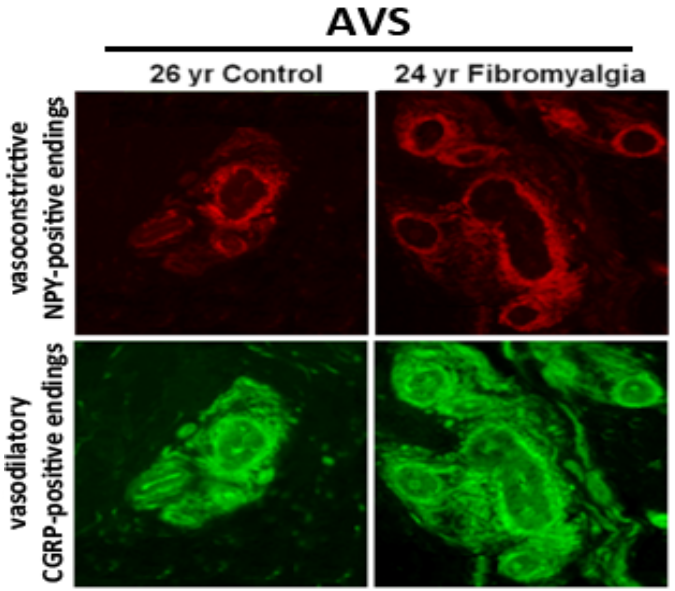
- Arteriovenous shunts (AVS) shift blood away from the muscles to the skin for heat regulation
- Small-fiber innervation of AVS controls if they open or shut
- Dilated AVS in fibromyalgia may contribute to muscle ischemia, aches and exercise intolerance





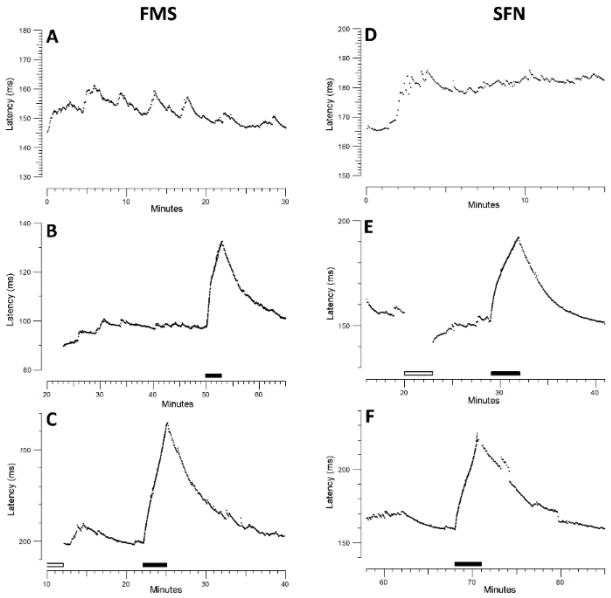
* AVS



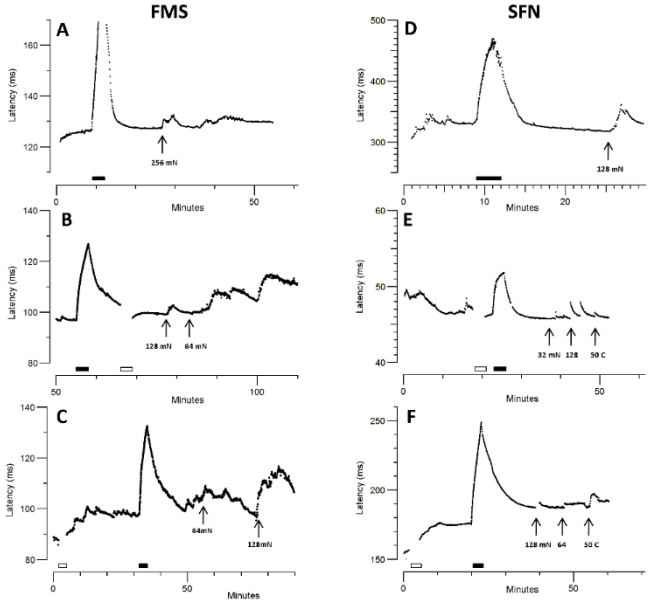


Microneurography showed that C-fibers fire spontaneously and abnormally in fibromyalgia as in SFPN

Spontaneous activity



Peripheral sensitization



Group	n
Fibromyalgia	30
Small fiber neuropathy	17
Normal controls	9

Hyperexcitable C nociceptors in fibromyalgia. Serra, Collado, Solà, Antonelli, Torres, Salgueiro, Quiles, Bostock Annals of Neurology 2014;75:196-208.


