Pathology and Functional Diagnosis of Small-fiber Painful Neuropathy

Sung-Tsang Hsieh

Abstract-

Small-fiber sensory neuropathy with neuropathic pain had been a diagnostic challenge for neurologists. We and several groups have developed skin biopsy with quantitation of intraepidermal nerve fiber (IENF) density as a diagnostic approach. In the skin with small-fiber sensory neuropathy, there are pathological hallmarks: reduced IENF density with degeneration of subepidermal nerve plexuses and dermal nerves. Skin denervation is a major presentation of diabetic neuropathy and inflammatory neuropathies including Guillain-Barr? syndrome and chronic inflammatory demyelinating polyneuropathy. The skin biopsy approach also provides an opportunity to examine dermal vasculature and inflammatory vasculopathy is demonstrated in vasculitic neuropathy, systemic lupus erythematosus, and eosinophilia-associated neuropathy. In addition to neuropahtologic evidence, the functional consequences of cutaneous nerve degeneration can be assessed with quantitative sensory testing (QST), contact heat evoked potential (CHEP), and functional magnetic resonance imaging (fMRI). One major etiology of small-fiber sensory neuropathy is familial amyloid polyneuropathy caused by mutations of transthyretin (TTR). We recently conducted studies on a large cohort of unique TTR mutation on Ala97Ser in Taiwan. These patients had significant skin denervation in addition to motor and autonomic neuropathy. Taken together, the skin biopsy with quantitation of IENF density provides diagnostic utility for small-fiber sensory neuropathy and the combination of psychophysical, physiological, and neuroimaging examinations offer comprehensive assessments for patients with neuropathic pain due o cutaneous nerve degeneration.

Key Words: skin biopsy, contact heat evoked potential, functional magnetic resonance imaging, amyloid neuropathy, transthyretin

Acta Neurol Taiwan 2010;19:82-89

INTRODUCTION

Neuropathic pain is a major symptom after nerve injury, which can be caused by degeneration of large-diameter sensory nerves (large fibers) or small-diameter sensory nerves (small fibers). Sensory nerves are the cytoplasmic extensions of dorsal root ganglion (DRG) neurons and are dichotomized into two classes: large-

From the Department of Neurology, National Taiwan University Hospital and Department of Anatomy and Cell Biology, National Taiwan University College of Medicine.
Received May 25, 2010. Revised May 27, 2010.
Accepted May 31, 2010.

Reprint requests and correspondence to: Sung-Tsang Hsieh, MD. Department of Anatomy and Cell Biology, National Taiwan University College of Medicine, 1 Jen-Ai Road, Sec, 1, Taipei, 10051, Taiwan.
E-mail: shsieh@ntu.edu.tw

diameter (large DRG neurons and large fibers) and small-diameter (small DRG neurons and small fibers) (Fig 1)[1]. Large sensory nerves terminate in the muscles, joints, and tendons and are responsible for proprioceptive sensations. Small sensory nerves terminate in the skin and visceral organs and transmit thermonociceptive stimuli, which form important protective sensations. Although sensory symptoms due to either type of nerve degeneration might be different in some patients, there are not distinct features to differentiate both. Practically, large fiber neuropathy can be examined by nerve conduction studies. Small-fiber sensory neuropathy, however, traditionally had depended on subjective description of symptoms by patients. Because small-diameter sensory nerves terminate in the skin, several groups including ours have developed skin biopsy with quantification of intraepidermal nerve fibers (IENF) density as a diagnostic approach for small-fiber sensory neuropathy[2-7]. There are two major approaches to quantitatively assess skin innervation, i.e. immunofluorescence with confocal microscopy and immunohistochemisty with conventional light microscopy[4]. The European Federation of Neurological Societies and Peripheral Nerve Society have formed a task force to set up guidelines for skin biopsies, the interpretations, and applications[8].

