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Valvular lesions in connective tissue dysplasia: clinical manifestations characteristics, the prognosis of the course

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Summary

Objective

To conduct a prospective study of young patients with undifferentiated form of connective tissue dysplasia (CTD) and analyze their valve syndrome course.

Materials and methods

Five hundred forty nine (549) patients aged 18-45 years (men = 330, 60.11%; women = 219, 39.89%) were enrolled in the study. They all had symptoms of CTD. Valve syndrome was indicated in 281 patients (51.18%; 95% CI 46.91-55.43) combined with arrhythmic (71.89%) and vascular (63.35%) CTD syndromes.

Results

Subjective status of patients with valve syndrome was characterized by numerous cardiovascular and other, less informative adverse effects.

The severity of CTD predicted valve syndrome formation. Low tolerance to physical activity and subsequent formation of dystonic reactions and left ventricle diastolic dysfunction were revealed more often among patients with valve syndrome. Valve syndrome progression was revealed in 2.85% of cases (8/281), average age of progression

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detection – 27.13±3.94 years. Arachnodactyly, combined valve pathology, bicuspid mitral valve prolapse, valve myxomatous degeneration were found more often among patients with severe form of valve syndrome and CTD.

Conclusion

Valve syndrome was revealed in 51% of young patients with undifferentiated CTD and is often combined with congenital subvalvular anomalies, arrhythmic and vascular CTD disorders. Valve syndrome is characterized with diverse and nonspecific complaints. It's associated with greater CTD severity, exerts regular influence on formation of left ventricle diastolic dysfunction and maladaptive reactions to physical activity. Combined valve pathology, bicuspid mitral valve prolapse, mitral valve myxomatous degeneration and arachnodactyly are predictors of progressive form of valve syndrome.

Keywords

Connective tissue dysplasia, valve syndrome, course of disease

Introduction

Cardiovascular symptoms of connective tissue dysplasia (CTD) including valve, vascular and arrhythmic syndromes can directly threaten health and life of patients because of progressive course with development of clinically significant unfavorable manifestations like aorta and other arteries aneurisms or dissections, life-threatening arrhythmias, myxomatously changed left ventricle cord avulsion, progressive insufficiency of heart valves, early and sudden death [1-3]. Course of disease and unfavorable outcomes of cardiovascular lesions are studied better for syndromal forms of CTD: Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome and others [4. 5]. Recently published data indicate that undifferentiated forms of CTD can manifest as the same cardiovascular syndromes and complications with increased frequency of early and sudden death comparing with general population. It does not go along with the idea of unambiguously benignant course of undifferentiated CTD and implies prognostic heterogeneity of this patients' group. There is a contradiction between contemporary knowledge about imperative clinical significance of CTD cardiovascular manifestations in definition of individual life and health perspectives and lack of possibility to make prognosis of cardiovascular syndromes course because of insufficient knowledge about factors that are associated with their formation and course.

The aim of this study is to make analysis of valve syndrome course in CTD during prospective observation of young patients with undifferentiated CTD.

Materials and methods

This research has been done of Western Syberian medical center, Omsk Regional Clinical Hospital, during the period of 2004–2013 years. We performed screening study of 752 patients, after which we selected 549 patients who had signs of dysmorphogenesis of connective tissue in the age of 18–45 years, (330 (60.11%) males and 219 (39.89%) females) according with inclusion/exclusion criteria.

We used the following inclusion criteria: presence of undifferentiated CTD, age of 18–45 years, signed informed consent. Presence of disorders underlying aorta lesions: atherosclerosis, syphilitic aortitis, We chose the following conditions as an exclusion criteria: Takayasu arteritis, giant cell arteritis, mycotic aneurism, chest trauma or/and cerebral arteries (craniocerebral trauma), use of narcotic drugs, alcohol abuse at the moment of inclusion, hereditary syndromes of connective tissue dysplasia in patient or in its first generation relatives. Patients were included with the trial during examination after independent appealing for medical help, during follow-up observation or being referred for advice of medical specialist. CTD was diagnosed according with the complex of phenotypic signs of connective tissue dysmorphogenesis[6]. Average age of patients was 23.51±8.67 years (95% CI: 22.78–24.24).