Symptoms, mechanisms, treatments
Diagnostic tests
Discovery of early-onset SFPN
Links between SFPN and fibromyalgia
Current Research研究进展

After we diagnose SFPN, we test blood for known causes of neuropathy

Tests for treatable causes of small-fiber polyneuropathy

Patient name
Medical record number
Date of birth

Date: ____/____/____

ordered today	not yet tested	abnormal value	normal value	BLOOD TESTS TO CONSIDER FOR ADULTS
☐	☐	☐	☐	Complete blood count (if low, consider B12 or copper deficiency, lead/arsenic toxicity)
☐	☐	☐	☐	Chemistries (if high glucose test for DM; if renal dysfunction consider Fabry, mercury toxicity)
☐	☐	☐	☐	AST, ALT (liver function; if abnormal consider hepatitis or alcohol)
☐	☐	☐	☐	Hemoglobin A1c (if elevated strongly consider testing for diabetes)
☐	☐	☐	☐	TSH thyroid screening
☐	☐	☐	☐	Vitamin B12 levels (if 200-500pg/dl consider testing for methylmalonic acid)
☐	☐	☐	☐	ESR (sedimentation rate; if elevated, consider inflammatory/dysimmune conditions)
☐	☐	☐	☐	ANA (antinuclear antibodies; higher titers suggest lupus or dysimmune conditions)
☐	☐	☐	☐	Complement components C3 and C4 (if low, consider dysimmune conditions)
☐	☐	☐	☐	Anti-Ro (SS-A) and anti-La (SS-B) (if present, consider Sjögren's disease)
☐	☐	☐	☐	CRP (C-reactive protein; if elevated, consider inflammatory/dysimmune conditions)
☐	☐	☐	☐	Hepatitis C serology (if abnormal consider testing for cryoglobulins)
☐	☐	☐	☐	Lyme antibodies by Western blot (for inhabitant or visitor to endemic area)
☐	☐	☐	☐	SPEP/IFIX (immunofixation tests for lymphoproliferative disorders)
☐	☐	☐	☐	Free κ/λ light chains (tests for less common lymphoproliferative disorders)
☐	☐	☐	☐	IgA anti-TTG (transglutaminase antibodies; if present consider celiac sprue)
				TESTS TO CONSIDER IN SPECIFIC POPULATIONS
☐	☐	☐	☐	2 hour, 75 g fasting glucose-tolerance test (strongly consider for all at risk for DM)
☐	☐	☐	☐	HIV (CDC recommends everyone ages 13-64 be tested ≥ once, high-risk more often)
☐	☐	☐	☐	Methylmalonic acid (consider if vitamin B12 level less than 500 pg/dL)
☐	☐	☐	☐	Thiamine (if low, consider vitamin B1 deficiency)
☐	☐	☐	☐	Pyridoxine (if elevated, consider vitamin B6 neurotoxicity)
☐	☐	☐	☐	Anti-ds DNA, anti-Smith (consider if ANA present)
☐	☐	☐	☐	Cryoglobulins, cryofibrinogens, viscosity (consider for myeloma, hep C, RA, SLE)
☐	☐	☐	☐	Fasting serum triglycerides (can worsen diabetic polyneuropathy)
☐	☐	☐	☐	Urine protein electrophoresis to identify Bence Jones paraproteins
☐	☐	☐	☐	24 hour urine for arsenic, lead, mercury, cadmium (for artists, welders, miners)
☐	☐	☐	☐	ACE (angiotensin converting enzyme; for sarcoidosis in patients with lung symptoms)
☐	☐	☐	☐	Phenotype-guided genetic sequencing esp. if family history (e.g., HSAN-1, SCN9A)
☐	☐	☐	☐	Abdominal fat-pad biopsy for amyloid
☐	☐	☐	☐	OTHER TEST PERFORMED_____

Check medications e.g., therapy for cancer or HIV, statins, colchicine, isoniazid, dapsone, hydralazine, lithium, phenytoin, vitamin B6, disulfiram, amiodarone, procainamide, perhexiline, streptokinase, nitrous oxide, metronidazole, nitrofurantoin, gold, thalidomide, TNF-antagonists, antimicrobials (chloramphenicol, fluoroquinolones, metronidazole, nitrofurantoin), history of GI surgery, malabsorption, alcoholism, exposure to inorganic arsenic, thallium, mercury, industrial toxins, organophosphate insecticides.

