SMALL HEART ANOMALIES AS CARDIAC MANIFESTATIONS OF HEREDITARY CONNECTIVE TISSUE DISORDERS

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Introduction. Small heart anomalies (SHA) are the morphological basis for functional changes in cardiac activity and can exacerbate the course of organic heart lesions. The most studied SHA include false chords of the left ventricle (FCLV) and mitral valve prolapse. Prevalence, association with external signs of dysembryogenesis, as well as the predictive value of SHA are not sufficiently studied.

Materials and methods. We examined 611 people between the ages of 18 and 23 (average age 20.3 ± 1.6 years), including 257 boys and 354 girls. All of the surveyed performed phenotypic, anthropometric and echocardiographic examinations. To identify the SHA links to heart rhythm disorders, the 205 surveyed performed Holter’s ECG monitoring.

Results. SHA identified in 90% of the individuals surveyed: atrial septum aneurysm (24%), tricuspid valve prolapse (23.4%), asymmetry of the aortic valve (20.6%), additional papillary muscles (39.4%) and FCLV (75.1%). Correlation analysis showed the presence of links between these SHA and bone signs of dysembryogenesis (chest deformities, arachnodactyly, dolistenomy and high palate), as well as heart rhythm disorders (supraventricular and ventricular extrasystoles, rhythm driver migration and episodes of AV-blockade 1 degree). Patients with marfanoid habitus have a higher average number of SHA (2.1 ± 1.4 vs 0.9 ± 0.7, p < 0.005).

Conclusions. SHA are identified in the vast majority of healthy people. Bone signs of dysembryogenesis are associated with significant SHA and can serve as a marker for the involvement of the heart in the dysplastic process. Patients with SHA have significant cardiac arrhythmias.

Keywords: small heart anomalies; bone signs of dysembryogenesis; hereditary disorders (dysplasia) of connective tissue; heart rhythm disorders; young people.

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Введение. Малые аномалии сердца (МАС) как морфологическая основа функциональных изменений сердечной деятельности способны усугублять течение органических поражений сердца. К наиболее изученным МАС относятся ложные хорды левого желудочка (ЛХЛЖ) и пролапс митрального клапана. Распространенность, связь с внешними признаками дизэмбриогенеза, а также прогностическое значение отдельных МАС изучены недостаточно.

Материалы и методы. Обследовано 611 практически здоровых людей в возрасте от 18 до 23 лет (средний возраст 20.3 ± 1.6 года), из них 257 юношей и 354 девушки. Всем обследованным выполнено фенотипическое, антропометрическое и эхокардиографическое обследование. Для выявления связей МАС с нарушениями сердечного ритма по 205 обследованным выполнено холтеровское мониторирование ЭКГ.
INTRODUCTION

One of the most complex and controversial aspects of modern cardiology is small heart anomalies (SHA), which are anatomical changes in the heart and great vessels’ architectonics not leading to gross functional disorders of the cardiovascular system [19]. As the morphological basis of functional changes in cardiac activity, SHA can worsen the heart’s course of organic lesions. National researchers’ interest in the problems of SHA classification and the assessment of their clinical significance is relatively high; however, despite this, the inconsistency of SHA diagnostic criteria remains. The data on the prevalence of individual SHA among healthy people (from 2.5% to 41.6%) also differ dramatically [1, 7]. This difference is due to the lack of unified approaches to SHA diagnostics and significant overdiagnostics in the pediatric and adolescent populations. There is no unified understanding of the possible relationship between individual SHAs to connective tissue defects.

Currently, the functional classification considers the localization and form of minor anomalies, the etiology of these changes, and possible complications and is used to diagnose SHA [2]. Over the years, ideas regarding some structural features of the heart have changed. Thus, the bicuspid aortic valve and the open foramen ovale are commonly referred to as congenital heart defects. In contrast, some SHA included in the working classification can be attributed to the elements of the typical heart structure (the moderator bundle of the right ventricle, Chiari malformation, and others) [3]. Mitral valve prolapse (MVP) and left ventricular pseudochords (LVPC) are worth noting separately. In the significant prolapse of mitral leaflets into the left atrium cavity by 3 mm or more, we should consider primary MVP as an independent nosological form. Small prolapses (by 1–2 mm) are called probable MVP, which can be considered SHA when combined with other heart development anomalies [12].

