Chapter One

General introduction and outline of the thesis

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CHARCOT-MARIE-TOOTH DISEASE TYPE 1A

Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathy (HMSN), refers to a heterogeneous group of slowly progressive motor and sensory neuropathies that are among the most common heritable disorders. It is characterized by slowly progressive distal muscle weakness, atrophy and sensory loss, with symptoms and signs most pronounced in feet and hands. The most frequent genetic form of CMT is CMT1A, which constitutes about 60-70% of CMT type 1 cases and 50% of all CMT cases. The estimated prevalence of Charcot-Marie-Tooth disease type 1A (CMT1A) is 1 per 5,000 people. CMT1A is caused by a 1.4 Mb duplication at chromosome 17p11.2 in the region containing the PMP22 gene. The mode of inheritance is autosomal dominant.

Figure 1
Jean-Martin Charcot, Pierre Marie & Howard Henry Tooth

HISTORICAL PERSPECTIVE

The first clear descriptions of a disease entity entitled peroneal type of progressive muscular atrophy were made simultaneously, but separately, by Charcot and Marie in France and Tooth in England in 1886 (Figure 1). They defined a disorder with its onset commonly in childhood and characterized by slowly progressive wasting and weakness of the muscles innervated by the peroneal nerve. Early involvement of the peroneal muscles, less severe sensory loss, tendency of the disorder to affect more than one member of the family, occurrence of foot deformities and the classical inverted champagne bottle configuration of the legs were emphasized. Progression to the hands was mentioned as a late feature of the disorder.
Based on nerve studies, Tooth suggested a peripheral neuropathy. Over the next several decades all sorts of hereditary peripheral neuropathies were reported. The introduction of nerve conduction studies in the 1950s began to shed light on the classification of this group of diseases. Severe slowing of motor nerve conduction velocities was found in some patients with peroneal muscular atrophy while other cases had normal or near normal motor nerve conduction velocities. In 1968, Dyck and Lambert found that severe conduction slowing was consistent within family members and could be found in patients with ‘hypertrophic’ changes in sural nerve biopsies. Patients with normal conduction velocities did not show these histologic features and were classified as the ‘neuronal’ type. After analysis of a large group of patients, a classification into seven types of hereditary motor and sensory neuropathies (HMSN) was composed. This classification, which was adopted by most neurologists, distinguished two major types. These two types were clinically identical but could be distinguished by nerve conduction studies: HMSN type I was considered to be a primary demyelinating neuropathy with reduced motor nerve conduction velocities. The second ‘neuronal’ type (HMSN type II) referred to individuals with relatively preserved nerve conduction velocity (> 40m/s). The term CMT-disease has been introduced by the molecular geneticists who were responsible for a complete reshuffling of the classification, which was thus far based on clinical and electrophysiological features.

The first genetic developments in CMT appeared in the early 1980s showing linkage to the Duffy (Fy) locus on chromosome 1q, in a family with the demyelinating form of HMSN. In 1993, a mutation in the myelin protein P0 (MPZ) gene located near the Duffy locus on chromosome 1 was found in this family. This form of HMSN was called CMT1B, whereas a family not showing linkage to the Duffy locus was called CMT1A since description of this family by Dyck took place in 1963. In 1991, Lupski et al. and Raeymakers et al. simultaneously discovered a duplication of a region on chromosome 17 containing the peripheral myelin protein 22 (PMP22) gene in CMT1A. With the discovery of new loci in various forms of CMT disease, the classification has been updated and changed.
PATHOGENESIS

Although the pathogenesis of CMT1A is still unknown several hypotheses have been put forward. Dyck et al. suggested a neuronal or axonal disorder, leading to distal axonal atrophy and degeneration, as the primary pathogenetic process. Others favoured a primary abnormality in the Schwann cell or myelin, resulting in uniform slowing of conduction velocity over all nerve segments and florid demyelination in early childhood followed by axonal loss at a later stage.

Recent advances in molecular genetics suggest that the peripheral nerve specific myelin protein PMP-22 is involved in mediating interactions between Schwann cells and the extracellular matrix, essential for the integrity of peripheral nerves. An extra copy of the PMP22 gene in each cell is the most common mutation that causes CMT type 1A. The extra gene leads to an overproduction of peripheral myelin protein 22, which clogs the Golgi apparatus in Schwann cells and prevents completion of the necessary processing steps. Myelin assembly is impaired due to the reduced availability of properly processed protein. The accumulation of unprocessed peripheral myelin protein 22 probably also disrupts other Schwann cell activities, leading to myelin loss and axonal dysfunction.

