CHARCOT-MARIE-TOOTH DISEASE: MODERN CLASSIFICATION AND CLINICAL FEATURES

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Summary: In this article consider classification and clinical features of Charcot-Marie-Tooth disease depending on the affection gene and inheritance type.

Keywords: Charcot-Marie-Tooth disease, classification, clinical features

Introduction

Charcot-Marie-Tooth disease – extensive group of genetically heterogeneous diseases of the peripheral nerves characterized by symptoms progressing polyneuropathies with primary defeat of muscles distal of departments of extremities [8]. The first clinical description of disease has been made by the French researchers J.Charcot, P.Marie (1886) and irrespective of them Englishman H. Tooth (1886) which have designated them as neural amyotrophy. This term is used till now for a designation of this group of diseases. However according to the international classification the term hereditary motor sensory neuropathies (HMSN) is accepted [7]. Frequency of all forms HMSN varies from 4,7 to 36 on 100 thousand population [12]. The greatest prevalence HMSN in Norway makes 36 cases on 100 thousand population, in Spain – 28,2 on 100 thousand population. Frequency in Cyprus has made 16 on 100 thousand population, in Serbia – 9,7 on 100 thousand population [13,23]. Result of Japanese research is frequency HMSN 10,8 on 100 thousand population. The least frequency is fixed in Nigeria – 0,14 on 100 thousand population. In Russia this indicator on the average makes 5,64 on 100 thousand population with fluctuations from 1,07 to 15,95 [1,11]. HMSN amazes all races and nationalities without age and gender distinctions, but people of young, able-bodied age (20-30 years) is more often suffer. The progressive course of disease with fast development of complications and absence of effective treatment in patients with HMSN leads to decrease in quality of life and early disability. In the families burdened on HMSN preventive maintenance of given hereditary disease is based on medical-genetic consultation and prenatal diagnostics [10]. Now it is identified about 30 various genes responsible for formation of phenotype HMSN. Till now new clinical variants, and also the new genes involved in formation of this pathology are described [26].

Classification

For more than centenary period, the past since the first description of Charcot-Marie-Tooth disease, sights at systematization and nosological independence of separate variants of this group

of diseases repeatedly changed. Creation of new classifications was promoted appreciably by development of diagnostic methods. Researches Dyck P. and Lambert E., performed in the sixties last century, it is shown that all hereditary polyneuropathies on the basis of the given electrophysiological and morphological methods of research it is possible to differentiate accurately 2 basic of type HMSN – HMSN I and HMSN II. Type HMSN I is characterized, by electrophysiological data, considerable decrease in speed of carrying out of nerve conduction velocity (than 38 km/s) and to sensitive fibers of peripheral nerves, and morphological – segmentary hypertrophic demyelination nerves with formation of "bulbous heads» («onion bulbs»). Thus, HMSN I type represents demyelination form of (mielinopathies). On the contrary, for HMSN type II primary defeat axonal peripheral nerves is characteristic, thus speeds of carrying out of an impulse on peripheral nerves within norm or are moderately lowered, and on a biopsy the myelin structure remains safe (axonal form of polyneuropathy, or axonopathies). As threshold value the indicator is accepted NCV (nerve conduction velocity) on impellent a component of a median nerve in 38 km/s. However families are described, at the amazed which members considerable variability of this parameter was observed (from 25 to 45 km/s), it has led to necessity of allocation of group of so-called, intermediate variants HMSN [3,7,8]. Besides the motor sensory polyneuropathies specified above two basic types, sometimes in the literature under heading HMSN allocate also a number of rather rare syndromes different from a classical phenotype by those CMT or other features of a clinical picture [2,25]:

a) HMSN III (Dejerine – Sottas disease) – is characterized by onset of symptoms throughout the first years of the life sharply expressed by a hypertrophy of peripheral nerves («hypertrophic neuritis»), the expressed decrease motor NCV (less than 10 km/s), early disability and quite often observable increase of level of fiber in spinal liquid;

b) HMSN IV (Refsum disease) – the independent disease connected with infringement of an exchange fitan of acid at which the impellent polyneuropathy is combined with an ataxy, an ichthyosis and other symptoms;

c) The rare forms HMSN characterized by a combination of mainly motor neuropathy with the bottom spastic paraparesis (HMSN V), an atrophy of optic nerves and deafness (HMSN VI), pigmentary retinitis (HMSN VII);

d) Congenital hypomyelination the polyneuropathy – is characterized by infringement of formation of a myelin cover of peripheral nerves since a birth, considerable backlog of the child in impellent development, sharp decrease in speed of carrying out of an impulse on peripheral nerves.

