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Identifying Dysplastic Stigmas in Female Patients with Acute Q-Wave Myocardial Infarction and Connective Tissue Dysplasia

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Abstract

Myocardial infarction (MI) remains the leading cause of mortality among individuals suffering from coronary heart disease (CHD) worldwide. In recent decades, there has been a significant increase in the prevalence of congenital connective tissue disorders. The significance of this issue extends beyond the increasing occurrence of undifferentiated connective tissue dysplasia (UCTD) and its complications, as it also presents medical and social challenges due to its association with various systemic conditions. Given the significant social impact of CHD in individuals with UCTD—particularly among the working-age population—this study focused on identifying dysplastic stigmas in women diagnosed with Q-MI in the presence of UCTD. The most common dysmorphic markers observed in these patients included abnormalities of the hands and feet (100%), ocular anomalies and auricular micro-malformations (90% each), lower extremity varicose veins (33.3%), and a tendency to form hematoma following minor trauma (20%). Significant correlations were identified in women with UCTD between the number of dysplastic markers and the occurrence of the diagonal earlobe crease ($r = +0.79$; $P < 0.05$), blue sclera ($r = +0.77$; $P < 0.05$), radial-lacunar iris pattern ($r = +0.66$; $P < 0.05$), lower limb varicose veins ($r = +0.73$; $P < 0.05$), and increased susceptibility to bruising with minimal trauma ($r = +0.51$; $P < 0.05$). These findings suggest that the aforementioned UCTD markers could serve as predictive indicators of the progression of more complex CHD, potentially guiding the development of improved diagnostic strategies and personalized therapeutic approaches.

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

Introduction

Cardiovascular disease (CVD) remains a leading global health concern, claiming more than 18.6 million lives annually. In many developed European nations, CVD accounts for nearly half of all adult deaths [1]. Among 30 European countries, Ukraine reports the highest incidence of CVD in women, including coronary heart disease (CHD), and ranks among the top for CHD-related male mortality. A striking disparity exists between Ukraine and developed European countries, particularly among younger populations, where CHD-related mortality rates are up to seven times higher. Alarmingly, both the incidence and mortality rates of CHD among young and middle-aged individuals continue to increase [2-5].

A considerable proportion of younger patients experience CHD with myocardial infarction (MI) as the initial manifestation, often accompanied by a high rate of prehospital fatalities. In certain cases, MI occurs despite the presence of structurally intact coronary vessels [6, 7]. Myocardial infarction (MI), often linked to coronary thrombosis, is traditionally understood to arise from a combination of well-known risk factors such as atherosclerosis, dyslipidemia, hypertension, diabetes, smoking, and genetic predisposition. These factors have been the focus of extensive research. However, the

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impact of other potential contributors to the development of acute coronary heart disease (CHD) and its complications has not been as thoroughly explored. Notably, studies involving coronary ventriculography have identified that up to 12% of MI patients present with no coronary vessel obstruction [8], suggesting that alternative factors, particularly undifferentiated connective tissue dysplasia (UCTD), may play a role in these cases [6, 9].

UCTD is a prevalent condition, affecting over half of the population in certain regions of Eastern Europe, with a higher incidence in women and those living in environmentally stressed areas. This disorder is characterized by structural abnormalities in collagen, elastic fibers, glycoproteins, and proteoglycans, driven by genetic mutations. These mutations impact genes involved in the synthesis of collagen, structural proteins, and protein-carbohydrate complexes, as well as those encoding enzymes and their cofactors [10].

The relatively common presence of undifferentiated connective tissue dysplasia (UCTD) in working-age individuals, particularly women, with coronary heart disease (CHD), underscores the need for a deeper exploration of this issue. This situation calls for the development of effective strategies for early diagnosis and prevention. Thus, the primary objective of the study is to examine the phenotypic and visceral markers of dysplasia in women who have experienced Q-wave myocardial infarction (Q-MI) in the context of UCTD.

Materials and Methods

The study involved 60 female patients, aged between 43 and 72 years, diagnosed with Q-wave myocardial infarction (Q-MI), who were admitted to the cardiology department of "Vinnytsya Regional Clinical Medical and Diagnostic Center for Cardiovascular Pathology" Diagnosis of Q-MI was confirmed through positive troponin test results, Raised levels of cardiac-specific enzymes, along with clinical symptoms and ECG findings, all following Global diagnostic standards and the clinical management protocol for acute coronary syndrome [11].

To achieve the study's goals, participants were categorized into two groups. The first group had 30 women diagnosed with myocardial infarction (MI) in association with undifferentiated connective tissue dysplasia (UCTD), aged between 43 and 69 years, with a mean age of 53.24 ± 5.08 years. The other group involved 30 women with MI but without UCTD (characterized by five or fewer phenotypic and visceral stigmas of UCTD), aged between 47 and 72 years, with a mean age of 56.30 ± 5.61 years.