Methods of examination included physical examination, laboratory and instrumental techniques including electrocardiography (ECG), Holter ECG monitoring with analysis of cardiac rhythm variability, 2D and 3D Doppler- echocardiography (Echo-CG), veloergometry, Doppler ultrasonography of intracranial and extracranial arteries supplying the brain, transcranial Doppler ultrasonography with functional tests, magnetic resonance imaging and magnetic resonance angiography.

Dynamic observation required making of actual medioprophylactic activities [7-9].

Statistical methods included descriptive and analytic statistics: parametric t-test, analysis of contingency tables – Fisher's exact test, χ^2,, dispersion analysis – single-factor dispersion analysis of quali-

tative (binary) characters. =Statistical tests like relative risk (RR), sensitivity (Se), specificity(Sp) were used for estimation of different factors' and clinical outcomes interrelations. The borderline of RR clinical significance for risk factor was 1.2, for a factor with protective action – 0.8. Estimation of information capability and prognostic (diagnostic) coefficient was performed with the use of summary prognostic table according with the Kullback test and statistic procedure of heterogeneous consequent recognition [10]. Statistical tests were performed using Microsoft Excel, Statistica 10,0 (StatSoft Inc., USA) software.

Results

Cardiovascular lesions took second position among registered dysplastic changes after musculoskeletal manifestations (table 1).

In absolute majority of patients (88,71%; n=487) CTD manifestations involved 2-4 systems: two systems were affected in 35.52% of patients (n=195), three systems – in 36.43% of patients (n=200), four systems – in 16.76% of patients (n=92). Lesions of one and five systems were registered in 6.16% (n=34) and in 4.74% (n=26) of patients respectively. Involvement of 6 systems mentioned above occurred significantly more rarely (0,36%; n=2). Involvement of each system had the following pattern: musculoskeletal system – 3.00 (2.00–4.00) symptoms, cardiovascular system – 1.00 (1.00-2.00) symptoms. Number of respiratory symptoms ranged from 0 to 3, gastrointestinal symptoms – from 0 to 4, ophthalmic symptoms – from 0 to 2, urogenital symptoms – from 0 to 1. Average diagnostic coefficient in general group of patients was 28,84±10,76 (95% CI – 27,94–29,74). It was detected that patients with severe form of CTD (n=339, 61,75%). Average diagnostic coefficient in mild CTD subgroup of patients was 20,12±2,07 (n=210, 38,25%, 95% CI: 34,19-42,48), the same rate for severe CTD was 34,25±10,65 (95% CI 33,10-35,39; t-value 19,321; p=0,000). System involvement score was 3.00 (2.00-4.00). Estimation of CTD symptoms according with National Guideline (2012) revealed that the most frequent manifestations are: increased dysplastic stigmatization/ increased mainly visceral dysplastic stigmatization (59.19%), mitral valve prolapsed syndrome (28.23%). Such signs right benignant hyper mobility of joints (8.93%), Marfan-like appearance (1.46%), Ehlers-like phenotype (1.46%), unclassified phenotype (0.55%), MASS-phenotype (0.18%).

Table 1. **Distribution of CDT manifestations**

System/organ	Number. (n)	%
Musculoskeletal system	549	100,00
Cardiovascular system	413	75,23
Skin manifestations	169	30,78
Respiratory system	119	21,68
Ophtalmic manifestations	120	21,86
Urogenital system	87	15,85
Gastrointestinal tract	81	14,75

Valve syndrome was diagnosed in 281 patients (51, 18%, 95% CI 46.91-55.43). Mitral valve prolapse (MVP) was the most frequent CTD valve manifestation (98.53% of all valves' prolapses), in 47.76% of cases (n=96) was combined with anomalous left ventricle cords, and in 35.32% (n=71) of cases – with myxomatous degeneration of valve (1–2 stage). In absolute majority of patients 1stage MVP was registered / (n=181; 90,05%), MVP of 2 stage occurred considerably less frequently (n=20, 9.95. Intensity of regurgitation didn't exceed 2 grade in all regurgitation variants: mitral, tricuspid and aortic (table 2).

