HEREDITARY CONNECTIVE TISSUE DISORDERS: A MODERN APPROACH TO CLASSIFICATION AND DIAGNOSIS (REVIEW)

UDC 577.17:616–018.2–07
Received 21.02.2014

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Hereditary connective tissue disorders — a genetically and clinically heterogeneous group of diseases united by common congenital mesenchymal abnormalities — is one of the most debatable problems of clinical medicine. A great while, from the whole variety of hereditary connective tissue disorders, only "differentiated" (with concerted diagnostic recommendations), monogenic syndromes registered in OMIM, have been the focus of attention of medical community. However, numerous unclassifiable forms with multi-factorial development mechanisms or so called dysplastic phenotypes have not been taken into account when estimating the disease prognosis and determining treatment policy. The review represents the current concepts of the nomenclature of hereditary connective tissue disorders, and considers the diagnostic criteria of the classified monogenic syndromes (Marfan syndrome and Ehlers–Danlos syndrome, MASS-phenotype, primary mitral valve prolapse, joint hypermobility syndrome) and unclassifiable dysplastic phenotypes (MASS-like phenotypes, marfanoid appearance, Ehlers-like phenotype, benign joint hypermobility, unclassifiable phenotype) in the view of recent international and domestic recommendations. Congenital mesenchymal disorders have been represented in the form of a continuous list in order of decreasing clinical intensity of their manifestations and prognostic value reduction ("phenotypic continuum"): from monogenic syndromes through dysplastic phenotypes to unclassifiable phenotypes. The authors have laid emphasis on the difficulties of clinical identification of hereditary connective tissue disorders related to non-specificity of external and visceral markers of connective tissue weakness and certain conventionality of diagnostic criteria. The review has shown the debating aspects of diagnosis and interpretation of clinical significance of some hereditary connective tissue disorders.

Key words: hereditary connective tissue disorders; phenotypic connective tissue continuum; dysplastic syndromes and phenotypes.

Hereditary connective tissue disorders (HCTD), a genetically and clinically heterogeneous group of diseases united by common congenital mesenchymal abnormalities, is one of the most debatable problems of clinical medicine. Only "differentiated", monogenic syndromes with concerted diagnostic recommendations associated with the mutation of extracellular matrix protein genes, growth receptor factors and matrix metalproteinases have been the focus of attention of medical community for many years. Although the number of such syndromes, many of which being registered in the Online Mendelian Inheritance in Man (OMIM) database, now exceeds 250 [1], their prevalence in the population and medical and social significance, accordingly, is not relatively high. More often we have to deal with numerous undifferentiated (unclassifiable) forms of HCTD with multi-factorial development mechanisms (so called dysplastic phenotypes). Their manifestations (commonly not so remarkable) do not fit any of the classified hereditary diseases, and the range of clinical features extends up to transitional, hardly differentiated from normal ones. While the clinical significance of monogenic syndromes being studied in detail and diagnosis criteria known, dysplastic phenotypes continue to be a kind of homogeneous mass, usually ignored in practice. The first attempt to systematize and formulate diagnostic criteria was made in the national guidelines for HCTD (Russia), adopted in 2009, [2] and revised in 2012 [3].

The review is aimed to show a clinical diversity of congenital mesenchymal disorders, to stress difficulties in their identification, show controversial and unsolved issues related to concerning HCTD diagnosis and clinical significance.

HCTD with concerted diagnostic recommendations include Marfan syndrome and Ehlers–Danlos syndrome, MASS-phenotype, primary mitral valve prolapse, joint hypermobility syndrome.

Marfan syndrome is an autosomal dominant pathology with underlying fibrillin-1 (FBN1) gene mutation. Despite apparent success of medicinal therapy and surgical treatment [4–7], Marfan syndrome continues to pose a serious problem associated with the risk of aortic dissection, hazardous to, at least, every tenth patient aged under 40 years [8, 9]. Determining the pathogenic role of the transforming growth factor (TGF-β) allowed a better understanding of the origin of the known Marfan's syndrome clinical manifestations and identification

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of new opportunities of conservative treatment of the given pathology with the use of pharmacological agents reducing TGF-β concentration [10–16].