The majority of forms (HMSN I and II type) have autosomal dominant type of inheritance, considerably smaller number of forms is inherited on autosomal recessive type (HMSN III and

IV type), some forms have X-linked recessive (Xq24) and the X-linked dominant inheritance (locus Xq13) with intermediate values NCV (from 30 to 40 km/s) [7]. Now the classification structure NMSN based on etiological distinctions is offered (see the table).

Features of a clinical picture.

For HMSN development of chronically progressing weakness and an atrophy distal muscles of feet, depression tendon reflexes (first of all Achillov´s reflexes), sensitivity frustration on polineurithic to type, deformation of feet («foot of Friedreich´s»), gait frustration on type «steppag» are characteristic; at a late stage weakness and an atrophy distal departments of hands, deformation of brushes (drawing see) can join. We will consider the basic types HMSN.

HMSN1 Type. The most common form is HMSN1A with autosomal dominant type of inheritance which according to research Saporta, etc. (2011) is revealed at 55 % of the surveyed patients with HMSN [15]. The reason is the mutation in gene PMP22 (peripheral myelin protein). The basic type of a mutation in this gene – duplication of 1,5 Mb in area chromosome 17p11.2-12 [14,21,33,34]. HMCH1A begins on 1-2 decade of life, extremely seldom arises after 30 years. The first symptoms, as a rule, are exhaustion in feet at long walking, static loadings, instability of gait, frequent stumble, and incomplete dislocations of ankle joints. In process of progressing of disease gait gets character "cock" («steppag»). To thicket originally atrophies arise in muscles of feet, is more rare in muscles of a shin, the bottom third of hip. Later atrophy extends on muscles of the top extremities in a direction from distal departments to the proximal. On occasion atrophy at HMCH1 type is limited to selective defeat distal departments of extremities. Bone deformations of feet are regarded by the majority of researchers as obligate sign HMSN1 of type. Foot get the hollow form with the high arch, sometimes in the form of "stick" or « Friedreich´s» hollow foot with the high arch and extension a thumb. Owing to atrophical changes of muscles of a foot have the form of "the overturned bottle», "riding breeches", «feet of a stork». Limitation of volume of active movements, weakness and decrease in muscular force varies in a wide range: from an easy paresis to bottom distal paraplegias. An early symptom of illness is decrease Achillov´s reflexes which is observed practically at all patients. Frequent display HMCH of 1 type are sensitivity frustration. Patients complain of pains of various character (aching, shooting, painful muscular reductions on type crampy), paresthesia. Changes both superficial, and deep sensitivity come to light. Disturbance of superficial sensitivity on polineurithic to type, in a kind hyposthesia [11].

Exists allelic variant HMSN 1A type – hereditary neuropathy with liability to pressure palsies which results deletion from gene PMP22 in the field of a chromosome 17p11.2-12 [2,20]. Has autosomal dominant type of inheritance. Disease is shown recurrence by the paresis of peripheral nerves arising sharply after small traumas or pressure palsies. Duration of impellent

infringements fluctuates from one day about several months then there is a complete recovery of functions. In process of illness progressing hanging down foot, oppression tendon reflexes, "spotty" or total sensitivity frustration that pulls together clinical picture HNPP with semiology HMSN1 [4,18] can gradually develop symmetric or asymmetric an amyotrophy in distal departments of the extremities.

Other variants HMSN1. Rare enough variant HMSN1B which makes from 5 % to 7 % of all hereditary demyelination polineuropathies [11]. It is caused by mutations in a gene of the basic fiber of a myelin (MPZ – myelin protein zero), mapped on a chromosome 1q22.1 [16,27]. For this variant considerable decrease is characteristic NCV on peripheral nerves (indicators on a median nerve don't exceed 10 km/s). Mutations in gene MPZ, breaking adgezive to fiber function lead to occurrence demyelation polineuropathies, characterized by the early beginning, the expressed atrophies and weakness of muscles of shins, stop and brushes and considerable decrease NCV on peripheral nerves.