Subjective health status of CTD patients with valve syndrome was characterized with numerous complaints related to cardiovascular system (cardialgia, undefined discomfort in heart area, palpitation, intermittence, etc) and general complaints (general weakness, fatigability, bad tolerance of physical activity, headache, non-rotatory vertigo) with poor level of informativity (0.52–0.80), significant diagnostic threshold wasn't achieved, total diagnostic coefficient was less than +13.

Table 2. **Clinical manifestations of valve syndrome, n=281**

	Number, (n)/%
Prolapses of heart valves	204/72,60
Mitral valve prolapse, classic	77/27,40
Mitral valve prolapse, non-classic	124/44,13
Tricuspid valve prolaps	20/ 7,12
Aortic valve prolapse	1/0,36
Combined prolapses	18/6,41
Myxomatous degeneration of valve	106/37,72
Isolated myxomatous degeneration	29/10,32
Associated with valve prolapse	77/ 27,40
Valvular regurgitation	157/55,87
MV: regurgitation (grade 1).	69/24,56
MV: regurgitation (grade 2).	11/3,91
Tricuspid valve: regurgitation (grade 1).	54/19,22
Tricuspid valve: (grade 2).	1/0,36
Aortic valve: regurgitation (grade 1).	28/ 9,96

Comment: MV – mitral valve

In majority of cases (n=202; 71,89%) patients with valve syndrome had arrhythmias, in 63.35% (n=178)

of cases vascular manifestations of CTD were detected. There were no gender differences between patients with valvular manifestations and without them: male – n=166, 59,07%, female – n=164, 61.19% in corresponding groups (χ^2 0,18; p=0,675). Presence of valve syndrome didn't affect significantly the development of orthostatic reactions in patients (n=47; 16,73%); (χ^2 2,641: p=0,104). At the same time patients with valve syndrome demonstrated significantly poorer tolerability of physical exercise (veloergometry) comparing with patients without valve syndrome: 79/28.11% and 46/17.16% respectively ((χ^2 8,74; p=0,003). Presence of valve syndrome increased the possibility of reducing physical exercise tolerability and/or development of distonic reactions to physical exercise by two times (χ^2 8,741; p=0,004); OR 1,89 (95%CI 1,23-2,91); Se 0,63 (95%CI 0,55-0,71); Sp 0,52 (95%CI 0,50-0,55). Valve syndrome was identified as a significant factor for diastolic dysfunction development — (χ^2 110,406; p=0,001); OR 10,06 (95%CI 6,13–16,56); Se 0,77 (95%CI 0,69-0,83); Sp 0,75 (95%CI 0,73-0,77) with sufficiently strong influence on formation of resultant sign diversity – 25,7% (F=140,486, p=0,000; df1=1; df2=547; η^2=0.257). Valve syndrome formation was predicted with severity of CTD, sign "involvement ≥3 systems" (F=25.777, p=0,000; η^2=0.045, "DC≥23" (F=27,091, p=0,000; η^2=0.047).