Marfan syndrome diagnosis is based on the Ghent criteria (Ghent nosology, 1996; 2010). The final, revised version [17] lacks the division into major and minor signs and a number of minor signs have been excluded. At the same time two most specific features — dilatation and/or aortic dissection and ectopic lens have been identified and numerical scoring of other features for calculating the degree of connective tissue systemic involvement have been proposed and the diagnostically significant threshold of 7 points determined. The advantages and limitations of the revised version of the Ghent criteria remain debatable. Comparison of the diagnostic values of the old and new criteria on the evidence of 1009 samples with confirmed FBN1 gene mutation showed that the diagnosis of Marfan syndrome according to the 2010 version may be found in 83% of the investigated patients, and according to the 1996 version in 89% [18]. Applying the new criteria for the disease diagnosis in 164 patients with established Marfan syndrome did not allow to confirm the diagnosis in 9% of cases due to the minor diagnostic significance of ectasia in dura mater and undervaluation of the aortic dilatation in patients with a high value of the total body area [19].

Ehlers–Danlos syndrome is a heterogeneous group of collagenopathies with different types of inheritance and common clinical manifestations of joint hypermobility and increased skin elasticity. Collagen gene, proteoglycans and tenascin-X or enzyme mutations involved in post-translational collagen modification, underlie these changes [16, 20–24]. The diagnosis of Ehlers–Danlos syndrome is based on the Villefranche criteria (Villefranche nosology 1997) [25].

Six disease modifications instead of ten ones previously recognized are identified for these criteria: classical, hypermobile, vascular, kyphoscoliotic, arthrochalasic and dermatosparactic; availability of at least one of the criteria is sufficient for clinical diagnosis [3, 23, 25, 26]. However, reports of new genetic and clinical syndrome modifications continue to be published, inviting to discuss the need of clarifying the Villefranche criteria [24, 27, 28]. A classic type of syndrome is the most common one accounting for up to 90% of patients [29, 30]; COL5A1 or COL5A2 gene mutation is identified approximately in 50% of them [31]. Major criteria of a classic type of Ehlers–Danlos syndrome include skin hyperextensibility, joint hypermobility and wide atrophic scars; the availability of at least one of the criteria is sufficient for clinical diagnosis [25].

MASS-phenotype (Marfan-like syndrome) is an acronym describing mitral valve prolapse, myopia, aortic dilatation, skin and skeletal bones changes. MASS-phenotype can be diagnosed with borderline and non-progressive aortic root dilatation, occurrence of at least one skeletal manifestation, chest malformation in particular [32], and signs of systemic connective tissue involvement with the score of 5 and more. Because MASS-phenotype as well as Marfan syndrome may be caused by FBN1 gene heterozygous mutations [33], it is difficult (if possible) to distinguish it from Marfan syndrome with an incomplete set of signs or “arising” Marfan syndrome when examining an individual, particularly in childhood.

Mitral valve prolapse is diagnosed at systolic shift of one or both cusps of the mitral valve off the line of the valve ring in the parasternal longitudinal position by more than 2 mm [3, 34]. The morphological substrate of ***primary mitral valve prolapse*** as an HCTD modification is valve cusps myxomatosis, reflecting collagenous febriles disorganization and the accumulation of acidic glycosaminoglycans in them [35–38]. Knowing the TGF-b effect on progressing mixomatous degeneration [35, 39, 40] facilitates the explaination of this phenomenon nature and provides new opportunities for the prevention of mitral regurgitation in those patients.

