REVIEW ARTICLE

Pes cavus and hereditary neuropathies: when a relationship should be suspected

S. Piazza · G. Ricci · E. Caldarazzo Ienco ·
C. Carlesi · L. Volpi · G. Siciliano ·
M. Mancuso

Abstract The hereditary peripheral neuropathies are a clinically and genetically heterogeneous group of diseases of the peripheral nervous system. Foot deformities, including the common *pes cavus*, but also hammer toes and twisting of the ankle, are frequently present in patients with hereditary peripheral neuropathy, and often represent one of the first signs of the disease. *Pes cavus* in hereditary peripheral neuropathies is caused by imbalance between the intrinsic muscles of the foot and the muscles of the leg. Accurate clinical evaluation in patients with *pes cavus* is necessary to exclude or confirm the presence of peripheral neuropathy. Hereditary peripheral neuropathies should be suspected in those cases with bilateral foot deformities, in the presence of family history for *pes cavus* and/or gait impairment, and in the presence of neurological symptoms or signs, such as distal muscle hypotrophy of limbs. Herein, we review the hereditary peripheral neuropathies in which *pes cavus* plays a key role as a "spy sign," discussing the clinical and molecular features of these disorders to highlight the importance of *pes cavus* as a helpful clinical sign in these rare diseases.

Keywords *Pes cavus* · Hereditary peripheral neuropathy · Neurological evaluation · Multidisciplinary management

S. Piazza · G. Ricci · E. Caldarazzo Ienco · C. Carlesi ·
L. Volpi · G. Siciliano · M. Mancuso (✉)
Department of Neuroscience, Neurological Clinic,
University of Pisa, Via Roma 67, 56126 Pisa, Italy
e-mail: mmancuso@inwind.it

Introduction

Pes cavus is a foot deformity characterized by a high arch of the foot that does not flatten with weight bearing; the deformity can be located in the forefoot, midfoot, hindfoot, or in a combination of all these sites (Figs. 1, 2). *Pes cavus* is a common finding in the general population, with prevalence of approximately 10% [1].

Frequently, *pes cavus* may be a sign of an underlying neurological disorder, including spinal cord and peripheral nerve pathologies, such us spino-cerebellar ataxia and hereditary peripheral neuropathies. A previous retrospective analysis of patients undergoing *pes cavus* surgery [2] revealed that almost one-third of apparently idiopathic cases suffered from a neurological disease.

Herein, we discuss the hereditary peripheral neuropathies (HPN) in which *pes cavus* plays a key role as a "spy sign." A clear, complete, and detailed review of clinical and molecular features of these rare disorders may be useful in clinical management and differential diagnosis of patients who present with *pes cavus* as almost single sign of disease.

Hereditary peripheral neuropathies (HPN) are a heterogeneous group of peripheral nerve disorders, clinically characterized by sensorial and/or motor impairment, with reduction or absence of deep tendon reflexes [3].

Foot deformities, including *pes cavus*, hammer toes, and twisting of the ankle, are commonly present in some HPN forms, such as Charcot–Marie–Tooth (CMT) disease, hereditary neuropathy with predisposition to pressure palsies (HNPP), and distal hereditary motor neuropathy (DHMN) [4], but are uncommon in the other HPN. We will therefore discuss only the clinical features and genetic basis of HPN associated with *pes cavus*.

Fig. 1 *Pes cavus* and *main en griffe* in a patient with CMT1A

Fig. 2 *Pes cavus* in a patient with CMT1A

HPN associated with *pes cavus*

Charcot–Marie–Tooth disease

The most common form of HPN is hereditary motor and sensory neuropathy (HMSN), also called Charcot–Marie–Tooth (CMT) disease. Prevalence is estimated at about 17–40 per 100,000 [5].

