RESEARCH REPORT

Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study

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Abstract The diagnostic reliability of skin biopsy in small fiber neuropathy depends on the availability of normative reference values. We performed a multicenter study to assess the normative values of intraepidermal nerve fiber (IENF) density at distal leg stratified by age deciles. Eight skin biopsy laboratories from Europe, USA, and Asia submitted eligible data. Inclusion criteria of raw data were healthy subjects 18 years or older; known age and gender; 3-mm skin biopsy performed 10-cm above the lateral malleolus; bright-field immunohistochemistry protocol, and quantification of linear IENF density in three 50-μm sections according to published guidelines. Data on height and weight were recorded, and body mass index (BMI) was calculated in subjects with both available data. Normative IENF density reference values were calculated through quantile regression analysis; influence of height, weight, or BMI was determined by regression analyses. IENF densities from 550 participants (285 women, 265 men) were pooled. We found a significant age-dependent decrease of IENF density in both genders (women $p < 0.001$; men $p = 0.002$). Height, weight, or BMI did not influence the calculated 5th percentile IENF normative densities in both genders. Our study provides IENF density normative reference values at the distal leg to be used in clinical practice.

Key words: intraepidermal nerve fiber density, neuropathy, neuropathology, neuropathic pain, skin biopsy, small fiber neuropathy

Introduction

Skin punch biopsy with measurement of intraepidermal nerve fiber (IENF) density has become a valuable tool in the evaluation of patients with neuropathy. For some patients, especially when small nerve fibers appear to be predominantly affected, this may be the only test that objectively shows abnormalities and thus confirms the diagnosis of small fiber neuropathy (SFN) *(England et al., 2009; Joint Task Force of the EFNS and the PNS, 2010)*. Although skin biopsy with IENF quantification has become standard and many laboratories have reported their own normal values, questions remain. First, two different techniques

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are used (e.g., bright-field immunohistochemistry and indirect immunofluorescence with or without confocal microscopy), which diagnostic yield has not been compared so far. Second, and most important, the effect of anthropomorphic and demographic parameters, including age, height, weight, and body mass index (BMI) on IENF density values is unknown and stratified normative data are lacking. Indeed, most articles reported the difference between cohorts of patients and healthy subjects in terms of mean, median, or cut-off values *(Kennedy et al., 1996; Holland et al., 1998; Herrmann et al., 1999; Periquet et al., 1999; Nolano et al., 2001; Pan et al., 2001; 2003; Chiang et al., 2002; Hoitsma et al., 2002; Polydefkis et al., 2002; Lauria et al., 2003; Pittenger et al., 2004; Goransson et al., 2006a; 2006b; Loseth et al., 2006; 2008; Sorensen et al., 2006; Gorson et al., 2008)*. Some have demonstrated differences between men and women, a decline of IENF density with increasing age, or confounding influence of height and weight *(Chien et al., 2001; Pan et al., 2001; Goransson et al., 2004; Umapathi et al., 2006)*. More recently, some of us reported the results of a multicenter study showing age and gender-dependent IENF density values in healthy subjects *(Bakkers et al., 2009)*. Because it is debated whether these values are representative for other centers, we aimed to calculate the normative reference values of IENF density at the distal leg through a worldwide multicenter collaboration in order to support a general standardized use of skin biopsy in the diagnosis of SFN.

Materials and Methods

Nine groups who previously reported normative IENF density values at the distal leg using bright-field immunohistochemistry were approached for collaboration. They were invited to provide the coordinating center (Milan, Italy) with their available IENF density data for healthy subjects. Eight centers decided to participate in the project. Eligibility criteria for inclusion of raw data were: (1) healthy subjects 18 years or older, free of neurological signs and symptoms, and conditions known to be at risk for neuropathy; (2) known age and gender; (3) specimens obtained through 3-mm punch skin biopsy 10 cm above the lateral malleolus, in the territory of the sural nerve; (4) use of bright-field immunohistochemistry protocol according to published guidelines *(Lauria et al., 2005)*; (5) quantification of linear IENF density (number of fibers/millimeter) in at least three sections of 50-μm thickness according to published counting rules (IENF have to cross or originate at the dermal–epidermal junction, and secondary branches and fragments are not counted) *(Kennedy et al., 2005)*. Data on height and weight were recorded when available, and body mass index (BMI = weight [kg]/height[cm] × height[cm]) was calculated in subjects with both available data.