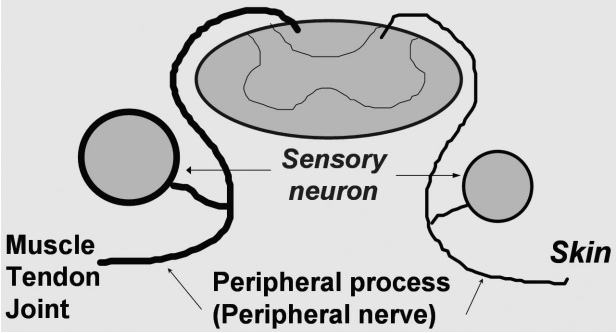

Figure 1. Structural organization of peripheral sensory nerves. Peripheral sensory nerves consist of (1) proprioceptive nerves from large-diameter sensory neurons of dorsal root ganglia which terminate in skeletal muscles, tendons, and joints and (2) nociceptive and thermal nerves from small-diameter sensory neurons of dorsal root ganglia which terminate in the skin.

SMALL-FIBER NEUROPATHY IN DIABETES

Small-fiber neuropathy is an important component of peripheral neuropathies in diabetes. Skin denervation is a major manifestation of neuropathy in type 2 diabetes [9]. In patients with stocking-glove sensory symptoms, 81.6% of them had reduced IENF densities and the reduction was correlated with diabetic duration. In contrast, only 50% of these patients had abnormal results on conventional nerve conduction studies, indicating that small-fiber sensory neuropathy is far more prevalent than large-fiber sensory neuropathy (Fig 2)[9]. In type 1 diabetes, there was also significant reduction of intraepidermal nerves[10]. Skin biopsy offers the potential for repeated examinations of skin innervation to understand cutaneous nerve regeneration. With this approach, it is clear that cutaneous nerve regeneration is impaired in diabetic patients [11,12].

SKIN DENERVATION IN INFLAMMATORY NEUROPATHIES

An important extension is the application of skin biopsy to explore small-fiber neuropathy in inflammatory neuropathies, in particular, Guillain-Barré syndrome (GBS)[13] and chronic inflammatory demyelinating polyneuropathy (CIDP) [14]. Traditionally, GBS is considered a large-fiber neuropathy. However, the presence of neuropathic pain and dysautonomia in GBS patients raises the possibility of small-fiber sensory and autonomic neuropathy. In the demyelinating form of GBS patients, IENF densities were reduced compared with age- and gender-matched control subjects. Among these patients, 55% of them had reduced epidermal innervation with pathological evidence of active nerve degeneration in the dermis, such as fragmentation of subepidermal nerve plexuses and dermal nerves. Additionally, reduced IENF density was associated with an elevated warm threshold, ventilatory distress, and dysautonomia. In GBS, IENF densities were negatively correlated with disability grade

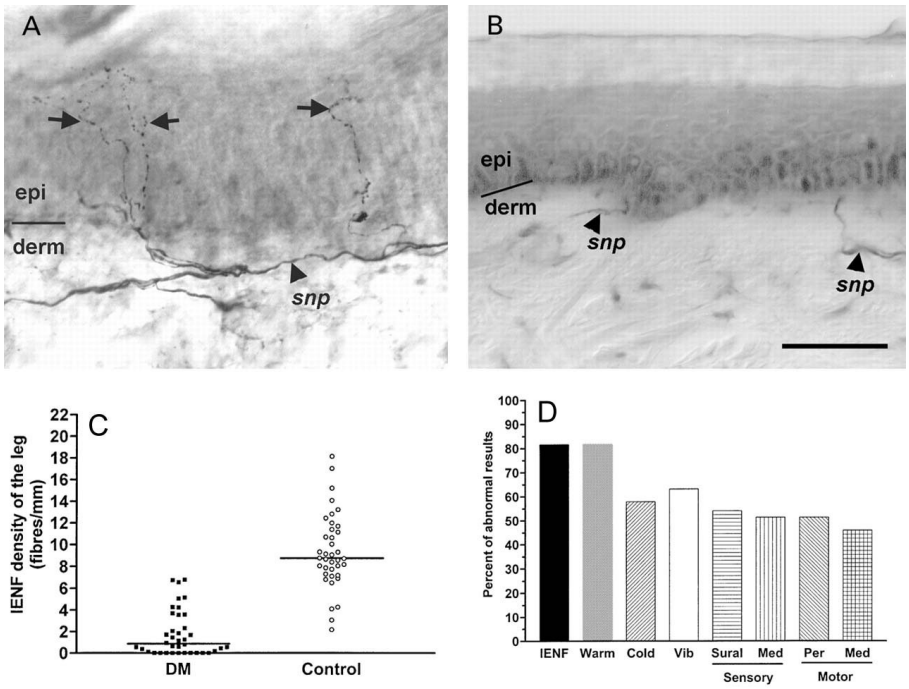

Figure 2. Skin innervation in type 2 diabetic neuropathy and its diagnostic value compared with quantitative sensory testing and nerve conduction studies.

