Pathophysiology of claw toes and forefoot cavus in children with Charcot-Marie-Tooth disease type 1A: an experience-based review

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ABSTRACT

Introduction. Charcot-Marie-Tooth disease type 1A (CMT1A) represents around two-thirds of dominant demyelinating phenotypes. Claw toes and forefoot cavus are cardinal manifestations of the disease. Based on our clinical, electrophysiological and imaging (MRI) studies, the objective of this review was fourfold: *i)* to describe the assessment of pes cavus in clinical practice; *ii)* to propose a new mechanism for the development of claw toe and forefoot cavus; *iii)* to recall our description of the physiological maturation of nerve conduction over the first five years of life; and *iv)* to highlight the contribution of MRI in characterizing the progression over time of the topography of foot and lower-leg muscle atrophy.

Development. A glossary of foot deformities in CMT is reported. In our initial cross-sectional research on CMT1, and afterwards in a longitudinal clinical-electrophysiological study of 12 patients with CMT1A aged zero to four years, with a mean follow-up period of 7.7 years, it was demonstrated that claw toes and forefoot cavus appeared much earlier than lower-leg amyotrophy. These findings suggested that intrinsic foot muscle involvement plays a pathological role in the development of this foot semiology. This hypothesis was corroborated by our MRI study of the leg and foot muscles showing a dual pattern: selective fatty atrophy of the foot muscles in young, paucisymptomatic patients with CMT1A, and fatty atrophy of muscles of the legs and the feet in adult patients with more advanced symptoms. Complete nerve conduction maturation occurs during the first five years of life.

Conclusions. The initial pathogenic mechanism of claw toes and forefoot cavus in CMT1A is denervation of the intrinsic foot muscles. This notion has therapeutic implications.

KEYWORDS

Charcot-Marie-Tooth disease type 1A; claw toes; electrophysiology; extrinsic foot muscles; forefoot cavus; intrinsic foot muscles; lunge test; magnetic resonance imaging; maturation of nerve conduction parameters; muscle denervation; muscle fatty atrophy; pathophysiology; peroneal muscular atrophy

1. Introduction

Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathy (HMSN), is the most frequent form of inherited polyneuropathy, with a prevalence rate of 28.2 cases per 100 000 population.[1] CMT was initially classified according to the mode of transmission (autosomal dominant [AD], autosomal recessive [AR], or X-linked) and the electrophysiological pattern or nerve biopsy features (demyelinating, axonal, or intermediate). Seven main disease categories were distinguished, although most cases could be categorized as HMSN-I/CMT1 (demyelinating pattern with AD or X-linked transmission), HMSN-II/CMT2 (axonal pattern with AD, AR, or X-linked transmission), or HMSN-III/CMT4 (severe demyelinating neuropathy with AR transmission).[2,3] Characteristically, motor conduction velocity in upper-limb nerves is < 38 m/s

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in CMT1, > 38 m/s in CMT2, and 25-45 m/s in the intermediate form of CMT.[4,5] With advances in molecular genetics, including next-generation sequencing (panels; whole-genome and whole-exome sequencing), CMT has become one of the most complex neurological syndromes, with more than 130 mutant genes having been discovered.[6,7]

CMT1A, usually caused by a large duplication on the short arm of chromosome 17[8-10] is by far the most frequent form of CMT, with its prevalence ranging between 66.8% and 76.3% of dominant demyelinating phenotypes[11-13]; furthermore, it accounts for 55% of all patients with genetically defined CMT.[12] The hallmark of the disease is a peroneal muscular atrophy syndrome of variable severity and marked, diffuse slowing of nerve conduction velocity.[14-17] Symptoms present during the first decade of life in over 60% of cases.[4] Foot deformity, basically forefoot cavus and (considerably less frequently) pes planus, is a cardinal manifestation of any CMT subtype, although it is significantly more common in patients with CMT1 than in those with CMT2.[18]

Based upon our clinical, neurophysiological, and MRI studies of CMT1A patients, the objective of this review is fourfold: *i)* to describe the assessment of pes cavus in clinical practice; *ii)* to propose a new mechanism for the development of claw toes and forefoot cavus from early childhood to adolescence; *iii)* to describe the maturation of nerve conduction velocity, both motor and sensory (MCV and SCV, respectively), in the first five years of life; and *iv)* to highlight the contribution of MRI in characterizing the progression over time of the topography of foot and lower-leg muscle atrophy.

2. Basic clinical definition of forefoot cavus

This section, dedicated to the semiology and examination of anterior pes cavus, is taken almost verbatim from previous works, particularly one of our own.[19-22] Forefoot cavus is defined as elevation of the medial longitudinal arch with marked forefoot drop and pronation, with additional drop and pronation of the first metatarsal below the lateral heads, with variable degrees of claw toes and hindfoot supination.[19] It is worth noting that in a plantigrade foot, the sole of the foot dorsiflexes to neutral (90º angle) in relation to the tibia. Forefoot cavus is not usually plantigrade.[20]

2.1. Foot examination in CMT patient

To provide a description that is as accurate and concise as possible, we reproduce the definitions provided by Guyton[21] and Berciano et al.[22] verbatim, always accompanied by our own illustrations. Examination of the feet demonstrates characteristic findings that may be summarized as follows (Figure 1)[21,22]:

— *Claw toes*. Balance in the toes results from the modifying force of the intrinsic muscles (mainly, the lumbricals) to flex the metatarsophalangeal joints and extend the interphalangeal joints. When intrinsic muscle function is lost, as characteristically occurs in CMT1A (see below), the unopposed force of the extrinsic muscles dorsiflexes the metatarsophalangeal joints and flexes the interphalangeal joints, resulting in a claw toe deformity (see Figure 1A, E).[22]

— *Forefoot cavus* is a term used to imply that cavus-varus foot results from the plantarflexion of the first ray. The plantarflexed first ray increases the height of the arch and secondarily forces the subtalar joint into a varus position (see Figure 1C, D, E, G, H).[22] Most authors consider forefoot pes cavus to be caused primarily by the action of the spared peroneus longus on the first ray, which serves to plantarflex the first metatarsal, and overpowers the affected tibialis anterior muscle; alternatively, muscle imbalance between the tibialis posterior and peroneus brevis may also be the chief contributor to this pathological foot posture.[19,23-25] Despite controversy regarding the role of intrinsic foot muscle atrophy in the development of forefoot cavus,[1] in a then unique orthopedic evaluation of foot semiology in a large CMT1 pedigree comprising affected children in early stage of disease, Sabir and Lyttle[26] proposed that the initial formation of pes cavus is caused by selective atrophy of the intrinsic foot muscles, as illustrated in Figure 2.[26,27] During the surgical correction of pes cavus in their patients with CMT, these Canadian orthopedic surgeons performed biopsies of the plantar muscles, revealing neurogenic atrophy: certainly, an unprecedented occurrence in the history of CMT!

— *Hindfoot varus* in CMT results from either an indirect compensatory mechanism of abnormal plantarflexion of the first ray, or from a direct mechanism consisting of an imbalance between the spared tibialis posterior muscle and the weakened peroneus brevis muscle.

— *Foot drop* results simply from failure of the tibialis anterior muscle while the plantar flexors are spared.

— *Clawed hallux* is a special case. In patients with CMT sparing the extensor hallucis longus, a severe claw toe deformity develops with marked hyperextension at the metatarsophalangeal joint; in this situation, the extensor hallucis longus serves as an accessory dorsiflexor of the ankle, replacing the weakened tibialis anterior muscle (Figure 3).[22]

2.2. Examining patients with CMT: specific tests

In current neurological practice, given the good correlation between quantitative and manual muscle strength tests, a manual assessment of the foot evertors/invertors, plantar extensors/plantar flexors, and ideally of lumbricals and flexor hallucis brevis, would be sufficient.[28,29] For monitoring disease progression or in a research setting, it is recommended to test the isometric muscle strength of foot inversion/eversion and ankle plantarflexion/dorsiflexion using a handheld dynamometer.[30,31] Specific difficulties in heel walking should be screened, since this is one of the earliest signs of the disease (Figure 1A).[17,22,30-32] Using conventional goniometry, the normal ankle may be expected to permit dorsiflexion of the foot to approximately 70° (anatomic, 20°) and plantarflexion to 135° (anatomic, 45°).[22]

The CMT Neuropathy Score[33] and Functional Disability Scale (FDS)[11] are simple, extremely useful tools for evaluating patients' disability in routine clinical practice.