Statistical analysis

Normative IENF density reference values were then calculated through quantile regression analysis *(Gould and Rogers, 1994)*. Possible influence of height and weight (or BMI) on IENF density in men and women was determined by regression studies. The median values and chosen cut-off at the 5th percentile are presented for men and women per age decade.

Results

Eight centers decided to participate in the study and provided data on 550 healthy subjects (women: n = 285, age: mean 44.9 years [SD 15.2], range 19–92 years; men: n = 265, age: mean 49.0 [SD 15.8], range 18–84 years). There was a significant age-dependent decrease of IENF density values in both genders (in women: $p < 0.001$; in men: $p = 0.002$). Up to 70 years, the normative IENFD findings were lower in men compared to women, but became equivalent in the older age groups (70 years plus) (Fig. 1 and Table 1).

Data on height were available from 320 subjects (161 women and 159 men) and on weight from 247 subjects (117 women and 130 men). Women had a mean height of 163 cm (SD 10; range 141–198) and men of 173 cm (SD 9; range 150–196). Women had a mean weight of 65.3 kg (SD 13.8; range 40–132) and men of 75.6 kg (SD 16.8; range 48.6–164). Multivariate regression analysis did not show any significant impact of weight on IENF density in women, whereas in men there was a minor but significant inverse correlation that explained a proportion of 12% of IENF density findings ($R^2 = 0.12$; $p < 0.001$). The BMI values demonstrated similar findings: in women (mean 24.1 ± 5.0 SD), where it explained only 3% ($R^2 = 0.028$; $p = 0.02$) and in men (mean 24.7 ± 4.4 SD), where it explained 13% ($R^2 = 0.13$; $p = 0.001$) of IENF density findings. Height did not influence IENF densities in men or women. However, for the calculated IENF density normative scores (5th percentile values), no influence of height, weight, or BMI was seen in both genders.

Discussion

This report presents the pooled normative IENF density values at the distal leg from eight skin biopsy