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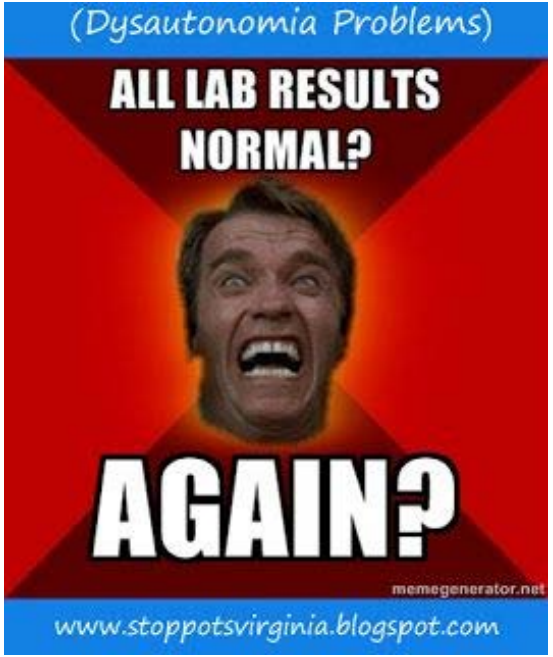
Author: A.L. Oaklander MD PhD 09/30/15

Curing the cause of disease is more effective than just treating its symptoms

治本重于指标



Blood-test list available at NeuropathyCommons.org website

Diagnostic yield of blood tests in "idiopathic" SFPN
对"不明原因"的SFPN的血液化验诊断

An IRB-approved retrospective study of 21 widely available blood tests for causes of SFPN

Inclusion required objective confirmation of SFPN during calendar year 2013

Among 195 qualifying patients, 70% female, 95% Caucasian, mean age 43.0 ± 18.6 y

Blood tests identified potential medical causes in 57% of SFPN patients 血液化验对**57%SFPN**患者可确认潜在病因

Hyperglycemia was not a major cause of idiopathic SFPN in New England 高血糖不是主要病因

- Only 2% had diabetes; below population prevalence
- Only 22% had pre-diabetes; below population prevalence of 37%

42% had at least one marker of dysimmunity 42%有至少一个免疫缺陷标记

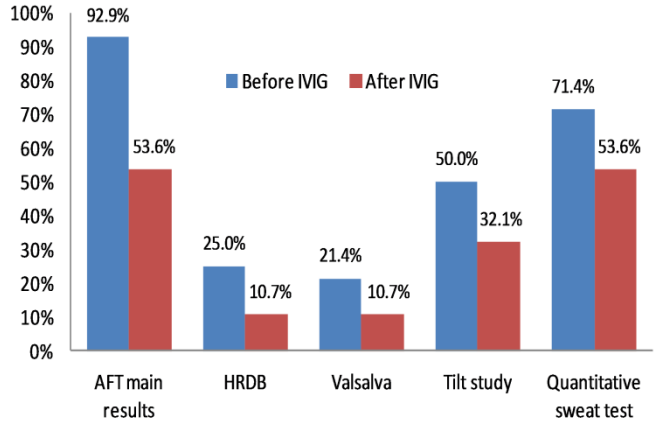
Most common blood test abnormalities were high ESR (28%), ANA ≥ 1:160; (27%), low C4 (16%)