Objective measurement of foot structure and ankle flexibility is better performed with the Foot Posture Index (FPI), lunge test, and weight-bearing anteroposterior and lateral radiographs.[22] The FPI is a validated method for quantifying standing foot posture, which evaluates the multi-segmental and multi-planar aspects of the foot using six criteria that, together, result in a score along a continuum of cavus (supinated) to planus (pronated) features.[34-36] The six components provide an aggregate score ranging from –12 for marked pes cavus (scores of –12 to –1) to +12 for marked pes planus (+6 to +12; normal FPI scores: 0 to +5).

Flexibility of weight-bearing ankle dorsiflexion is measured using the lunge test.[31,34] Compared to mean values for age-equivalent norms (> 30°), the lunge test shows a decrease in mean ankle dorsiflexion flexibility from early childhood (27°) to adolescence (23°).[34] In children, normal values for toe-to-wall distance are 7-11 cm. As illustrated by Figure 4, the lunge test may be abnormal when no other signs of CMT1A are detected. The flexibility of the hindfoot varus may be evaluated using the Coleman block test.[23]

On standard weight-bearing lateral radiographs, the following measurements are routinely performed[37]: *i)* calcaneal pitch angle, to distinguish hindfoot cavus (normal, 18°-30°) characteristic of acquired neurogenic syndromes, from forefoot cavus; *ii)* the talar-first metatarsal angle (Meary's angle; normal 0° ± 4°); and *iii)* and calcaneal–first metatarsal angle (< 120°), to corroborate the clinical diagnosis of forefoot cavus and eventually to evaluate its severity.[23,38,39]

It is important to note that chronic neuropathies developing before cessation of the growth period frequently give rise to foot, hand and spinal deformity.[23,40] Focusing on foot deformity, toe clawing may develop in a chronic neuropathy beginning at any age, whereas the presence of forefoot cavus indicates onset in childhood. This point is sometimes of diagnostic importance; indeed, presence of pes cavus is often taken as evidence of an inherited neuropathy, such as CMT.[40]

3. A summary of our contributions to the topic in question

We will consider this issue in three chronologically separate paragraphs.

3.1. Initial stage (1983-1989): studies in CMT1

Our initial CMT1 studies were carried out before the discovery of the CMT1A genetic mutation. In 1983, Combarros et al.[41] reported four CMT1 families with a total of 26 affected and 21 unaffected individuals. This series included two patients aged < 10 years and eight patients aged between 10 and 20 years. The majority of symptomatic cases (14 out of 26) developed during the first decade of life and very few (five cases) became symptomatic in the second decade or afterwards. The main presenting symptoms were foot deformities and difficulty walking. Decreased conduction velocity values were detected even in an affected 2.5-year-old family member. A few years later, after performing clinical-electrophysiological examinations of 11 CMT1 families, including 73 affected patients out of 99 individuals examined, we suggested that penetrance was complete since childhood; in fact, from the age of

six months, an individual showing normal clinical and electrophysiological features probably presents zero risks of having inherited the gene mutation causing the disease.[42] Our results contradicted the prevailing view at that time, which was that complete penetrance of the CMT1 gene was not achieved until the second decade of life.[43] Be that as it may, in 1992 four Cantabrian CMT1 families were included in an international study comprising eight families with 57 affected individuals, which demonstrated 17p duplication in all of them.[10] Eventually, all 11 of our CMT1 pedigrees would be found to exhibit 17p duplication.[22]

3.2. Longitudinal clinical - electrophysiological studies in children with CMT1A and normative nerve conduction parameters in controls (up to 2003)

In the following stage, hoping to understand the maturation of conduction velocity parameters during the first years of life, we carried out two parallel projects[17,32,44,45]: *i)* a cross-sectional study of 92 control children (without neurological disease) divided into six groups (first month of life, two to six months, seven to 12 months, 13-24 months, 25-48 months, and 49-72 months); and *ii)* a longitudinal study of 20 preschool children (0-5 years) at risk of CMT1A from six unrelated families studied by us. The findings will be presented separately.

Physiological maturation of MCV and SCV occurs in the first five years of life.[44] The parallel progression of distal motor latencies is explained by applying a correction that considers the distance between the cathode and the recording electrode. Modifications of F-wave latencies are explained both by the increase in MCV and by limb growth. The results of this control electrophysiological study were extremely helpful in interpreting our findings in children with CMT1A, which are presented below.

By definition, the 20 children at risk of CMT1A were assessed within the first five years of life, between one month and four years (mean, 1.5 years); at the end of the study, ages ranged between four and 19 years (mean, 9).[17,32,45] Mean follow-up was 7.7 years. Twelve (seven boys and five girls) of the 20 (60%) individuals at risk were affected. Each of these 12 patients underwent two or more consecutive neurophysiological examinations. Clinical progression of semiology is illustrated in Figure 5,[17] showing a clear progression of disease symptoms and signs, although peroneal muscular atrophy was only observed in the second decade of life. The percentage of symptomatic patients (essentially, unsteady gait) was 17% in the youngest group (zero to four years) and 42% in the second decade of life. The frequency of neuropathic signs amounted to 50% at the beginning of the study and 83% at the end. The most frequent signs were lower-limb areflexia, nerve enlargement and foot abnormalities, which included a variable combination of clawing toes, forefoot cavus, atrophy of intrinsic foot muscles (Figure 6),[45] difficulty in heel walking, and flattening of the transverse arch (Figure 1).[22] The onset of forefoot pes cavus clearly occurs much earlier than peroneal muscle atrophy, which led us to propose that its initial development depended not on peroneal weakness, as suggested in the literature, but on the involvement of the intrinsic foot muscles (see MRI studies below). From the age of two years, all 12 affected children presented alteration of nerve conduction parameters (Figure 7).[17] As illustrated in Figure 6,[45] motor signs depend not on the degree of MCV slowing, but rather on the degree of attenuation of distal motor potentials, that is, the degree of secondary and length-dependent axonal degeneration.

3.3. Magnetic resonance imaging study of the leg and foot muscles (2006)

MRI plays an important role in the detection and characterization of pathological conditions of the skeletal muscle that cause changes in muscle signal intensity.[46] Having demonstrated that pes cavus and intrinsic foot atrophy usually precede peroneal muscle atrophy in CMT1A, we hypothesized that initial walking difficulties were correlated with abnormal foot architecture owing to selective denervation of the intrinsic foot muscles. In this context, we planned a clinical/MRI study of the foot and leg muscles in CMT1A in two case groups: *i)* six patients (aged between eight and 24 years; median, 20) with no or minimal disability on the FDS[16] and no weakness of ankle flexor/extensor muscles; and *ii)* five patients (aged between 32 and 61 years; median, 45) with FDS scores indicative of mild or moderate gait impairment and paresis of the ankle dorsiflexor muscles.[47,48] If we were right, MRI study would show abnormal signal in the foot muscles in the first group and in both foot and leg muscles in the second group. And in effect, our MRI study demonstrated that all six patients in the first group showed abnormal muscle signal restricted to the intrinsic foot muscles (Figures 8 and 9),[47] which reinforces the pathogenic role of these

muscles in the initiation of pes cavus (see above). In the older group, and in parallel with the observed clinical data, both foot and leg muscles were involved (Figures 8 and 10).[47] At this stage, lower-leg muscle imbalance would most likely have a pathogenic influence on the progression of forefoot cavus. These pioneering findings were soon corroborated by other authors.[49]

3.4. Evidence for a good clinical-electrophysiological-imaging correlation

We may cite as an example the case of the patient in Figure 3[22] who presented with deformed feet (for details, see figure caption). Clinical examination revealed forefoot cavus and severe restriction of passive ankle extension, but with relative sparing of muscle strength in both peroneal compartment muscles. The electrophysiological recording of the peroneal nerve is shown in Figure 11[22]; as one might expect, there was an absence of compound muscle action potentials in the extensor digitorum brevis, while motor responses were preserved in the muscles of the peroneal compartment. Similarly, MRI examination (Figure 12)[22] shows relative preservation of peroneal compartment muscles (minimal fatty infiltration of the peroneus brevis) and marked fatty atrophy of the more distal plantar muscles of the foot (lumbricals and interossei). As mentioned above, the preferential involvement of the most distal muscles, both in electrophysiological and in imaging tests, indicates that disease semiology is the expression of a secondary, length-dependent axonal degeneration.