Researchers’ attitudes toward SHAs, such as LVPC, are also ambiguous. There is currently no precise classification and generally accepted terminology for these SHAs. LVPC are divided depending on their number (single and multiple), localization (right ventricular and left ventricular), according to the ventricle part (basal, median, apical), and direction (transverse, longitudinal, diagonal) [9, 13]. Data on the prevalence of LVPC range from 7.2% to 80% in the healthy population. Some researchers recognize the independent clinical significance of LVPC: ischemic heart disease is more severe, signs of early ventricular repolarization pattern and various cardiac arrhythmias, and left ventricular myocardium remodeling are more often revealed in such patients [8, 15, 17, 21]. On the other hand, no significant differences in the frequency of cardiac arrhythmias and the early repolarization pattern and ventricular pre-excitation phenomena were found in children with isolated LVPC (without combination with other SHA). This polarity of opinions is related to the fact that most researchers do not consider the characteristics of LVPC: their localization, number, and relationship with other structural changes in the heart.

Data on the prevalence and clinical significance of other SHAs are limited. The relationship between pronounced aortic valve asymmetry and the development of sclerodegenerative changes in the aorta has been shown [18]. The clinical significance of atrial septal aneurysm, the prevalence of which is approximately 1% remains essentially unexplored [6, 10]. Many authors also recognize the frequent combination of various SHA, which does not allow assessing the contribution of each of them to certain functional cardiovascular system disorders. Most researchers place all SHA in the same row without assessing their specificity. When any three
SHA are identified, it is proposed to isolate the connective tissue dysplasia syndrome of the heart [3]. The prevalence of individual SHAs and their various numbers in healthy people has not been previously considered. A few studies show a relationship between individual SHAs, primarily MVP, and external signs of dysembryogenesis [15, 20]. Simultaneously, the relationship of other SHAs with hereditary connective tissue disorders, particularly with dysplastic phenotypes, also remains unstudied. The contribution of SHA to the structure of cardiac arrhythmias and conduction disorders was not evaluated.

The aim of this work is to establish the prevalence of individual SHAs among essentially healthy young people and their relationship with external signs of dysembryogenesis and to assess the prognostic value of SHAs in detecting cardiac arrhythmias.

MATERIALS AND METHODS

This study enrolled 611 essentially healthy people aged 18–23 years old (mean age 20.3 ± 1.6 years), including 257 boys and 354 girls were examined. All patients underwent a phenotypic and anthropometric examination to identify the bone signs of dysembryogenesis. Funnel-shaped and keeled chest deformities, symptoms of arachnodactyly (thumb and wrist symptoms), high arched palate, flat feet, and scoliotic spinal deformity, and dolichostenomelia were identified. Diagnostics of the marfanoid appearance were performed according to generally accepted recommendations considering the specificity of individual bone signs [4, 5]. The marfanoid habitus included persons with at least four bone features, including a combination of arachnodactyly and dolichostenomelia and at least one particular feature – chest deformity or high arched palate. The control group included persons with no more than two bone signs.

All examined patients underwent echocardiographic examination using ultrasound apparatus Vivid 7 Dimension (General Electric, matrix phased transducer 3.5 MHz), in 2D, Doppler, and color M-mode according to the generally accepted technique, to identify SHA. The study protocol was supplemented by the targeted search for minor heart anomalies. The following SHAs were revealed: atrial septal aneurysm, which was differentiated with the open oval window, increased trabecularity of the right and left ventricles, tricuspid valve prolapse, pulmonary valve prolapse, aortic valve asymmetry, aortic valve prolapse, and accessory papillary muscles.

SHA connections with cardiac arrhythmias were identified in 205 patients who underwent daily Holter electrocardiogram monitoring (the average monitoring duration was 23.1 ± 0.9 h).

Statistical data processing was performed using Statistica 8 software (StatSoft, Inc.). The differences’ significance between qualitative characteristics was determined using Fisher’s nonparametric method ($p < 0.05$). The relationship between bone signs, SHA, and heart rate characteristics was determined by performing a Spearman correlation analysis ($p < 0.05$).

