Original Article

Markers of Undifferentiated Connective Tissue Dysplasia in Female Patients with Acute Q-myocardial Infarction

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Abstract

Myocardial infarction (MI) remains the leading cause of death in patients with coronary heart disease (CHD) worldwide. Over the past twenty years, there has been a tendency to increase the prevalence of congenital disorders of connective tissue. The relevance of this problem is due not only to the growing occurrence of undifferentiated connective tissue dysplasia (UCTD) and a variety of complications but also to medical and social problems resulting from associated somatic diseases. Considering the high social significance of the problem of CHD on the background of UCTD, and because it affects mainly people of working age, this study aimed to investigate stigmas of dysplasia in women with Q-MI on the background of UCTD. The most common stigmas of dysembryogenesis in patients with UCTD were various anomalies of the hands and feet (100%), ophthalmic stigmas and microanomalies of the auricles (90% each), varicose veins of the lower extremities (33.3%) and easy formation of hematomas at insignificant damage (20%). Correlations were found in women with UCTD between the number of markers and the frequency of detection of the diagonal fold of the earlobe ($r=+0.79$; $p<0.05$), blue sclera ($r=+0.77$; $p<0.05$), radial-lacunar type of iris ($r=+0.66$; $p<0.05$), varicose veins of the lower extremities ($r=+0.73$; $p<0.05$) and easy formation of hematomas at insignificant damage ($r=+0.51$; $p<0.05$). Thus, the above markers of UCTD can be considered as prognostic criteria for the complicated course of CHD, which will allow further development of new approaches to the detection of such individuals and their differentiated therapy.

Keywords: Myocardial infarction, Coronary heart disease, Undifferentiated connective tissue dysplasia, Stigmas of dysembryogenesis

Introduction

More than 18.6 million people die each year from cardiovascular disease (CVD). In developed European countries CVD is responsible for almost 50% of all causes of death of adults [1]. Ukraine has the highest rates of CVD in women among 30 European countries, including coronary heart disease (CHD), as well as one of the highest rates of male mortality from CHD. It is also noteworthy that the largest differences in the levels of these indicators between Ukraine and developed European countries were observed in the younger age categories, reaching seven times the difference. It is worrying that the incidence and mortality from CHD in young and middle-aged people have been rising [2-5].

In a significant number of patients at a young age, CHD debuts with the myocardial infarction (MI) with a high level of prehospital mortality, and in some cases intact coronary vessels were detected [6, 7].

According to conventional view, MI on the background of coronary thrombosis develops under the influence of the several risk factors, among which atherosclerosis and dyslipidemia, hypertension, diabetes, smoking, and adverse heredity are the most studied. However, the influence of other factors on the occurrence of acute CHD and its complications have been studied much worse. Although, coronary ventriculographic studies indicate a significant percentage (up to 12%) of patients with MI and with intact coronary vessels [8], which may be associated, in particular, with undifferentiated connective tissue dysplasia (UCTD) [6, 9].

UCTD is a common background pathology (in more than 50% of the population, among which women predominate, in environmentally unfavorable regions of Eastern Europe), morphologically characterized by changes in collagen, elastic fibrils, glycoproteins, and proteoglycans, which are based on inherited mutations in genes that synthesize collagen,

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structural proteins, and protein-carbohydrate complexes, as well as mutations in genes of enzymes and cofactors to them [10].

The fairly widespread occurrence of UCTD among patients of working age with CHD, women, in particular, creates the preconditions for a more in-depth analysis of this problem and the search for optimal solutions in primary diagnosis and prevention. Therefore, the aim of this study is to investigate the phenotypic and visceral stigmas of dysplasia in women with Q-MI on the background of UCTD.

Materials and Methods

60 female patients with verified Q-MI, aged 43 to 72 years, who were hospitalized in the cardiology department No1 "Vinnytsya Regional Clinical Medical and Diagnostic Center for Cardiovascular Pathology" (Vinnytsya, Ukraine), were examined.