4. Applicability to the treatment of CMT1A children

Our studies in children with CMT1A have contributed to establishing that the initial semiology in the foot results from the denervation of its intrinsic muscles, particularly the lumbricals. At this early stage of the disease, there is no evidence of involvement of lower leg muscles, from which we may infer that neither the tibialis (anterior and posterior) nor peroneus (longus and brevis) muscles are significant pathogenic factors. Early forefoot cavus is nearly always correctable, as was rightly noted by Sabir and Lyttle.[26] Under these circumstances, treatment should always be conservative and carried out in collaboration with a multidisciplinary team including rehabilitation specialists, physical therapists, and orthotic/prosthetic technicians.[6,26,37,50] Both at these early stages and later in the clinical course, when surgical treatment may be required, we recommend following the stepwise treatment algorithm reported by Nonnekes et al.[50]

Wicart's recommendations[37] on orthotic treatment for children with CMT are very useful, so that allows us to reproduce them verbatim: "Orthotic treatment is classically described as ineffective. This view is wrong. When a child with pes cavovarus deformity is in the supine position, the cavus deformity worsens and clawing of the toes appears. These findings indicate a need for orthotic treatment at night. An orthotic treatment protocol has been developed based on pathophysiological consideration. *Untwisting plaster boot cast:* the objective is to correct established pes cavovarus. *Untwisting Perlstein-type orthosis for night wear:* use of this orthotic device is rational […] at onset of the first evidence of pes cavovarus (to prevent or slow progression); and as follow-on therapy after the use of a derotating plaster boot cast […]."

5. Conclusions

Our clinical, electrophysiological and imaging studies in children with CMT1A, carried out over three decades, allow us to propose that the initial pathogenic mechanism of claw toes and forefoot cavus, the cardinal manifestations of the disease, is denervation of the intrinsic foot muscles, particularly affecting the lumbricals. With this proposed pathogenesis, early treatment should almost always be conservative, reserving surgical procedures for more advanced stages of the clinical course.

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Conflicts of interest

The author has no conflicts of interest to declare. This study has received no public or private funding.



Figure 1. Composite figure illustrating foot semiology in patients with CMT1A duplication. A, B) Incipient difficulties in standing on the heels in an asymptomatic patient, aged 5 years, who exhibits prominent tendo Achillis. C, D) Mild and severe hindfoot varus deformity in two patients aged 23 and 54 years, respectively. E) Close-up picture of the right foot, showing marked cavus deformity with toe clawing in a patient aged 23 years. F) Atrophy of the extensor digitorum brevis muscle in a patient aged 16 years. G) Close-up picture of the sole of the right foot, which shows incipient pes cavus in the patient illustrated in panels A and B. H) Close-up picture of the soles of the feet of a patient aged 38 years, showing marked pes cavus with flattening of the transverse arch and callosity over the metatarsal heads and external borders of the feet, and atrophy of the abductor hallucis muscles. Taken from Berciano et al.[22]

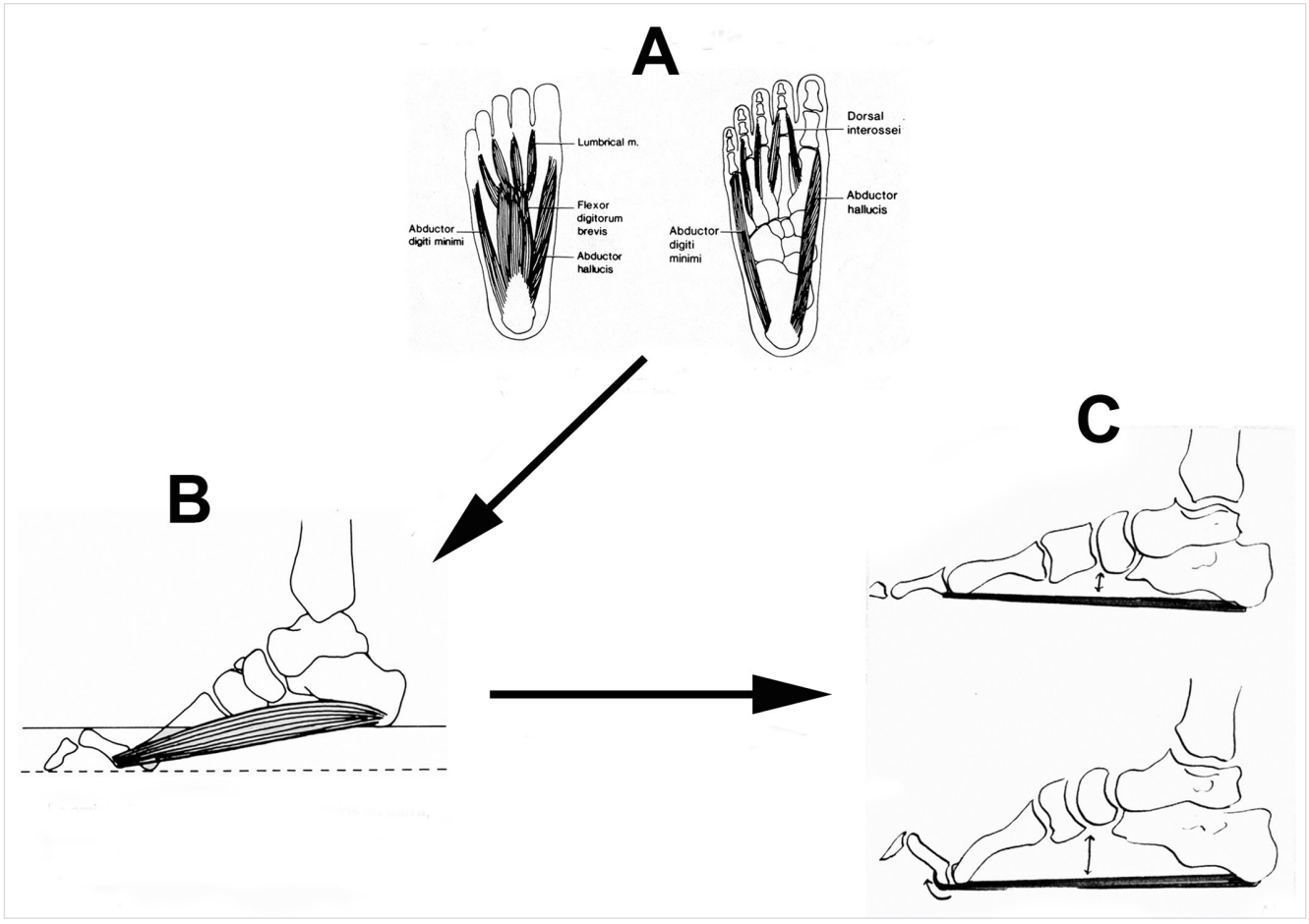


Figure 2. Pathophysiological interpretation of pes cavus in early stages of CMT1A, based on images taken from Sabir and Lyttle[26] and foot muscle MRI findings (see further on in the text). A, B) The initial step would consist of denervation and weakening of the lumbricals, leading to unopposed action of flexor digitorum longus and extensor digitorum longus, producing claw deformity. C) During gait, prior to toe-off, as the metatarsophalangeal joints extend, the plantar fascia is wrapped around the metatarsal heads, and the short flexors contract cause a "windlass effect," approximating the pillars of the longitudinal arch and thus increasing the height of the arch; another dynamic consequence may be prominent tendo Achillis (see Figure 1B). At this stage, foot deformity is correctable. Later in the clinical course, short plantar flexors (flexor digitorum brevis, flexor accessorius, abductor hallucis, and abductor digiti minimi) undergo denervation, atrophy, fibrosis and shortening, acting as a "tie beam" between the anterior and posterior pillars of the arch, drawing them closer together, thereby further raising the height of the medial longitudinal arch and producing equinus of the forefoot, varus of the hindfoot, and flattening of the transverse arch (see Figure 1). A contracture of the plantar fascia follows. At this stage, the deformity is not correctable. Adapted from Berciano et al.[27]