RESULTS

The prevalence of SHA in the population is relatively high: on average, 2–3 SHA were found in each person examined, whereas no SHA were found in only 10% of healthy young people. The results obtained when assessing the prevalence of individual SHAs among essentially healthy young people are shown in Table 1.

Certain SHAs are widespread among essentially healthy young people. The most common were developmental anomalies such as LVPC, accessory papillary muscles, and prolapse of the mitral valve leaflets up to 2 mm. Increased right and left ventricular trabecularity was found somewhat less frequently; pulmonary valve prolapse was noted in rare cases. The average number of SHA does not depend on the sex of the individuals surveyed; however, some SHA are unequally distributed among men and women. Thus, in young men, aortic valve asymmetry and increased right ventricular trabecularity were found significantly more often. On the contrary, girls showed a higher frequency of increased trabecularity of the left ventricle and accessory papillary muscles.

Further, LVPC were assessed depending on their location and quantity. The most common (65.8%) were LVPC of apical localization that allows them to be regarded as variants of the norm. Median (38.1%) and basal (10.0%) LVPC were less common. Significant LVPC, which included median, mid-basal, and basal LVLC, were found in almost half of the subjects (45.4%). At the same time, there were no significant features in the prevalence of LVPC at various localization among boys and girls.

In 36% of essentially healthy individuals, at least three SHA were identified. When using a quantitative approach, they created the prerequisites for overdiagnosing connective tissue dysplasia syndrome of the heart. In addition, it seems that it is not very promising to consider all SHA in
Prevalence of small heart anomalies in healthy young people
Распространенность малых аномалий сердца среди практически здоровых молодых людей

| Small heart anomalies / Малые аномалии сердца | All / Всего (611, 100%) | Men / Юноши (257, 100%) | Women / Девушки (354, 100%) | p |
|-----------------------------------------------|-------------------------|--------------------------|-----------------------------|---|
| Atrial septum aneurysm / Аневризма межпредсердной перегородки | 146 (24.0) | 68 (26.5) | 78 (22.0) | 0.20 |
| Mitral valve prolapse 1–2 mm / Пролапс митрального клапана 1–2 мм | 150 (24.5) | 58 (22.6) | 92 (26.0) | 0.33 |
| Pulmonary valve prolapse / Пролапс пульмонального клапана | 5 (0.8) | 4 (1.6) | 1 (0.3) | 0.20 |
| Tricuspid valve prolapse / Пролапс трикуспидального клапана | 143 (23.4) | 60 (23.3) | 83 (23.4) | 0.97 |
| Asymmetry of the aortic valve / Асимметрия аортального клапана | 126 (20.6) | 69 (26.8) | 57 (16.1) | 0.001 |
| Increased trabecularity of the left ventricle / Повышенная трабекулярность левого желудочка | 128 (20.9) | 39 (15.2) | 89 (25.1) | 0.002 |
| Increased trabecularity of the right ventricle / Повышенная трабекулярность правого желудочка | 176 (28.8) | 116 (45.1) | 60 (16.9) | 0.0001 |
| Additional papillary muscles / Добавочные папиллярные мышцы | 241 (39.4) | 75 (29.2) | 166 (46.9) | 0.0001 |
| False chords of the left ventricle / Ложные хорды левого желудочка | 459 (75.1) | 190 (73.9) | 269 (76.0) | 0.56 |
| Average of small heart anomalies / Среднее количество малых аномалий сердца | 2.2 ± 1.4 | 2.2 ± 1.5 | 2.2 ± 1.4 | 1.0 |

The existence of a close relationship between SHA and bone signs of dysembryogenesis is confirmed by the high frequency of individual SHA detected in young people with a marfanoid appearance (Fig. 2). Young people with marfanoid habitus are characterized by the more frequent detection of significant LVPC, tricuspid valve prolapse, aortic valve asymmetry, and atrial septal aneurysm (p < 0.01). The average number of SHA in the group with marfanoid habitus was more than two times higher, than in the control group (2.1 ± 1.4 vs. 0.9 ± 0.7, p < 0.005).
DISCUSSION