Skin tissues from control (A) and diabetic (B) subjects were immunostained with protein gene product 9.5 (PGP 9.5). The boundary between the epidermis (epi) and the dermis (derm) is marked by a line.

(A) In the skin of a normal subject, PGP 9.5 (+) nerves appear in the epidermis and dermis. Typical epidermal nerves (arrows) arise from the subepidermal nerve plexuses (snp).

(B) In the skin of a diabetic patient, the epidermis is completely denervated. The staining of the subepidermal nerve plexus (snp) has become faint, and the number of dermal nerve fascicles is markedly reduced. (bar = 80 ?m).

(C) The intraepidermal nerve fibre density (IENF density) of the leg in diabetic patients (filled squares) is markedly reduced compared with that in age- and gender-matched control subjects (open circles) ($P < 0.0001$) (bar = mean value).

(D) The graph shows the proportion of diabetic patients with abnormal results on the intraepidermal nerve density of the leg (IENF); warm threshold at the foot dorsum (Warm); cold threshold at the foot dorsum (Cold); vibratory threshold (Vib); and nerve conduction studies on motor nerves (Motor) and sensory nerves (Sensory). The latter include sural (Sural), peroneal (Per) and median (Med) nerves.

This Figure is reproduced and modified from Shun et al, 2004 [9].

and patients with skin denervation tended to have a slower recovery than those with normal skin innervation. Similarly, IENF densities of patients with CIDP were lower than those of controls and skin denervation was associated with autonomic symptoms and elevation of thermal thresholds. The mechanisms of cutaneous nerve degeneration in GBS and CIDP remain obscured. Nevertheless, the presence of small-fiber neuropathy in inflammatory neuropathies indicates that these inflammatory neuropathies should be considered as a pan-neuropathy. In patients with paraproteinemic neuropathy, the IENF densities was reduced and the antibody against myelin-associated glycoprotein was deposited in the dermal nerves which provided a foundation of the mechanisms of paraprotein-induced sensory neuropathy [15,16].

In addition to demonstrate skin denervation, the der-

mal vessels are also targets of vasculitis and we have applied this approach to examine dermal microvasculitis in various types of inflammatory and autoimmune diseases, which are often associated with undiagnosed neuropathies. This new approach has important implications because traditionally vasculitis could only be diagnosed with nerve and muscle biopsies [17-19]. We first demonstrated dermal microvasculitis in patients with vasculitis syndrome [20]. In addition to vascular injury, there was perivascular inflammation of macrophage and T cells, indicating the immune-mediated nature of nerve injury [20]. All these patients also exhibited skin denervation, suggesting the association of both conditions. We then demonstrated that dermal vasculitis was associated with skin denervation in systemic lupus erythematosus (SLE), i.e. the higher the degree of vasculitis, the lower the IENF density [21]. IENF densities were associated with clinical deficits. These include the negative correlation with the SLE disease activity index and cumulative episodes of lupus flare-up within 2 years before the skin biopsy. In addition to being present in the patients with sensory neuropathy, skin denervation also existed in the patients with neuropsychiatric syndrome involving the central nervous system. In neuropathy due to eosinophilia and Churg-Strauss syndrome [22], there is also significant skin denervation and IENF density is negatively correlated with the disability grade and associated with cutaneous vasculitis. These studies raise the possibility that skin biopsy may provide another approach to diagnose vasculitis [23].