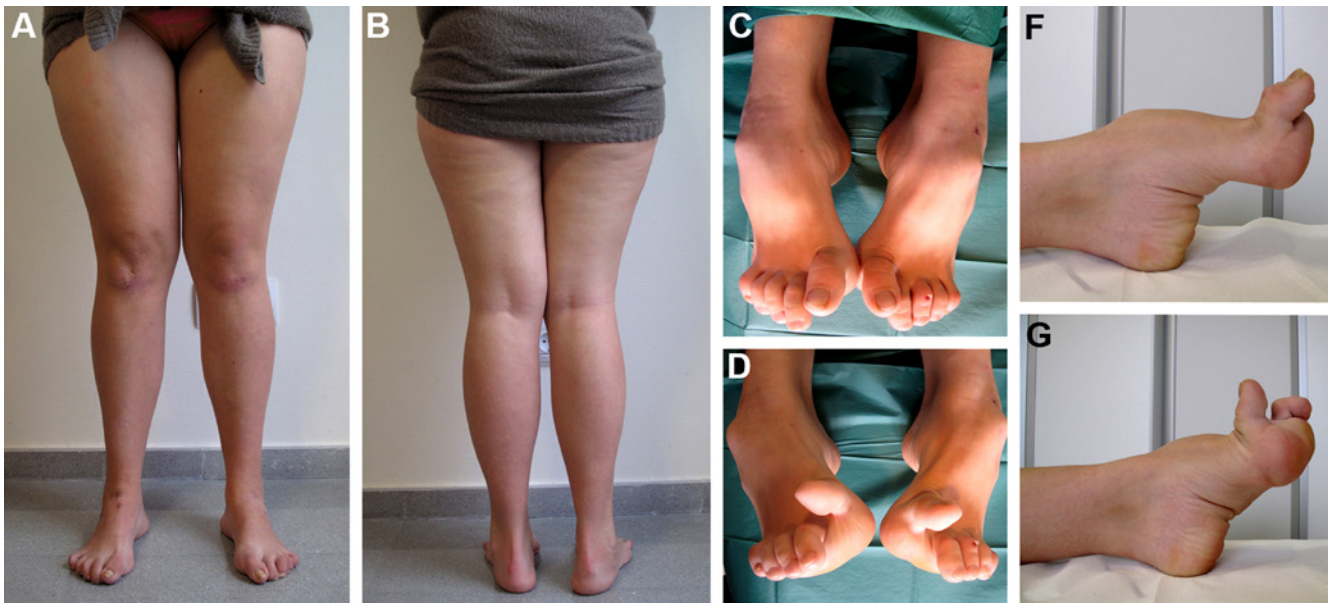


Figure 3. Composite figure of a 17-year-old girl with CMT1A presenting with foot deformity. She showed a CMT Neuropathy Score of 18 (moderate score), Functional Disability Scale score of 3 (unable to run), ankle flexibility of 20° in the lunge test (toe-to-wall distance 10 cm), and preserved plantar flexion to 135° (anatomic, 45°) whereas dorsiflexion was restricted to 100° (anatomic, –10°) (for explanation, see text). A, B) Note the absence of the lower-limb amyotrophy; there may be incipient involvement of the distal part of peroneal muscles. In a standing position, toe clawing is evident; note also mild bilateral hindfoot varus deformity. C) Close-up picture of the feet showing pes cavus and toe clawing. D) When the patient is asked to raise all her toes, the big toes display hyperextension, whereas the lesser toes do not extend at all, as if they were completely paretic. E, F) Similarly, with the patient lying down, when she is asked to raise her foot, there is mild dorsiflexion, with the foot passing from 145° to 133°, with the extensor hallucis longus serving as an accessory dorsiflexor. Severe restriction of passive ankle dorsiflexion to –10°, caused by forefoot cavus, may limit the action of the tibialis anterior, which is otherwise spared according to electrophysiological and MRI findings (see Figure 11, 12). Taken from Berciano et al.[22]

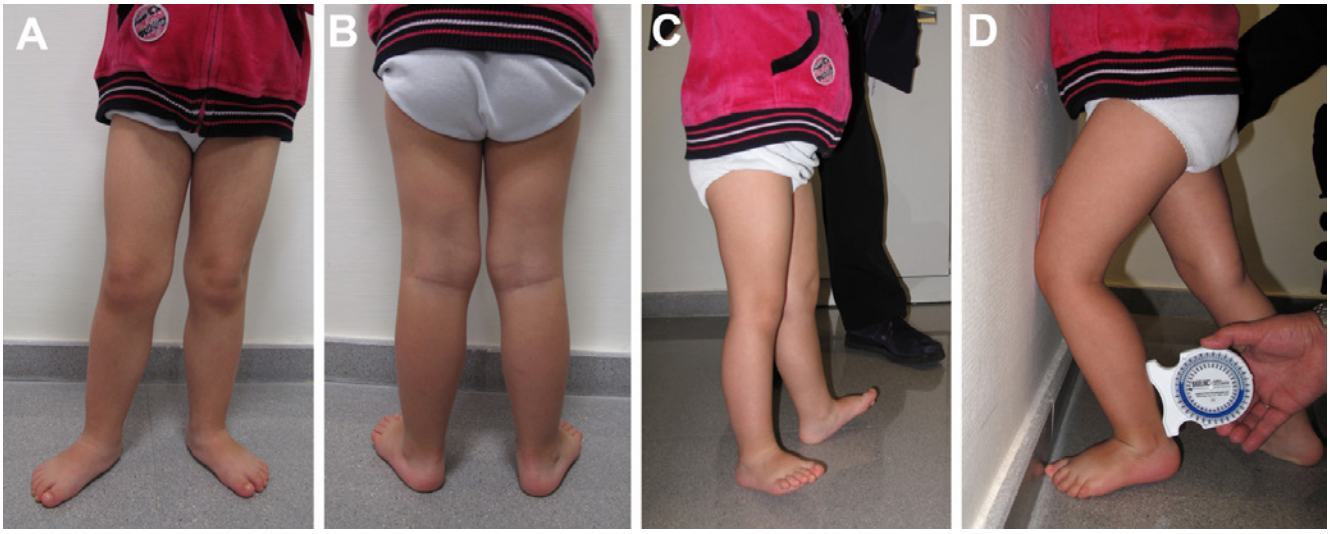


Figure 4. A three-year-old girl with subclinical CMT1A. Neither lower-leg amyotrophy (A, B) nor difficulty in standing on the heels is noted (C). D) The results of the lunge test, however, are abnormal as the patient needs to bring the big toe closer to the wall, with ankle flexibility being reduced to 20°.

