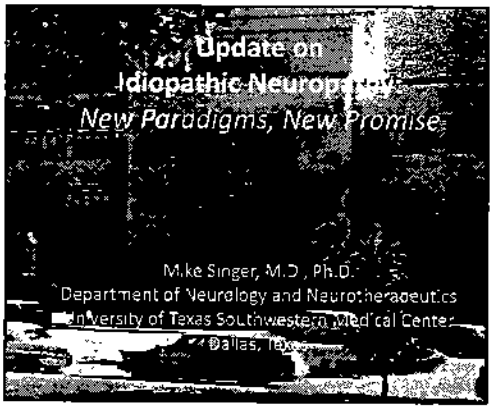
Idiopathic Polyneuropathies

Mike Singer, MD, PhD
Assistant Professor of Neurology
UT Southwestern Medical School
Dallas, TX

Objectives: Outline the challenges when the evaluation of your neuropathy patient is normal - what's next?



Terminology

Unclassified peripheral neuropathy

Idiopathic neuropathy

Chronic polyneuropathy of undetermined cause

Cryptogenic sensory polyneuropathy

Cryptogenic polyneuropathy

Chronic idiopathic axonal polyneuropathy (CIAP)

Idiopathic Neuropathy is a Major Public Health Problem

An estimated 5 to 8 million Americans have idiopathic neuropathy.
Bright et al, 1995, Gregg et al 2004 Smith and Singleton, 2006

Alzheimer's disease *National Institute on Aging*	2.4 to 5.1 million
Parkinson's disease *National Institutes of Health*	500,000
Multiple sclerosis *National Multiple Sclerosis Society*	400,000
Amyotrophic lateral sclerosis *ALS Association*	30,000

How Often is Neuropathy Idiopathic?

Matthews (1952)	70%
Rose (1960)	56%
Prineas (1970)	38%
Dyck (1981)	24%
Fagius (1983)	74%
Konig (1984)	14%
McLeod (1984)	13%
Corvisier (1987)	11%
Notermans (1983)	10%
Wolfe (1999)	23%
Jann (2001)	18%
Rosenberg (2004)	6%
De Sousa (2006)	61%

Initial Paradigm: Improved Recognition of Familiar Etiologies

Enhanced identification of hereditary neuropathies
Dyck et al, 1981

Chronic inflammatory demyelinating polyneuropathy
Dyck et al, 1975

Neuropathy associated with monoclonal gammopathies
Latov et al, 1981; Gosselin et al, 1991; Pestronk et al, 1991

A New Paradigm: Idiopathic Neuropathy as a Distinct Entity

"Late-life chronic peripheral neuropathy of obscure nature"
CM Fisher, 1982

Systematic study of patients with chronic idiopathic axonal polyneuropathy
Notermans et al, 1993

Establishment of specific criteria for diagnosis
Wolfe et al, 1999

Characterization: Diagnosis of Exclusion

Personal, Social, and Family History
- History of exposure to toxins
- History of alcohol abuse
- Family history of neuropathy

General
- Complete blood count
- Comprehensive metabolic panel

Endocrine
- Thyroid function
- 2-hour glucose tolerance test

Metabolic
- Vitamin B12 (with methylmalonic acid and homocysteine)
- Thiamine
- Pyridoxine

Infectious
- Hepatitis B and C serologies
- HIV
- Syphilis testing
- Lyme serology

Toxins
- Heavy metals screen

Autoimmune/ Inflammatory
- Erythrocyte sedimentation rate
- Antinuclear antibodies
- Anti-neutrophil cytoplasmic antibodies
- SSA and SSB
- Rheumatoid factor
- Serum protein electrophoresis
- Urine protein electrophoresis
- Gliadin and transglutaminase antibodies
- Paraneoplastic antibodies

Characterization: General Clinical Features (I)

Onset in age 50s-60s.

Acquired sensorimotor polyneuropathy or exclusively sensory polyneuropathy.

Idiopathic sensory polyneuropathy may evolve into sensorimotor polyneuropathy over time.

Patients with only sensory symptoms and signs on clinical evaluation may demonstrate motor nerve involvement on EMG/NCS.

Insidious onset and slowly progressive.

Cheema and Wolfe, 2003, De Sousa et al 2006, de Schryver et al, 2010, Traub et al 2010

Characterization: General Clinical Features (II)

Symmetric sensory loss or altered sensation beginning in the distal limbs, typically in the feet.

Not limited to region of a single nerve.

May affect one or more sensory modality.

Present for over 3 months; not rapidly progressive.

Strength is usually preserved.

Neurologic examination may identify minimal weakness or atrophy in the fingers or toes.

Characterization: General Clinical Features (III)

Reflexes may be diminished or absent.

Several studies have shown male predominance, up to 2:1 or 3:1 …

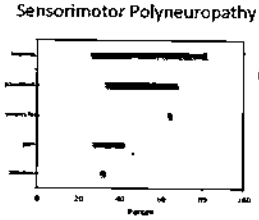
Primeas et al, 1970, Notermans et al, 1993; Jann et al, 2001, Lindh et al, 2005

… although other series have had similar numbers of men and women.