Primary mitral valve prolapse proved to be the most prevalent disorder among the classifiable HCTD [41]. Its detection rate substantially depends on the chosen diagnostic threshold of prolapsing depth, cusps thickness, as well as the age of patients selected. In young people, with using ultrasound threshold of 2 mm or more, prolapse was diagnosed in 10% of cases, 3 mm or more — in 4.3% of cases [42, 43]. The “classical” prolapse prevalence (cusps thickening of 5 mm and more), according to Framingham research, is not more than 1.3% [34, 44]. Non-classical pathology variant (prolapsing of more than 2 mm without thickening of the valve cusps) was found in the young population more often — in 3% of cases [42, 43], which, however, is much smaller than previously reported [45–50]. The prior reports of higher prevalence of mitral valve prolapse was due to its over diagnosis at the dawn of introduction in clinical practice of echocardiography, extrapolating the results of separate observations on the population in the whole and the lack of clear criteria for diagnosis [51–55].

Old beliefs about the prevalence and severity of complications of primary mitral valve prolapse were subject to revision. The opinion that severe complications do not occur in patients with mitral valve prolapse more often than in individuals lacking that defect was upheld in the articles published at the turn of the XXI century with expressive titles: “Misteries of mitral valve prolapse”, “Time for a fresh look”, “Old beliefs yield to new knowledge”, “The merchant of Venice or much ado about nothing”, “When should mitral valve prolapse be considered a real disease?” [52, 56–59]. A number of studies, in particular, did not confirm the information about close association of mitral prolapse with cerebral stroke [51, 60], infectious endocarditis [61], other complications [51, 52], however, other observations suggest otherwise [62–66]. It is not ruled out that a pathogenetic relationship of primary mitral

valve prolapse with some complications (cerebral stroke, serious cardiac rhythm disturbance) can be supported without direct involvement of the "valve" mechanism, for example, due to the inherent HCTD activation of the vegetative nervous system, neuroendocrine dysfunction or bleeding abnormalities [63, 67–71].

At present clear diagnostic mitral valve prolapse criteria have been developed [34, 63, 72, 73], and pathology modifications associated with a different degree of risk and various prognosis, including serious ones have also been determined [52, 63, 74–76]. For risk stratification in patients with mitral valve prolapse the parameters of prolapsing depth, cusp thickness and the degree of mitral regurgitation are essential [72].

With high mitral regurgitation and cusp thickness of more than 5 mm (a sign of its mixomatous degeneration) the probability of hemodynamic disorders significantly increases [73]. The genetic homogeneity as well as clinical and prognostic differences of diffused (Barlow's valve) and partial myxomatosis of valve cusps are in doubt so far [37, 63]. Besides, as shown in the literature [7, 43, 77, 78], disturbed circulation in primary mitral valve prolapse occurs not only through the mechanism of mitral insufficiency, but also through diastolic dysfunction and reduced contractility, conditioned by intramyocardial connective tissue involvement.

Mutation of genes encoding collagen, elastin, fibrillin and tenascin X, resulting in joint ligament weakness, underlies ***joint hypermobility syndrome.*** Currently joint hypermobility is diagnosed on the P. Beighton stanine [79], its comparison with previously proposed scales (Carter and Wilkinson, Rotès-Quérol) has demonstrated its validity [80]. Joint hypermobility of no less than 4 points on the Beighton scale, and arthralgia in no less than four joints with three and more month duration are significant diagnostic criteria for the disorder. A major clinical problem of joint hypermobility is a chronic pain syndrome [81–83] often inducing depression and anxiety [84–86]. Arthralgia associated with joint hypermobility syndrome rather often becomes the cause of prolonged diagnostic seeking [87, 88] and diagnostic errors [89, 90]. Presumable relationship between joint hypermobility and osteoarthrosis still remains unproven [81].

Accompanying pathology of the urogenital system as the reflection of systemic connective tissue defect is one more problem for patients with joint hypermobility syndrome. The prevalence of genital prolapse [87, 91–93] and urinary incontinence [87, 93–96], vesicoureteral reflux [97] and urinary tract infections [87], the frequent combination of these disorders with fecal incontinence [91, 94, 95] disproves the idea of "benign joint hypermobility syndrome".