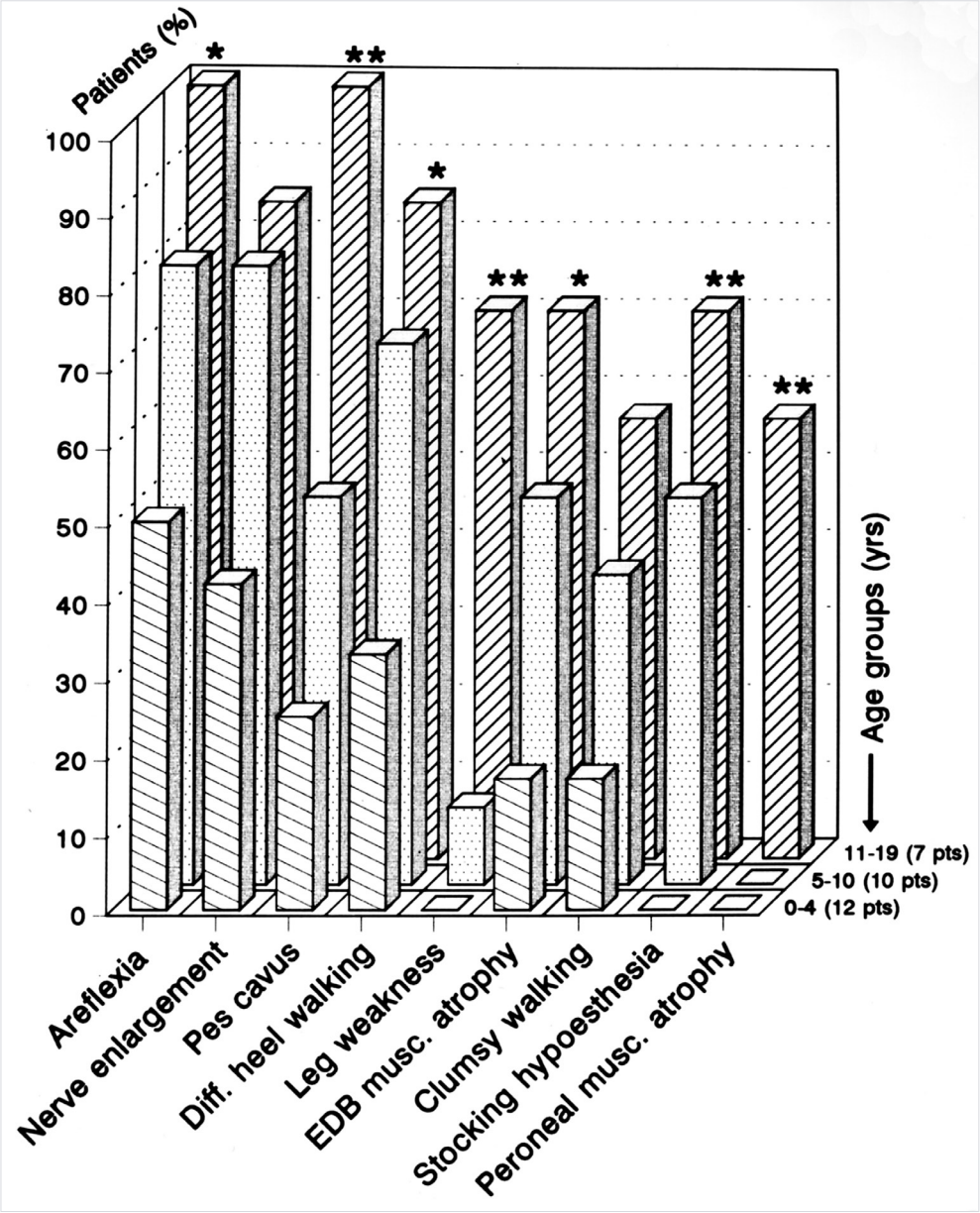


Figure 5. Frequency of clinical signs and symptoms according to age groups. Asterisks indicate significant differences between older and younger groups (*$P < .05$; **$P < .01$). Taken from García et al.[17]

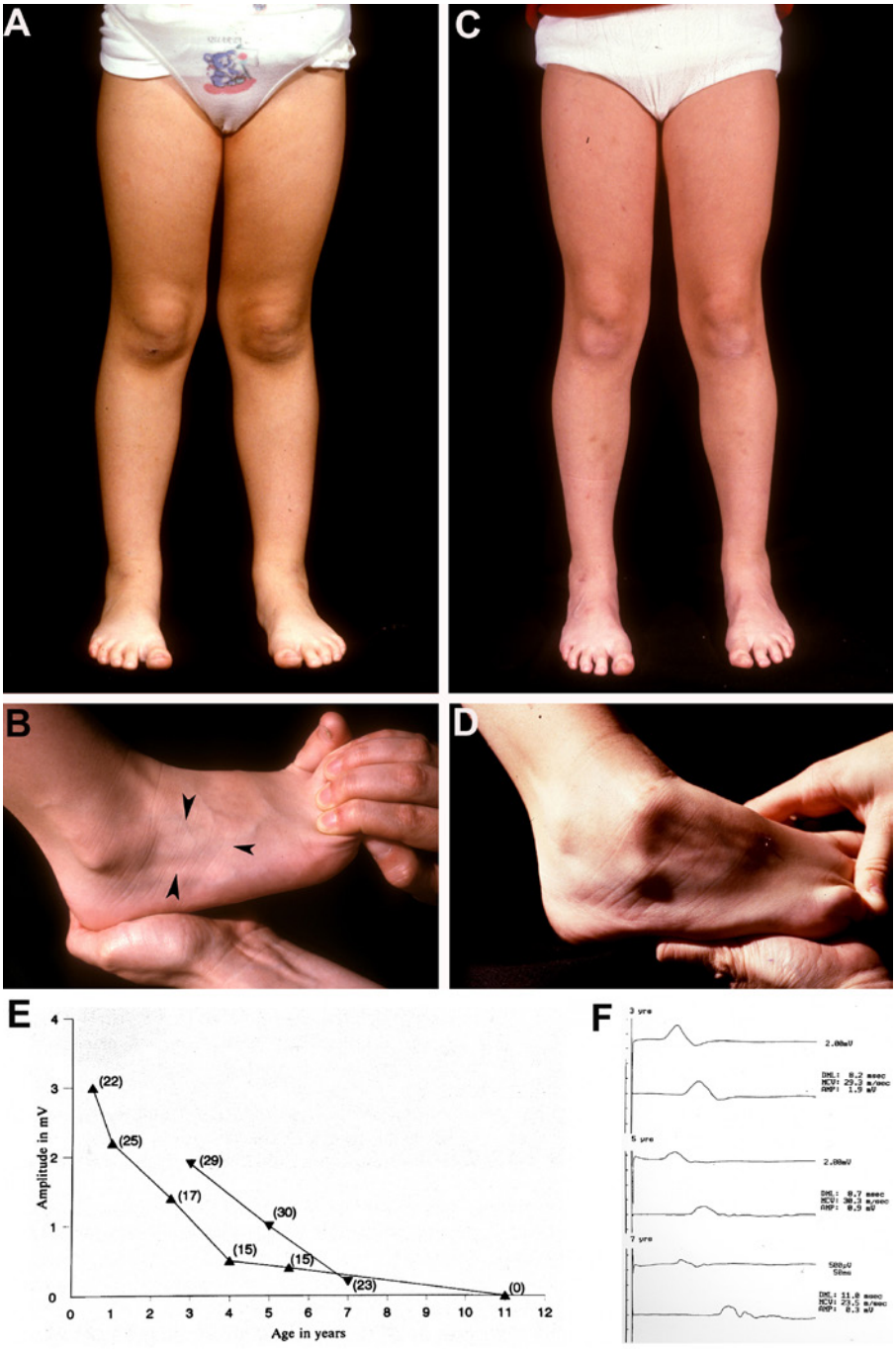


Figure 6. Consecutive images of a patient with asymptomatic CMT1A at age four (A, B) and eight years (C, D). The extensor digitorum brevis muscle (EDB) was initially flattened upon palpation, but this sign is barely visible in the close-up image (B, arrowheads). Four years later, muscle atrophy was very visible, leaving a pronounced hollow (D). No peroneal muscle atrophy is observed (A, B); therefore, the disease first affects the intrinsic foot muscles and later extends to the leg (see text). (E) Compound muscle action potential (CMAP) amplitudes of the EDB in two patients with CMT1A. The connected symbols correspond the values of consecutive amplitudes (y-axis, expressed in mV) as a function of age (x-axis); numbers in parentheses correspond to motor conduction velocity in the peroneal nerve. EDB atrophy was detected between the ages of six and eight years. Drastically reduced amplitudes in motor potentials are observed with relatively preserved conduction velocities, which are only reduced when the amplitude is close to or below 1 mV. F) CMAP recording in the EDB after proximal and distal stimulation of the peroneal nerve in the patient represented with inverted triangles in panel E at the ages of three, five, and seven years. Potentials show progressive attenuation with temporal dispersion only in the last recording (seven years), when amplitude was severely reduced (0.3 mV). Total recording time was 50 ms. Vertical calibration was 2 mV in the recordings performed at three and five years of age, and 500 μV at seven years. Adapted from Berciano et al.[45]

