Small Fiber Neuropathy and Related Syndromes: Pain and Neurodegeneration

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Sung-Tsang Hsieh dedicates this book to
beloved family (Whei-Min, Paul-Chen, and Christine Yi-Chen) and
mentor (late Professor Jack Griffin)

Foreword

This is a very good book focusing on small fiber neuropathy (SFN), an important and interesting disease. When I was a young neurologist in the 1980s, there were few clinicians or researchers whose main theme was SFN; since it was a very complicated disease entity, there were few practical tests for its diagnosis; and it was very difficult or impossible to care for patients with SFN. In fact, as written in Chap. 1 (Overview) by Prof. Hsieh, chief editor of this book, "SFN is a commonly encountered clinical entity that significantly compromises patients' overall quality of life. Patients having SFN are heterogeneous in clinical presentation, underlying causes, and pathophysiology. The presence of symptoms and/or signs of small fiber damage warrant a thorough evaluation for SFN. Furthermore, a diagnosis of SFN should also be considered in patients with chronic pain and autonomic dysfunctions with unclear causes."

However, due to the tireless efforts by some clinicians and researchers including the authors of this book, causes of SFN have been gradually clarified, and treatments for some diseases have been established, as shown clearly in this book. In addition, some clinical testing methods are now used to make a diagnosis of SNF.

I strongly recommend this book to not only experts of SFN but also junior clinicians to study SFN, since this book clearly covers both basic and up-to-date knowledge on the disease.

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Foreword

If your feet hurt, everything hurts. (widely attributed quote)

Springtime in nerveland (one of my patients with HIV neuropathy)

Two illuminating quotes from patients with neuropathic pain of small fiber neuropathy illustrate the tremendous constant impact of this disease entity or syndrome on quality of life. The incidence and prevalence of neuropathic pain continues to rise, and a recent systematic review estimated the prevalence of painful diabetic peripheral neuropathy ranging from 15.3 to 72.3/100,000 PY. Diabetes mellitus is certainly the most common trigger for painful neuropathy, and rates will likely to continue to rise with the epidemic of obesity and overconsumption of refined carbohydrates. Considering the wide range of systemic and primary neurological conditions associated with neuropathic pain related to small fiber neuropathy, this is clearly an affliction that is often misdiagnosed or inadequately treated. In recent years, considerable research has been dedicated to understanding its mechanisms, and new techniques have been developed for diagnosis including the much wider use of genetic testing, at substantially lower costs, and punch skin biopsy that has now entered the field as a simple and reliable tool to assess intra-epidermal nerve fiber densities and sweat gland innervation. Despite these advancements, there have been few advances in definitive treatments, with the exception of ASO therapies silencing therapies (siRNA and antisense oligonucleotide) for amyloid neuropathy, approved in 2018. In contradistinction, we now have a much better understanding of effective use of combination pain-modifying agents and increasingly of neuromodulatory strategies using devices such as the Scrambler™ and Rebuilder™. There are several new elements, however, that have changed the landscape for the management of neuropathic pain in small fiber neuropathy. First, these symptomatic therapies have developed in the setting of the opioid crisis that kills on average 116 people daily in the USA. Since the late 1990s, pharmaceutical companies reassured the medical community that patients would not become addicted to opioid pain relievers and healthcare providers began to prescribe them at greater rates. This led to widespread misuse of both prescription and nonprescription opioids before it became clear that these medications could indeed be highly addictive. According to the 2015 National Survey on Drug Use and Health (NSDUH), approximately 91.8 million adults aged 18 or older were users of prescription pain relievers in 2015, representing more than one-third (37.8%) of the adult US population. About 11.5 million adults misused pre-

scription pain relievers at least once in the past year. The most common reason for their last misuse of pain relievers was to relieve physical pain (63.4%). In 2017, HHS declared a public health emergency and announced a 5-point strategy to combat the crisis. A second element is the spreading legalization of marijuana. Medical marijuana is now legal in 30 states in the USA, and public support reached new levels in 2018 with 64% of Americans favoring legalization. It is highly likely that legal forms of marijuana will increasingly be used to treat small fiber neuropathy-related neuropathic pain. Finally, I believe that the future of developing even more effective therapies for small fiber neuropathy will predictably involve a "precision medicine" approach incorporating genetic testing (e.g., COMT and the variant allele V158M), metabolic parameters (diabetic control, hypertriglyceridemia, and inflammatory markers), and comorbid conditions.

