Medische update: ontwikkelingen in het onderzoek naar erfelijke polyneuropathieën

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Ontwikkelingen

Classificatie

Diagnostiek

Behandeling

Classificatie erfelijke neuropathieën

(Poly)neuropathie: beschadiging van (meerdere) zenuwen

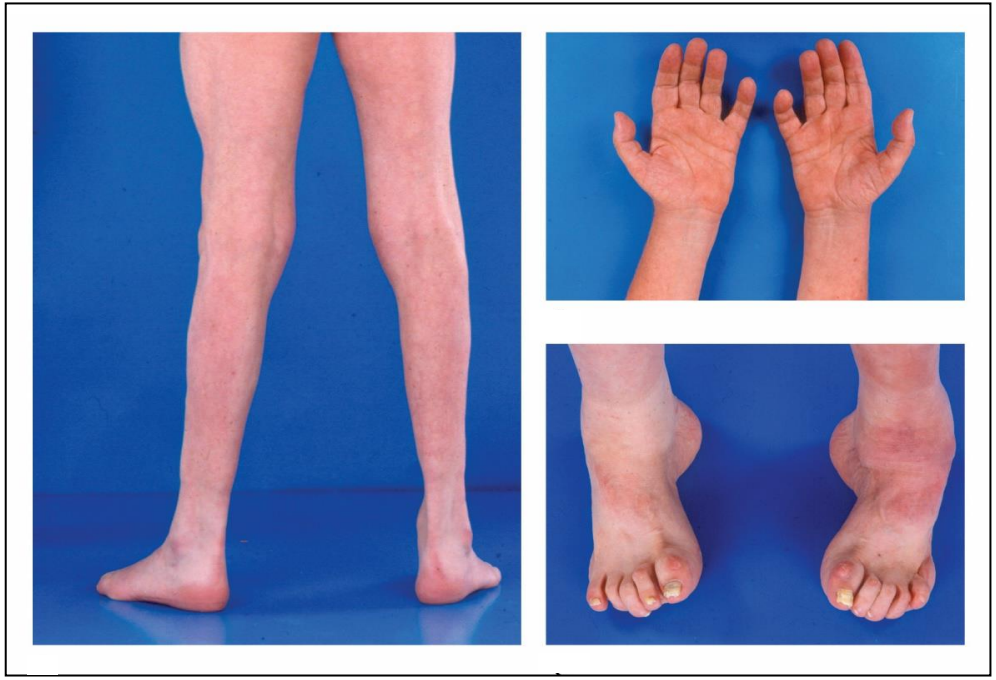
- Op zichzelf staande aandoening

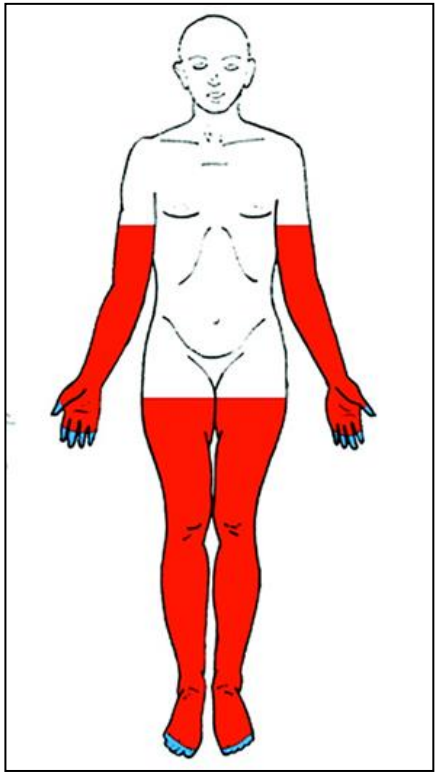
  Charcot-Marie-Tooth (**CMT**) en gerelateerde aandoeningen
  - hereditaire motorische en sensorische neuropathie - HMSN
  - erfelijke drukneuropathie - HNPP