FUNCTIONAL EXAMINATIONS OF THERMONOCICEPTIVE NERVES

Functional assessments provide another domain of small-fiber painful neuropathy, including psychophysical, neurophysiological, and functional imaging approaches. Among these, quantitative sensory testing (QST) has been the earliest examination to measure thresholds. QST is a psychophysic approach and there are two algorithms to measure thermal thresholds, i.e. limits and level [24]. The method of limits directly measures the thermal thresholds and therefore might be affected by reaction time. This algorithm is highly correlated with the method of level and is less time-consuming compared with the method of level. Briefly, the sensory analyzer delivers a stimulus from a baseline temperature of 32.0 ˚C with an initial increment (for warm stimuli) or decrement (for cold stimuli) of 1.0 ˚C. The temperature of the next stimulus is either increased or decreased by a fixed ratio (2:1) according to the response of the subject, i.e., whether or not the subject had perceived the thermal stimulus. The mean intensity of the final two thermal stimuli is the thermal threshold temperature, and is expressed as the warm threshold or the cold threshold temperatures (˚C), respectively. QST is noninvasive and can be repeated for following up the progression of the disease or assessing the effects of new therapies. QST is a functional assessment of the entire thermonociceptive pathway from nerve terminals, through peripheral nerves, DRG, and spinal cord to the cerebrum. There are, however, several drawbacks for using QST. For example, QST is unable to define the site of nerve injury and QST could be influenced by emotional and environmental effects. QST could be used for a large-scale screening of small-fiber neuropathy. For example, thermal thresholds are elevated in diabetic patients and the elevation of thermal thresholds is correlated with diabetic control parameters, particularly glycated hemoglobin, HbA1C [25].

Heat or pain-evoked potentials studies provide neurophysiological evidence of small-fiber painful neuropathy. Traditionally, laser-evoked potential has been a research tool for assessing thermonociceptive pathway [26]. Laser-evoked potential was reduced in patients with painful neuropathy. Painful signals stimulated by electric currents through delicate epidermal electrodes demonstrate pain-evoked potential. The amplitude was reduced and correlated with IENF density in HIV-induced sensory neuropathy [27]. The above three types of pain- or heat-evoked potentials all activate Aδ fibers. Contact heat evoked potential (CHEP) appears to have additional advantages [28,29]. Together with the ability to adjust the heat intensity and stimulation paradigms, C-fiber evoked potentials can be recorded. A punctuate stimulation site for inducing laser is small and may not simulate the real

experience of pain or heat. In contrast, the probe for contact heat stimulation is larger than that for laser- or pain-evoked potential stimulator, which could mimic real-life heat perception. We have showed that CHEP amplitude was linearly correlated with IENF density, providing a link between the structure and functions of small-diameter sensory fibers [30].

In addition to exploring neurophysiologic evidence, we further investigated the patterns of brain activation to innocuous and noxious heat stimulations on functional magnetic resonance imaging (fMRI). Previously, the prevailing thought has been that the areas activated by innocuous heat were also activated by noxious heat [31-34]. We hypothesized that different cerebral areas might be activated by innocuous heat and noxious heat respectively and adopted a paradigm of 38 ˚C for innocuous heat and 44 ˚C for noxious heat. Our study indicated that there are unique spatial and temporal patterns of brain activations on either type of heat stimuli, i.e. distinct areas activated by innocuous heat and noxious heat and shared areas activated by both innocuous heat and noxious heat. In particular, the inferior parietal lobule is a innocuous heat-exclusive area (Table 1) [35].

FAMILIAL AMYLOID POLYNEUROPATHY DUE TO TRANSTHYRETIN MUTATIONS

Small-fiber painful neuropathy is a syndrome of different etiologies. These include diabetic and autoimmune diseases. Among these causes, familial amyloid polyneuropathy (FAP) constitutes a unique disease entity. The most common form of FAP is due to mutations of transthyretin (TTR). Mutations of TTP have previously reported in Portugal, Sweden, and Japan. Originally considered as endemic in certain ethnic groups, it is clear that neuropathies due to TTR mutations have a worldwide distribution. TTR mutation of V30M appears the most common mutation causing FAP [36-41]. In contrast, A97S compared with other mutations seems to be the most common mutation of TTR in Taiwanese [42-44]. We have recently completed a study on a cohort of 19 A97S patients to characterize this unique neuropathy in Taiwan [45]. Neuropathy due to A97S TTR is a late-onset global

Table 1. *Functional magnetic resonance imaging (fMRI) patterns of brain activations to contact innocuous heat (IH) and noxious heat (NH) based on the entire section of fMRI scanning*