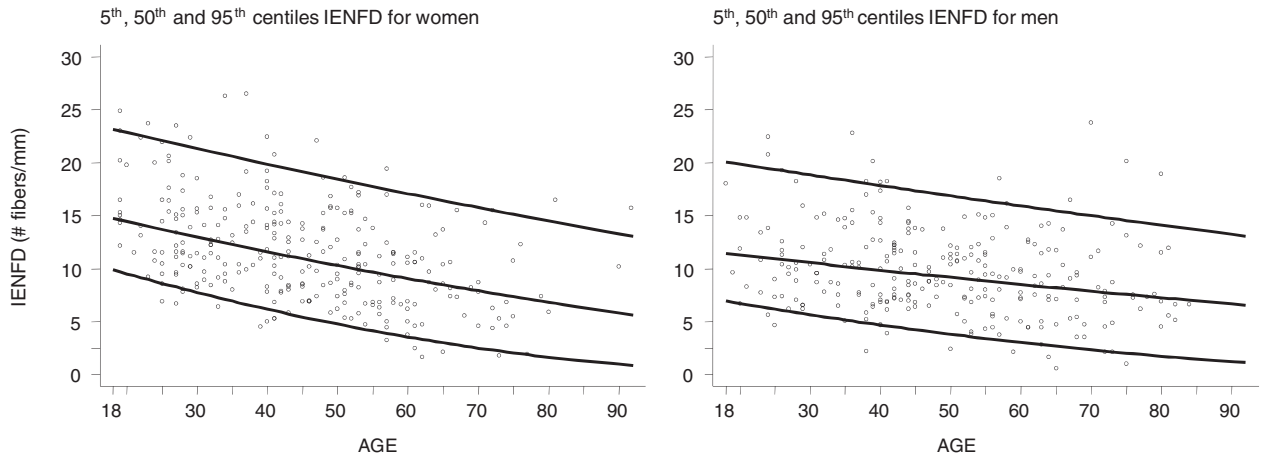

Figure 1. Scatterplot showing intraepidermal nerve fiber density (IENFD) values in healthy individuals (n = 285 women; n = 265 men). Lines depict 5th, 50th, and 95th percentiles.

Table 1. Intraepidermal nerve fiber density (IENFD) normative values for clinical use.

	Females (n = 285)			Males (n = 265)		
Age (years)	Number of subjects	0.05 Quantile IENFD values per age span	Median IENFD values per age span	Number of subjects	0.05 Quantile IENFD values per age span	Median IENFD values per age span
20–29	57	8.4	13.5	36	6.1	10.9
30–39	47	7.1	12.4	40	5.2	10.3
40–49	70	5.7	11.2	62	4.4	9.6
50–59	59	4.3	9.8	53	3.5	8.9
60–69	32	3.2	8.7	43	2.8	8.3
70–79	16	2.2	7.6	22	2.1	7.7
≥80	4	1.6	6.7	9	1.7	7.2

laboratories. The findings demonstrated that IENF density gradually declines with increasing age. Up to 70 years, the normative values were higher in women compared to men. In the higher age groups (70 years plus), the normative values became quite equivalent between the two genders. Moreover, we found that height does not influence IENF densities, whereas weight and BMI had a small inverse correlation in men. However, none of these parameters (height, weight, or BMI) demonstrated a significant impact on the 5th percentile IENF normative densities in both genders. Therefore, the 5th percentile values provided can be used in clinical practice without adjustment to these anthropomorphic parameters.

These results confirm previous observations (Table 2) and definitely establish the normative reference values of IENF density at the distal leg to be used in clinical practice and research. Data originate from the largest sample size ever analyzed with the same methods, and are valid for bright-field immunohistochemistry using specific counting rules, which exclude IENF fragments from quantification. Fragments have been formerly included in the quantification of IENF density *(McArthur et al., 1998)*. Whether different counting rules would give different cut-off values needs to be investigated by a focused comparative study including healthy subjects and neuropathy patients.

The decrease of IENF density values with age is in line with studies reporting an age-related decline of other direct or indirect measures of neurological functions, such as grip strength, sensory testing, sensory nerve action potential amplitude, and Meissner and Pacinian corpuscle density *(Bruce and Sinclair, 1980; Martina et al., 1998; Merkies et al., 2000; Rivner et al., 2001; Lin et al., 2005; Roglio et al., 2008)*. However, the correlation between age and loss of unmyelinated axons in human beings is controversial *(Verdu et al., 2000)*. The reasons for the age-related decline in IENF density are likely related to the physiological processes of aging. The differences in epidermal innervation density between men and women may be related to gender-related hormonal status *(Roglio et al., 2008)*. It has been shown that progesterone stimulates axonal growth and myelination, and may have a neuroprotective effect

Table 2. Published studies addressing normative values for intraepidermal nerve fiber density (IENFD).