Verification of the diagnosis of Q-MI has been performed based on a positive result of the troponin test and elevated levels of cardiospecific enzymes in the presence of pain and relevant ECG changes, taking into account international standard criteria and according to medical care protocol for patients with acute coronary syndrome [11]

To achieve the goal of the study, patients were divided into two groups. The main group included 30 women with MI on the background of UCTD, aged from 43 to 69 years, mean age (53.24 ± 5.08) years. The comparison group consisted of 30 women with MI without UCTD (number of phenotypic and visceral stigmas of UCTD – 5 and less), aged from 47 to 72 years, mean age (56.30 ± 5.61) years.

Exclusion criteria were concomitant nosologies that affected the structural and geometric parameters of the heart muscle, clinical features, and development of CHD complications: hypertension, obesity, diabetes, other severe comorbidities (chronic obstructive pulmonary disease, malignant neoplasms), primary and secondary mitral valve prolapse.

The main group and the comparison group were representative by the age of patients, risk factors, and features of family history of CVD.

All patients underwent clinical and instrumental studies, followed by statistical processing of the obtained data. In particular:

- somatometric examination (analysis of the following anthropometric features by the method of Bunak modified by Shaparenko [12], such as body weight, body length, torso length, neck length, chest length, lower length limbs, head circumference, chest circumference). UCTD-specific symptoms were also identified: joint hypermobility, increased skin elasticity, high palate, and abnormal tooth position. Ocular signs (radial-lacunar iris, "blue sclera" - thinning of the sclera and lumen of the vascular tract, myopia, close or wide eye slits, short or narrow eye slits) UCTD was evaluated anamnestically, during clinical examination, and ophthalmoscopically. Ear markers (protruding ears, diagonal fold of the earlobe, small lobe, absence of tragus, congenital deafness) were to detect during a clinical examination [10].

The following vertebrogenic symptoms were diagnosed by X-ray examination and clinical examination: lumbar hyperlordosis and scoliosis.

- survey of patients. All subjects were surveyed using a specially designed original questionnaire based on the phenotypic map of Glesby in the modification of Martinov and co-authors [10, 13]. The questionnaire included 54 positions of microanomalies. The number of phenotypic and visceral stigmas of UCTD was counted, based on examination. The diagnosis of UCTD was established by detecting 6 or more positions of microanomalies [14].

- Instrumental methods: All patients underwent electrocardiographic examination (ECG) in 12 standard leads on an electrocardiograph "Heart Screen 112 D" (Hungary) to diagnose focal changes in the ventricular myocardium, and primary screening for arrhythmias and conduction disorders. Abnormalities of the kidneys (dystopia, ectopia, partial doubling of the pelvis and ureters, cysts, nephroptosis) and gallbladder (single or multiple constrictions, inflections, and deformation of the gallbladder) were determined using ultrasound apparatus General Electric «Logic-7» (Vivid – 3) (USA).

Prolapse of the gastric mucosa into the lumen of the esophagus, hernia of the esophageal orifice of the diaphragm, gastroptosis, visible gastroduodenal reflux have been diagnosed with the help of endoscopic methods. Esophagofibrogastroduodenoscopy was performed if patients had complaints of heartburn and/or abdominal pain, particularly in the epigastric region.

Chest radiography was performed to detect focal pathologies of the lungs and mediastinum and to detect visceral abnormalities of the chest.

- Data analysis was performed in SPSS Statistics v.23. Summary statistics of mean, standard deviation, and percentiles were used for quantitative measurements. The association between measures was assessed using the correlation test and t-test. The probability value was estimated at 0.05 confidence level (P=0.05).

Results and Discussion

Analysis of UCTD markers in the main group and the comparison group revealed that the average number of stigmas in patients of main group was 8.45 ± 0.31, and in patients of comparison group - 4.44 ± 0.17. Among persons with UCTD: one patient (3.3%) had 13 markers, 2 (6.7%) -

12 signs, 3 (10.0%) - 11 signs, 3 (10.0%) - 10 signs, 4 markers were found in 4 people (13.3%), 8 markers were found in 6 (20%), 5 people (16.7%) had 7 signs of UCTD and 6 (20%) - 6 markers.