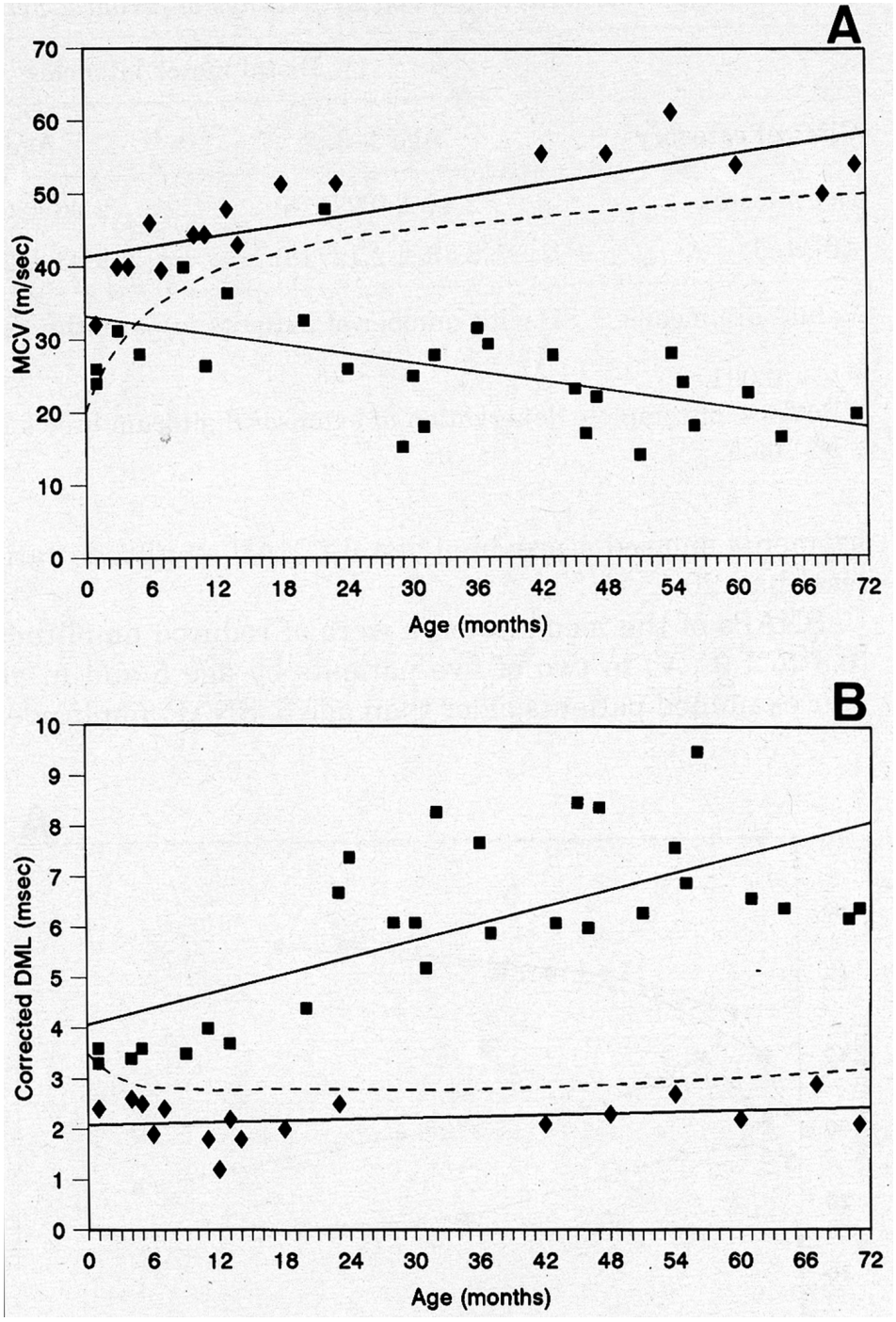


Figure 7. Result of all measurements of motor conduction velocity (MCV) (A) and corrected distal motor latencies (DML) (B) in the median nerve in affected (squares) and unaffected individuals (lozenges). Continuous lines correspond to regression lines and dashed lines indicate the lower limit of normal for MCV and upper limit of normal for DML. Taken from García et al.[17]

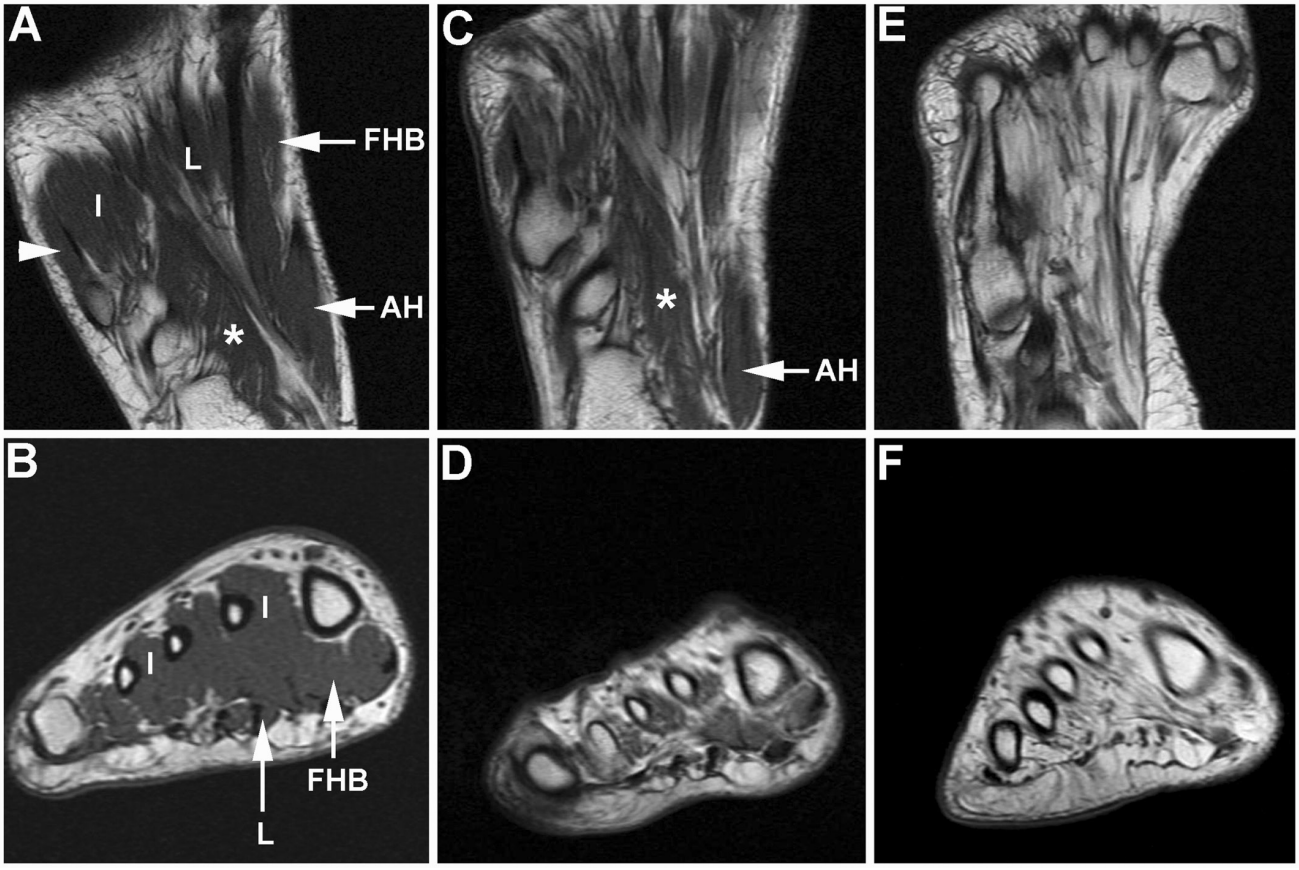


Figure 8. T1-weighted images of the intrinsic foot muscles in a control subject (A, B), in a patient with CMT1A aged 17 years with a Functional Disability Scale (FDS) score of 0 (normal) (C, D), and in another patient aged 41 years with mild peroneal paresis and FDS score of 2 (inability to run) (E, F), obtained at the same level on the long and short foot axes. A) Normal (intermediate to low signal) identified muscles in this axial section, including the lumbricals (L), abductor hallucis (AH); interossei (I), and flexor digitorum accessorius (asterisk), and flexor digiti minimi brevis (FDMB, arrowhead), are partially visualized. B) Normal muscles clearly identified in this coronal section include the interossei (I), lumbricals (L), and flexor hallucis brevis (FHB). C, D). Note evident but incomplete fatty infiltration of the lumbricals, FHB, FDMB, and interossei; the AH and flexor digitorum accessorius (asterisk) are relatively spared. E, F) Compared with the previous case, note the massive fatty infiltration of all mentioned foot muscles. Taken from Gallardo et al.[47]