The following variant demyelination polineuropathies with autosomal dominant type of inheritance – 1C is caused missens by mutations in gene LITAF localized on a chromosome 16p13 [28]. This variant meets extremely seldom and has no specific clinical features. Variant HMSN1D is caused by mutations in gene EGR2 (early grow response), mapped on a chromosome 10q21-q22 [30]. Mutations in this gene stop an expression of structural genes of a myelin, such as MBP (myelin basic protein) and MPZ.

HMSN2 Type. The most common variant axonal HMSN is 2A type on which share it is necessary, by estimations of different authors, from 12 to 23 % of all diseases of this genetically heterogeneous group neurodegenerative to a pathology [6]. In overwhelming majority of cases the reason of development of disease are mutations in gene MFN2 mapped in the field of a chromosome 1p36 [22], and only in one family from Japan in quality etiological the factor the mutation in gene KIFlfiB localized in the same chromosomal region is considered [17]. Feature of this genetic variant, in comparison with widespread variants demyelination polineuropathies, the expressed defeat of muscles of shins and feet is, thus foot seldom gets the form eqinovarus or foot of Friedreich´s. More often it to become hollow or flat. It is in most cases observed frustration of deep sensitivity while superficial sensitivity changes not sharply. At patients with this genetic variant occurrence neurosensory relative deafness and atrophies of disks of optic nerves [7] is described.

Prominent feature HMSN 2B the type, caused by mutations in gene RAB7, is the expressed touch component and development of trophic ulcers of the bottom extremities. At HMSN2D – more distinct and early involving of hands. Other variants autosomal dominant axonal HMSN meet equal frequency and have no features of clinical displays [2].

HMSN4 Type. The most widespread variant autosomal recessive HMSN is 4A the type caused by mutations in gene GDAP1, localized on a chromosHMSN4 Type. The most widespread variant autosomal recessive HMSN is 4A the type caused by mutations in gene GDAP1, localized on a chromosome 8q13-q21.1 [24,29]. For this variant early demonstration of process which arises at the age from 1 year till 5 years, and also process distribution on muscles of hips, in communication is chromosome 8q13-q21.1 [24,29]. For this variant early demonstration of process which arises at the age from 1 year till 5 years, and also process distribution on muscles of hips, in communication is characteristic than, at duration of disease more than 10 years at patients can appear receptions of Govers. Deformation of feet and deformation of brushes on type of "a sharp-clawed paw» is marked also expressed eqinovarus. Early loss tendon reflexes from the bottom and top extremities, and also the expressed frustration of deep sensitivity, at a long absence superficial hypesthesia was prominent feature HMSN 4A type [5]. Other genetic variants HMSN 4 types meet extremely seldom and are described in individual families.

X-linked HMSN. Not less than 90 % from all X-linked HMSN it is necessary on share HMSN1X. Reason HMSN 1X are mutations in gene GJB1 localized on a long shoulder of the X-chromosome (Xq13.1). A product of this gene is connexin 32 [7,8,9,19]. It is By this time identified more than 300 various mutations in gene GJB1. The basic type of point-mutations: missens - and a nonsense-. Mutations with shift of a framework of reading [8] in rare instances come to light. Mutations in gene GJB1 are characterized varying expression and incomplete penetration at patients of a female. For the first time a family with neural an amyotrophy with the X-linked dominant type of inheritance has described Herringham in 1889. Disease demonstrates in an age interval from 10 till 35 years from occurrence of weakness and an atrophy of muscles distal departments of the bottom extremities, leading to occurrence steppag gait. In process of disease progressing are marked involving in process of interosseous muscles of brushes and occurrence of deformation of feet as "horse", "hollow" or eqynovarus, and brushes – on type of «a monkey's paw» or «a sharp-clawed paw». Characteristic signs of illness are frustration of all kinds of sensitivity in the field of the amazed muscles, and also tendon hypo- or areflexia. Frequent clinical display of disease happen a tremor of fingers of outstretched arms and fasciculation muscles which are regarded by a number of authors as consequence of interest of motor-neurons of a spinal cord. At 80 % of patients signs of an is sensitive-cerebellar ataxy come to light. By electroneuromiological data decrease in speeds of carrying out of an impulse on impellent fibers of all peripheral nerves and amplitudes of M-answers, along with increase distal the latent periods and duration of M-answers comes to light [9].