Lang, Treister, Oaklander

Presented to the American Neurological Association, 2015

Retrospective study of IVIg for SFPN
免疫球蛋白治疗SFPN的回顾性研究

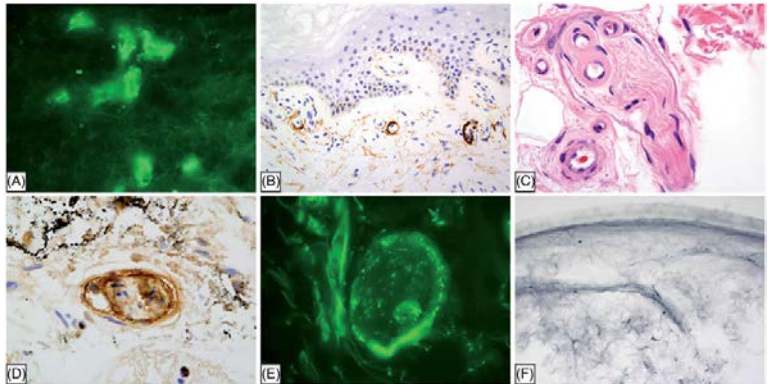
- **Inclusion criteria:**
  - "Gold standard" SFPN confirmed by biopsy or AFT
  - Evidence of immune causality; other causes excluded
  - At least 3 month trial of IVIG at 2 grams/kg/4 weeks
- **55 patients studied:**
  - Mean age 41 years, 78% female
  - IVIg treatment averaged 28 months
- **Primary Symptom Outcome: Pain scores among all patients with baseline pain ≥ 3**
  - Baseline pain of 6.3 ± 1.7 dropped to 5.2 ± 2.1; p = 0.007
- **Primary Function Outcome: AFT among all patients with AFT before and after IVIG**
  - Abnormal AFTs dropped from 88% to 55%; p = 0.001
- **Secondary Outcomes**
  - Good safety profile, no serious AE, 1 moderate AE (hemolytic anemia), standard infusion reactions
  - 74% of patients and 77% of physicians rated SFPN as improved; 15% remission rate

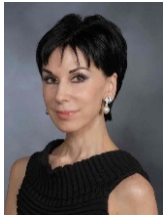


Liu, Treister, O'Neil, Lang, Oaklander, submited for publication

Dermatopathology can identify cellular, molecular mechanisms

皮肤病理学能够确认细胞、分子机制





Liu, Magro, Loewenstein, Makar, Stowell, Dzik, Hochberg, Oaklander, Sobrin.

A man with paraneoplastic retinopathy plus small fiber polyneuropathy associated with Waldenström macroglobulinemia (lymphoplasmacytic lymphoma): Insights into mechanisms. *Ocul.Immunol.Inflamm. 2014*

Pathologic analyses from distal-leg skin biopsies of patient with SFPN

A. Extensive IgM deposits in microvessels

B. Prominent granular labeling of microvessels for C3d

C. Severe hyalinizing vasculopathy of blood vessels supplying nerves

D. Extensive perineurial deposition of IgM

E. Extensive perineurial deposition of C5b-9

F. Preservation of some deep microvascular innervation after PLEX

Our Gulf War Illness research projects

海湾战争疾病研究项目

Gulf War Illness Research Program grant GW093049

Undiagnosed small-fiber polyneuropathy-Is it a component of GWI?

To measure prevalence of SFPN in deployed veterans of first Gulf War (1990 - 1991)

Gulf War Illness Research Program grant GW130109

Characterizing treatable causes of SFPN in Gulf War veterans

To develop a global case definition of SFPN, use it to reassess prevalence of SFPN in deployed veterans of first Gulf War (1990 - 1991), and look for causes

Gulf War Illness Research Program grant GW140169

Diagnosis of late-stage, early-onset SFPN

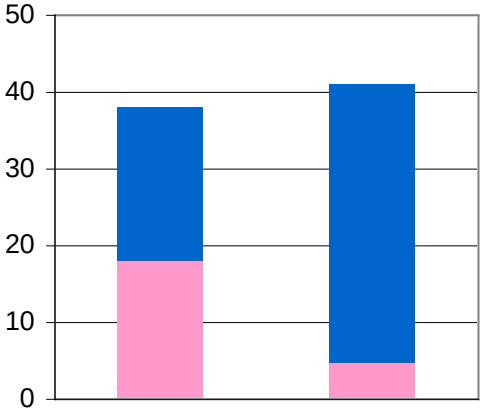
To determine how to diagnose and monitor early-onset SFPN of 25 years duration

Jorge Serrador PhD
East Orange VA WRIISC

Max Klein PhD
Mass General Hospital

Symptomatic Gulf War veterans have evidence of SFPN

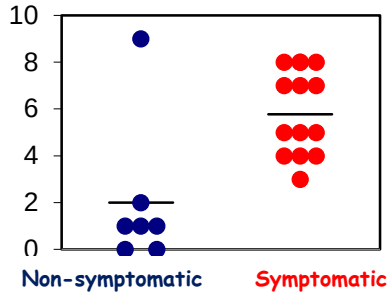
Subjects with objective test evidence of SFPN