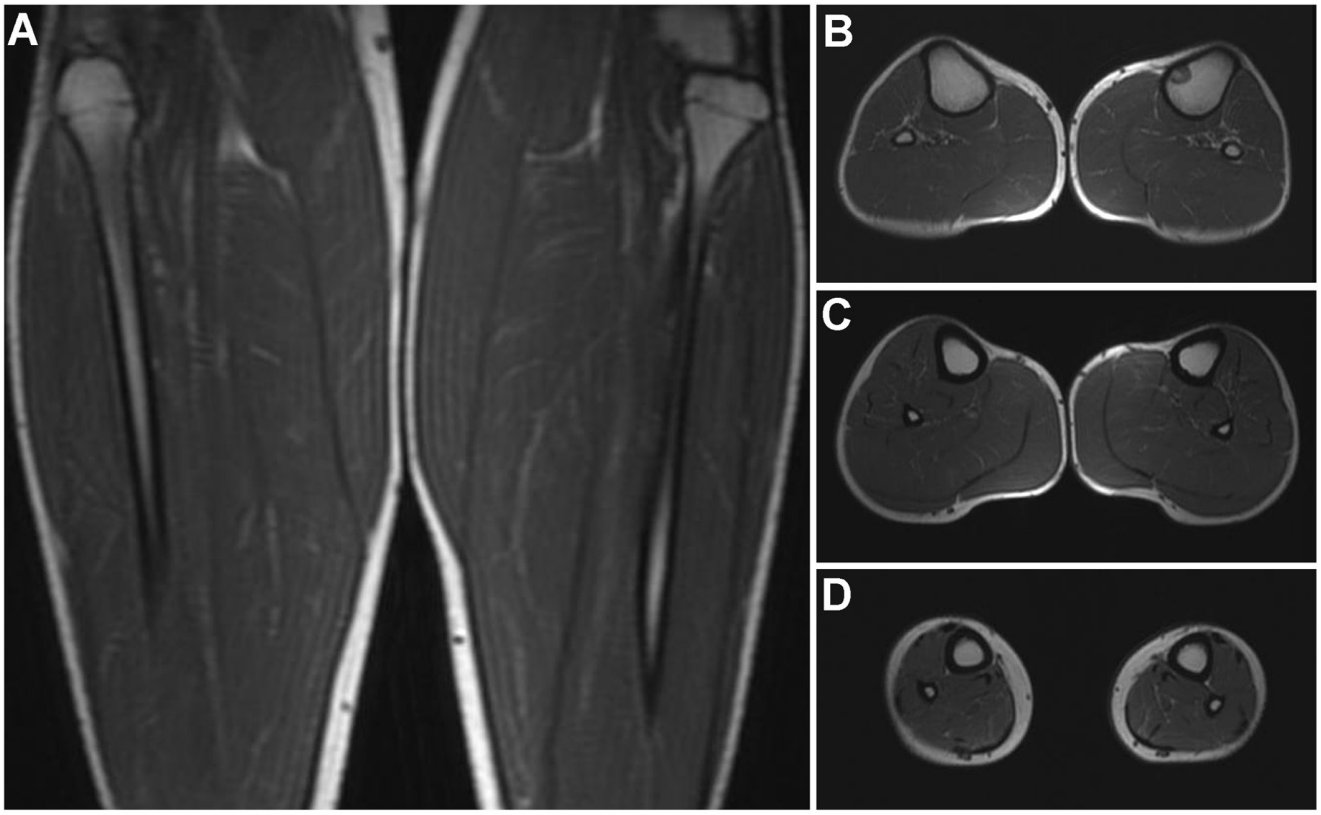


Figure 9. MRI study in the patient illustrated in Figure 8C, D. Coronal (A) and axial (B: proximal calves; C: mid-calves; and D: lower calves) T1-weighted images showing that all four leg compartments are spared. Taken from Gallardo et al.[47]

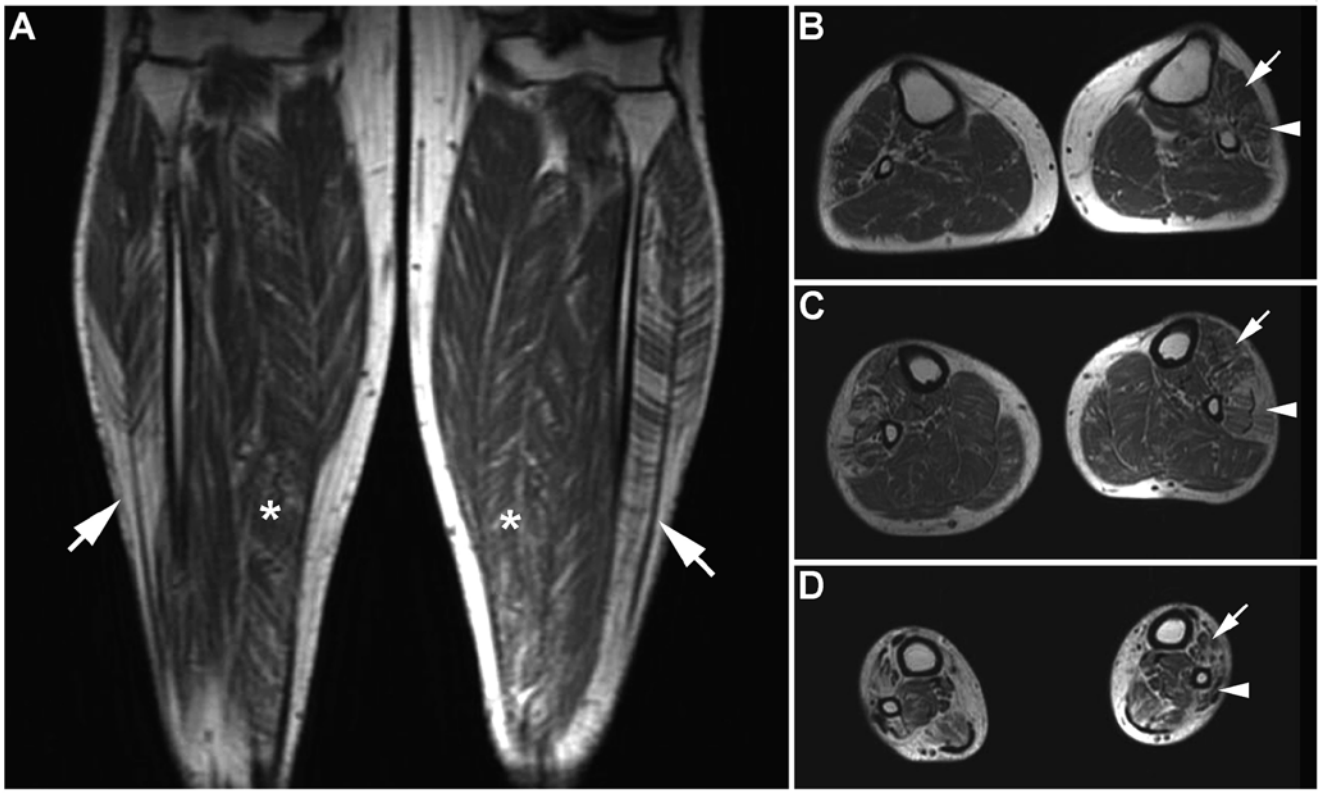


Figure 10. MRI study in the patient illustrated in Figure 8E, F. A) Coronal T1-weighted image of the legs showing extensive and striped fatty infiltration of the peroneal muscles, which is distally accentuated (arrows). Distal soleus muscles (asterisks) are less severely affected. Axial T1-weighted images (B: proximal calves; C: mid-calves; and D: lower calves) showing distally accentuated fatty infiltration of the lateral (arrowheads) and anterior (arrows) muscle compartments. There is also fatty infiltration of the soleus muscles (D), but other muscles of the superficial and deep posterior compartments are spared. Taken from Gallardo et al.[47]