Qualitative analysis of stigmas of dysembryogenesis in the main group by the topic of lesions revealed the following features **(Figure 1)**. Connective tissue anomalies of the hands and feet were observed in all patients. Ophthalmic stigmas (radial-lacunar iris, blue sclera) and microanomalies of the auricles (diagonal fold of the earlobe, small lobe) occurred in the vast majority of patients and were registered with the same frequency - in 27 people (90.0%). Changes in the oral cavity (occlusal abnormalities, predisposition to early caries, diastema) were detected in 24 patients (80%). Stigmas of dysembryogenesis of the skin and its appendages were registered in 18 patients (60%). The frequency of visceral stigmas was lower (gastroesophageal reflux disease - in 2 patients, gallbladder abnormalities - 1, polycystic kidney disease - 1, easy formation of hematomas at insignificant damage - 6, varicose veins of the lower extremities - 10) - 13 patients (43.3%). With the lowest frequency, connective tissue anomalies have been registered in body structure - 8 people (26.7%) and craniocephalic area - 3 patients (10.0%).

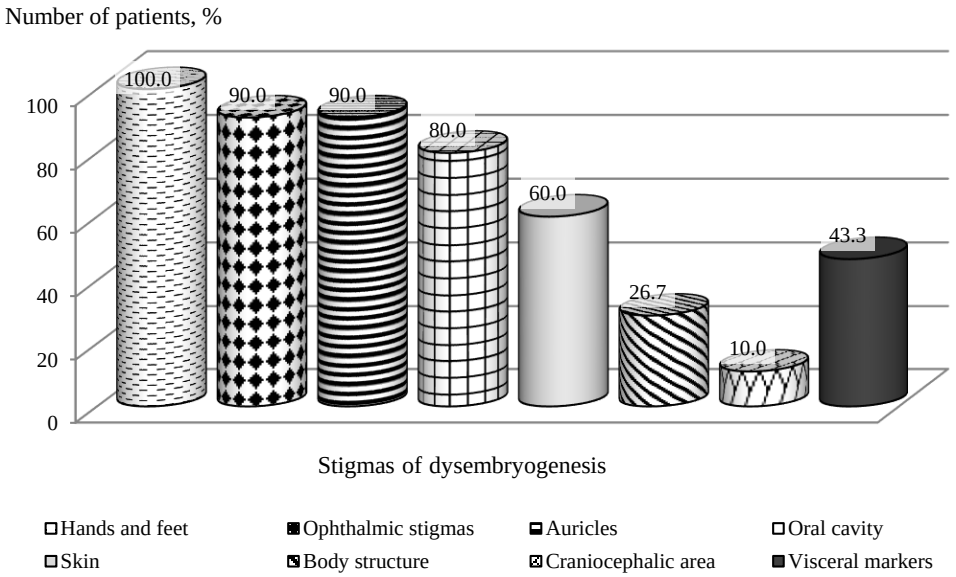

Figure 1. Distribution of stigmas of dysembryogenesis in women of the main group

In the comparison group, the frequency of lesions of the anatomical areas differed from the main group **(Figure 2)**. Stigmas of dysembryogenesis on the hands and feet were observed in all women. The phenotypic marker from the auricles (diagonal fold of the earlobe) was determined in 20 patients (66.7%). Oral changes (occlusion anomalies, predisposition to early caries) were detected in 18 patients (60%). In contrast to the main subgroup, changes in the eyes (radial-lacunar iris, blue sclera) were observed in a much smaller number of patients - 10 (30.0%). Connective tissue anomalies of the skin and its appendages were registered in 7 patients (23.3%), and visceral stigmas of dysembryogenesis - only in 5 (16.6%). In turn, changes in body structure and craniocephalic area were found in only 3 (10.0%) and 1 (3.3%) patients, respectively.

