

Update on the role of immunology in Inflammatory Neuropathies

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ABBREVIATIONS

<i>Class of Evidence for Therapy</i>	
<i>Class I</i>	-High quality randomized controlled trials (RCTs).
<i>Class II</i>	-Prospective matched group cohort studies or randomized controlled trials lacking adequate randomization concealment or blinding or potentially liable to attrition or outcome ascertainment bias.
<i>Class III</i>	-Other studies such as natural history studies.
<i>Class IV</i>	-Uncontrolled studies, case series or expert opinion.
<i>Strength of the Recommendations</i>	
<i>A</i>	-established as effective, ineffective, or harmful or as useful/predictive or not useful/predictive.
<i>B</i>	-Probably useful/predictive or not useful/predictive for the given condition in the specified population.
<i>C</i>	-Possibly effective, ineffective, or harmful or as useful/predictive or not useful/predictive.
<i>U</i>	-Data inadequate or conflicting. Treatment, test, or predictor unproven.

Abbreviations

AGEs	-Advanced Glycation End products
AIDP	-Acute Inflammatory Demyelinating Polyneuropathy
AIDS	-Acquired Immunodeficiency Syndrome
AMAN	-Acute Motor Axonal Neuropathy
AMSAN	-Acute Motor and Sensory Axonal Neuropathy
APOE	-Apolipoprotein E
AZT	-Zidovudine
BBB	-Blood-Brain Barrier
BNB	-Blood-Nerve Barrier
BNF	-Brain-derived Neurotrophic Factor
CANOMAD	-Chronic Ataxic Neuropathy, Ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies
CB	-Conduction Block
CBZ	-Carbamazepine
CD	-Cluster of Differentiation
Cer	-Ceramide
CIDP	-Chronic Inflammatory Demyelinating Polyneuropathy
CIDP-DM	-Chronic Inflammatory Demyelinating Polyneuropathy with Diabetes Mellitus
C.jejuni	-Cambylobacter jejuni

Abbreviations

<i>CMV</i>	-Cytomegalovirus
<i>CNS</i>	-Central Nervous System
<i>CR</i>	-Complement Receptor
<i>CSF</i>	-Cerebrospinal Fluid
<i>DRG</i>	-Dorsal root ganglion
<i>DADS</i>	-Distal Acquired Demyelinating Predominantly Sensory
<i>ddC</i>	-Zalcitabine
<i>ddI</i>	-Didanosine
<i>DN</i>	-Diabetic neuropathy
<i>DRG</i>	-Dorsal root ganglion
<i>EAN</i>	-Experimental Autoimmune Neuropathy
<i>EFNS/PNS</i>	-European Federation of Neurological Societies/Peripheral Nerve Society
<i>EMG</i>	-Electromyography
<i>Gal</i>	-Galactose
<i>GalNAc</i>	-N-acetylgalactosamine
<i>GBP</i>	-Gabapentin
<i>GBS</i>	-Guillain-Barre syndrome
<i>Ig</i>	-Immunoglobulin
<i>GALOP</i>	-Gait Ataxia and Late Onset Neuropathy
<i>GDNF</i>	-Glial cell line–derived neurotrophic factors
<i>Glc</i>	-Glucose

Abbreviations

<i>GlcNAc</i>	-N-acetylglucosamine
<i>GlcUA</i>	-Glucuronic acid
<i>HAART</i>	-Highly Active Antiretroviral Therapy
<i>Hex-LM1</i>	-SLPG, Sialosyllactosaminyllparagloboside
<i>HIV</i>	-Human Immunodeficiency Virus
<i>HLA</i>	-Human Leukocytic Antigen
<i>HS</i>	-Heat Stable
<i>IDDM</i>	-Insulin dependant diabetes mellitus
<i>ILs</i>	-Interleukins
<i>INCAT</i>	-International Neuropathy Cause and treatment
<i>IVIg</i>	-Intavenous Immunoglobulin
<i>LIF</i>	-Leukeamia Inhibitory Factor
<i>LL</i>	-Lepromatous Leprosy
<i>LM1</i>	-SPG, sialosylparagloboside
<i>LOS</i>	-Lipooligosaccharides
<i>LPS</i>	-Lipopolysaccharides
<i>LTG</i>	-Lamotrigine
<i>MAC</i>	-Membrane Attack Complex
<i>MASAM</i>	-Multifocal Axonal Sensory and Motor Neuropathy
<i>MAG</i>	-Myelin-Associated Glycoprotein
<i>MCV4</i>	-quadrivalent Conjugated Meningococcal Vaccine
<i>MDSAM</i>	-Acquired Demyelinating Sensory and Motor
<i>MFS</i>	-Miller Fisher Syndrome