- Onderdeel van uitgebreidere aandoening

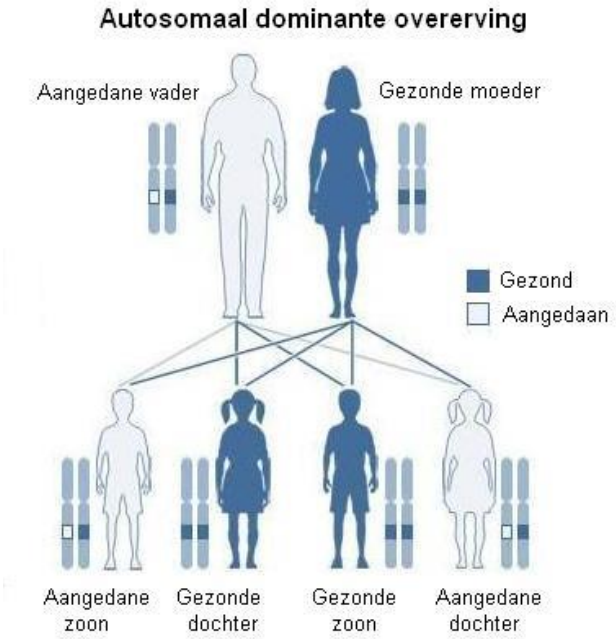
HMSN	HNPP
1 : 2.500	1 : 20.000-50.000
Meest voorkomend	zeldzaam
Autosomaal dominant; autosomaal recessief; X-gebonden	Autosomaal-dominant
verschillende genen; oa PMP22 duplicatie	PMP22 deletie
Alle leeftijden	Alle leeftijden (meest 20-30 jr)
	mechanische stress
Natuurlijk beloop studies	Natuurlijk beloop ? Geen