Some SHA are a frequent finding during echocardiographic examinations. According to our data, only 10% of healthy young people did not have a single SHA. At the same time, distinct features of the prevalence of individual SHA are specific depending on the sex of the surveyed individuals: aortic valve asymmetry, increased right ventricular trabecularity were revealed more often in men and increased left ventricular trabecularity, and accessory papillary muscles were found more often in women. SHA, such as mitral, tricuspid,
or pulmonary valve prolapse, were detected with the same frequency among boys and girls. The high incidence of LVPC in the population (75%) does not determine their clinical significance without considering their number (single or multiple) and localization. Most often, LVPC is found in the apex of the left ventricle. Obviously, with such localization, they do not significantly affect intracardiac hemodynamics and do not interfere with blood flow. This idea is consistent with data published in the literature data that the clinical significance is mainly the LVLH located closer to the base of the heart – median and basal parts [3, 17]. This assumption is confirmed by the direct correlation between LVPC of the median and basal localization with conduction disturbances; episodes of AV block 1 degree during the day were significantly more often detected in young people with LVPC. It can be assumed that there are foci of myocardial fibrosis at the site of the basal pseudochords attachment, which leads to a slowdown in the electrical impulse conduction in the interventricular septum’s upper third, in the AV node region and atriocentric trunk. The development of such fibrosis development is facilitated by the TGF-β signaling pathway activation, which is characteristic of patients with hereditary connective tissue disorders, particularly marfan syndrome and marfanoid habitus [14, 16].

Individual SHAs are not equally related to external signs of dysembryogenesis. Bone signs were chosen as the defining external signs characterizing the bone system’s involvement in the dysplastic process. Many bone signs of dysembryogenesis are combined with signs of involvement of other body systems in the dysplastic process, primarily the cardiovascular system [12]. Bone signs of dysembryogenesis are associated with SHAs such as pulmonary and tricuspid valve prolapse, atrial septal aneurysm, aortic valve asymmetry, and significant LVPC. The close relationship of the listed SHAs with systemic connective tissue defect is confirmed by their more frequent detection in patients with marfanoid habitus. Thus, the signs of a marfanoid habitus can be regarded as a marker of the involvement of the heart’s connective tissue frame in the dysplastic process, which is manifested by a large number of SHAs.

The clinical significance of SHAs is confirmed by their association with cardiac arrhythmias. Aneurysm of the interatrial septum is associated with supraventricular extrasystole of high gradations (more than 10 per hour) and paired and group atrial extrasystole. Incomplete fusion of the oval window with a thin fibrous septum formation between the atria creates conditions for impulse circulation around the electrically inactive area, which forms re-entry type atrial rhythm disturbances. On the other hand, the atrial septal defect can interfere with normal impulse conduction to the left atrium, which causes electrical uncoupling of the atria and can lead to the activation of ectopic foci of the rhythm. In this case, episodes of pacemaker migration through the atria are recorded. The prolapse of the tricuspid valve due to the tension of the papillary filaments creates stress foci in the wall of the right ventricle, which is a prerequisite for the formation of high-grade ventricular extrasystoles (more than 10 per hour). In addition, pulmonary and tricuspid valve prolapses are associated with impaired autonomic regulation of the heart rate – an increase in the circadian index and a decrease in heart rate variability. It will be recalled that young people with marfanoid habitus are characterized by low values of spectral and temporal indicators of variability increasing the difference between the values of heart rate in the daytime and at night (circadian index) [11]. It can be assumed that this is realized due to the more frequent detection of right heart valve prolapse in such people.

CONCLUSIONS

1. Separate SHAs were found in 90% of essentially healthy young people. The most common SHAs are left ventricular pseudochords, accessory papillary muscles, asymmetry of the aortic valve, and prolapse of the mitral and tricuspid valves. When LVPC is detected, it is necessary to assess their localization (apical, basal, and median) and number (single and multiple).

2. SHA, such as aortic valve asymmetry, tricuspid valve prolapse, atrial septal aneurysm, multiple LVPC of median and basal localization, are associated with systemic connective tissue defects. These SHAs are associated with atrial and ventricular extrasystoles, episodes of pacemaker migration through the atria, slowing of atrioventricular conduction (1st degree AV block), and a decrease in spectral and temporal parameters of heart rate variability.