Abbreviations

<i>MMN</i>	-Multifocal Motor Neuropathy
<i>MMPs</i>	-Matrix Metalloproteinases
<i>MRI</i>	-Magnetic Resonance Imaging
<i>NeuNAc</i>	-N-acetylneuraminic acid
<i>NCV</i>	-Nerve Conduction Velocity
<i>NF</i>	-Neuclear Factor
<i>NGF</i>	-Nerve Growth Factor
<i>NMJ</i>	-Neuromuscular junction
<i>NIDDM</i>	-Non Insulin Dependant Diabetes Mellitus
<i>NISLL</i>	-Neuropathy Impairment Score in the Lower Limbs
<i>OXC</i>	-Oxcarbazepine
<i>PCR</i>	-Polymerase Chain Reaction
<i>PE</i>	-Plasma Exchange
<i>POEMS</i>	-Polyneuropathy, organomegaly, endocrinopathy or edema, monoclonal protein, skin changes
<i>PNS</i>	-Peripheral Nervous System
<i>pSC</i>	-Perisynaptic Schwann cell
<i>PSSD</i>	-Peripheral Specified Sensory Device
<i>QST</i>	-Quantitative Sensory Testing
<i>RAGEs</i>	-Receptors for Advanced Glycation End products
<i>SGLPG</i>	-Sulfated Glucuronyl Lactosaminyl Paragloboside
<i>SGPG</i>	-Sulfated Glucuronyl Paragloboside
<i>SNAP</i>	-Sensory Nerve Action Potentials

Abbreviations

<i>SNRI</i>	-Serotonin-Noradrenaline Reuptake Inhibitors
<i>SOD3</i>	-Superoxide Dismutases
<i>SPG</i>	-Sialosylparagloboside
<i>SSR</i>	-Sympathetic Skin Response
<i>SSRIs</i>	-Selective Serotonin Reuptake Inhibitors
<i>SWM</i>	-Semmes-Weinstein Monofilaments
<i>TCA</i>	-Tricyclic Antidepressants
<i>TNF</i>	-Tumor Necrosing Factor
<i>TST</i>	-Triple Stimulation Technique
<i>TT</i>	-Tuberculoid Leprosy
<i>US</i>	-United States
<i>VEPs</i>	-Visual Evoked Potentials
<i>VPT</i>	-Vibration Perception Threshold

INTRODUCTION

Peripheral neuropathy is a generic phrase denoting functional and /or pathological changes in peripheral nerves. The disorder varies in severity , but in some cases it can be crippling and , if vital organ function is affected , even fatal. it is often symmetric , but can be asymmetric (*Donofrio, 2003*).

Inflammatory neuropathies represent a heterogeneous spectrum of peripheral nerve disorders that can be classified according to time , course, predominant involvement of motor and sensory fibers, distribution of deficits and paraclinical parameters such as electrophysiology and serum antibodies (*Kieseier , 2004*).

The nature of the underlying mechanisms in inflammatory and immune-mediated neuropathies continues to represent an intensive area of research. It was found that 32-70% of all peripheral neuropathy are idiopathic, but with the development of autoimmune and genetic tests ,the cause of this idiopathic neuropathies can be identified and can be treated (*Kieseier , 2004*).Different auto-antibodies that are thought to cause specific neuropathic syndromes have been described. The involvement of T cells, cytokines, complement and class II molecules in the pathogenesis has also been studied. There is also intensive investigation into the area of immunotherapy, in particular in the

use of intravenous immunoglobulin (Ig) (*Steck, 1992*).

The prototypic immune-mediated peripheral neuropathy is the Guillain–Barre´ syndrome (GBS), which is now recognized as a group of conditions with diverse pathology and pathogenesis (*Hughes & Rees, 1997; Hahn, 1998*). The therapeutic window for GBS is short, and the current optimal treatment with whole plasma exchange or intravenous immunoglobulin (Ig) therapy lacks immunological specificity and only halves the severity of the disease (*Visser et al., 1999; Raphael et al., 2001; Hughes et al., 2004a; 2004b*). Thus, there is an incentive to understand GBS pathogenesis as a prerequisite to developing and instituting effective, contemporary immunotherapies. Other dysimmune neuropathies can also be recognized such as, for instance, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and nonsystemic vasculitic neuropathies (*Hughes et al, 2008*).

Immune mechanisms has been postulated also in other types of neuropathies as diabetic neuropathy. Diabetic neuropathy (DN) is the most common and troublesome complication of diabetes mellitus, leading to great morbidity and mortality. Epidemiologic data suggest that approximately 30% to 40% of people with type 2 diabetes have a distal peripheral neuropathy and is responsible for 50% to 75% of nontraumatic amputations

(*Holzer ,1998; Hink,2001*). It now seems that the pathogenesis of diabetic neuropathy is heterogeneous. New therapies are aimed at the underlying pathogenesis as well as the symptom complex (*Guo , 2001; Hyllienmark 1995*) . Electrophysiology, particularly conduction velocity alone, may provide a poor measure of early dysfunction in some patients, because there is little demyelination in the early stages (*Holland et al.,1997;Lauria et al., 2007*).

In practice, many of the autoimmune neuropathies are difficult to diagnose, due to a lack of generally accepted clinical diagnostic criteria, or availability of reliable serological tests. Consequently, many patients with autoimmune neuropathies are diagnosed as having “idiopathic neuropathy” instead, and left untreated despite progression of their disease (*Kieseier et al., 2004*). In the last few years, significant advances in molecular immunology and biotechnology have been achieved in elucidating underlying pathomechanisms, which made it possible to identify potential therapeutic targets and selecting the correct strategies for novel therapeutic interventions and the management of patients with this class of disorders.