Study	Thermal stimulus		Temperature (˚C)	Brain activation		
	Ramp rate	Site	(IH / NH)	IH only	NH only	IH and NH
Tseng et al, 2010 [35]	20 ˚C/s	foot	38 / 44	IPL	S1, S2, pIC, PMA	MFG, IFG, aIC, Cb, SFG, SMA, Th, ACC, LN, Mb
Moulton et al., 2005 [34]	4 ˚C/s	foot	41 / 46.4, 47.4	-	pIC	S1, S2, ACC, SMA, IFG
Brooks et al., 2002 [33]	N/A	hand	40 / 46-49	-*	IC, ACC, S2, Cb, MFG, IFG	-
Becerra et al., 1999 [32]	4 ˚C/s	hand	41 / 46	-	MTG	MFG, IC, ACC, PCC, Th, S1, S2, SMA, PMA, STG, Cb
Davis et al., 1998 [31]	N/A	hand	40-43 / 47.5	-	S2	Th, LN, IC

N/A: information not available; * no activation to IH.

ACC, anterior cingulate cortex; Cb, cerebellum; aIC, anterior insular cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; LN, lentiform nucleus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; pIC, posterior insular cortex; PMA, premotor area; R, right; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SMA, supplementary motor area; STG, superior temporal gyrus; Th, thalamus.

This Table was reproduced from Tseng et al, 2010 [35].

neuropathy, i.e. involving motor, sensory, and autonomic components of peripheral nerves. Reported patients had onset > 50 years of age and exhibited significant autonomic dysfunction including chronic diarrhea and postural hypotension. Sensory nerves of large and small-fiber categories were affected. All patients had skin denervation which was correlated with the elevation of thermal thresholds. This form of neuropathy could be an under-diagnosed neuropathy in Taiwan and it is mandatory to perform genetic screening of A97S in patients with adult-onset idiopathic motor, sensory, and autonomic neuropathy.

PERSPECTIVES

In conclusion, the skin biopsy with quantitation of IENF density provides diagnostic utility for small-fiber sensory neuropathy and the combination of psychophysical (QST), physiological (CHEP), and neuroimaging (fMRI) examinations may offer comprehensive assessments for patients with neuropathic pain due to cutaneous nerve degeneration. In Taiwan, TTR (A97S)-amyloid neuropathy appears a unique neuropathy involving the motor, sensory, and autonomic components.

ACKNOWLEDGEMENT

The works are supported by grants from the National Health Research Institute, Taiwan, the National Science Council, Taiwan, and the Excellent Translational Medicine Research Projects of NTUMC and NTUH.

REFERENCES

1. Hsieh ST. Toxic neuropathies. In: Schmidt RF, Willis WD. Eds. Encyclopedia of Pain. Berlin, Germany: Springer-Verlag, 2007: 2493-2498.
2. Hsieh ST, Chiang HY, Lin WM. Pathology of nerve terminal degeneration in the skin. J Neuropathol Exp Neurol 2000;59:297-307.
3. Pan CL, Lin YH, Lin WM, Tai TY, Hsieh ST. Degeneration of nociceptive nerve terminals in human peripheral neuropathy. NeuroReport 2001;12:787-792.
4. Chien HF, Tseng TJ, Lin WM, Yang CC, Chang YC, Chen RC, Hsieh ST. Quantitative pathology of cutaneous nerve terminal degeneration in the human skin. Acta Neuropathol (Berl) 2001;102:455-461.
5. Sommer C, Lauria G. Skin biopsy in the management of peripheral neuropathy. Lancet Neurol 2007;6:632-642.
6. Lauria G, Devigili G. Skin biopsy as a diagnostic tool in peripheral neuropathy. Nat Clin Pract Neurol 2007;3:546-557.
7. England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, Asbury AK, Szigeti K, Lupski JR, Latov N, Lewis RA, Low PA, Fisher MA, Herrmann DN, Howard JF Jr, Lauria G, Miller RG, Polydefkis M, Sumner AJ; American Academy of Neurology. 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 2009;72:177-184.
8. Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, Nolano M, Merkies ISJ, Polydefkis M, Smith AG, Sommer C, Valls-Sole J. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol 2010; in press.
9. Shun CT, Chang YC, Wu HP, Hsieh SC, Lin WM, Lin YH, Tai TY, Hsieh ST. Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. Brain 2004;127:1593-1605.
10. Kennedy WR, Wendelschafer-Crabb G, Johnson T. Quantitation of epidermal nerves in diabetic neuropathy. Neurology 1996;47:1042-1048.
11. Rajan B, Polydefkis M, Hauer P, Griffin JW, McArthur JC. Epidermal reinnervation after intracutaneous axotomy in man. J Comp Neurol 2003;457:24-36.
12. Polydefkis M, Hauer P, Sheth S, Sirdofsky M, Griffin JW, McArthur JC. The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. Brain 2004;127:1606-1615.
13. Pan CL, Tseng TJ, Lin YH, Chiang MC, Lin WM, Hsieh