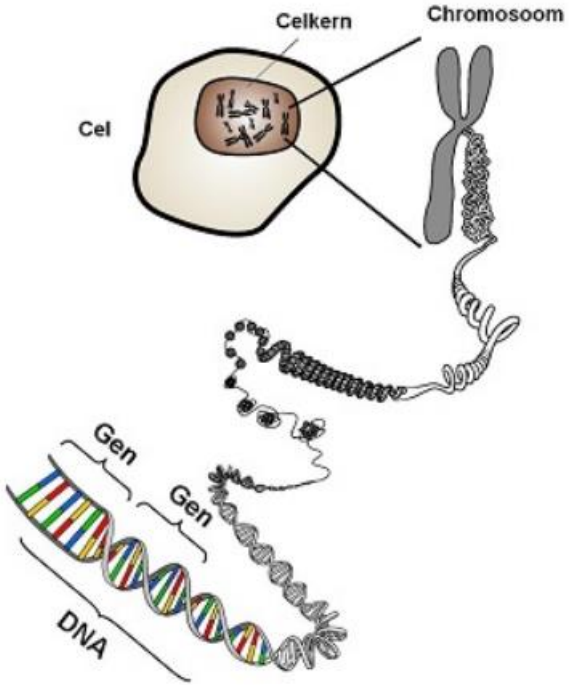
CMT/HMSN





Erfelijk



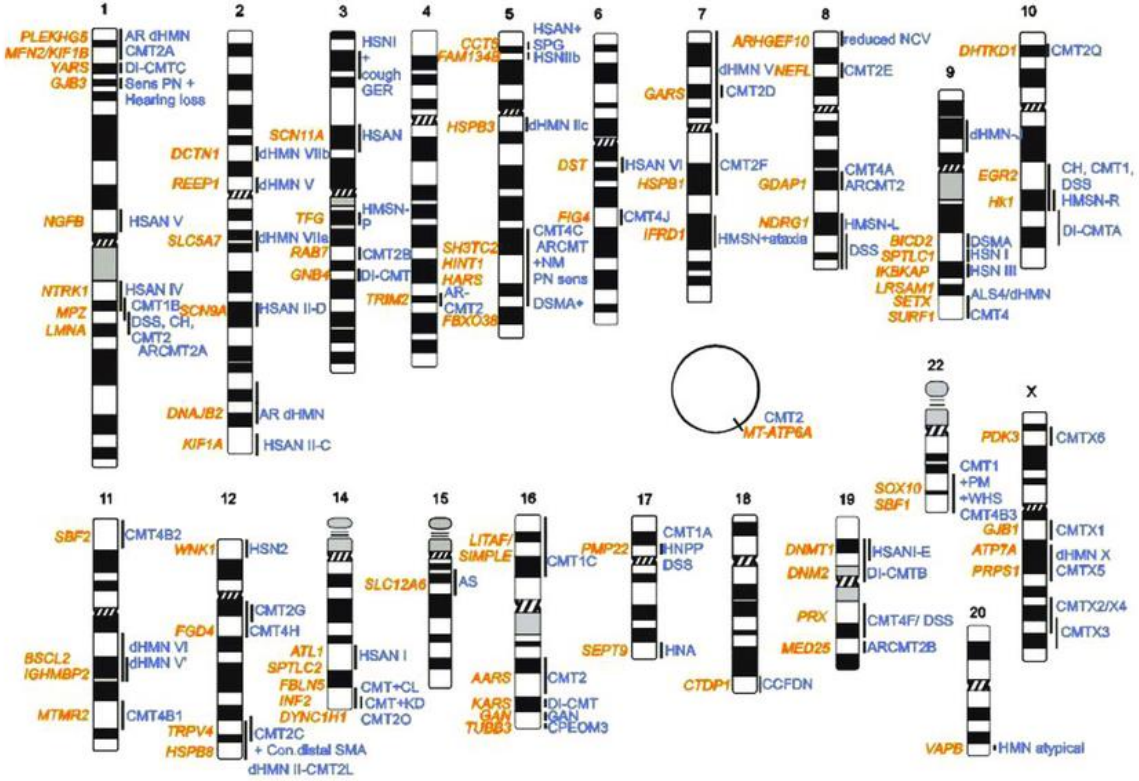


www.erfelijkheid.nl

Genetisch verschillend

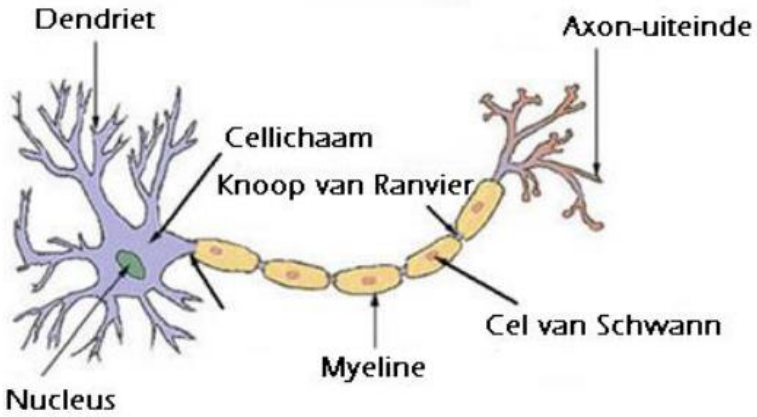
>100 genen

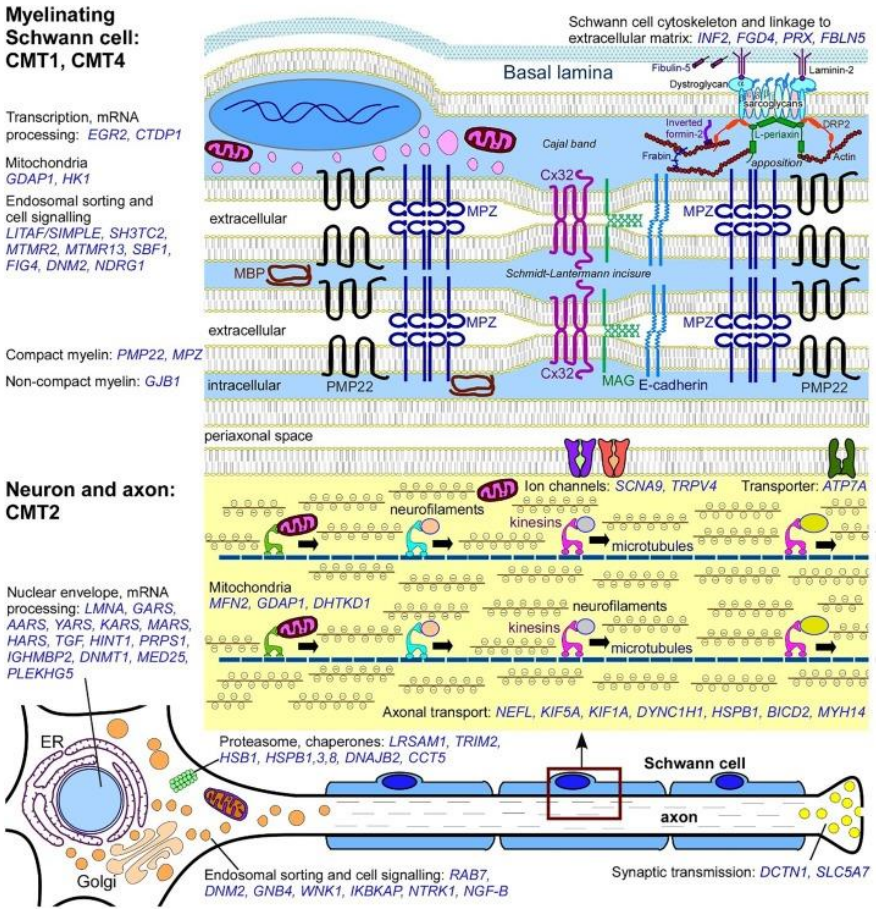
Uiting redelijk hetzelfde



Timmerman et al, 2014

Myeline - axon





Stavrou, Neuroscience letters, 2021 https://doi.org/10.1016/j.neulet.2020.135357

DNA diagnostiek

Van: gericht per gen (stukje DNA)

Naar:

Next generation sequencing

1. Gen panels
2. Whole exome
3. Whole genome

CMT1A - PMP22

CMT1B - MPZ

CMTX1 - Cx32

CMT2A - MFN2

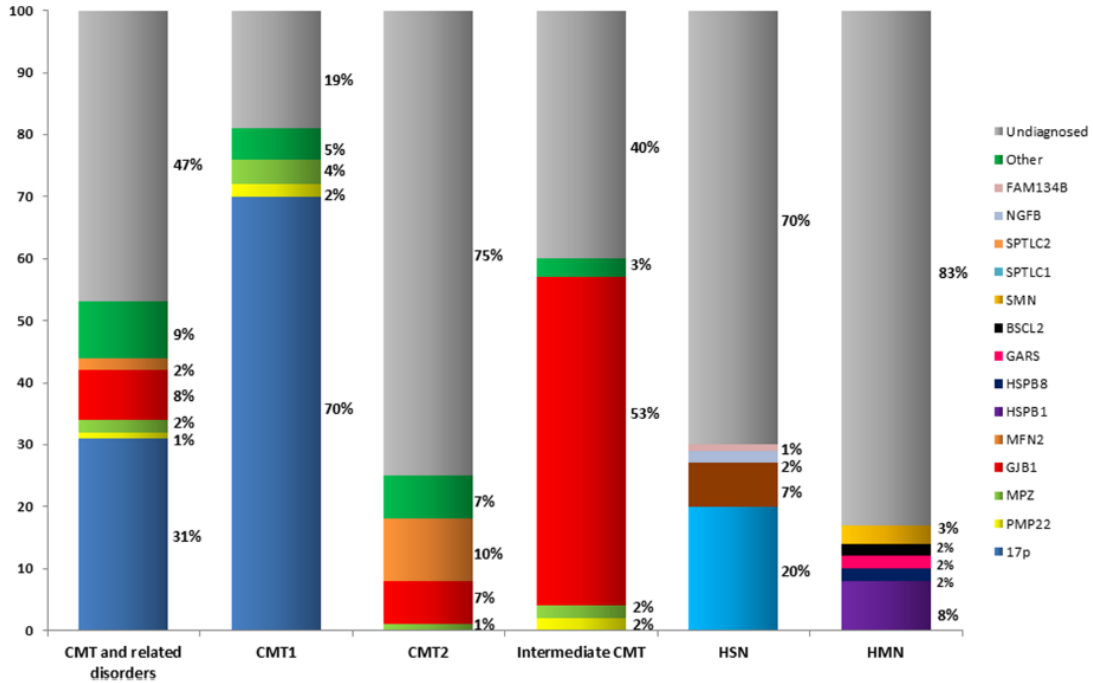


Figure 1 Genetic diagnoses in Charcot–Marie–Tooth disease (CMT) and related disorders in patients attending a specialist CMT clinic in the UK (inherited neuropathy clinic, National Hospital for Neurology and Neurosurgery, Queen Square).[17] It can be seen that for the majority of patients with CMT2, hereditary sensory neuropathy (HSN) and hereditary motor neuropathy (HMN) the underlying genetic defect is unknown. BSCL, Berardinelli-Seip congenital lipodystrophy; GARS, glycyl tRNA synthetase; HSPB8, heat shock protein 22kDa protein 8; MFN, mitofusin 2; MPZ, myelin protein zero; NGFB, nerve growth factor β; PMP, peripheral myelin protein; SPTLC, serine palmitoyltransferase, long-chain; SMN, survival of motor neuron.