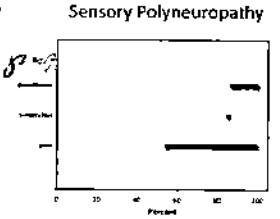
Wolfe et al, 1999, De Souza, 2006

Characterization: Common Presenting Symptoms

Sensorimotor Polyneuropathy



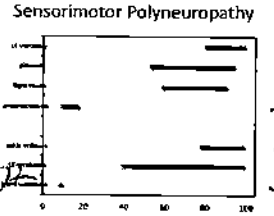
Sensory Polyneuropathy



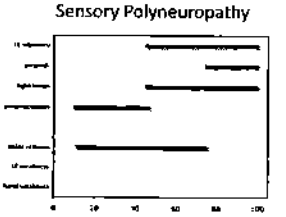
McLeod et al, 1984, Notermans et al, 1993; Gorson and Ropper, 1995; Periquet et al, 1999; Wolfe et al, 1999, Jann et al, 2001, Hughes et al, 2004, Lindh et al 2005

Characterization: Common Examination Findings

Sensorimotor Polyneuropathy



Sensory Polyneuropathy



Notermans et al, 1993; Gorson and Ropper, 1995, Periquet et al, 1999; Wolfe et al, 1999, De Sousa et al 2006

Characterization: Electrophysiology

Nerve conduction studies are abnormal in >75% of patients.

Most common finding is reduced-amplitude or absent sural sensory response, consistent with axonal pathology.

EMG abnormalities have been observed in a majority of patients, including patients with no motor symptoms or findings on neurologic examination.

This finding is consistent with more widespread subclinical sensorimotor polyneuropathy.

Gorson and Ropper, 1995, Periquet et al, 1999, Wolfe et al 1999

Characterization: Additional Tests

For detection of small-fiber neuropathy (sensitivity):

Skin biopsy for epidermal nerve fiber density: 88%

Quantitative sensory testing: 84%

Autonomic symptoms or prominent distal small-fiber neuropathy:

Autonomic testing, including quantitative sudomotor axon reflex testing and heart-rate variability

Limited utility:

Cerebrospinal fluid is generally unremarkable in CIAP.

Sural nerve biopsy typically demonstrates axonal pathology.

Gorson and Ropper, 1995, McArthur et al, 1998, Periquet et al, 1999, Wolfe et al, 1999; Low et al 2006; Devigili et al, 2008

Characterization: Natural History

Stable or slowly progressive over years.

Sensory polyneuropathy may reach a stable plateau.

Nearly all patients maintain the ability to walk independently, but may require cane or ankle braces.

Important to address ambulation, fatigue, and pain to minimize limitations from disease.

Prineas, 1970, Grahmann et al 1991, Notermans et al, 1994, Wolfe et al, 1999, Jann et al 2003, Vrancken et al, 2002; Erdmann et al, 2007

Characterization: Pain Treatment

Based on treatment of neuropathic pain, primarily from diabetic neuropathy or HIV-associated neuropathy.

Primary medications:

Tricyclic antidepressants (eg, amitriptyline, nortriptyline)

Calcium-channel alpha-2-delta ligands (gabapentin, pregabalin)

SNRI antidepressants (venlafoxine, duloxetine)

Opiods can be used successfully with skilled management

Less effective:

SSRI antidepressants

Anti-epileptic medications

Traub et al, 2010, O'Connor and Dworkin, 2009

A Second New Paradigm: Search for Treatable Risk Factors

Impaired glucose tolerance
Smith and Singleton, 2001; Novello et al, 2001

Hypertension, hypercholesterolemia, current smoking
Teunissen et al, 2002

Hypertriglyceridemia (but not hypercholesterolemia or impaired glucose tolerance)
Hughes et al, 2004

Metabolic syndrome
Smith and Singleton, 2006

UT Southwestern Retrospective Study of Risk Factors for Chronic Idiopathic Axonal Polyneuropathy *[126 patients] [Singer et al, manuscript in preparation]*

Methods (I)

Retrospective case-control study, examining records of patients evaluated in the neuromuscular clinic at UT Southwestern.

Cases: 126 patients with CIAP

Controls: 98 patients with amyotrophic lateral sclerosis (ALS)

Cases and controls were matched for sex and age (within 10 years).

Methods (II)

The control group was selected to:

Minimize referral bias, since like the cases, the controls are also patients referred to our neuromuscular clinic, typically by neurologists.

Minimize diagnostic (and ideally, pathologic) overlap, since ALS is a disorder of motor rather than sensory, neurons.

Inclusion Criteria

Men and women over 18 years old.

Cases:

Clinical diagnosis of CIAP based on history and neurologic examination demonstrating approximately symmetric loss of sensation, pain, tingling or numbness in the distal extremities for >3 months.

Thorough laboratory evaluation, including EMG/NCS, to exclude known causes of neuropathy.

Controls:

Diagnosis of ALS following generally-accepted clinical criteria, as per World Federation of Neurology Revised El Escorial guidelines.