In general group of CTD patients 217 clinically significant unfavorable cardiovascular manifestations were detected in 156 (28.42%) cases with average duration of observation 7,49±3,44 years, 95%CI 7,21–7,79. Average age of patients during control visit was 31,01±8,58 years, 95%CI 30,29–31,73. The most frequent unfavorable cardiovascular manifestations were dilatation/aneurism of thoracic aorta (27.19%), symptomatic vascular lesions of brain: arteriovenous malformations, intracranial arterial aneurisms (26.73%), clinically significant arrhythmias (23.04%). Valve syndrome progressing, progression of mitral valve prolapse grade and mitral valve insufficiency, spontaneous cord avulsion were registered in 2.85% (8/281) of cases, average age of progression detection was 27,13±3,94 years, 95% CI – 23,7–27,3. Estimation of CTD manifestation revealed that the patients with unfavorable course of CTD valve syndrome have some lesions more often comparing with the other patients with valvular manifestations:combined valvular lesions (4/50,00% and 14/4,98%, respectively(χ^2 19,155; df=1; p=0,001)), bicuspid mitral valve prolapse (2/25,00% and 4/1,47%, respectively (χ^2 10,878; df=1; p=0,002)), myxomatous valve degeneration (6/75,00% and 59/21,61%, respectively (χ^2 9,637; df =1; p=0,003)), arachnodactyly – (2/25,00% and 4/1,47%, respectively (χ^2 10,880; df =1; p=0,001)). The risk of valve syndrome unfavorable course increased in case of associated valvular lesions in the form of prolapses by 10 times: RR 9,97 (95%CI 1,88-70,85); Se 0,75 (95%CI 0,36-0,96); Sp 0,78 (95%CI 0,77-0,79); mitral valve myxomatous degeneration – by 15 times – RR 14,61 (95% CI 3,22-65,24); Se 0,50 (95%CI 0,18-0,82); Sp 0,95 (95%CI 0,94–0,96); bicuspid mitral valve prolapse – by 15 times: – RR 15,28 (95% CI 2,22-54,75); Se 0,25 (95% CI 0,05–0,54); Sp 0,98 (95%CI 0,98–0,99), and also "aracnodactyly RR 33,81 (95%CI 4,45–179,25); Se 0,33 (95%CI 0,06–0,72); Sp 0,99 (95%CI 0,98–0,99). To define the effect of factors mentioned above (validity and power of influence) we performed one-factor dispersion analysis for qualitative (binary) symptoms. factor «combined valvular lesions» had the biggest impact on valve syndrome progressing: 11,30% (F=61,988, p=0,000; df1=1; df2=547; η^2=0.113); factor "bicuspid mitral valve prolapse" took the second position – 8,50% (F=46,396, p=0,000; df1=1; df2=547; η^2=0.085); "arachnodactyly" – 8,5% (F=46,396, p=0,000; df1=1; df2=547; η^2=0.085); «myxomatous valve degeneration» – 5,9% (F=32,767, p=0,000; df1=1; df2=547; η^2=0.059). Chosen complex of independent factors had summarized impact on the formation of the diversity of the resultant sign "valve syndrome progression" around 34.2%. Such components of valve syndrome like myxomatous degeneration of heart valves and associated CTD valvular manifestations were identified as potent predictors of clinically significant arrhythmias development: risk of arrhythmia onset increased twice in case of myxomatous degeneration of heart valves (– χ^2 6,619; p=0,011; RR 2,15; 95% CI 1,18–3,82) and in case of associated CTD valvular manifestations it had three-fold increase (χ^2 5,679; p=0,018; RR 3,28; 95% CI 1,20–6,85).

Discussion

Studying of systemic dysmorphogenesis morphofunctional cardiovascular manifestations has always been one of important research topics because of evident impact on patient's life and health prognosis. Valve syndrome is one of the most frequent cardiovascular manifestations of CTD [11–15]. Many works are dedicated to prevalence, clinic and laboratory signs, ultrastructural and immunohistochemical characteristics of heart valves as in syndromal CTD as in undifferentiated CTD [11, 12, 14, 16-18]. Factors determining CTD development in the form of heart valves lesions