Unclassifiable HCTD being, as a rule, of multifactorial origin and unfitting concerted diagnostic criteria occur more often in daily practice. Their clinical diversity is classified into the following modifications: (MASS-like phenotypes, marfanoid appearance, Ehlers-like phenotype, benign joint hypermobility, unclassifiable phenotype. The first two of them phenotypically remind Marfan syndrome, the following two ones remind Ehlers–Dunlos syndrome, not meeting completely the diagnostic criteria of these conditions. The diagnosis of unclassifiable HCTD is based on the same principles (a constellation of external and visceral phenotypic manifestations) that are applied to identify HCTD with concerted guidelines, though the diagnostic criteria are "softer" at that [41, 98].

MASS-like (Marfan-like) phenotype is characterized by the borderline value of the aortic root size in combination with myopia and/or mitral valve prolapse and signs of the systemic connective tissue involvement of less than 5 points (unlike MASS-phenotype in which involvement is 5 points or more).

Marfanoid appearance is characterized only by the signs of the skeletal system involvement (with no less than four signs [41]) and no visceral changes. Less strict skeletal changes than those required for diagnosing Marfan syndrome are accepted but dolichostenomelia and arachnodactyly are obligatory [3]. The opinions about the harmless nature of marfanoid appearance (due to no changes of visceral organs) seem to be subjected to revision in light of the latest findings. Young individuals with Marfanoid appearance are shown [99] to significantly differ from their peers by a higher activity of the sympathoadrenal system and more significant (though within normal) values of the diameter of the aortic root, wall thickness and myocardium mass. The idea of Marfanoid appearance as a predictor of atrial fibrillation and sclero-degenerative lesions of the aortic valve is undoubtedly of interest [100–102].

The main prerequisite of referring a patient to the ***Ehlers-like phenotype*** is the availability of at least two signs of the skin involvement, excluding the major criteria of Ehlers–Danlos syndrome.

Benign joint hypermobility is diagnosed at the identification of excessive movement range in the joints, but (unlike joint hypermobility syndrome) without clinical symptoms [3]. Benign joint hypermobility turned out to be the most prevalent dysplastic phenotype, however, as the range of values for its prevalence, given by different authors, is wide (4–13% [103] to 44–50% [41, 104]), the necessity of toughening diagnostic criteria is discussed [41, 105].

The cases of detection of at least six minor external and/or visceral signs of connective tissue congenital "weakness" that do not meet the criteria of the mentioned above syndromes and phenotypes are referred to the ***unclassifiable phenotype*** [3]. Its prevalence has caused showing thought for it; the clinical significance of this phenotype needs specification [2, 106]

Non-specificity of external and/or visceral markers of connective tissue congenital "weakness", certain conditionality of the diagnostic criteria of dysplastic phenotypes (some of which differ not in quality, but

quantitatively, i.e. by the number of identified signs) impedes the identification of some HCTD. The diagnosis should be guided by a distinctive hierarchy of HCTD: from monogenic syndromes through dysplastic phenotypes to unclassifiable phenotype and norm. Following Glesby M.J. and Pyeritz R.E. [107] the similar continuous list is accepted terminologically as "phenotypic continuum" [108]. According to this approach the availability of Marfan or Ehlers–Dunlos syndrome excludes the diagnosis of unclassifiable HCTD. Availability of MASS-phenotype criteria (including mitral valve prolapse and skeletal changes) does not give evidence to indicate primary mitral valve prolapse or marfanoid appearance. Similarly, the diagnosis of primary mitral valve prolapse turns down the conclusion about any dysplastic phenotype. Finally, the least clinical and diagnostic significance belongs unclassified phenotype.

Thus, to date, the concept of HCTD as an extensive and non-discrete multitude of various by symptoms and prognosis congenital connective tissue disorders has taken shape; the classification of these pathological conditions has been developed and their diagnostic criteria have been formulated. In the course of further investigations the clinical significance of individual classified HCTD and, particularly, dysplastic phenotypes will have to be specified.

Study Funding and Compenting Interests. The study has not been funded by any sources, and conflicts of interests relating to this study are not available.

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