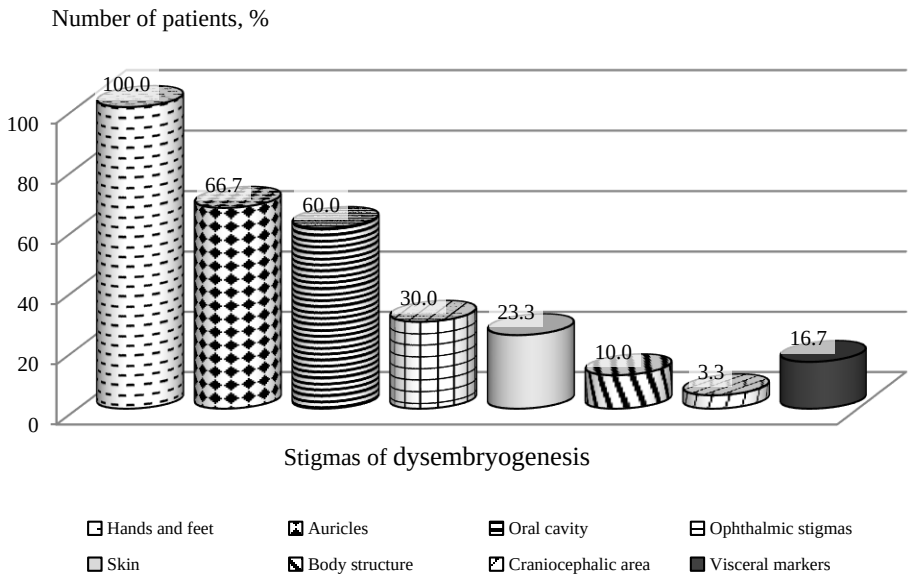

Figure 2. Distribution of stigmas of dysembryogenesis in women of the comparison group

Next, we decided to investigate the frequency of detection of UCTD markers in patients of the main group and the comparison group. So, in the main group such phenotypic and visceral stigmas of UCTD have been dominated: anomalies of the auricles (diagonal fold of the earlobe, small lobe (90.0%)), medial and/or lateral clinodactyly (83.3%), radial-lacunar type of iris eyes and blue sclera (63.3% each), predisposition to early caries (43.3%). In addition, direct strong correlations were found in women with UCTD between the whole number of UCTD markers and the frequency of the diagonal fold of the earlobe ($r=+0.79$; $p<0.05$), blue sclera ($r=+0.77$); $p<0.05$), varicose veins of the lower extremities ($r=+0.73$; $p<0.05$); direct correlations of medium strength - for the radial-lacunar type of the iris ($r=+0.66$; $p<0.05$) and easy formation of hematomas at insignificant damage ($r=+0.51$; $p<0.05$).

In patients of the comparison group with the highest frequency revealed: anomalies of the auricles (diagonal fold of the earlobe (63.3%), medial and/or lateral clinodactyly (40.0%), the predominance of the length of the fourth finger of the hand over the second (33.3%)), sandal-shaped first interdigital slit of the foot (26.7%), predisposition to early caries (23.3%), blue sclera (23.3%), radial-lacunar type of iris (20.0%). In patients of this group, the following markers of UCTD were detected significantly less often than in the main group: radial-lacunar type of iris, blue sclera, anomalies of the auricles, predisposition to early caries, varicose veins of the lower extremities. No scoliosis, chest deformity, increased skin elasticity (3 cm), flat feet, tendency of easy formation of hematomas at insignificant damage, changes in the shape of the gallbladder, gastroesophageal reflux disease, and polycystic kidney disease were detected.

A detailed analysis of the frequency of UCTD markers combinations on the affected systems revealed the following features. The skeletal system is affected in 100% of patients in the main group and the comparison group. Among the patients of the main group, the largest part were patients with a combination of lesions of the skeletal system and eyes - 25 people (83.3%). The next was the combination of UCTD markers from the skeletal system, eyes, and ears, which was observed in 23 patients (76.7%) of the main group.