The contributors to this book are internationally renowned leaders in the field of small fiber neuropathy. They discuss clinical approaches to diagnosis and treatment of small fiber neuropathy neuropathic pain and its underlying mechanisms. This book will serve as a useful guide for diagnostic approaches and treatment of small fiber neuropathy for the student, resident, practicing physician or advanced practice provider, researcher, and neuromuscular specialist.

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Preface by Sung-Tsang Hsieh

Small fiber neuropathy or syndrome of small fiber pathology has become a recognized disease entity due to improvement in diagnostic tools during the past decades. The development of skin biopsy is a key step to revolutionize assessments of small fiber neuropathy by providing objective and quantitative evidence of nociceptive nerve degeneration at the level of pathology. During the past 20 years, additional examinations on psychophysics and physiology such as quantitative sensory testing, pain-evoked potentials including laser-evoked potentials, and contact heat-evoked potentials offer complementary evaluations for functional deficits of small fiber neuropathy. Initially small fiber neuropathy was recognized as the major manifestations of neuropathies mainly affecting nociceptive and autonomic nerves, for example, diabetic neuropathy and familial amyloid polyneuropathy. With the applications of these advanced and integrated examinations including pathology of skin innervation, psychophysics of quantitative sensory testing, and physiology of pain evoked potentials, the spectrum of small fiber pathology actually extended to neuropathies in which large fiber deficits were considered as the main presentations, e.g., Guillain-Barré syndrome and vasculitic neuropathy. In addition to documenting nociceptive nerve degeneration in small fiber neuropathy of sensory type, skin biopsy also provides assessments for small fiber neuropathy of autonomic type including sudomotor, pilomotor, and vasomotor innervation. Furthermore, the applications of these tests expanded our understanding of neurodegenerative disorders and complex pain syndrome: Parkinson's disease, fibromyalgia, etc. This is an intriguing topic which certainly provides foundations for future studies to test whether small fiber pathology in the periphery could serve as a window to neurodegenerative disorders in the central nervous system.

This contributed volume intends to provide updated and concise information in the field of small fiber neuropathy and syndrome. Such a book project would never become a reality without the tremendous expertise and efforts of all coeditors, Professors Anand, Sommer, and Gibbons. I am indebted to the excellent editorial assistance from Springer Nature, particularly Xuewen, who enthusiastically initiated this project. Forewords by Professors Kakigi and McArthur are greatly appreciated which point the significance of this field. This work is in memorial for late Professor Jack Griffin, a great mentor in my research career, and also dedicated to my wife,

Whei-Min, who took care of checking the format of the writing with my son, Paul-Chen, and daughter, Christine Yi-Chen, and offer endless support with my works.

Neurology is in rapid progress, and the information needs update continuously. We look forward to comments from colleagues and readers.

Taipei, Taiwan Sung-Tsang Hsieh
October 15, 2018

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Abbreviations

AAN	American Academy of Neurology
ABCA1	Adenosine triphosphate-binding cassette transporter 1
ACC	Anterior cingulate cortex
ACCORD	Action to Control Cardiovascular Risk in Type 2 Diabetes
ALS	Amyotrophic lateral sclerosis
anti-dsDNA	Anti-double-stranded DNA
ApoA1	Apolipoprotein A1
ASIC	Acid-sensing ion channel
BDNF	Brain-derived neurotrophic factor
BMS	Burning mouth syndrome
BOLD	Blood-oxygen-level-dependent
BoNT/A	Botulinum toxin
BPS/IC	Bladder pain syndrome/interstitial cystitis
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAN	Cardiac autonomic neuropathy, cardiovascular autonomic neuropathy
CASPR2	Contactin-associated protein-like 2
CB1	Cannabinoid receptor 1
CBD	Corticobasal degeneration
CCI	Chronic constriction injury
CCM	Corneal confocal microscopy
CGRP	Calcitonin gene-related protein
CHEP	Contact heat-evoked potential
CIDP	Chronic inflammatory demyelinating polyneuropathy
CIPN	Chemotherapy-induced peripheral neuropathy
CMAP	Compound muscle action potential
CMT	Charcot-Marie-Tooth neuropathy (disease)
CMT2	Charcot-Marie-Tooth neuropathy type 2
CNS	Central nervous system
CRPS	Complex regional pain syndrome
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DAB	3,3′-Diaminobenzidine
DBH	Dopamine beta-hydroxylase
DCCT	Diabetes Control and Complications trial
DLPFC	Dorsolateral prefrontal cortex