remain poorly undertood. Some data propose that development of mitral valve prolapse is associated with magnesium deficiency [19, 20]. This research identified some factors with predictor role in severe CTD development: "involvement of more than 3 systems", and "diagnostic coefficient CTD ⩾23" that can be a prove of already known CTD characteristics like system involvement and similarity of connective tissue dysmorphogenesis in different organs. Results of this observation proved existing ideas about non-specific complaints of patients with CTD because subjective manifestations of valve syndrome have low informative value. From the one side, it is possible to talk about overdiagnosis problem at the stage of anamnesis and complaints estimation that, on the one part, goes along with specific psychological condition (increased anxiety, lowered self-esteem) that brings them down to their disease, from the other side, complaints of young patients are often considered as vegetative dysfunction and overstrain and lead to ill-timed diagnostics and prevention and development of negative consequences related to dysplastic-dependent conditions and associated pathology. They can threaten patient's health and even life. Clinical significance of CTD valvular manifestations is defined by their involvement into formation of left ventricle diastolic dysfunction, deconditioning reactions to physical exercise and progressing in a few percent of cases. Impact of valve syndrome in dysplastic dysfunction can be determined by the changes of blood pressure inside atria and the volume of transmitral blood flow that changes the phase of early diastolic filling. The presence of anomalous left ventricle cords can interfere with synchronous contraction and relaxation of left ventricle, increase the volume of mitral regurgitation and worsen its consequences [21, 22]. The majority of works investigating the prognosis of CTD course are dedicated to studying of mitral valve prolapse natural course, that demonstrated the crucial role of TNFβ in pathogenesis of matrix remodeling, fibrosis and oxidative stress [23–26]. It gives future prospects to the components of TNFβ-signaling pathway as predictors of myxomatous valve degeneration formation and progressing. Nevertheless some authors consider clinical symptoms more informative for estimation of the prognosis of mitral valve prolapse progression [17, 27]. According with these data dysmorphogenetic symptom arachnodactyly and non-modifiable factors describing morphofunctional condition of heart valves (myxomatous degeneration in mitral valve prolapsed), prolapsed of both valvular cusps, association with other heart valves' prolapses are the predictors of dysplastic-dependent valvular lesions.

Conclusion

The results of this study demonstrate that valve syndrome is present in 51% of young patients with undifferentiated CTD and it manifests as heart valve prolapse: mitral valve prolapse 1–2 grade prevails with functional insufficiency 1–2 grade or without it in 72.6% of patients, myxomatous degeneration of valves, isolated or combined with prolapse, is present in 37.72% of patients, often it is also combined with congenital anomalies of subvalvular structures (50.89%), arrhythmic (71.89%) and vascular syndromes (63.35%) of CTD. Valve syndrome is characterized with diverse and non-specific patient's complaints; it is associated with more severe forms of CTD. It has an impact on the formation of left ventricle diastolic dysfunction, causes low tolerability of physical exercises and distonic reaction on it. Combined lesions of heart valves, bicuspid mitral valve prolapse, myxomatous degeneration of mitral valve and arachnodactyly are found to be predictors of valve syndrome progressive course.

Conflict of interest: None declared.

References

1. Shilova MA, Konev VP, Tsaregorodtsev AG. Vascular pathology in patients with connective tissue dysplasia in the aspect of sudden death. Kazan med J. 2007; 88(5):33-5. Russian.
2. Yakovlev VM, Karpov RS, Belan YuB. Heart rhythm and conduction disturbances in the heart connective tissue dysplasia. Omsk: Agentstvo kurer; 2001.- 160p. Russian.
3. Crawford MH, DiMarco JP, Paulus WJ. Cardiology 3rd ed. MOSBY Elsevier; 2010.- 1878p.
4. Caglayan AO, Dundar M. Inherited diseases and syndromes leading to aortic aneurysms and dissection. Eur J Cardiothorac Surg. 2009;35(6): 931-40.
5. Vanakker OM, Hemelsoet D, De Paepe A. Hereditary Connective Tissue Diseases in Young Adult Stroke: A Comprehensive Synthesis [Electronic resource. Stroke Res Treat. 2011. – Access mode: http: dx.doi.org/ 10.4061/2011/712903
6. MakKonki E. Human Genom. Moskva: Tehnosfera; 2008.-288p. Russian.
7. Kadurina TI, Gorbunova VN. Connective tissue dysplasia: a guide for doctors. Sankt-Peterburg : Elbi-SPb, 2009. Russian.
8. Nechaeva GI, Konev VP, Viktorova IA, et al. Methodology for Supervision of patients with connective tissue dysplasia family physician in terms of prevention of early and sudden death. Rossijkie medicinskie vesti. 2004;3:25-32. Russian.