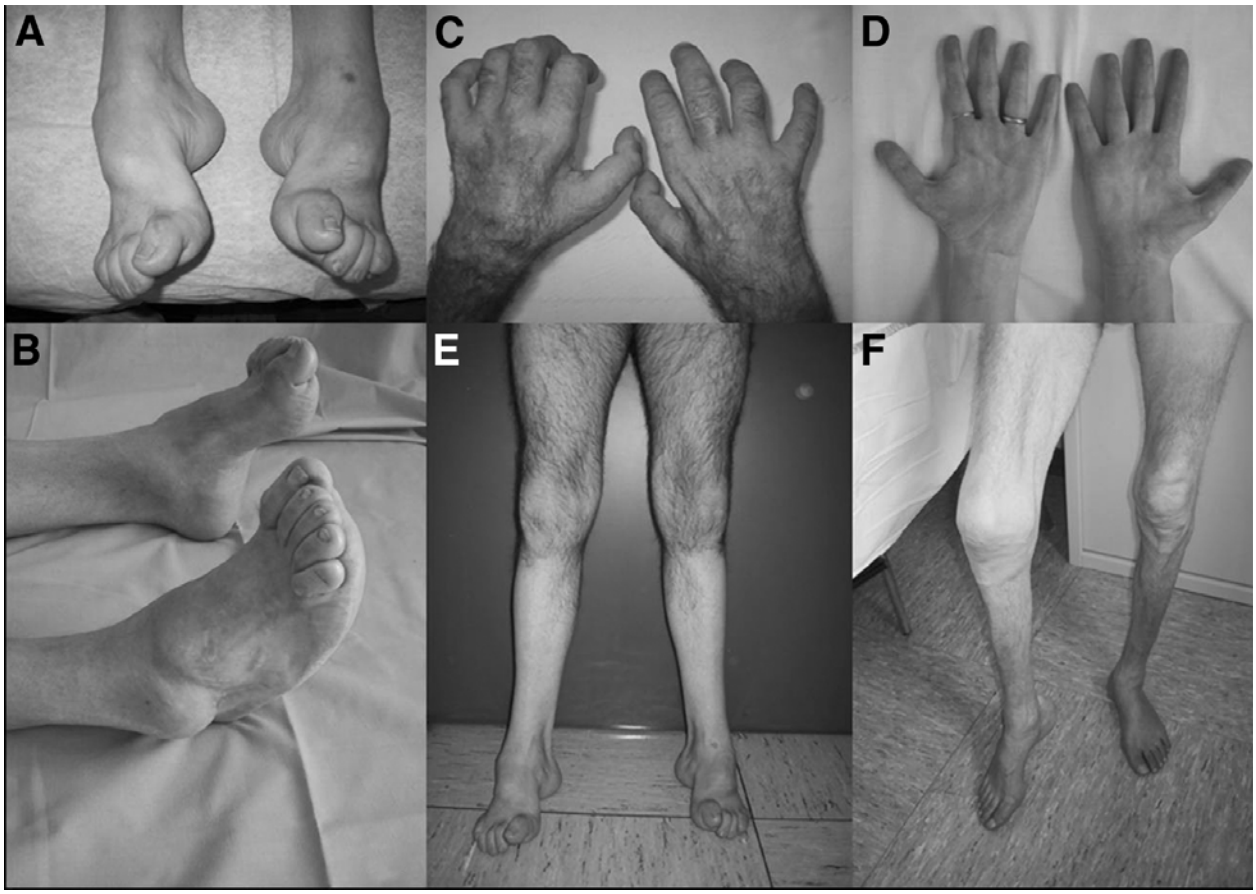
The conclusion

In a kind of the expressed heterogeneity hereditary motor and sensory neuropathies at considerable similarity of clinical displays there are considerable difficulties at identification of a genetic variant with use of expensive methods of DNA-analysis. However, considering high enough prevalence of separate forms hereditary neuropathies and their late diagnostics in daily neurologic practice, increase of vigilance of practising doctors (neurologists, pediatrists, general practitioners) for the purpose of early revealing of disease when therapy and rehabilitation actions are most effective is necessary. It will allow to slow down rates of progressing hereditary neuropathies and to improve social adaptation of patients.