ST. Cutaneous innervation in Guillain-Barre syndrome: pathology and clinical correlations. Brain 2003;126:386-397.

14. Chiang MC, Lin YH, Pan CL, Tseng TJ, Lin WM, Hsieh ST. Cutaneous innervation in chronic inflammatory demyelinating polyneuropathy. Neurology 2002;59:1094-1098.
15. Lombardi R, Erne B, Lauria G, Pareyson D, Borgna M, Morbin M, Arnold A, Czaplinski A, Fuhr P, Schaeren-Wiemers N, Steck AJ. IgM deposits on skin nerves in anti-myelin-associated glycoprotein neuropathy. Ann Neurol 2005;57:180-187.
16. McArthur JC, Griffin JW. Another tool for the neurologist's toolbox. Ann Neurol 2005;57:163-167.
17. Collins MP, Mendell JR, Periquet MI, Sahenk Z, Amato AA, Gronseth GS, Barohn RJ, Jackson CE, Kissel JT. Superficial peroneal nerve/peroneus brevis muscle biopsy in vasculitic neuropathy. Neurology 2000;55:636-643.
18. Bennett DL, Groves M, Blake J, Holton JL, King RH, Orrell RW, Ginsberg L, Reilly MM. The use of nerve and muscle biopsy in the diagnosis of vasculitis: a 5 year retrospective study. J Neurol Neurosurg Psychiatry 2008;79:1376-1381.
19. Magy L, Vallat JM. Nerve biopsy without muscle sampling: is it enough for diagnosing vasculitis? J Neurol Neurosurg Psychiatry 2008;79:1307.
20. Lee JE, Shun CT, Hsieh SC, Hsieh ST. Skin denervation in vasculitic neuropathy. Arch Neurol 2005;62:1570-1573.
21. Tseng MT, Hsieh SC, Shun CT, Lee KL, Pan CL, Lin WM, Lin YH, Yu CL, Hsieh ST. Skin denervation and cutaneous vasculitis in systemic lupus erythematosus. Brain 2006;129:977-985.
22. Chao CC, Hsieh ST, Shun CT, Hsieh SC. Skin denervation and cutaneous vasculitis in eosinophilia-associated neuropathy. Arch Neurol 2007;64:959-965.
23. Pleasure DE. Dwindling indications for sural nerve biopsy. Arch Neurol 2007;64:935-936.
24. Lin YH, Hsieh SC, Chao CC, Chang YC, Hsieh ST. Influence of aging on thermal and vibratory thresholds of quantitative sensory testing. J Peripher Nerv Syst 2005;10:269-281.
25. Chao CC, Hsieh SC, Yang WS, Lin YH, Lin WM, Tai TY, Hsieh ST. Glycemic control is related to the severity of impaired thermal sensations in type 2 diabetes. Diabetes Metab Res Rev 2007;23:612-620.
26. Chao CC, Hsieh ST, Chiu MJ, Tseng MT, Chang YC. Effects of aging on contact heat evoked potentials: the physiological assessment of thermal perception. Muscle Nerve 2007;36:30-38.
27. Obermann M, Katsarava Z, Esser S, Sommer C, He L, Selter L, Yoon MS, Kaube H, Diener HC, Maschke M. Correlation of epidermal nerve fiber density with pain-related evoked potentials in HIV neuropathy. Pain 2008;138:79-86.
28. Le Pera D, Valeriani M, Niddam D, Chen AC, Arendt-Nielsen L. Contact heat evoked potentials to painful and non-painful stimuli: effect of attention towards stimulus properties. Brain Topogr 2002;15:115-123.
29. Granovsky Y, Granot M, Nir RR, Yarnitsky D. Objective correlate of subjective pain perception by contact heat-evoked potentials. J Pain 2008;9:53-63.
30. Chao CC, Hsieh SC, Tseng MT, Chang YC, Hsieh ST. Patterns of contact heat evoked potential (CHEP) in neuropathy with skin denervation: correlation of CHEP amplitude with intraepidermal nerve fiber density. Clin Neurophysiol 2008;119:653-661.
31. Davis KD, Kwan CL, Crawley AP, Mikulis DJ. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. J Neurophysiol 1998;80:1533-1546.
32. Becerra LR, Breiter HC, Stojanovic M, Fishman S, Edwards A, Comite AR, Gonzalez RG, Borsook D. Human brain activation under controlled thermal stimulation and habituation to noxious heat: An fMRI study. Magn Reson Med 1999;41:1044-1057.
33. Brooks JC, Nurmikko TJ, Bimson WE, Singh KD, Roberts N. fMRI of thermal pain: effects of stimulus laterality and attention. NeuroImage 2002;15:293-301.
34. Moulton EA, Keaser ML, Gullapalli RP, Greenspan JD. Regional intensive and temporal patterns of functional MRI activation distinguishing noxious and innocuous contact heat. J Neurophysiol 2005;93:2183-2193.
35. Tseng MT, Tseng WY, Chao CC, Lin HE, Hsieh ST. Distinct and shared cerebral activations in processing innocuous versus noxious contact heat revealed by functional magnetic resonance imaging. Hum Brain Mapp

