Nerves and Neuropathy

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Structure of a neuron

- Dendrite
- Cell body
- Axon
- Axon terminal
- Node of Ranvier
- Schwann cell
- Myelin
- Nucleus

users.tamuk.edu
What is an Axon?

• An axon is the arm-like extension of a nerve cell (neurons)
• There are motor, sensory and autonomic neurons which send out axons
• The neurons are located in or near the spinal cord
What is a Nerve?

- A nerve is a cable-like bundle of axons that runs between the spinal cord and the periphery.
- Axons transmit information by an electrical current that runs along the axon like a wire in your home.
- The axons are each surrounded by a fatty coating, called myelin, that acts like insulation on a wire.
Cross Section of a Nerve

Nerve

www.axogeninc.com
Normal Nerve – Longitudinal Section
3 Types of Axons

1. Motor
   - Information runs from cell bodies in the spinal cord to muscle
   - These axons are thick with a heavy fatty coating

2. Sensory
   - Information runs from nerve endings in the skin and organs to the spinal cord and up to the brain
   - These axons are thin with less fatty coating
3 Types of Axons

3. Autonomic ("automatic")

Information runs out from the spinal cord to:
- Salivary glands in the mouth
- Tear glands in the eye
- Muscle in the walls of blood vessels
- Muscle in the walls of the stomach and intestine
- Sweat glands in the skin
- Blood vessels in the genitals

• These axons are the thinnest, with almost no fatty coating
What is Neuropathy?

- Neuropathy is a general term meaning damage to a nerve
- One nerve = mononeuropathy
  - Example carpal tunnel syndrome
- Many nerves = polyneuropathy
  - Also called peripheral neuropathy
Nerve Damage in Amyloidosis

• Seen in two types
  – Primary (AL, problem in bone marrow)
  – Inherited
    • TTR – also called Familial Amyloid Polyneuropathy
    • Gelsolin
    • ILE122 (though not common)
  – Not typically seen
    • AA amyloid
    • Focal amyloid
What the heck is amyloidosis?

• A general term that refers to a number of diseases that result from extracellular deposition of insoluble proteins in tissues and organs.
• The diseases are a subset of disorders caused by misfolding of protein.
• Many different proteins can make amyloid fibrils
• All have a β-pleated sheet conformation which confers unique staining properties
Beta-Pleated Sheet

From *Biochemistry* 2nd Ed. by Garrett and Grisham (Harcourt, Brace & Company)
Birefringence

www.neuro.wustl.edu/neuromuscular
Birefringence
Nerve Damage in Amyloidosis

- Can be one nerve
  - Carpal tunnel syndrome

- Can be generalized disorder of nerves
  - Amyloid polyneuropathy = peripheral neuropathy
Amyloid Polyneuropathy

- Axonal, length-dependent, symmetrical, dying-back neuropathy
  - Axon itself is damaged
    - Compression by amyloid deposits
    - Amyloid compresses blood vessels to nerve and prevents blood flow
  - The area that surrounds the dorsal root ganglia, where sensory axons are located, has a poor blood/nervous system barrier and amyloid can infiltrate here and damage sensory neurons and axons
Nerve with amyloid deposit

Amyloid surrounding an artery
Normal nerve cross-section  Nerve with amyloid

Missinglink.ucsf.edu  Wustl.....
Amyloid Polyneuropathy

• Longest nerves affected first – why?
  – High metabolic load
• Symmetrical
• The nerve degenerates from the end, upward
• Thin axons affected first (pain and autonomic)
• Thick axons affected later (to muscle)
Symptoms of Polyneuropathy

- Tingling, numbness, burning, electrical shocks, feeling cold, feeling like walking on cotton/something in your shoe
- Often feel worse at night
  - Off your feet
  - Not distracted
Symptoms of Polyneuropathy

- Same in amyloid as in neuropathy due to other causes such as diabetes, kidney failure or alcohol use.
- Start in feet, slowly climbs up the legs. When the symptoms are at knee level symptoms start in the hands.
Symptoms of Polyneuropathy

• Why does it feel numb and painful at the same time?
  – Different axons mediate different sensations
  – Thin axons mediate pain sensation
    • When damaged, they fire – brain “feels” it as pain
  – Thick axons mediate touch and pressure sensation
    • When damaged, do not transmit information to the brain – so brain does not “feel” touch
Diagnosis of Amyloid Polyneuropathy

- History
- Examination
- Nerve Conduction Studies
- Electromyography (EMG)
- Blood work
- Biopsies
- “Rule out” other causes
Think about other causes of PN

• Are symptoms directly related to amyloid deposition or to something else?
  – Organ damage due to amyloidosis
    • Kidney failure
    • Malnutrition
  – Other medical problems
    • Diabetes
    • Vitamin deficiency
    • Thyroid disease
  – Medications and other toxins
    • alcohol
Treatment

1. Etiologic
   Treating the cause of neuropathy

2. Symptomatic
   Treating the symptoms
If the cause is treated will my nerves grow back?

• Maybe
• Nerves regrow best in people who are young and otherwise healthy
• Nerves grow back slowly
  – 1 mm a day = 1 inch a month = 1 foot a year
Etiologic Treatment of ATTR

- Molecules that stabilize TTR so it does not fall apart, change confirmation and deposit in tissues
  - Diflunisal
  - Tafamidis
Etiologic Treatment of ATTR

- Preventing the liver from making mutant TTR
  - Liver transplantation

- Medications that prevent liver cells from making TTR
  - RNA antisense/interfering molecules
    - ISIS
    - Alnylam
Can amyloid be removed from tissues once it deposits?