47% of veterans had abnormal skin biopsy or AFT vs. 12% of controls

P = 0.0010

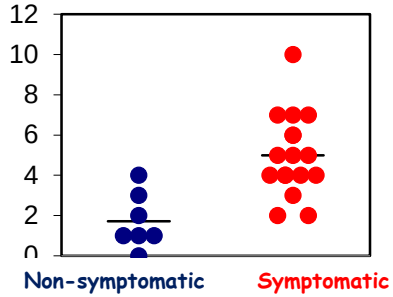
Pain Scores



Bars are mean scores

P = 0.0014

Michigan Neuropathy Screening Instrument MNSI



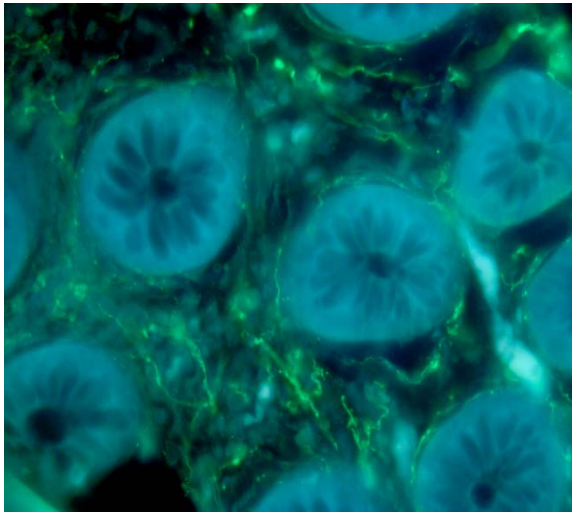
Bars are mean scores

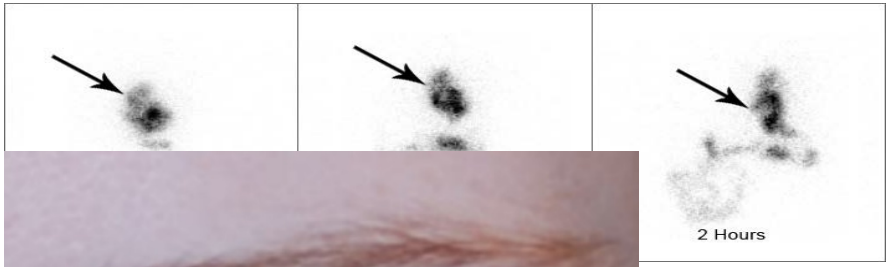
P = 0.0029

From the East Orange VA to the Institute of Medicine (National Academy of Medicine)

work of Max Klein PhD
Mass General Hospital

SFPN Symptoms: Gastrointestinalof SFPN





Upper GI symptoms of SFPN:
nausea and vomiting after
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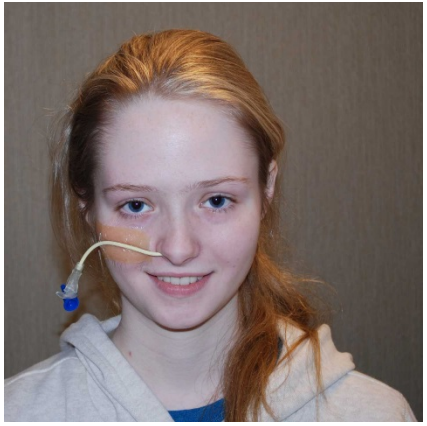
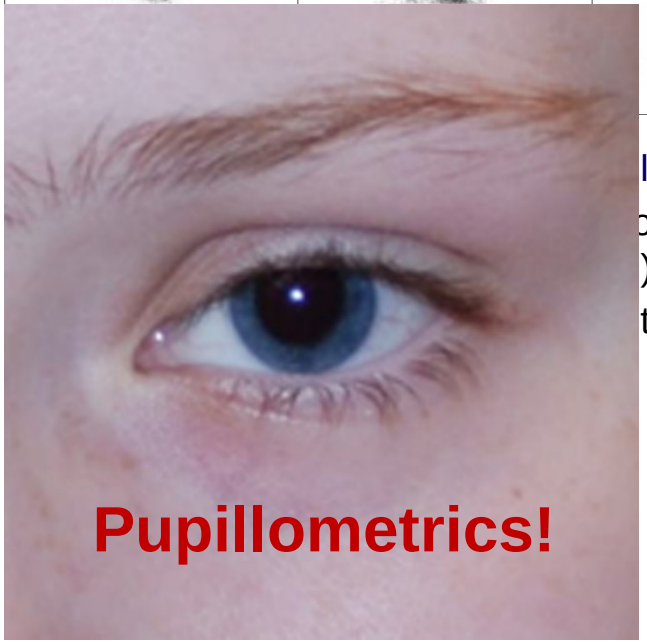