Rossor, 2015

Behandeling

Medicatie

- Ondersteunend
- Gericht op de ziekte

Gentherapie

Ondersteunend

In pijplijn….

CMT1A - PMP22

CMT1B - MPZ

CMTX1 - Cx32

CMT2A - MFN2

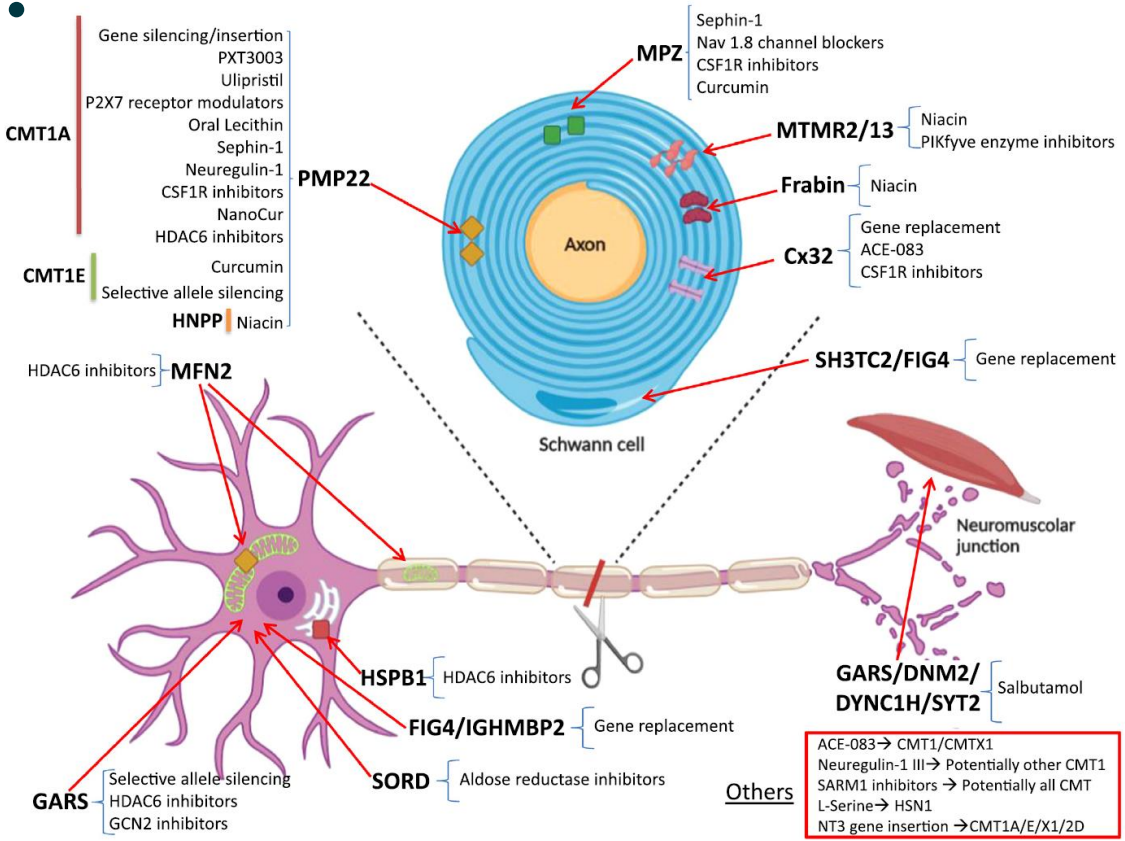


Fig. 1. Schematic representation of a motor neuron with its myelinated axon, neuromuscular junction and innervated muscle fiber. A transversal section of an internode with the myelinating Schwan cell is also shown. A list of potential treatments already tested, under evaluation, or under development is provided for each CMT type or related protein.