• Maybe
  – Doxycycline trial
  – Monoclonal antibodies
Treatment of Polyneuropathy

• First ask – Do I Need To Be Treated?
  – Is underlying disease being treated?
  – No treatment to make nerves grow back
  – Treatment is symptomatic
    • Crazy-making: Yes or No??
Symptomatic Treatment of Polyneuropathy

• Without Medication
  – Foot rub or warm water foot massage before bed
  – Acupuncture: Anecdotal reports only (but check with your doctor regarding risk of infection!!!)
Symptomatic Treatment

• Topical Medication
  – Lidoderm patch – topical anesthetic
  – Anesthetic cream
  – Capsacin
    • causes release of Substance P (causes pain)
    • initially increases pain
    • must be used 2-3 times/day
Symptomatic Treatment

Medication

• Anti-seizure medications
  – Lyrica (pre-gabalin)
  – Neurontin (gabapentin)
  – others

• Antidepressants
  – Cymbalta (duloxetine)
  – “tricyclic antidepressants” like Elavil – not typically used in amyloid

• Anti-inflammatory
  – Aspirin-like drugs
  – Tylenol
Treatments for severe pain

- Narcotics
  - Extended release pill or patch
- Intravenous lidocaine
- Marijuana
- Percutaneous nerve stimulation
- Nerve stimulation (TENS) unclear if effective
- Spinal cord stimulation
  - Very invasive, risk of infection
Symptoms of Autonomic Dysfunction

• Dry eyes and mouth
  – Nerves to the glands are damaged

• Trouble accommodating to bright light
  – Autonomic nerves control how constriction of the pupil in the eye

• Lightheadedness when standing
  – Blood vessels do not constrict when you stand up
  – Heart rate does not increase when you stand up

• Diarrhea

• Constipation

• Erectile dysfunction

• Talk to your doctor about symptomatic treatment for these symptoms
Beware

ReBuilder

$500-700

Neuracel

$70 for one month
A word about foot care

• Foot care is important
• If you can’t feel your feet you can’t feel cuts or sores that can become infected.
• Foot care tips
  – Look between and under your toes every day
  – Wear soft, well fitting shoes
  – Do not walk barefoot, particularly outside
  – Keep feet soft and well moisturized
  – Have nails filed rather than cut
    • A podiatrist or specialized pedicurist can help
    • Don’t cut your own nails
• We want you have all 10 toes, all of the time!
Carpal Tunnel Syndrome

www.carpal-tunnel-syndrome.com
Carpal tunnel syndrome (CTS)

- Common in the general population over age 50 and common in TTR amyloidosis
- Also seen with diabetes and low thyroid function
- May have this many years before diagnosis is made.
- The median nerve runs down from the neck into the hand
- At the wrist, the nerve runs under a band of connective tissue that encircles the wrist
- Amyloid deposits in the connective tissue and compresses the nerve
CTS Symptoms

- Tingling, pain, numbness in the thumb, forefinger and middle finger
- Weakness of the thumb and of grip
- Trouble opening jars and buttoning
- Worse at night, with driving, typing
CTS Treatment

• Ergonomic adjustment
• Wrist brace
• Local injection of steroid
• Surgery
  – Always make sure the surgeon sends a sample of the connective tissue band to pathology!!
Carpal Tunnel Syndrome

wikipedia
What you can do for healthy nerves

1. CUT DOWN ON ALCOHOL – IT IS DIRECTLY TOXIC TO NERVES

2. STOP SMOKING – WITH EVERY PUFF YOU CAUSE CONSTRICTION OF THE BLOOD VESSELS THAT NOURISH NERVES

3. EAT A LOT OF FRUITS AND VEGETABLES, ESPECIALLY DARK GREEN LEAFY VEGETABLES WHICH CONTAIN B VITAMINS (but not if you are taking coumadin)

4. MUSCLES DEPEND ON THEIR NERVE SUPPLY TO STAY HEALTHY – USE THEM BOTH
Resources

• Healthy Nerves pamphlet on ASG website
• Boston University Amyloid Treatment and Research Website
  – Podcasts
  – Healthy Nerves pamphlet

http://www.bu.edu/amyloid/resources/patient-resources/