First author	Publication year	Sample size	Stratification	Reliability			Validity	Conclusion
				Interobserver	Intraobserver	Between centers		
McArthur (*McArthur et al., 1998*)	1998	98	Yes, however uneven distributed	0.74–0.86	0.86–0.94	—	—	IENFD 13.8 ± 6.7 Teenagers have significantly higher IENFD
Pan *(Pan et al., 2001)*	2001	55	Not reported	—	—	—	—	IENFD 13 ± 5.3
Chang *(Bianchi et al., 2004)*	2004	87	Not reported	—	—	—	Correlation age and IENFD: −0.462	IENFD age 40<: 13.6 ± 0.85 IENFD age>60: 7.8 ± 0.78 Males have lower IENFD
Goransson *(Goransson et al., 2004)*	2004	106	Not reported	Mean interobserver difference: 0.4 +/− 1.5	Mean intraobserver difference: 0.2 +/− 1.2	—	—	IENFD females: 13.6 ± 4.6 IENFD males: 10.5 ± 3.9 IENFD = 13.92 + 2.25 (gender) − 0.6 × age
Umapathi *(Umapathi et al., 2006)*	2006	84	Not reported	—	—	—	—	IENFD decreases with age (16.1 − 10.8)
Bakkers *(Bakkers et al., 2009)*	2009	188	15 men and 15 women per decade	0.94	0.90–0.95	0.78–0.91	Decrease in symptoms inventory questionnaire (SIQ) score in sarcoidosis ($p < 0.001$)	Decrease with aging, women higher scores

on IENF. Furthermore, nerve sprouting, regeneration, and remyelination have been demonstrated to occur at a more rapid speed in female rats *(Koenig et al., 2000; Kovacic et al., 2003)*.

Skin biopsy with quantification of IENF density at the distal leg is considered a reliable tool to confirm the clinical diagnosis of SFN *(England et al., 2009; Joint Task Force of the EFNS and the PNS, 2010)*. Although conclusive diagnostic criteria for SFN are not yet available, most authors used a similar definition based on normal sural nerve conduction study, clinical symptoms and signs considered suggestive, and altered skin biopsy or quantitative sensory testing (QST) findings *(Holland et al., 1998; Lacomis, 2002; Mendell and Sahenk, 2003; Said, 2003; Sommer, 2003; Herrmann et al., 2004; Hoitsma et al., 2004; Lauria, 2005; Sommer and Lauria, 2006; Goodman, 2007; Devigili et al., 2008; Bakkers et al., 2009; Nebuchennykh et al., 2009; Tavee and Zhou, 2009)*. However, in most clinical series patients were compared to normative mean or cut-off values of IENF density obtained from nonstratified control groups. These values are higher than the age-related normative values, possibly leading to an overdiagnosis of SFN. The availability of cut-off values stratified per age decade and gender will allow the definition of the clinical diagnosis of SFN with a higher certainty.

The 5th percentile cut-off values in this study were only slightly higher than those recently reported, with comparable age-related decrease of IENF densities, even though the subjects were not exactly stratified as it was presented by Bakkers *et al. (2009)*. However, there are still some unresolved issues regarding the reliability of normative IENF density values. The 5th percentile was used as cut-off value in previous works *(McArthur et al., 1998; Bakkers et al., 2009)*. In a recent paper, Nebuchennykh and colleagues compared the diagnostic yield of skin biopsy at the distal leg in 45 patients with SFN and 134 healthy subjects using three statistical methods: (1) Z-scores, calculated from multiple regression analysis, which cut-off values were estimated for each patient and adjusted for age and gender; (2) 5th percentile with 6.7 IENF/mm cut-off value; and (3) receiver operating characteristic (ROC) analysis with a cut-off value of 10.3 IENF/mm *(Nebuchennykh et al., 2009)*. Z-scores and 5th percentile showed higher specificity (98% and 95%, respectively) but lower sensitivity (31% and 35%, respectively) compared to the ROC analysis that showed specificity of 64% and sensitivity of 78%. We agree that the diagnostic yield of skin biopsy may depend on how the reference and cut-off values have been assessed and on the diagnostic criteria for SFN which still need to be defined. Further studies are warranted to establish specificity and sensitivity values of IENF density using the reference normative values provided by this work, which we consider valid for clinical practice use.

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