Pisciotta, 2023

Gericht medicamenteus

CMT1A

Vitamine C: geen effect

PXT3003 bij CMT1A

Naltrexone
Baclofen
Sorbitol

Verlagen PMP22

Attarian et al. Orphanet J Rare Dis (2021) 16:433
https://doi.org/10.1186/s13023-021-02040-8

Orphanet Journal of Rare Diseases

RESEARCH Open Access

A double-blind, placebo-controlled, randomized trial of PXT3003 for the treatment of Charcot–Marie–Tooth type 1A

Shahram Attarian[1*], Peter Young[2], Thomas H. Brannagan[3], David Adams[4], Philip Van Damme[5,6], Florian P. Thomas[7,8], Carlos Casanovas[9,10], Céline Tard[11], Maggie C. Walter[12], Yann Péréon[13], David Walk[14], Amro Stino[15], Marianne de Visser[16], Camiel Verhamme[16], Anthony Amato[17], Gregory Carter[18], Laurent Magy[19], Jeffrey M. Statland[20] and Kevin Felice[21]

Vervolgstudie:

Geen verschil in effect tussen placebo en medicijn

Alleen persbericht

CMT-SORD

CMT2 en distale HMN

SORD – Sorbitol dehydrogenase

Betrokken bij de omzetting van sorbitol - giftig voor zenuwen bij overmatige ophoping

Klinische studie: govorestat: blokkeert sorbitolproductie

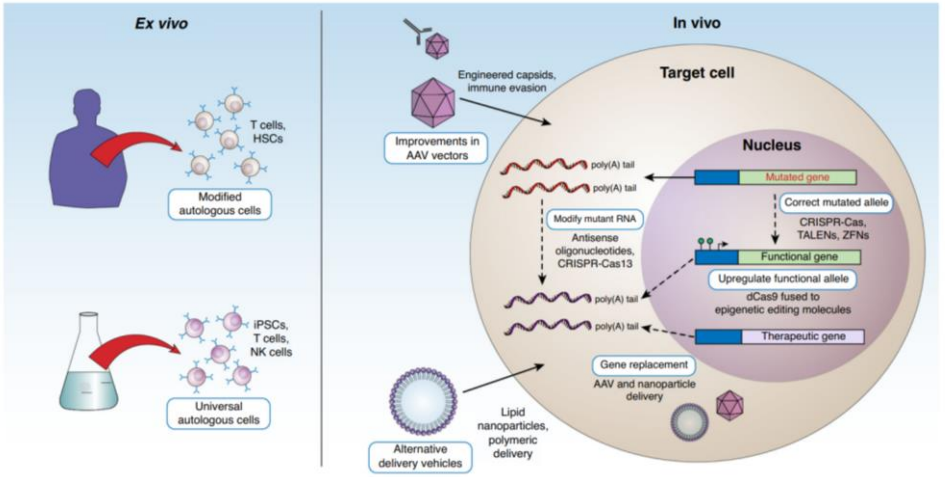
Sorbitol niveaus werden verlaagd; ziektelast verbeterde;

behandeling wordt goed verdragen

Gen therapie

NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-020-19505-2

- Repareren afwijkende gen
- Afschermen (afwijkende) gen
- Toevoegen therapeutisch gen
- Verhoogd afschrijven funktioneel allel
- Modificeren RNA



Inbrengen door een drager (vector)

Virus; Stamcellen

Prof. dr. Erik Storkebaum is hoogleraar moleculaire neurobiologie aan de Radboud Universiteit. Hij doet onderzoek naar HMSN.

De magie van onderzoek

Mensen denken soms dat fundamenteel wetenschappelijk onderzoek saai is, maar we boren juist al onze creativiteit en kennis aan om iets unieks tot stand te brengen. Toen ik 16 jaar geleden met onderzoek naar HMSN begon, wist niemand waar het bij deze ziekte precies fout gaat. Gelukkig is daar de afgelopen jaren verandering in gekomen.

Wat we hebben ontdekt, is dat je bij een vorm van HMSN (type 2D) ziek wordt omdat je te weinig tRNA hebt. tRNA is essentieel voor het aanmaken van eiwitten. Als er te weinig van deze eiwitten worden aangemaakt, sterven de zenuwen af. Die ontdekking was een doorbraak, want toen we wisten wat er misgaat, konden we heel gericht op zoek gaan naar een oplossing."