Modern classification HMSN [Shagina O. A. et al., 2009]

The disease form	Inheritance type	Loci	Gene
HMSN tupe 1 (mielinopathia)			
HMSN1A	AD	17p11.2	PMP22
HMSN1B	AD	1q22-q23	MPZ (Po)
HMSN1C	AD	16p13.1-p12.3	LITAF (SIMPLE)
HMSN1 (HMSN1D)	AD	10q21.1-q22.1	EGR2
HMSN1 (HMSN1E)	AD	8p21	NEFL
DCC	AD	8qter	unknown
HMSN type 2 (axonopathia)			
HMSN2A	AD	1p35-p36	MFN2
HMSN2A	AD	1p35-p36	KIFIB
HMSN2B	AD	3q13-q22	RAB7
HMSN2C	AD	12q23-q24	unknown
HMSN2D	AD	7p14	GAPS
HMSN2E	AD	8p21	NEFL
HMSN2A	AD	7q11-21	HSPB1 (HSP2)
HMSN2П	AD	12q12-q13.3	unknown
HMSN2	AD	1q22-q23	MPZ
HMSN2L	AD	12q24	HSPB28
Autocomal-dominant HMSN intermediate type			
DI-HMSNA	AD	10q24.1-q25.1	unknown
DI-HMSNB	AD	19p12-p13.2	DNM2
DI-HMSNC	AD	1p34-p35	YAPS
DI-HMSN	AD	1q2-q23	MPZ
HMSN-P	AD	3q13.1	unknown
Low NCV	AD	8p23	APHGEF10
HMSN type 4 (autocomal-recessive mielinopathia)			
HMCH4A	AR	8q13-q21	GDAP1
HMCH4B2	AR	11p15	SBF2 (MTMR13)
HMCH4B1	AR	11q23	MTMR2
HMCH4C	AR	5q23-q33	SH3TC2 (KIAA1985)
HMCH4D	AR	8q24	NDRG1
HMCH4E	AR	10q21.1-q22.1	EGR2
HMSN4F	AR	19q13.1-q13.3	PRX
CCFDN	AR	18q23-gter	CTDP1
HMSN4G	AR	10q23	unknown
HMSN4H	AR	12p11.1-q13.11	FGD4
HMSN4J	AR	6q21	FIG4
HMCH type 4C (autosomal-recessive axonopathia)			
AP-HMSN2A (HMSN4C1)	AR	1q21.2-q21.3	LMNA
AP-HMSN2 (HMSN4C2)	AR	8q21.3	unknown
AP-HMSN2B (HMSN4C3)	AR	19q13.3	unknown
AP-HMSN2 (HMSN4C4)	AR	8q21	GDAP1

X-linked HMSN			
HMSN1X	XR/XD	Xq13.1	GJB1 (Cx32)
HMSN2X	XR	Xq24-q26	unknown
HMSN3X	XR	Xp22.2	unknown
HMSN4X	XR	Xp26-q28	unknown
HMSNX5	XR	Xq21.32-q24	PRPS1



Clinical features of Charcot-Marie-Tooth (CMT) disease. (**A,B**) Moderate to severe foot deformities in CMT1A and note the pes cavus, hammer toes, and callosities. (**C**) Severe wasting of intrinsic hand muscles in a male patient with CMT. (**D**) Wasting of hand muscles in a female patient with CMTX. Note that muscles of the thenar eminence are more severely involved than hypothenar muscles, suggesting that the median nerve is more severely affected than the ulnar nerve. (**E**) Patient with CMT1A and note the pes cavus, moderate wasting of leg musles and of the lower third of the thigh. (**F**) Patient with late-onset CMT2 associated with an MPZ gene mutation. Foot drop, severe wasting of lower limb muscles, no evidence of foot deformities. Differential diagnosis with acquired axonal polyneuropathy is extremely difficult in the absence of family history of neuropathy.

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