CLINICAL FEATURES IN CMT1A

The general clinical picture of CMT1A is that of a distal length-related neuropathy affecting the lower limbs to a greater extent than the upper limbs, and motor function more than sensory function. There is a remarkable diversity in clinical presentation in CMT1A, ranging from severe distal weakness and atrophy resulting in deformities of the feet and hands to slightly affected or even asymptomatic individuals. The clinical features of CMT1A have been analyzed, among others, by Thomas et al. and Birouk et al. The peak onset of the disease was found in the first decade of life. Symmetrical muscle wasting and weakness was the most consistent clinical abnormality, involving both the lower and upper limbs in about two-thirds of the patients. Tremor and ataxia were found less frequently. On clinical assessment, sensory loss was evident in 72% of the patients; presenting as loss of pain and touch and loss of proprioception in predominantly the lower limbs. Parents of children with CMT1A may report ‘unsteady ankles’, stumbling, late walking in infancy, running abnormally, or not picking up their feet. Abnormalities of the feet, such as pes cavus, pes equinovarus, hammertoes, or symptoms related to painful calluses are present in most cases.
When the upper limbs are involved, loss of hand strength and manual dexterity are common complaints. Patients with CMT1A may have difficulties with the manipulation of small objects such as coins or buttons or with grasping large, heavy objects.

Not all patients with CMT1A seek the help of their neurologist or rehabilitation physician for the neuromuscular symptoms and loss of dexterity due to their neuropathy. Due to the slow progression of the disease they may have become accustomed to their symptoms or not seldom, they might have been told that there is nothing that can be really done for them.

THE HAND IN CMT1A

In the literature, little attention has yet been paid to the impairments in hand function and the following functional restrictions of patients with CMT1A. This is surprising, since loss of hand function, especially bi-lateral loss, may have major impact on the performance of our daily life activities. In their descriptions, Charcot, Marie and Tooth emphasize that feet and legs are affected primarily, and they mention the involvement of hands and forearms as a late feature of the disorder. Only recently, a study among young children with CMT1A showed that hand weakness and dysfunction can be present at even early age.

In the hands of CMT1A patients, the intrinsic muscles become primarily affected. These muscles are innervated by the ulnar and median nerves. The motor branches of the ulnar nerve innervate the m. palmaris brevis, the abductor digiti minimi, all interossei, the two ulnar lumbricales, the adductor pollicis, and generally the deep head of the flexor pollicis brevis muscle. The median nerve innervates the two radial lumbricales and the muscles of the thenar, the superficial head of the flexor pollicis brevis, the opponens pollicis and the abductor pollicis brevis. The sensory branches of the ulnar nerve innervate the medial half of the fourth and the entire fifth digit of the hand, the ulnar part of the palm, and the ulnar portion of the posterior aspect of the hand. The median nerve supplies sensory innervation to the lateral aspect of the palmar skin, lateral (radial) three and a half digits on the palmar side and index, middle and ring finger on dorsum of the hand.

Median and ulnar nerve pathology may result in a variety of clinical features:
An intrinsic-minus hand

A hand without intrinsic muscle function is generally known as an intrinsic-minus or claw hand\textsuperscript{24}. In CMT1A, wasting of the intrinsic musculature can be observed especially at the dorsum of the hand, as grooves between the metacarpalia. The normal cupping of the hand diminishes, giving the hand a flattened appearance (Figure 2).

A (mild) clawing position of the fingers may arise due to an imbalance between the intrinsic and extrinsic muscles of the hand\textsuperscript{25}. The intrinsic muscles are the only prime flexors of the metacarpal phalangeal (MP) joints. The long flexor muscles do flex these joints, but only secondarily; their first action is on the interphalangeal joints\textsuperscript{24}. In intrinsic palsy the flexion vector, induced by the intrinsic muscles, across the MP joints is lost while the long extrinsic extensor muscles hyperextend the MP joints and the extrinsic flexors flex the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of the fingers. The result is an ‘intrinsic minus’ or ‘clawing hand’, with the MP joints in hyperextension and the PIP and DIP joints in flexion (Figure 3). The deformity is present in varying degrees, depending on the extent of the paresis and the suppleness of the digits. It involves the four fingers in cases of associated paralysis of the ulnar and median nerves. It involves only the ring and small fingers in cases of predominantly ulnar paralysis\textsuperscript{26}.

\textbf{Figure 2}
\textit{A hand of a CMT1A patient with distinct intrinsic muscle atrophy}
Loss of finger function

With ulnar-nerve deficits the ability of the fingers to abduct (spread) and adduct (close) is lost and an abducted resting position of the little finger can be observed (Wartenberg's sign) (Figure 4). Due to wasting of the interosseous muscles patients with ulnar nerve pathology are also not able to actively flex the MP joints of the ring and little fingers with simultaneous active IP extension, as in holding cards.