REFERENCES

1. Ахтарова Ф. М., Муратходжаева А. В. Особенности малых аномалий развития и дисплазии соединительной ткани у детей // Лучшая научная статья 2017: сборник статей VII Международного научно-практического конкурса под общ. ред. Г.Ю. Гуляева. – М.: МЦНС «Наука и просвещение», 2017. – С. 228–232.
10. Нечаева Г.И., Викторова И.А., Конев В.П. Выявление предикторов ранней и внезапной смерти при дисплазиях соединительной ткани как основа ее профилактики // Кардиология. – 2006. – № 4. – С. 18–26. [Nechaeva GI, Viktorova IA, Konev VP. Vyyavlenie prediktorov rannei i vnezapnoi smerti pri displaziyah soedinitel'noj tkani kak osnova ee profilaktiki. Kardiologiya. 2006;4:18-26. (In Russ.)]

11. Тимофееv Е.В. Распространенность дисплазических синдромов и фенотипов и их взаимосвязь с особенностями сердечного ритма у лиц молодого возраста: Автореф. … дис. канд. мед. наук. – СПб., 2011. 22 с. [Timofeev EV, Malev EG, Zemtsovsky EV. A differentiated approach to variability of abnormally located chords of the left ventricle. Kazanskij medicinskij zhurnal. 2010;91:36-37. (In Russ.)]

12. Серженко Н.П., Болотова В.С. К вопросу о структуре и распространенности малых аномалий развития сердца // Журнал анатомии и гистопатологии. – 2013. – Т. 2. – № 1. – С. 53–57. [Serezhenko NP, Bolotova VS. On the structure and occurrence of small anomalies of development of the heart. Zhurnal anatomii i gistopatologii. 2013;2(1):53-57. (In Russ.)]

13. Тимофееv Е.В., Зарипов Б.И., Малев Е.Г., Земцовский Э.В. Алгоритм диагностики распространенных дисплазических синдромов и фенотипов. Теоретические подходы и практическое применение классификации // Артериальная гипертензия. – 2009. – № 15. – С. 162–166. [Zemtsovsky EV, Malev EG, et al. Algorithms of diagnostics of widespread dysplastic syndromes and phenotypes. Theoretical approaches and practical application of classifi cation. Arterial'naya Gipertenziya. 2009;15(2):162-165. (In Russ.)] https://doi.org/10.18705/1607-419X-2009-15-2-162-165.

14. Серженко Н.П., Болотова В.С. К вопросу о структуре и распространенности малых аномалий развития сердца // Журнал анатомии и гистопатологии. – 2013. – Т. 2. – № 1. – С. 53–57. [Serezhenko NP, Bolotova VS. On the structure and occurrence of small anomalies of development of the heart. Zhurnal anatomii i gistopatologii. 2013;2(1):53-57. (In Russ.)]

15. Тимофееv Е.В. Распространенность дисплазических синдромов и фенотипов и их взаимосвязь с особенностями сердечного ритма у лиц молодого возраста: Автореф. … дис. канд. мед. наук. – СПб., 2011. 22 с. [Timofeev EV, Malev EG, Zemtsovsky EV. The prevalence of dysplastic syndromes and phenotypes and their relationship with the features of heart rhythm in young people [dissertation abstract]. Saint Petersburg; 2011. 22 p. (In Russ.). Режим доступа: https://static.freereferats.ru/_avtorefers/01005084276.pdf.}

16. Тимофееv Е.В. Распространенность дисплазических синдромов и фенотипов и их взаимосвязь с особенностями сердечного ритма у лиц молодого возраста: Автореф. … дис. канд. мед. наук. – СПб., 2011. 22 с. [Timofeev EV, Malev EG, Zemtsovsky EV. The prevalence of dysplastic syndromes and phenotypes and their relationship with the features of heart rhythm in young people [dissertation abstract]. Saint Petersburg; 2011. 22 p. (In Russ.). Режим доступа: https://static.freereferats.ru/_avtorefers/01005084276.pdf.]