"Uit ons onderzoek in het lab blijkt dat een extra voorraad tRNA ervoor zorgt dat er genoeg eiwit wordt aangemaakt en de zenuwen gezond blijven. Kortom: met extra tRNA word je niet ziek. Maar hoe krijg je het tRNA in de cel? Dat bleek nog best een uitdaging. Eerst hebben we het verpakt in microscopisch kleine druppeltjes vet (nanodeeltjes), die we lieten samensmelten met de

Spierkrant mei 2024

Science. 2021 September 03; 373(6559): 1161–1166. doi:10.1126/science.abb3356.

tRNA overexpression rescues peripheral neuropathy caused by mutations in tRNA synthetase

Amila Zuko[1,†], Moushami Mallik[1,2,†], Robin Thompson[3], Emily L. Spaulding[4,5,‡], Anne R. Wienand[1], Marije Been[1], Abigail L.D. Tadenev[4], Nick van Bakel[1], Céline Sijlmans[1], Leonardo A. Santos[3], Julia Bussmann[2], Marica Catinozzi[1,2], Sarada Das[3], Divita Kulshrestha[1,2], Robert W. Burgess[4,5], Zoya Ignatova[3], Erik Storkebaum[1,2,*]

Drosophila – fruitvlieg

Muismodellen voor CMT2D (GARS)

Transgene overexpressie van tRNAGly geeft verbetering

Gen therapie

Afwegingen:

- Te behalen effect
- Wijze en frequentie van toedienen
- Bijwerkingen
- Kosten

Nog met name in dierexperimenteel, eerste trials bij CMT1A

Revalidatie

Orthoses

RESEARCH ARTICLE

Effects of specialist care lower limb orthoses on personal goal attainment and walking ability in adults with neuromuscular disorders

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I’M FINE Beweegprogramma

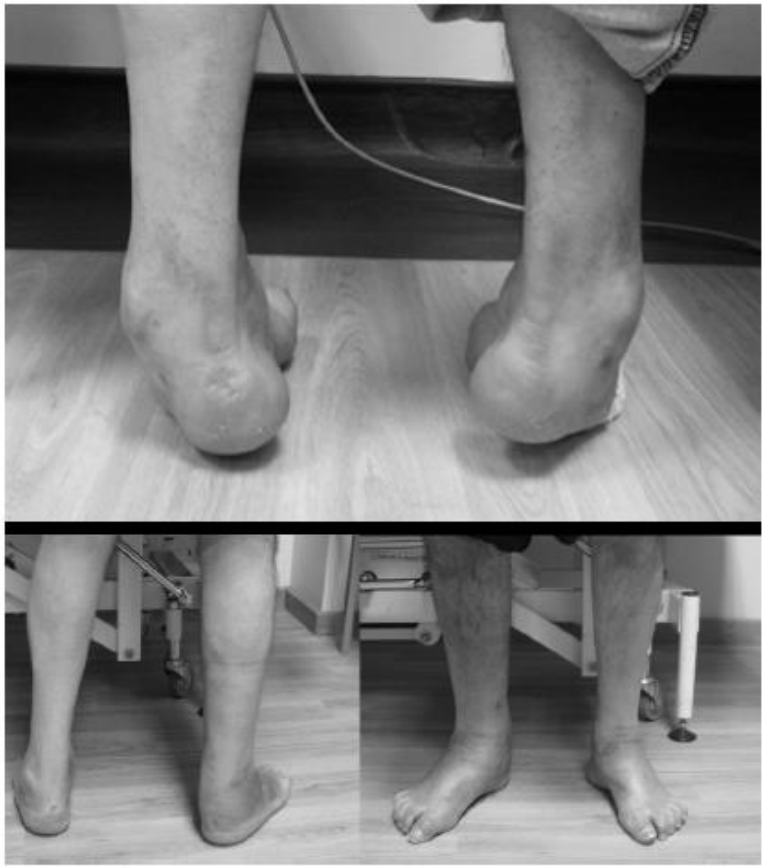
IMproving Fitness in Neuromuscular disease

Fysieke training

Coaching

Op het individu afgestemd

Chirurgie



Preoperative (row above) and postoperative (row below) images of bilateral cavovarus correction including ankle fusion and dorsiflexion osteotomy in a CMT1A patient.