2010;31:743-757.

36. Misu K, Hattori N, Nagamatsu M, Ikeda S, Ando Y, Nakazato M, Takei Y, Hanyu N, Usui Y, Tanaka F, Harada T, Inukai A, Hashizume Y, Sobue G. Late-onset familial amyloid polyneuropathy type I (transthyretin Met30-associated familial amyloid polyneuropathy) unrelated to endemic focus in Japan: clinicopathological and genetic features. Brain 1999;122:1951-1962.
37. Hund E, Linke RP, Willig F, Grau A. Transthyretin-associated neuropathic amyloidosis: pathogenesis and treatment. Neurology 2001;56:431-435.
38. Ikeda S, Nakazato M, Ando Y, Sobue G. Familial transthyretin-type amyloid polyneuropathy in Japan: Clinical and genetic heterogeneity. Neurology 2002;58: 1001-1007.
39. Ando Y, Nakamura M, Araki S. Transthyretin-related familial amyloidotic polyneuropathy. Arch Neurol 2005; 62:1057-1062.
40. Planté-Bordeneuve V, Ferreira A, Lalu T, Zaros C, Lacroix C, Adams D, Said G. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). Neurology 2007;69:693-698.
41. Hou X, Aguilar MI, Small DH. Transthyretin and familial amyloidotic polyneuropathy. Recent progress in understanding the molecular mechanism of neurodegeneration. FASEB J 2007;274:1637-1650.
42. Yamamoto K, Hsu SP, Yoshida K, Ikeda S, Nakazato M, Shiomi K, Cheng SY, Furihata K, Ueno I, Yanagisawa N. Familial amyloid polyneuropathy in Taiwan: identification of transthyretin variant (Leu55-->Pro). Muscle Nerve 1994;17:637-641.
43. Pica EC, Pramono ZA, Verma KK, San LP, Chee YW. A novel transthyretin mutation V32A in a Chinese man with late-onset amyloid polyneuropathy. Muscle Nerve 2005; 32:223-225.
44. Liu YT, Lee YC, Yang CC, Chen ML, Lin KP. Transthyretin Ala97Ser in Chinese-Taiwanese patients with familial amyloid polyneuropathy: genetic studies and phenotype expression. J Neurol Sci 2008;267:91-99.
45. Yang NC, Lee MJ, Chao CC, Chuang YT, Lin WM, Chang MF, Hsieh PC, Kan HW, Lin YH, Yang CC, Chiu MJ, Liou HH, Hsieh ST. Clinical presentations and skin denervation in amyloid neuropathy due to transthyretin Ala97Ser. Neurology 2010; in press.