Exclusion Criteria

History of diabetes mellitus (*in cases only, not in controls*), uncontrolled hypothyroidism, vitamin B12 deficiency, neoplasm, HIV/AIDS, uremia, connective tissue disease, syphilis, amyloidosis, or monoclonal gammopathy preceding onset of neuropathy.

Family history of neuropathy.

Known history of environmental or occupational toxin exposure.

Self-reported history of alcoholism.

Results (I): Population

	Men	Women	TOTAL
CIAP	55	71	126
ALS	46	52	98

	Mean Age (years)	SD	
CIAP	65.0	12.0	*t* test, p = 0.14
ALS	62.6	11.7	

No significant differences in sex or age distribution, or imbalance from unmatched CIAP patients.

Results (II): Frequencies

	CIAP	ALS
IGT	42 (43%)	9 (9%)
Hypertension	77 (62%)	41 (43%)
Hyperlipidemia	53 (44%)	32 (33%)
OSA	14 (11%)	2 (2%)
Alcohol use	62 (49%)	39 (40%)
Tobacco use	51 (40%)	37 (38%)

Results (III): Body-mass Index

Initial BMI in patients and controls:

	CIAP	ALS	p value
BMI (kg/m^2)	28.4 ± 5.8	26.2 ± 4.8	0.018

Results (IV):
Unadjusted odds ratios for CIAP vs controls

	OR	95% CI	p value
IGT	**7.33**	**(3.45, 17.1)**	**<0.0001**
Hypertension	**2.20**	**(1.28, 3.80)**	**0.0045**
Hyperlipidemia	1.63	(0.94, 2.86)	0.085
OSA	**5.94**	**(1.61, 38.4)**	**0.021**
Alcohol use	1.47	(0.86, 2.50)	0.16
Tobacco use	1.12	(0.65, 1.93)	0.68

A Third New Paradigm -- CIAP as an Oxidative Stress Disorder? (I)

Oxidative stress is one of several hypotheses suggested for CIAP
Hughes et al, 2004

Known vulnerability of the peripheral nervous system to oxidative stress
Vincent et al, 2004

Possible risk factors are associated with increased oxidative stress
Lavie, 2009

Similarity of CIAP to decline of peripheral nerve function with advanced age

A Third New Paradigm -- CIAP as an Oxidative Stress Disorder? (II)

Verghese et al, 2001
Idiopathic neuropathy is significantly more common in patients >80 years old, compared to younger patients:
39% vs 9% ($p < 0.001$)

Vrancken et al, 2006
Meta-analysis of 50 studies (9,996 patients) from 1960-2004.
Examination findings in self-reported healthy individuals >60 years old, not seen in self-declared healthy patients <60 years old:

Absent vibration at hallux	29% (95% CI: 18, 38)
Absent vibration at ankle	15% (95% CI: 11, 20)
Absent ankle reflexes	23% (95% CI: 16, 30)

A Third New Paradigm -- CIAP as an Oxidative Stress Disorder? (III)

Rivner et al, 2001
Analysis of nerve conduction studies performed on 3969 patients deemed clinically normal, based on examination by a neurologist:

	Age (years)			
	<50	50-59	60-69	70-79
Absent sural response	< 1%	3%	5%	24%

A Third New Paradigm -- CIAP as an Oxidative Stress Disorder? (IV)

Jacob and Love, 1985; Swallow, 1966
Analysis of peripheral nerves from patients >50 years old shows axonal degeneration with attempted regeneration

Periquet et al, 2000
Skin biopsy shows decreased intraepidermal nerve fiber density in normal individuals >60 years old, compared to normal individuals aged 20-59.

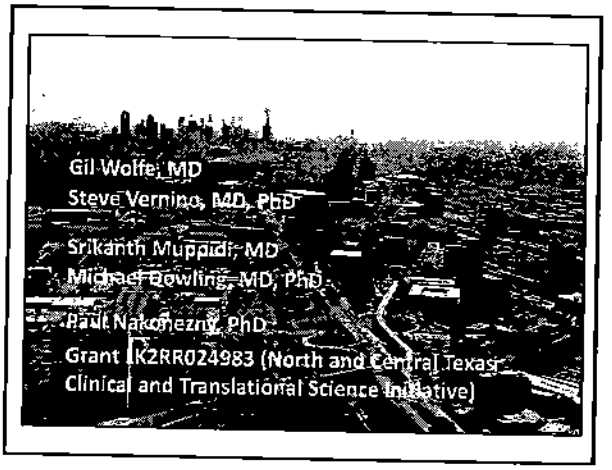
Future Directions

Genome microarray analysis of CIAP patients (with Dr. Benjamin Greenberg at UT Southwestern).

Investigation of oxidative stress biomarkers in CIAP patients compared to controls.

Prospective study of CIAP in patients with obstructive sleep apnea.

Online registry of CIAP patients, to facilitate collaboration and further studies, and provide information for patients and families.


Gil Wolfe, MD
Steve Vernino, MD, PhD
Srikanth Muppidi, MD
Michael Bowling, MD, PhD
Paul Nakonezny, PhD
Grant K2RR024983 (North and Central Texas Clinical and Translational Science Initiative)