Chirurgie

Landelijke richtlijn

A prospective study on surgical management of foot deformities in Charcot Marie tooth disease

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[2]Foot and ankle Unit, Royal National Orthopaedic Hospital, Stanmore, Middlesex, UK

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Abstract

Foot deformities are frequently observed in patients with Charcot Marie tooth disease (CMT) and orthopaedic surgery is often required. Currently there is no evidence-based guideline on surgical management and only a few studies which have evaluated long-term outcomes of surgical procedures. The aim of the study was to evaluate longitudinally the effect of foot surgery in a cohort of CMT patients. Twenty-five CMT adult patients were assessed using a comprehensive group of validated scales and questionnaires before and after surgery. A wide range of surgical procedures was performed by one team of dedicated foot ankle orthopaedic surgeons. Foot alignment as measured by the foot posture index, pain, quality of life and callosities significantly improved after one year and the improvement was maintained up to 4 years after surgery. There was a trend towards a reduction in the number of falls post-operatively. Surgery had no effect on fatigue, balance and CMT examination score. Our findings showed significant improvement of pain, foot alignment, callosities and quality of life after surgery and suggested that foot deformity correction in adults with CMT performed in a specialised foot and ankle unit is beneficial.

KEYWORDS
Charcot Marie tooth disease, foot and ankle surgery

Ontwikkelingen

Diagnostiek: next generation sequencing – steeds uitgebreider

Behandeling: veel in pijplijn

Kennis van onderliggende mutatie van groter belang; vroege diagnostiek

Opzet registratie in Nederland

In pijplijn….

Table 2
Main compounds tested/under study for treating CMT and related neuropathies.

Category / compound	Mechanism of action	CMT type involved	Potential application to human disease
Ascorbic acid	cAMP mediated decrease of PMP22 expression	CMT1A	No efficacy in phase II-III clinical trials (adults and children)
Progesterone antagonists/modulators: onapristone, ulipristil	Decreased PMP22 expression	CMT1A	Ulipristil phase III trial suspended
PXT3003 (mixture of baclofen, sorbitol and naltrexone)	Decreased expression of PMP22; baclofen = GABA-B receptor modulator	CMT1A	Phase II and III trials completed. Novel Phase III study ongoing
ACE-083	Myostatin pathway action	CMT1, CMTX1	No clinical benefit in phase II clinical trial
P2×7 receptor modulators	Decrease abnormal calcium influx in SCs	CMT1A	P2×7 inhibitor used in phase II trial in rheumatoid arthritis
Dietary lipid supplementation	Correction of defective lipid biosynthesis	CMT1A (other CMT?)	Oral lecithin trial planned in Germany
Curcumin	Several mechanisms (UPR modulation, oxidative stress, inflammation)	CMT1A, CMT1B, CMT1E	Poor absorption is an issue. NanoCur greatly increases bioavailability
Sephin-1	UPR modulation	CMT1A, CMT1B	Clinical trial(s) in CMT1A-CMT1B under consideration
GCN2 inhibitors	Integrated stress response inhibition	CMT2D (*GARS*) (and other AARS?)	CMT associated with AARS mutations possible candidates
Neuregulin-1 III (Neuregulin pathway)	Myelin thickness regulation	Hypo-demyelinating (including CMT1A) and hypermyelinating CMT (CMT4B, HNPP, CMT4H)	Niacin-niaspan possible candidate for CMT4B and HNPP (and CMT4H)
Targeting macrophages - CSF1R inhibitors	Decrease nerve macrophages number and activity	CMT1A, CMT1B, CMTX1	–
Sodium channel blockers	Block of Nav 1.8 channels	CMT1B and potentially other demyelinating CMT	Lamotrigine candidate compound
HDAC6 inhibitors	Action on microtubules, axonal and mitochondrial transport	CMT1A, CMT2A, CMT2D/dHMN5, CMT2F/dHMN2A (potentially all CMT)	Clinical trials under preparation
SARM1 inhibitors	Axonal degeneration prevention	Potentially all CMT	–
PIKfyve enzyme inhibitors	Decrease of PI(3,5)P2 levels	CMT4B1, CMT4B2	Considered for CMT4B1 and CMT4B2
L-Serine	Decrease production of neurotoxic deoxysphingolipids	HSN1	Phase II trial underpowered showed only a positive trend; novel trial will be conducted in UK
Aldose reductase inhibitors	Decrease production of sorbitol	CMT-SORD (recessive CMT2/dHMN)	Phase II-III trial ongoing

Pisciotta, 2023