We are putting SFPN on the map
SFPN全球努力

- DoD funded grant to assemble nerve experts from US, Europe, Asia, South America, Africa 资助和联合全球专家
- Scientific Advisory Board: Alain Créange, Peter J. Dyck, John England, Eva Feldman, Riadh Guider 科学顾问委员会
- Global experts will use modified Delphi process to formulate first Case Definition, Diagnostic Criteria for SFPN 全球专家制定SFPN定义、诊断标准
- For publication, will seek endorsement from World Federation of Neurology, Peripheral Nerve Society, American Academy of Neurology, European Academy of Neurology 寻求“世界神经内科联合会”、“外周神经学会”、“美国神经内科学会”、“欧洲神经内科学会”的支持
- **Should improve patient care around the world 将促进世界的患者医疗**
- **Should improve research on SFPN 将促进SFPN的研究**

A. Créange and A. Careyron. The diagnosis of chronic inflammatory demyelinating polyneuropathy: a Delphi-method approach. J.Neurol, 2013

Passive immune transfer with patient sera

- 200 g male Sprague-Dawley rats; 5 day habituation to day/night reversal
- Baseline behavioral data collected, then wait 7 days to dehabituate
- IP injection with sera from patients or matched screened controls
  - 2 ml/day x 4 days
- Monitor for mechanical allodynia
  - von Frey thresholds for hindpaw withdrawal
- Monitor for development of C-fiber degeneration
  - hindpaw skin biopsies for PGP9.5 immunohistochemistry

Linda Sorkin PhD
UCSD Dept. Anesthesiology

Identifying genetic risk factors for autoimmune SFPN
确认自主免疫SFPN风险因素

- HLA Class I molecules are ligands for the killer immunoglobulin-like receptors (KIR)
- KIR molecules regulate cytokine production and activation of NK cells
- Variability in HLA Class I and II loci influences specificity of binding to foreign peptides and risk of inflammatory disease
- Isolating mononuclear cells (PBMC) from SFPN patients permits identifying activated B or T-cell subsets
- Cells frozen, viable for years, source of DNA