CMT is a genetically heterogeneous disorder (Table 1), classified into demyelinating (CMT1 and CMT4), axonal (CMT2 and CMT4), and intermediate (CMT, CMTX,

CMT2E) forms, and caused by mutations in several genes coding for structural myelin proteins, gap-junction proteins, cytoskeleton components, enzymes, or transcription factor. CMT is usually transmitted as an autosomal dominant trait, although rarer X-linked (CMTX) or recessive forms have been reported [6, 7]. CMT is a slow progressive disease, usually with onset in the second or third decade. Rarely, CMT arises in early infancy (Dejerine–Sottas and congenital hypomyelination diseases) [8] with a severe phenotype characterized by hypotonia and delay in motor milestones. CMT onset may also occur later, generally with a less aggressive clinical course [9].

The most common features in classical CMT phenotype are skeletal deformities such as *pes cavus* with hammer toes; less frequent skeletal signs are *pes planus*, twisting of ankle and tripping, and painful foot callosities. Scoliosis could be present in 10% of affected people [10, 11]. Neurological examination shows characteristic signs of a sensorimotor peripheral neuropathy. Sensory signs are usually less prominent (70%) than motor ones [12]. The most frequent findings [13] are ataxia, hypoesthesia, and loss of vibration, two-point discrimination, and joint position sense. Motor impairment, which usually became evident during the course of disease, is responsible for upper and lower limb weakness and atrophy, with *main en griffe* (Fig. 1) and "inverted champagne bottle" legs. Steppage gait and foot drop are the first most common motor signs. Deep tendon reflexes are diminished or absent [14]. Muscle cramps, cold feet, acrocyanosis, and postural tremor are frequent complaints.

Electroneurography allows classification of CMT disease into two main forms: CMT1 or demyelinating form, characterized by a marked slowing in nerve conduction velocities (by definition, <38 m/s in upper limb motor nerves) and by a primary myelinopathy; and CMT2 or axonal form, in which nerve conduction values are preserved or only mildly slowed (>38 m/s in upper limb motor nerves) and the axon is the primary disease target [15]. The existence of a CMT subgroup showing nerve conduction velocity (NCV) values "intermediate" between CMT1 and CMT2 has been also reported [16, 17].

As previously reported, CMT diagnosis is based on clinical examination, electrophysiological findings, and molecular testing. In selective cases, such as in patients with sporadic form or in whom molecular investigations result unable to demonstrate DNA defects, nerve biopsy might give relevant information for diagnosis and differential diagnosis. In particular, the typical histological marker of demyelinating neuropathies is represented by the presence of basal lamina "onion bulbs," determined by concentric proliferation of Shawn cell cytoplasmic processes during the demyelination phenomenon and the remyelination tentative. In the advanced phase, loss of normal myelin covering ("nude axon") has also been reported.

Table 1 Genetic classification of hereditary motor and sensory neuropathies

	Gene	Inheritance	Locus
HMSN1-CMT1			
CMT1A:	PMP-22	Dominant/sporadic	17p11
CMT1B:	P0 protein	Dominant	lq22
CMT1C:	LITAF	Dominant	16pl3
CMT1D:	EGR2	Dominant	10q21
CMT1E:	P0 protein	Dominant	lq22
CMT1F:	Neurofilament light chain	Dominant/sporadic	8p21
HMSN2-CMT2			
CMT2A1:	KIF1B	Dominant	lp36
CMT2A2:	MFN2	Dominant	lp36
CMT2B:	RAB7	Dominant	3ql3-q22
CMT2C:	TRPV4	Dominant	12q23-q24
CMT2D:	GARS	Dominant	7pl5
CMT2E:	Neurofilament light chain	Dominant	8p21
CMT2F:	HSPB1	Dominant/recessive	7q11-q21
CMT2G:		Dominant	12ql2
CMT2I:	PO	Dominant	lq22
CMT2J:	PO	Dominant	lq22
CMT2L:	HSPBE	Dominant	12q24
AR-CMT2A	Lam in A/C	Recessive	lq21.2
AR-CMT2E	Med25	Recessive	19ql3.3
CMT2K:	GDAP1	Dominant/recessive	8q21
HMSN3—DSN/CHN			
DSNA	PMP-22	Dominant/recessive	17p11-2
DSNB	MP2	Dominant/recessive	lq22
DSNC	EGRP2	Dominant	10q21/EGR2
DSND		Dominant	Sq23-24
DSN	PRX	Recessive	19ql3.1-13.2
DSN	GDAP1	Recessive	8ql3-21.1
Congenital hypomyelination			
CHA	PMO-22	Dominant	17p11.2
CHB	MP2	Dominant	lq22
CHC	EGRP2	Dominant/recessive	10q21
HMSN4-CMT4			
CMT4A:	GDAP1	Recessive	8q21
CMT4B1:	MTMR2	Recessive	11q23
CMT4B2:	SBF2	Recessive	11p15
CMT4C:	SH3TC2 (KLAA1985)	Recessive	5q32
CMT4D:	NDRG1	Recessive	8q24
CMT4E:	EGR2	Dominant/recessive	10q21
CMT4F:	Periaxin	Recessive	19ql3
CMT4H:	FGD4	Recessive	12ql2
CMT4J	FIG4	Recessive	6q21
HSMN5			
Silver syndrome	Seipin/BSCL2	Dominant	11ql3
Troyer syndrome	SPG20	Recessive	13ql2.3

