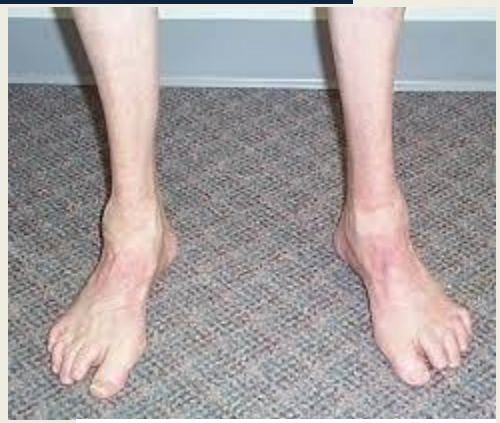
Charcot-Marie-Tooth Disease Type 1A

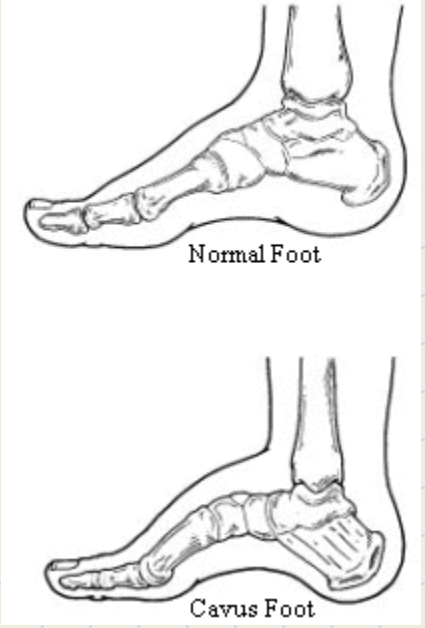
A GENETIC DISEASE

By Allen Na

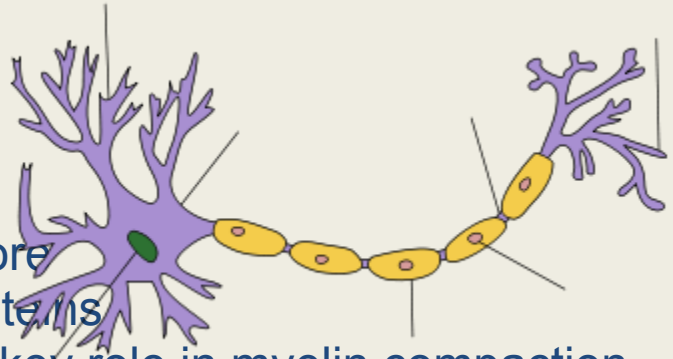
PHYSIOLOGY

- 15 in 100,000 occurrence rate
- Age of onset: Childhood to adulthood
- Progressive distal muscle weakness and wasting
- Foot deformities, unorthodox gaits
- Sometimes hard to diagnose because symptoms appear gradually
- Hyporeflexia
- Symptoms begin in the lower legs but can expand upwards
- Trouble with fine motor skills-- fingers, toes, tongue





MOLECULAR CAUSE



- Autosomal Dominant
- Duplication of peripheral myelin protein 22 (PMP22) gene on chromosome 17
- Gene is coded correctly, just too much of it
- PMP22 tends to misfold a lot normally, so more of the gene means more of the misfolded proteins
- PMP22 is an integral glycoprotein and has a key role in myelin compaction
- Lots of misfolded proteins overload the proteasome, so some misfolded ones escape and aggregate in the cytoplasm or move to cell membrane
- Misfolded proteins are not efficient at their job-- myelin is not compact
- Demyelination causes symptoms such as hyporeflexia, not muscle weakness. Motor nerve conduction velocity shows no correlation with distal muscle weakness
- Demyelination is linked to axonal degeneration
- Axonal loss shows significant correlation with weakness

Treatments/Risks and Limits

- No cure
- Symptom managements
- Daily exercise
- Physical therapy
- Brace, orthosis, splint for support
- <5% severely affected patients need wheelchairs
- Pills to treat pain
- Cures on the horizon
  - Anti-progesterone: Less PMP22 mRNA but may mess with female progesterone levels
  - Stem cells: Potential to regenerate axons. Hard to control differentiation of cell. May be rejected and may cause cancers
  - Exogenous growth factors: Rescue generating neurons by stimulating regeneration. Needs to be deployed in early stages in order to combat symptoms

PROPOSED CURE/LIMITS

- Chaperone proteins help the cell repair and traffic other proteins, and are more prominent when the cell is under stress
- Upon heat shock, the number of misfolded proteins greatly increase, and to counter this, heat shock proteins(HSPs), a subclass of chaperones, are deployed.
- Proposal is to induce heat shock response in order to release chaperones
- Celastrol, a HSP90 inhibitor found in some plants activates heat shock transcription factor 1(HSF1) similarly to what heat stress would do
- HSPs can help relieve stress on the proteasome, and clear the aggregation of misfolds in the cytoplasm. The working proteins would prevent demyelination, axonal loss, and finally, the symptoms
- Would help many diseases related to protein misfoldings
- Celastrol induced heat shock response still not strong enough--chaperones deployed not enough
- Foot deformities would remain

Citations

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Images(in order they appear)
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