The combination of lesions of the skeletal system and joints; skeletal system, eyes, and joints, and lesions of the skeletal system, eyes, ears, and joints occurred in 63.3, 60.0, and 53.3% of patients, respectively. The least common combinations were: skeletal system, eyes, cardiovascular system (CVS) and skin - 16.7% of patients; skeletal system, eyes, joints and CVS; skeletal system, eyes, joints, CVS and auricles - 13.3% of patients.

In patients of the comparison group, the combination of external and internal signs of UCTD was quite different. The most frequently observed in this category were lesions of the skeletal system and eyes - 15 patients (50.0%). In 11 patients (36.7%) a combination of stigmas from the skeletal system and joints was found. The combination of UCTD markers from the skeletal system, eyes, and auricles was observed in 6 patients (20.0%); bones, eyes, and skin - in 5 people (16.7%). Other combinations of phenotypic and visceral stigmas of dysembryogenesis were detected with very low frequency.

According to the number of affected systems, patients from the main group were distributed as follows: 6.7% of patients had stigmas in 3 systems; 26.7% - 4 systems; 43.3% - 5 systems; 23.3% - in all 6 systems. Phenotypic and visceral stigmas in 2 systems were not detected in any patient.

Among patients of comparison group 10.0% had lesions of 2 systems; 43.3% - 3 systems; 36.7% - 4 systems and 10.0% - 5 systems. Combinations with lesions of 6 systems in this cohort of patients were not detected at all. Thus, according to our data, patients with UCTD were significantly more likely to have a larger quantity of systems affected.

Therefore, all our patients with UCTD had different microanomalies of the connective tissue of the hands and feet; at the same time, according to various authors [10, 14-16], anomalies of the skeletal system were detected more often among the phenotypic stigmas, such as asthenic constitution, chest deformity, flat feet, postural disorders, and joint hypermobility, positive wrist symptom and "gothic palate". This can be explained by the fact that the above studies were conducted mainly either in mixed groups or among patients who did not have CHD.

Among patients with UCTD in our study, the second in frequency were ocular stigmas and ear microanomalies. The obtained data are consistent with the results of previous studies [10], which revealed a large number of patients with radial-lacunar type of iris. According to the existing observations [14], in patients with CHD, there was also a large number of such phenotypic stigmas of UCTD as multiple caries and diastema of the teeth of the upper jaw. In other studies [15, 17], increased skin elasticity was observed in only 1.47% of patients with UCTD and mitral valve prolapse. According to our data, this stigma was also found in a small percentage of patients – in 3.3% of patients in the main group.

Studies of the last decade suggest that there is a close relationship between the number of dysplasia phenotypic markers and the detection frequency of stigmas of internal organs dysembryogenesis, and, above all, CVS [10, 18].

In our study, visceral stigmas of dysembryogenesis were found in fewer patients than phenotypic ones – in 13 women of the main group (43.3%). Among the visceral markers of UCTD in patients of the main group most often were observed varicose veins of the lower extremities, easy formation of hematomas at insignificant damage, gastroesophageal reflux disease. In patients of the main group significantly more often than in women of the comparison group were found varicose veins of the lower extremities ($p<0.05$). It should be noted that the occurrence of varicose veins of the lower extremities in patients with small structural abnormalities of the heart on the background of UCTD, according to various authors, is 4.8 – 12.9% [10, 15, 16, 19, 20]. However, in our study, the number of such women was higher – 33.3% patients with MI on the background of UCTD, which is also most likely due to mixed gender of studied groups in previous researches.

Thus, such dysplasia stigmas of the phenotypic and visceral level as radial-lacunar iris and diagonal fold of the earlobe, as well as the symptom of blue sclera, varicose veins of the lower extremities, and easy formation of hematomas at insignificant damage can be considered as prognostic criteria of complicated CHD course.

Conclusion

The results of the study indicate the need for a detailed examination of patients with acute Q-MI on the background of UCTD, which includes, along with protocol examination methods, the detection of phenotypic and visceral markers of UCTD. This, in turn, will allow to predict the adverse course of CHD in patients with UCTD and to develop new approaches, including the genetic level ones, to the differentiated therapy of this group of patients.

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