Figure 3
A CMT1A patient with clawing of the fourth and fifth fingers; hyperextension of the MP joints and flexed PIP and DIP joints

Figure 4
Wartenberg's sign; abducted resting position of the fifth finger
Dyskinetic finger flexion

Normally, finger flexion begins at the base of the fingers, at the PIP and MCP joints and is followed by flexion at the DIP joint. In the case of an interosseous paralysis, the sequence of flexion is altered\(^{24}\). Finger flexion is now accomplished by the long flexors alone, which acts first on the distal phalanges\(^ {26}\). With a dyskinetic finger flexion it is difficult for the hand to grasp large objects. The help of the contra-lateral hand is needed, or objects such as a cup of coffee are most likely to be pushed away or pushed over (Figure 5).
**Froment’s sign**

With ulnar-nerve pathology, a flexed position of the IP joint of the thumb can be observed when the patient is asked to adduct the thumb (Figure 6) or when the patient attempts to make a firm pinch grip (Figure 7). This is called Froment’s sign. When a firm pinch grip is made, the adductor pollicis and the first dorsal interosseous muscles are particularly active. The adductor stabilizes the thumb during pinch and helps extend the IP joint of the thumb through its attachment into the dorsal apparatus. When the adductor pollicis muscle is weak, the extrinsic flexor pollicis longus muscle pulls the IP joint into hyper-flexion.

**Loss of thumb opposition**

Signs of median-nerve involvement include atrophy of the thenar eminence, a resting posture of the thumb in the plane of the palm of the hand and loss of thumb opposition (Figure 8). One of human’s differences in anatomy, from that of our predecessor the ape, is the ability to oppose the thumb. Therefore this characteristic deformity is sometimes called the ‘ape’ or ‘simian hand’. During opposition of the thumb to the fifth finger, both fingertips are extended as they meet pulp-to-pulp and the fingers form a vertical arch. In the absence of the opponens pollicis, pseudo-opposition can occur by a combination of the flexor pollicis brevis (deep head) muscle, which acts to flex the thumb in the carpometacarpal and MCP joints, and the adductor pollicis muscle, which acts to slide the thumb across the palm. The result is that the flexed thumb advances to the lateral aspect of the fifth finger and rotation does not take place.
The hand in Charcot-Marie-Tooth disease 1A

Figure 6
Froment’s sign occurs when the patient is asked to adduct the thumb

Figure 7
Froment’s sign during pinch grip

Figure 8
Atrophy of the thenar eminence and loss of thumb opposition
**A weak pinch**

If all, or parts of the intrinsic muscles of the thumb are weak, its stabilization is lost resulting predominantly in limited functional pinch grips such as the two-point pinch, the tripod pinch and the lateral pinch. Loss of the first dorsal interosseous muscle contributes to the pinch instability, as it is predominantly responsible for stabilizing the thumb metacarpal and for providing stability for lateral pinch against the index finger.

When the intrinsic muscles are paralyzed, patients are unable to make an “O” with their thumb and index finger. During a two-point or tripod pinch the pressure from the index finger is exerted on the dorso-ulnar aspect of the distal phalanx of the thumb, forcing the thumb into supination, called the ‘Crank-handle’ effect (Figure 9) 24,26.

Finally, sensory loss of the volar radial side of the hand may also contribute to a weak and disturbed pinch grip (Figure 10).

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**Figure 9**
The ‘crank-handle’ effect

**Figure 10**
Disturbed pinch grip in CMT1A
MANUAL DEXTERITY

It has long been recognized that the sensory and motor capabilities of the human hand endow it with unique properties and a degree of specialization not evident in other structures of the body. Although of great importance for our daily activities and individual independence, literature on hand function and manual dexterity in patients with CMT1A has been sparse. The attention given to the problems of the lower extremity may have often overshadowed the disabling deformities seen in the upper extremity.

Manual dexterity is classified in the International Classification of Functioning, Disability and Health (ICF), in the Chapter Mobility (d440) on the level of Activity and Participation and defined as “fine hand use”27. A more extended description is provided by the American Society of Hand Therapists (ASHT): “the ability to move the hands easily and skilfully and to work with the hands in turning and placing motions”28. It involves working with arms and hands when for example objects are stacked or in other situations in which wrists and hands are used in turning and placing movements. Finger dexterity, which is defined as “the ability to move fingers, and manipulate small objects with fingers, rapidly or accurately”, may or may not accompany manual dexterity28.

For the rehabilitation management of patients with upper limb related disabilities, the evaluation of manual dexterity with a dexterity test, qualified in the perspective of the ICF as capacity, is of great importance. It provides information about the patient’s ability to execute a task or action. Because activities are to be considered as the primary focus of rehabilitation29, manual dexterity needs to be objectified, not merely as an outcome measure, but also for a better understanding of the causes of activity limitations and of the consequences of the impairments in body functions for hand use.