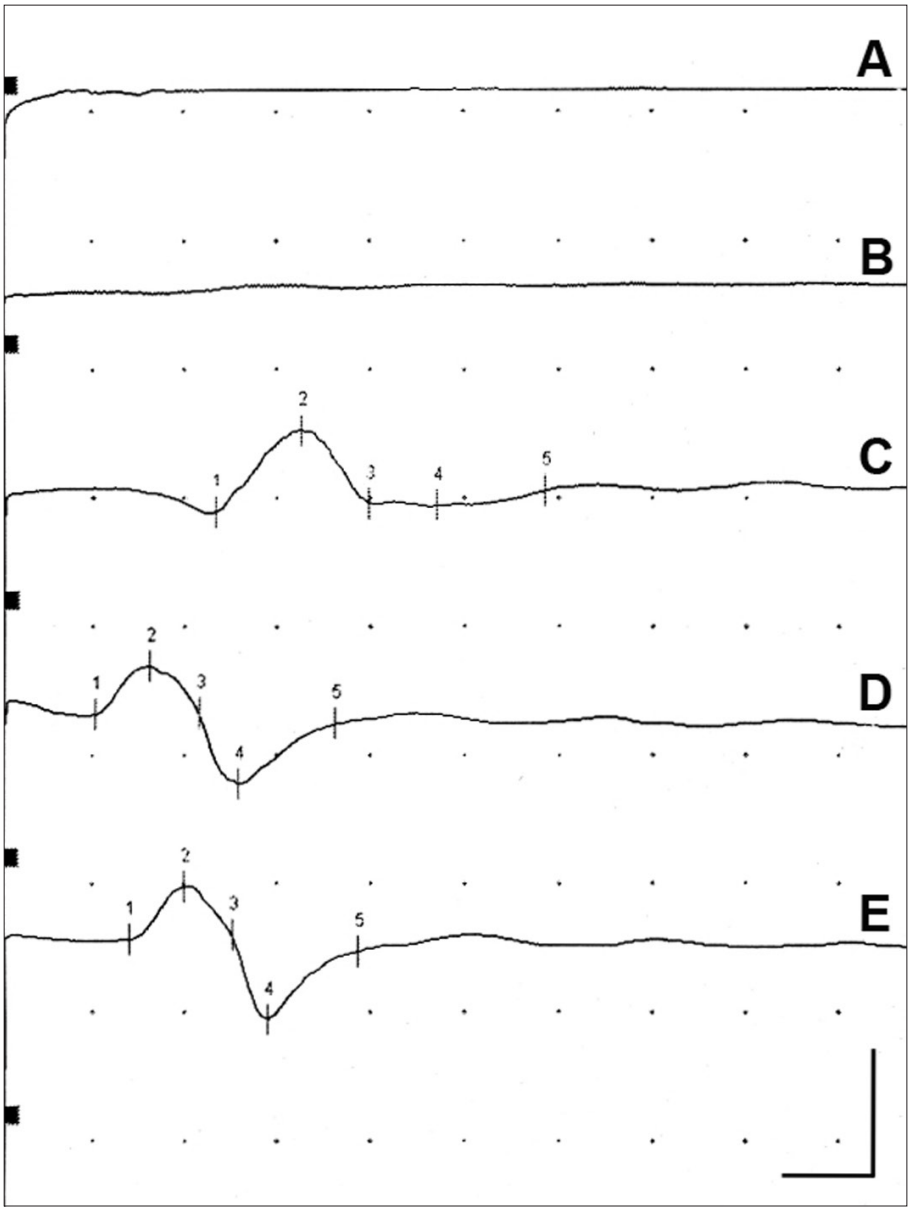


Figure 11. Electrophysiological study of the peroneal nerve in the patient from Figure 3. Note the absence of compound muscle action potentials (CMAP) in the extensor digitorum brevis after stimulation of the nerve at the extensor retinaculum (A) and peroneal head (B). Preserved CMAP recorded at the distal third of the lower leg (8 cm above the bimalleolar line of the ankle, just lateral to the crest of the tibia) after stimulation at peroneal head (C); the only muscle belly at this point is that of the extensor hallucis longus. CMAPs are preserved in the tibialis anterior after stimulation at the peroneal head (D) and popliteal fossa (E); motor conduction velocity for this segment was 17.8 m/s. Bars: 10 ms and 1 mV (A, B), 10 ms and 2 mV (C), and 10 ms and 5 mV (D, E). Taken from Berciano et al.[22]

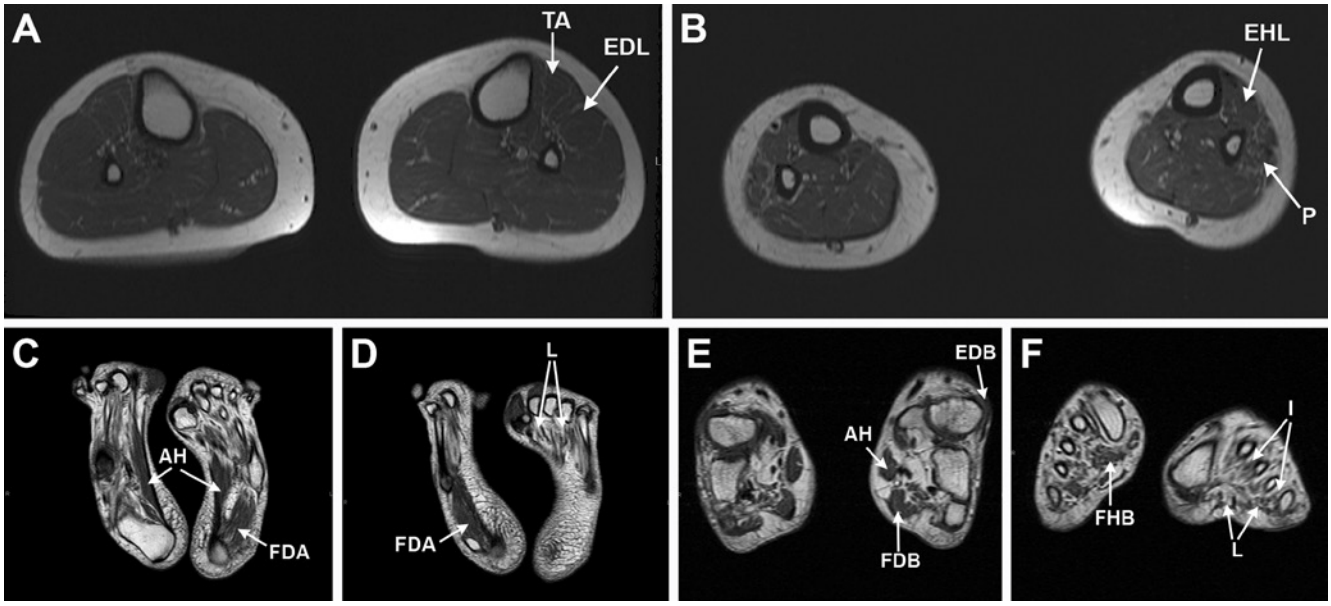


Figure 12. T1-weighted MRI from the patient in Figure 3. A) Axial image passing through the proximal third of the lower legs, showing normal intermediate signal in all muscle compartments; note the preservation of tibialis anterior (TA) and extensor digitorum longus (EDL). B) Axial image passing through distal third of lower legs, showing only slight infiltration of the peroneus brevis (P), with normal signal in the extensor hallucis longus (EHL). C, D) Images of the long axis of the feet, showing fatty atrophy of the lumbricals (L), but relative preservation of other more proximal muscles, the abductor hallucis (AH) and flexor digitorum accessorius (FDA). E) Image of the feet (short axis), passing through the navicular bones and showing fatty atrophy of extensor digitorum brevis (EDB), but relative preservation of the proximal muscles of the feet, including the abductor hallucis (AH) and flexor digitorum brevis (FDB). F) Image of the feet (short axis), passing through the metatarsals and showing marked fatty atrophy of the lumbricals (L) and interossei (I); note that on the right side, the flexor hallucis brevis (FHB) is still visible, with its physiological intermediate signal being relatively preserved. Asymmetry of MRI foot images is accounted for by the clinical asymmetry of forefoot deformity. Taken from Berciano et al.[22]

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