DLRPN	Diabetic lumbosacral radiculoplexus neuropathy
DRG	Dorsal root ganglion/ganglia
DSPN	Distal symmetric polyneuropathy
EFNS	European Federation of Neurological Societies
EMG	Electromyography
EPO	Erythropoietin
EPSC	Excitatory postsynaptic current
EPSP	Excitatory postsynaptic potential
ESCS	Electrical spinal cord stimulation
FAC	Familial amyloid cardiomyopathy
FACT/GOG-Ntx	FACT/GOG-Neurotoxicity subscale
FAP	Familial amyloid polyneuropathy
FDA	Federal Drug Administration
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
GAP-43	Growth-associated protein 43
Gb3	Globotriaosylceramide
GBS	Guillain-Barré syndrome
GDNF	Glial cell-derived neurotrophic factor
GERD/GORD	Gastroesophageal (esophageal) reflux disease
GL3	Globotriaosylceramide
HbA_{1C}	Hemoglobin A_{1C}
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HSN/HSAN	Hereditary sensory (and autonomic) neuropathies
HSV	Herpes simplex virus
IASP	International Association for the Study of Pain
IB4	Isolectin B4
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IDO	Idiopathic detrusor overactivity
IENF(s)	Intraepidermal nerve fiber(s)
IENFD	Intraepidermal nerve fiber density
IgM	Immunoglobulin M
IL-1β	Interleukin-1β
IL-2	Interleukin-2
iRBD	Idiopathic rapid eye movement (REM) sleep behavior disorder
IVIg	Intravenous immunoglobulin
LDI_{FLARE}	Laser Doppler imager-FLARE
LEP	Laser-evoked potential
LGI-1	Leucine-rich glioma-inactivated 1
LTD	Long-term depression
LTP	Long-term potentiation
M-CSF	Macrophage colony-stimulating factor
mGluR5	Metabotropic glutamate receptor subtype 5
MPEP	2-methyl-6-(phenylethynyl)-pyridine
MSA	Multiple system atrophy

Na_v	Voltage-gated sodium channels
NCS	Nerve conduction studies
NeuPSIG	Neuropathic Pain Special Interest Group of International Association for the study of Pain
NFκB	Nuclear transcription factor κB
NGF	Nerve growth factor
NK1	Neurokinin-1
NMDA	*N*-methyl-D-aspartate or *N*-methyl-D-aspartic acid
NNH	Number needed to cause harm
NNT	Number needed to treat
NPY	Neuropeptide Y
NSAID	Nonsteroidal anti-inflammatory drug
NT-3	Neurotrophin-3
PAG	Periaqueductal gray
PD	Parkinson's disease
PENS	Percutaneous electrical nerve stimulation
PEPD	Paroxysmal extreme pain disorder
PGP9.5	Protein gene product 9.5
PHN	Postherpetic neuralgia
PKA	Protein kinase A
PKC	Protein kinase C
PMP22	Peripheral myelin protein 22
PNQ	Participant Neurotoxicity Questionnaire
PNS	Peripheral nervous system
POEMS	Polyneuropathy associated with organomegaly, endocrinopathy, monoclonal gammopathy, and skin hyperpigmentation
POTS	Postural tachycardia syndrome
PPI	Psychophysiological interaction
PSP	Progressive supranuclear palsy
QSART	Quantitative sudomotor axon reflex test
QST	Quantitative sensory testing
RA	Rheumatoid arthritis
RAGE	Receptors for advanced glycation end products
RBD	Rapid eye movement (REM) sleep behavior disorder, REM sleep behavior disorder
RBP	Retinol-binding protein
REM	Rapid eye movement
RTX	Resiniferatoxin
RVM	Rostroventromedial medulla
SFN	Small fiber neuropathy
SGNFD	Sudomotor nerve fiber density/sweat gland nerve fiber density
SLE	Systemic lupus erythematosus
SNRI	Serotonin noradrenalin reuptake inhibitor
SP	Substance P
SSEP	Somatosensory-evoked potential
SSR	Sympathetic skin response

SSRI	Serotonin specific reuptake inhibitor
T4	Thyroxine
TCA	Tricyclic antidepressant
tDCS	Transcranial direct current stimulation
TGF	Transforming growth factor
TH	Tyrosine hydroxylase
TIND	Treatment-induced neuropathy of diabetes
TMS	Transcranial magnetic stimulation
TNFα	Tumor necrosis factor α
TNSc	Total Neuropathy Score clinical version
TRPV1	Transient receptor potential subfamily vanilloid 1
TST	Thermoregulatory sweat testing
tTMS	Repetitive TMS
TTR	Transthyretin
UC	Ulcerative colitis
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VGKC	Voltage-gated potassium channels
VIP	Vasoactive intestinal peptide
VZV	Varicella zoster virus
WHO	World Health Organization
WHOQoL	WHO quality of life
α-Gal A	α-galactosidase A