Criteria for exclusion were set to exclude patients with concurrent conditions that could affect the structure and function of the heart muscles, along with the progression of cardiovascular complications, the development of CHD complications these conditions included hypertension, obesity, and diabetes, serious comorbidities like chronic obstructive pulmonary disease or cancer, as well as both primary and secondary mitral valve prolapse.

Both the first and comparison groups were matched in terms of age, cardiovascular risk factors, and family history of cardiovascular diseases (CVD).

All participants underwent a series of clinical and instrumental assessments, followed by statistical analysis of the gathered data. Specifically:

Somatometric assessment: Various anthropometric features were measured using the Bunak method modified by Shaparenko [12], which included body weight, torso length, height, chest-length, neck length lower limb length, head circumference, and chest circumference. Furthermore, UCTD-related features were identified, such as joint hypermobility, increased skin elasticity, a high-arched palate, and abnormal tooth alignment. Ocular signs, including radial-lacunar iris, "blue sclera" (thinning of the sclera and narrowing of the vascular tract), myopia, varying eye slit widths, and short or narrow eyelids, were evaluated through patient history, clinical examination, and ophthalmoscopic evaluation.

Ear anomalies, including protruding ears, diagonal earlobe folds, small lobes, absence of the tragus, and congenital deafness, were also noted during the clinical examination [10].

Vertebrogenic symptoms: These were identified using X-ray imaging and clinical evaluation, with a particular focus on lumbar hyperlordosis and scoliosis.

Patient survey: Each patient was questioned and gathered data using a specially developed questionnaire, based on the phenotypic map of Glesby as modified by Martinov *et al*. The questionnaire consisted of 54 items related to microanomalies. The total number of phenotypic and visceral markers of UCTD was recorded based on the findings. UCTD was diagnosed when six or more microanomalies were detected [10, 13, 14].

Instrumental Techniques: All participants underwent electrocardiography (ECG) using a 12-lead electrocardiograph, to identify focal adaptations in the ventricular myocardium and to conduct preliminary screening for arrhythmias and conduction abnormalities. Ultrasound imaging, performed with a General Electric "Logic-7" (Vivid-3) (USA) device, was used to assess kidney abnormalities, including dystopia, ectopia, partial duplication of the pelvis and ureters, cysts, and nephroptosis, as well as gallbladder conditions, such as single or multiple constrictions, inflections, and deformations.

Endoscopic techniques were used to diagnose gastric mucosal prolapse into the esophagus, esophageal hiatus hernia, gastroptosis, and visible gastroduodenal reflux. Esophagofibrogastroduodenoscopy was conducted on patients reporting abdominal pain and heartburn, especially in the epigastric region.

Radiographs of the chest were obtained to identify focal lung and mediastinal pathologies and to detect visceral abnormalities within the chest.

Results and Discussion

Data analysis was conducted using SPSS version 23. Descriptive statistics, including mean, standard deviation, and percentiles, were employed for quantitative measurements. To assess the relationships between variables, correlation tests, and t-tests were used. A significance level of 0.05 was considered, with a P-value threshold of P = 0.05.

The analysis of UCTD markers in both the first group and the comparison group showed that the average number of stigmas in the first group was 8.45 ± 0.31, while in the comparison group, it was 4.44 ± 0.17. In the group with UCTD, the distribution of the number of markers was as follows: 1 patient (3.3%) had thirteen markers, two patients (6.7%) had 12 markers, three patients (10%) had 11 markers, three patients (10%) had 10 markers, four patients (13.3%) had 9 markers, six patients (20%) had 8 markers, five patients (16.7%) had 7 markers, and six patients (20%) had 6 markers.

A qualitative analysis of dysembryogenesis markers in the first group revealed the following findings based on the type of lesions **(Figure 1)**. Connective tissue abnormalities in the feet and hands were present in every patient. Ophthalmic markers, including radial-lacunar iris and blue sclera, as well as auricular microanomalies such as a diagonal fold of the earlobe and small earlobes, were observed in the majority of patients, with a frequency of 90% (27 patients). Oral Cavity changes, such as occlusal abnormalities, a tendency toward early caries, and diastema, were identified in 80% of patients (24 patients). Skin and its appendages exhibited signs of dysembryogenesis in 60% of patients (18 patients). Visceral markers were less common, with gastroesophageal reflux disease observed in two patients, gallbladder abnormalities in 1, polycystic kidney disease in 1, easy hematoma formation following minimal injury in 6, and varicose veins of the lower extremities in 10 patients, totaling 43.3% (13 patients). Connective tissue anomalies in body structure were seen in 26.7% (8 patients), while craniocephalic abnormalities were the least frequent, occurring in 10% (3 patients).