Hereditary motor and sensor neuropathy (http://www.ncbi.nlm.nih.gov/omim)

Large-caliber fiber reduction and formation of isolated monostratified "simple onion bulbs" have been described in CMT2 [3].

There are no pharmacologic cures for CMT. A well-balanced diet and weight control can help minimize disability. Dietary supplements such as creatine, and

co-enzyme Q have not been proven effective in treating CMT. Aerobic exercise and rehabilitation play an essential role in preserving quality of life of patients with CMT. A small percentage of patients with inherited neuropathy may respond to immunomodulatory therapy, such as prednisone or intravenous gammaglobulin (IVIG). Potentially neurotoxic medications, such as vincristine or cisplatinum, should be avoided [18]. Experimental studies showed that progesterone antagonist improves neuropathy in CMT1A rats, and it represents a promising pharmacologic target for CMT1A patients [19, 20].

Dejerine–Sottas neuropathy and congenital hypomyelinating neuropathy

Dejerine–Sottas (DSN) and congenital hypomyelinating (CHN) neuropathies are rare, severe, infantile-onset, demyelinating peripheral nerve diseases.

DSN is transmitted as an autosomal dominant or recessive trait (Table 1). Clinical onset occurs at up to 2 years of age, with motor and sensory impairment and skeletal deformities, more frequently represented by scoliosis. NCV of DSN patients is greatly compromised, with values <15 m/s. Sural nerve biopsies could show marked demyelination or predominant axonal loss [8, 18].

CHN, an autosomal dominant or recessive disease (Table 1), is characterized by severe hypotonia ("floppy infant"), dysphagia, and respiratory insufficiency, usually occurring within the first year of life. NCV is very slow (<10 m/s), and sural nerve biopsy presents pathological features similar to those of DSN [16, 17].

Hereditary neuropathy with liability to pressure palsies

The prevalence of hereditary neuropathy with liability to pressure palsies (HNPP) is estimated to be at least 16 per 100,000 [21].

HNPP is an autosomal dominant disorder due to a deletion in chromosome 17p11.2 which codes for peripheral myelin protein (PMP22), an integral membrane protein that is a major component of myelin in the peripheral nervous system [22].

Patients present acute and transient episodes of focal neuropathies, commonly affecting the ulnar, radial, and peroneal nerves and the brachial plexus. These episodes are typically painless, recurrent, and occur after trauma or pressure, or with no evident precipitating factor [23]. The palsies may be debilitating, last for days to weeks, and require installation of specific orthosis. Onset of HNPP is usually in adolescence, with a high degree of penetrance; however, clinically asymptomatic gene carriers are reported. Neurological examination could evidence hypoactive

deep tendon reflexes and mild *pes cavus*, even in clinically asymptomatic patients [24].

With ageing, these patients can have a significant clinical overlap with CMT1, as the repeated injuries to the nerve can prevent full reversal.