17. Тимофееv Е.В. Зарипов Б.И., Малев Е.Г., Земцовский Э.В. Алгоритм диагностики распространенных дисплазических синдромов и фенотипов. Теоретические подходы и практическое применение классификации // Артериальная гипертензия. – 2009. – № 15. – С. 162–166. [Zemtsovsky EV, Malev EG, etc. Algorithms of diagnostics of widespread dysplastic syndromes and phenotypes. Theoretical approaches and practical application of classification. Arterial'naya Gipertenziya. 2009;15(2):162-165. (In Russ.)] https://doi.org/10.18705/1607-419X-2009-15-2-162-165.
14. Тимофеев Е.В., Земцовский Э.В. Особенности регуляции сердечного ритма у лиц молодого возраста с марфаноидной внешностью // Медицина: теория и практика. – 2018. – Т. 3. № 2. – С. 26–34. [Timofeev EV, Zemtsovsky EV. Features of the regulation of cardiac rhythm in young age with marfanoid habitus. Medicina: teoriya i praktika. 2018;3(2):26-34. (In Russ.)]

15. Тимофеев Е.В, Земцовский Э.В. Распространенность внешних и кардиальных признаков дизэмбриогенеза у практически здоровых лиц молодого возраста // Медицина: теория и практика. – 2017. – Т. 2. – № 2. – С. 21–29. [Timofeev EV, Zemcovskij EV. The prevalence of external and cardiac signs of dysembryogenesis at the apparently healthy young people. Medicina: teoriya i praktika. 2017;2(2):21-29. (In Russ.)]

16. Тимофеев Е.В., Малев Э.Г., Лунева Е.Б., Земцовский Э.В. Активность трансформирующего фактора роста-β у лиц молодого возраста с марфаноидной внешностью // Педиатр. – 2019. – Т. 10. – № 1. – С. 49–56. [Timofeev EV, Malev EG, Luneva EB, Zemtsovsky EV. The activity of transforming growth factor-β in young age with marfanoid habitus. Pediatrician (St. Petersburg). 2019;10(1):49-56. (In Russ.)] https://doi.org/10.17816/PED10149-56.

17. Форстер О.В., Шварц Ю.Г. Имеется ли взаимосвязь между степенью дисплазии соединительной ткани, «эмоциональным статусом» и фибрилляцией предсердий у больных ишемической болезнью? // Вестник аритмологии. – 2004. – Т. 33. – С. 18–21. [Forster OV, Shvarc YuG. Imeetsya li vzaimosvyaz' mezhdu stepen'yu displazii soedinitel'noj tkani, emocional'nym statusom i fibrillyaciej predserdij u bol'nyh ishemi-cheskoj bolez'yu? Vestnik aritmologii. 2004;33:18-21. (In Russ.)]

18. Хасanova С.И. Роль соединительной ткани в формировании клео-дегенеративных поражений аортального клапана сердца: Дисс. … канд. мед. наук. – СПб., 2010. – 162 с. [Khasanova SI. The role of connective tissue dysplasia in the formation of sclero-degenerative lesions of the aortic valve of the heart [dissertation abstract]. Saint Petersburg, 2010. 22 р. (In Russ.)]. Режим доступа: https://rusneb.ru/catalog/000199_000009_004604986/.

19. Ягода А.В., Гладких Н.Н. Малые аномалии сердца. – Ставрополь: Изд. СГМА. 2005. – 248 с. [Yagoda AV, Gladikhi NN. Malye anomaliyi serdca. Stavropol': Izd. StGMA. 2005. 248 s. (In Russ.)]

20. Flack JM, Kvasnicka JH, Gardin JM, et al. Anthropometric and physiologic correlates of mitral valve prolapse in a biethnic cohort of young adults: the CARDIA study. Am Heart J. 1999;138(3 P. 1):486-492.

21. Hall ME, Halinski JA, Skelton TN, et al. Left ventricular false tendons are associated with left ventricular dilatation and impaired systolic and diastolic function. Am J Med Sci. 2017;354(3):278-284. https://doi.org/10.1016/j.amjms.2017.05.015.