Ideally, a CMT1A manual dexterity test should provide data about a variety of aspects such as speed, accuracy, and the quality of hand and finger use during unilateral and bilateral tasks. Although numerous manual dexterity tests exist, there are no tests developed specifically for CMT1A and no evaluation covers all aspects of dexterity.

PERCEIVED LIMITATIONS IN ACTIVITIES AND PARTICIPATION

For people with CMT1A disease, it is likely that the reduced motor and sensory functions in arms and legs might lead to limitations in daily activities and subsequently to restrictions in participation in life situations. Unfortunately, there is
currently no way to cure CMT1A or influence the progression. Therefore the rehabilitation of these patients aims to prevent complications, to reduce or postpone their limitations in activities, and to optimize their participation in society in the presence of a chronic illness. Participation is defined by the ICF as social involvement in a life situation. In the ICF, the need to assess patients’ own perceptions of their life situations are emphasized. Nevertheless, no reports have been published on either perceived upper limb functioning or patient participation in CMT1A.

AIM OF THE THESIS

This thesis focuses entirely on the hand in CMT1A and addresses upper limb involvement on all three levels of the International Classification of Functioning, Disability and Health (ICF); body functions and structures, activities and participation. The ICF is World Health Organization’s framework for measuring health and disability at both individual and population levels.

The research project is initiated to obtain more insight into the impairments in hand function, the perceived limitations in activities, the restrictions in participation and to identify important determinants of manual dexterity of patients with CMT1A. Although CMT1A is a demyelinating neuropathy, previous studies indicated that clinical disease severity is especially associated with the severity of axonal dysfunction. Therefore, the associations between motor axon loss, hand function and manual dexterity on CMT1A are explored additionally.

Insight into upper limb functioning, manual dexterity, daily life functioning and into its underlying factors is needed to design intervention strategies, effective to preserve or even enhance daily life functioning of patients with CMT1A.

The main objectives of this thesis are:

1. To evaluate, on the level of body functions and structures, hand function (hand strength and fatigue, joint mobility and sensory functions) of patients with CMT1A;

2. To investigate in CMT1A the relation between motor axon loss, as estimated with motor unit number estimation (MUNE) and compound muscle action potentials (CMAP), hand function and manual dexterity;
To evaluate, on the levels of activities and participation, manual dexterity, the perceived limitations in upper limb related activities and the restrictions in participation of CMT1A patients;

To assess the reproducibility of two manual dexterity test in patients with CMT1A

And to identify important determinants of manual dexterity.

**OUTLINE**

The first two studies are explorative by nature and performed in both type 1 and 2 CMT patients. In the first study, presented in chapter 2, maximal isometric strength of handgrip, two-point pinch, and lateral pinch of patients with CMT is compared with healthy age- and sex-matched controls, and fatigue (the rate of decline of maximal isometric handgrip strength during series of contractions) is examined. Additionally, the reproducibility of handgrip strength and fatigue measurements in CMT is determined. Chapter 3 consists of a pilot study in which we explore the impairments in manual dexterity and the perceived limitations in upper extremity-related activities of the same group of CMT patients.

In chapters 4, 5 and 6 upper limb involvement is evaluated extensively in a large and homogeneous sample of CMT1A patients. A homogeneous sample of DNA-confirmed CMT1A patients was chosen as study population to eliminate variation due to disease heterogeneity that might obscure the effects of variety in clinical manifestations of CMT1A, which was our primary focus of interest.

The study in chapter 4 assesses the prevalence and significance of impaired manual dexterity in CMT1A and compares the feasibility, reliability and agreement of two manual dexterity tests.

In chapter 5, clinical aspects of hand function (grip and pinch strength, mobility and sensory modalities) and motor axon loss, as estimated with motor unit number estimation (MUNE) and compound muscle action potentials (CMAP) are evaluated in CMT1A. The relation between motor axon loss and hand function and manual dexterity is investigated in this study as abundant evidence suggests that clinical disease severity is determined by axonal degeneration, secondary to the demyelination.

In chapter 6 we aim to gain insight into patients’ perception of functioning. Perceived upper limb functioning and perceived restrictions on participation of CMT1A patients are evaluated. Because both upper and lower limbs are affected in
CMT1A, the independent contribution of upper and lower limb functioning to participation restrictions is studied additionally. Finally, in chapter 7, we identify the major determinants of impaired manual dexterity in CMT1A. In order to elucidate the relative contributions of motor and sensory impairments to limited manual dexterity, grip and pinch strengths, joint motion and sensory functions of the hand are evaluated. In a motor and sensory neuropathy as CMT1A, sensory loss may also contribute to impaired dexterity and therefore we compare the results of the CMT1A group with a sample of patients with multifocal motor neuropathy (MMN), a pure motor neuropathy. Chapter 8 presents a general discussion were the main findings and limitations of this thesis are dealt with. Finally, clinical implications and future perspectives are considered.

REFERENCES