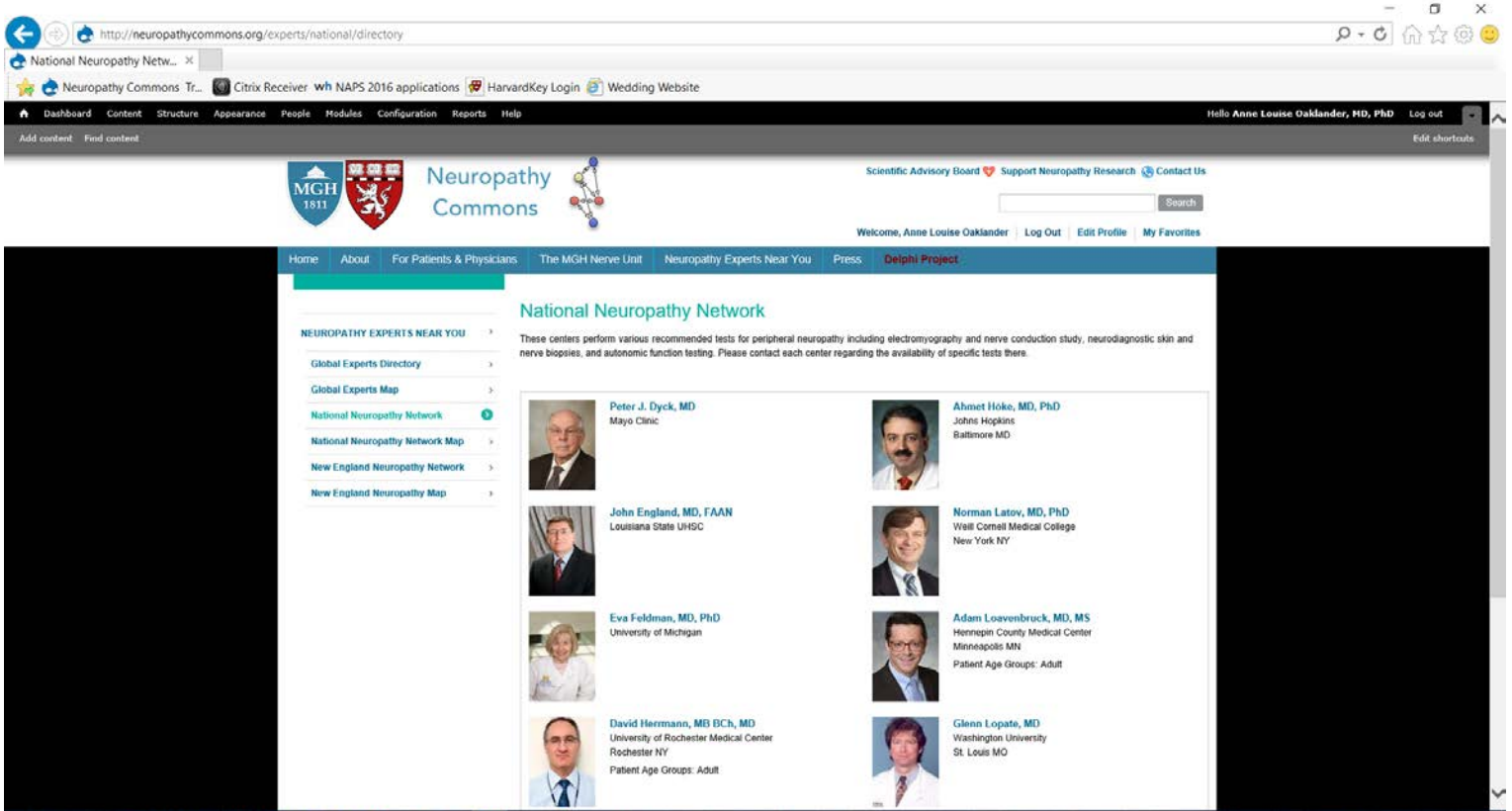
Mary Carrington PhD

Shiv Pillai, MD PhD

Ragon Institute of MGH, MIT and Harvard

Establishing Global and National Neuropathy Network

建立全球和国际神经病变网络



Summary and Conclusions:总结与结论

- Almost half of fibromyalgia patients have objective evidence of SFPN
  几乎一半纤维肌痛患者有SFPN证据
- SFPN can develop in children and young adults and can last into adulthood
  SFPN能够发现在儿童和年轻时期，并延续至成年
- Skin biopsy and AFT permit objective diagnosis and tracking treatment efficacy
  皮肤活检和AFT能够诊断和追寻治疗效果
- Blood tests can help identify underlying causes of SFPN 皮肤活检可确认SFPN病因
- Some types of SFPN seems to have autoimmune contribution 某些SFPN类型可能有自主免疫作用
  - Have we discovered the small-fiber correlates of Guillain-Barré and CIDP?
- Is immunotherapy an alternative to opioids for some chronic pain problems?
  自主免疫治疗是否是某些慢性疼痛问题治疗的阿片替代方法？

About 100 million patients have fibromyalgia phenotype (est 1% prevalence), how many could have SFPN? 大约一亿人有纤维肌痛表现(1%患病率)，多少是SFPN?

Do we need to re-engineer for population diagnosis and outcome monitoring?
是否需要建立人群诊断和结果检测？

Thanks to our contributors and funders

<u>Current MGH Contributors</u>
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Kate O'Neil BS
Xiaolei Liu MD
Mette Lodahl MD

<u>Dermatopathology</u>
Dr. Cynthia Magro
Weill Cornell

http://NeuropathyCommons.org/

Response to a short course of prednisone provides additional evidence of autoimmune causality in many patients with "idiopathic" SFPN

对短期强的松治疗的反应进一步为特发性SFPN与免疫因素相关提供证据

- IRB-approved retrospective review of 56 treated patients
- Had objective validation of SFPN diagnosis and comprehensive blood testing to rule out other causes.
- Autoimmune causality based on history of autoimmune illness or serologies.
- We gave prednisone 1 mg/kg for 4 weeks then rapid taper.

- Among all 36 patients with pain ≥ 3/10 at baseline, pain scores dropped from 6.6 ± 2.0 at baseline to 4.7 ± 2.5 ($p<0.001$).
- No significant adverse effects.

Liu, Treister, Oaklander
manuscript in preparation