Electrophysiological examination shows prolonged motor and sensory nerve conduction velocities (NCV) [25] and conduction blocks that are characteristic of the affected nerves, especially over entrapment sites. NCV abnormalities are also present in those nerves apparently unaffected by palsy and in asymptomatic gene carriers [26].

Histological analysis of sural nerve biopsies shows segmental area of de- and remyelination. The pathological hallmark of HNPP is presence of tomacula, consisting of massive variable myelin overfolding [27]. In rare of HNPP patients nerve biopsy could be present only the axonal regeneration signs [28].

There is no specific treatment for HNPP. Current management consists of early detection and diagnosis of the disease, to reduce excessive force or repetitive movements, or to avoid static joint positions. Chemotherapeutic agents, such as vincristine, should be used with great caution [29].

Distal hereditary motor neuropathies

Distal hereditary motor neuropathies (dHMNs) are very rare genetic disorders (approximately prevalence rate of 1/100,000) [30], inherited as an autosomal dominant, autosomal recessive or X-linked trait [31–33] (Table 2).

dHMN usually presents as a classical peroneal muscular atrophy syndrome without sensory symptoms [34]. The clinical picture consists of progressive weakness and wasting of the extensor muscles of the toes and feet. Later,

Table 2 Genetic classification of distal hereditary motor neuropathies

Type	Inheritance	Gene/locus
HMN I	AD	Unknown
HMN II	AD	HSP27 (HSPB1)
HMN II	AD	HSP22 (HSPB8)
HMN III	AR	11q13
HMN IV	AR	11q13
HMN V	AD	GARS
HMN V	AD	BSC12
HMN VI	AR	IGHMBP2
HMN VIIA	AD	2q14
HMN VIIB	AD	DCTN1
HMN/ALS4	AD	SETX
HMN-J	AR	9p21.1-p12
Congenital distal SMA	AD	12q23-12q24

Distal hereditary motor neuropathies (http://www.ncbi.nlm.nih.gov/omim)

weakness and wasting also involve the distal upper limb muscles. Foot deformity is a common feature. Additional features are represented by involvement of hands, vocal cord paralysis, diaphragm paralysis, and pyramidal tract signs [35].

In dHMN patients, electromyography evidences signs of chronic denervation, and motor NCV study shows an amplitude reduction of compound muscle action potentials or a moderate decrease in velocity. Sensory nerve conductions and amplitudes were normal [4, 36].

Sural nerve biopsy has rarely been performed in dHMN patients and usually showed normal findings [4]. Muscle biopsy shows neurogenic damage related to lower motor neuron degeneration [37].

dHMN has no specific treatment. Patients need neurological follow-up to evaluate the disease's clinical progression and for referral to rehabilitation or orthopedic service for correct management of complications.

Etiopathogenesis of *pes cavus* in HPN

Pes cavus in HPN derives from plantar flexion deformity of the first metatarsal due to imbalance between the intrinsic muscles of the foot and the muscles of the leg. The exact physiopathological mechanisms responsible for *pes cavus* genesis in HPN is not entirely clarified, even if two main hypotheses have been formulated [38].

The first hypothesis assigns an important role in the pathogenesis of this skeletal deformity to overaction of the peronei in comparison with the antagonist tibialis anterior, secondary to the leg muscle's amyotrophy pattern in the disease. In particular, it has been supposed that a weak peroneus brevis is overpowered by a relatively stronger tibialis posterior, causing adduction of the forefoot and inversion of the hindfoot. In addition, a weak tibialis anterior is overpowered by a stronger peroneus longus, causing plantar-flexion of the first metatarsal and anterior *pes cavus* [12, 39–41]. The intrinsic foot muscles develop contractures, while the long extensor to the toe muscles, recruited to assist in ankle dorsiflexion, causes claw toes deformity.

