Update on the role of immunology in Inflammatory Neuropathies

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Index

Tables

Figures

ABBREVIATIONS

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

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

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

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

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

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