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ETHNIC DIFFERENCES IN EPIDERMAL NERVE FIBER DENSITY

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Quantification of epidermal nerve fiber density (ENFD) is a validated tool to confirm the clinical diagnosis of small fiber neuropathy.¹ Several groups have published normative ENFD data in healthy controls.^{2–6} We assessed ENFD values in healthy ethnic Thais and report that values are significantly higher when compared with normative ENFD data from the United States.

Following local Institutional Review Board approval, distal leg and proximal thigh skin punch biopsies were performed on healthy Thai subjects free of neuropathic symptoms (persistent pain, tingling, or numbness of lower extremities) and signs (diminished or absent ankle reflexes, decreased vibratory, pin or temperature sensation, or contact allodynia). Subjects were excluded if they were pregnant or had disease or medication use known to cause neuropathy, including HIV, diabetes, vitamin B12 deficiency, excessive alcohol intake, or hepatitis C infection. Skin punch biopsy and processing were performed in strict adherence to guidelines of the Cutaneous Nerve Laboratory at Johns Hopkins (http://www.hopkinsmedicine.org/neurology_neurosurgery/specialty_areas/cutaneous_nerve_lab/), with on-site training in Bangkok. and quality control performed by Johns Hopkins.

Slides of 50- μ m-thick PGP9.5 immunostained sections were examined at Johns Hopkins for specimen and staining quality, and the number of unmyelinated nerve fibers per millimeter of length of epidermis was quantitated using established counting rules.^{2,7,8} All slides were blinded and clinical information masked. One author (G.J.E.) counted 95% of biopsies. Results were then compared with U.S. normative data using the same lab and counting techniques.²

Forty-nine healthy ethnic Thai subjects (21 men/28 women) were studied. The ages ranged from 25 to 44 years, with a mean (SD) of 33.2 (4.8) and median of 32. The mean (SD) and median height and body mass index (BMI) were 162.1 (6.2) and 161 cm, and 22.1 (2.4) and 22.0, respectively. The reference paper on U.S. normative range for ENFD used 98 healthy

controls with an age range of 13–82 years, 76% of whom were white and 18% black.² Height and BMI were not reported.

Results are shown in Table 1. The mean (SD) distal leg ENFD in our Thai subjects was 30.4 (10.4) mm (fifth percentile 16.5 mm) compared with 13.8 (6.7) mm (fifth percentile 3.8 mm) in the reference paper, with proximal thigh ENFD in Thais of 47.1 (12.5) mm (fifth percentile 27.0 mm) compared with reference values of 21.1 (10.4) mm (fifth percentile 5.2 mm). The thigh/distal leg ratios were similar.

In summary, our study found approximately 2–3× higher ENFD in healthy controls in Thailand compared with healthy subjects in the United States. Previous studies that have included Asians have not reported ethnic differences,^{3,4} but the credibility of our analysis is strengthened by the use of the same technique and laboratory that reported U.S. norms. The limitations include the 14-year difference between comparisons, and lack of height, BMI, and other relevant information to assess potential confounders. We conclude that substantial differences in ENFD may exist by ethnicity, and further investigation into the role of ethnicity is warranted.

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Table 1

Proximal thigh and distal leg epidermal nerve fiber density in Thai healthy controls compared to healthy controls in the United States* using 2-sample *t*-test.

Parameter	SEARCH 014		U.S. Norms*		P-value
	<i>n</i>	ENFD [mean (SD)]	<i>n</i>	ENFD [mean (SD)]	
Proximal thigh					
20–29 year olds	11	51.5 (9.3)	18	15.8 (5.9)	<0.01
30–29 year olds	32	45.7 (13.7)	20	17.8 (9.4)	<0.01
40–49 year olds	6	46.7 (10.6)	19	22.3 (7.4)	<0.01
Distal leg					
20–29 year olds	11	29.3 (8.2)	18	11.3 (5.3)	<0.01
30–29 year olds	32	29.7 (10.4)	20	11.9 (7.1)	<0.01
40–49 year olds	6	36.4 (13.4)	19	14.6 (5.6)	<0.01
Thigh/leg ratio					
20–29 year olds	11	Ratio 1.8 (0.4)	18	Ratio 1.6 (0.7)	0.34
30–29 year olds	32	Ratio 1.7(0.7)	20	Ratio 1.8 (1.1)	0.72
40–49 year olds	6	Ratio 1.4 (0.5)	19	Ratio 1.6 (0.7)	0.53

* McArthur JC, Stocks A, Hauer P, Cornblath DR, Griffin JW. Epidermal nerve fiber density: normative reference range and diagnostic efficacy. *Arch Neurol* 1998;55:1513-1519.