9. Heritable disorders of connective tissue in cardiology. Diagnosis and treatment. Russian recommendation (I revision). Russ cardiol J. 2013; 1(99), suppl. 1: 1-32. Russian.
10. Gubler EV, Genkin AA. Application of nonparametric statistics in biomedical research. Leningrad: Meditsina; 1973.- 141 p. Russian.
11. Klemenov AV. Primary mitral valve prolapse. ed. 3rd, revised. N. Novgorod; 2006.-72 p. Russian.
12. Martyinov AI, Stepura OB, Ostroumova OD, et al. Mitral valve prolapse. Part I. The phenotypic characteristics and clinical manifestations. Kardiologiya. 1998;1:72-80. Russian.
13. Yakovlev VM, Nechaeva GI, Bakulina EG. Fundamentals of clinical diagnosis of connective tissue dysplasia: a guide for practitioners. Stavropol: AGRUS; 2011.- 408 p. Russian.
14. Yakovlev VM, Karpov RS, Shvetsova EV. Connective tissue dysplasia of the mitral valve. Tomsk: Publishing House of the Siberian Publishing House, 2014. Russian.
15. Shabalina H. Mitral valve prolapse as display heart connective tissue dysplasia. Clinical and hemodynamic aspects. Eur J Int Med. 2013; 24 (Suppl. 1.): e17-8.
16. Zemtsovskiy EV. Dysplastic syndromes and phenotypes. dysplastic heart. St-Petersburg, 2007. Russian.
17. Storozhakov GI, Vereschagina NV, Malyisheva NV. Risk stratification and selection of clinical management of patients with mitral valve prolapse. Serdechnaya nedostatochnost. 2001;6:287-90. Russian.
18. Sho E, Sho E, Sho M, et al. Arterial enlargement in response to high flow requires early expression of matrix metalloproteinases to degrade extracellular matrix. Exp Mol Pathol. 2002; 73:142-53.
19. Kalacheva AG, Gromova OA, Kerimkulova NV, et al. Violations of the formation of connective tissue in children as a result of magnesium deficiency. Lechaschiy vrach. 2012;3:59-63. Russian.
20. Lichodziejewska B, Klos J, Rezler J. Clinical symptoms of mitral valve prolapse of related to hypomagnesemia and attenuated by maghesium supplementation. Am J Cardiol. 1997; 76:768-72.
21. Otto CM. Textbook of Clinical Echocardiography. Fifth Ed Elsevier, 2013. 552 p.
22. Silbiger JJ. Left Ventricular False Tendons: Anatomic, Echocardiographic, and Pathophysiologic Insights. J Am Soc Echocardiogr 2013; 26:582-8.
23. Aupperle H, März I, Thielebein J, Schoon H-A. Expression of transforming growth factor-beta1, -beta2 and -beta3 in normal and diseased canine mitral valves. J Comp Pathol. 2008;139:97-107.
24. Hulin A, Deroanne CF, Lambert CA, et al. Metallothionein-dependent up-regulation of TGF-ß2 participates in the remodelling of the myxomatous mitral valve. Cardiovascular Research. 2012; 93:480-9.
25. Geirsson A, Singh M, Ali R, Abbas H, et al. Modulation of transforming growth factor-beta signaling and extracellular matrix production in myxomatous mitral valves by angiotensin II receptor blockers. Circulation. 2012: 126: S189-97.
26. Hagler MA, Hadley TM, Zhang H, et al. TGF-ß signalling and reactive oxygen species drive fibrosis and matrix remodelling in myxomatous mitral valves. Cardiovascular Research. 2013;99:175-84.
27. Kühne K, Keyser B, Groene EF, et al. FBN1 gene mutation characteristics and clinical features for the prediction of mitral valve disease progression. Internat J Cardiol. 2013;168(2): 953-9.