The second hypothesis is that precocious and primary involvement of intrinsic foot muscles is responsible for the pathogenesis of *pes cavus*, because the deformity is observed in the early stages of the disease, also when there is not yet evidence of leg muscle weakness [42]. A magnetic resonance imaging (MRI) study of amyotrophic leg and foot muscles performed in patients with CMT [43] reported precocious fatty infiltration of intrinsic foot muscles, also when leg muscles are still preserved. The authors deduced that the weakness of the lumbricals and the other intrinsic foot muscles, due to selective denervation, could cause the dorsiflexion of metatarsophalangeal joints,

initially responsible for the flattening of the transverse arcus plantaris and the clawing of the toes. Dorsiflexion of metatarsophalangeal joints during gait could also determine the wrapping around the metatarsal head of the plantar aponeurosis and the contraction of the short flexors, with secondary shortening of the Achilles tendon and limitation of ankle dorsiflexion. A subsequent MRI muscle study in CMT patients also seems to confirm a possible primary role of intrinsic foot muscle in *pes cavus* pathogenesis [44]. The sensitivity of MRI for detecting precocious denervation changes in early stages of HMN and CMT has been also recently confirmed [45].

In conclusion, the foot deformity *pes cavus*, secondary to plantar flexion deformity of the first metatarsal, could be associated to several neurological disorders, including spinal cord and peripheral nerve pathologies, such us spino-cerebellar ataxia and hereditary peripheral neuropathies.

In this article, we have reported the HPN in which *pes cavus* plays a key role as a "spy sign" [46, 47], as a precocious manifestation of HPN. Accurate clinical evaluation in patients with *pes cavus* is therefore necessary to exclude or confirm the presence of contemporary involvement of peripheral nerves [48, 49], especially in the early stage of
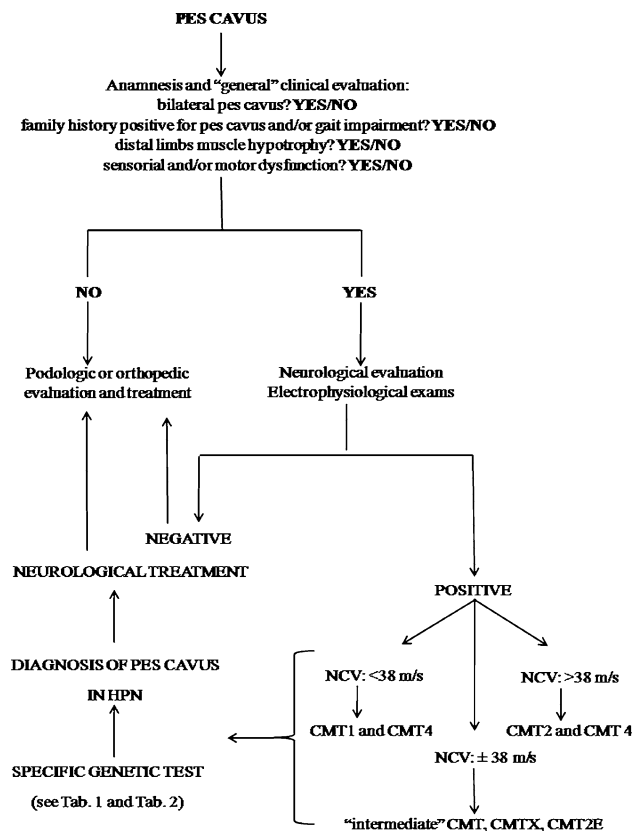

Fig. 3 When *pes cavus* might reveal HPN: a proposed diagnostic algorithm. *NCS* nerve conduction studies, *HPN* hereditary peripheral neuropathies

the disease, when other signs of HPN may not yet be present or evident.

When should HPN be suspected in a patient with *pes cavus*? Clinical data suggestive of HPN are represented by evidence of: bilateral *pes cavus*, positive family history for *pes cavus* and/or gait impairment, distal muscle hypotrophy of limbs, and sensorial and/or motor dysfunction.

When one or more of these signs are present, the patient should be subjected to neurological evaluation to complete the HPN diagnostic algorithm, based on electroneurograph-ysiological studies and, subsequently, molecular analysis (see Fig. 3).

Conflict of interest   None.

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