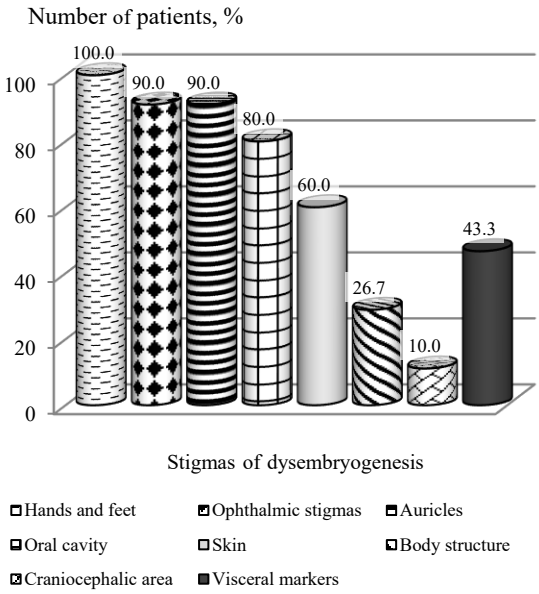

Figure 1. Distribution of stigmas of dysembryogenesis in women of the first group

In the comparison group, the occurrence of anatomical lesions showed significant differences compared to the first group **(Figure 2)**. All patients exhibited stigmas of dysembryogenesis in the feet and hands. The diagonal fold of the earlobe, a phenotypic marker, was present in 66.7% of the patients (20 individuals). Oral abnormalities, such as occlusion issues and a tendency toward early caries, were identified in 60% of the patients (18 individuals). However, ocular changes, such as radial-lacunar iris and blue sclera, were noted in a smaller proportion, affecting only 30% of the patients (10 individuals). Skin and appendage connective tissue

anomalies were observed in 23.3% of the patients (7 individuals), while visceral dysembryogenic signs were seen in only 16.6% (5 patients). Additionally, changes in the structure of the body and craniocephalic features were noted in a small percentage of patients, with 10% (3 patients) and 3.3% (1 patient), respectively.

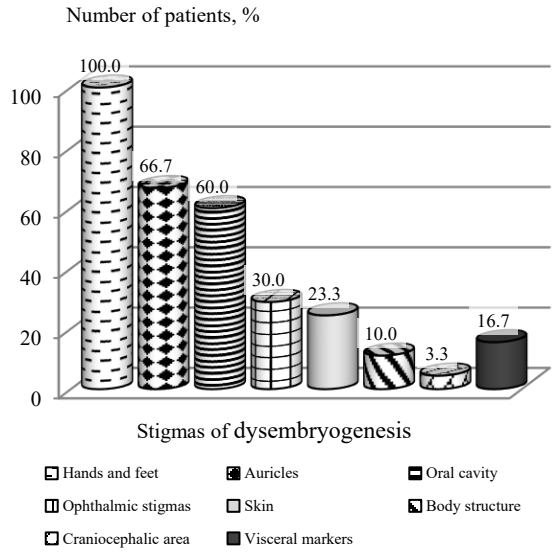

Figure 2. Distribution of stigmas of dysembryogenesis in women of the comparison group

We then analyzed the frequency of UCTD markers in both the first and comparison groups. In the first group, the most prevalent phenotypic and visceral signs of UCTD included ear anomalies (diagonal earlobe fold, small lobe) observed in 90% of patients, medial and lateral clinodactyly in 83.3%, radial-lacunar iris and blue sclera in 63.3% each, and early caries susceptibility in 43.3%. Moreover, we identified strong positive correlations between the total count of UCTD markers and the occurrence of specific traits. Notably, the frequency of the diagonal fold in the earlobe showed a strong correlation ($r = +0.79$; $P < 0.05$), as did blue sclera ($r = +0.77$; $P < 0.05$) and varicose veins in the lower limbs ($r = +0.73$; $P < 0.05$). Moderate correlations were found for radial-lacunar iris ($r = +0.66$; $P < 0.05$) and hematoma formation from minor injury ($r = +0.51$; $P < 0.05$).

In the comparison group, the most commonly observed UCTD markers included ear anomalies (diagonal fold of the earlobe in 63.3%), medial and lateral clinodactyly in 40.0%, a longer fourth finger compared to the second in 33.3%, and a sandal-shaped first interdigital space in the foot in 26.7%. Other notable markers were early caries susceptibility (23.3%), blue sclera (23.3%), and radial-lacunar iris (20.0%). When compared to the first group, the frequency of several UCTD markers was significantly lower in the comparison group, including radial-lacunar iris, blue sclera, ear anomalies, early caries predisposition, and varicose veins in the lower extremities. Additionally, no cases of scoliosis, chest deformities, increased skin elasticity (3 cm), flat feet, hematoma formation from minor injury, gallbladder shape abnormalities, gastroesophageal reflux disease, or polycystic kidney disease also were observed in this group.

A thorough examination of the combinations of UCTD markers across affected systems showed the patterns. In both the first and comparison groups, the skeletal system was involved in all patients (100%). Within the first group, the most common combination was the involvement of the skeletal system and eyes, observed in 25 patients (83.3%). The next most frequent combination included the skeletal system, ears, and eyes, which was present in twenty-three patients (76.7%) of the first group.

In the first group, the combinations of UCTD-related lesions involving the skeletal system, eyes, joints, the joints and skeletal systems and the skeletal system, ears, eyes, and joints were observed in 63.3%, 60.0%, and 53.3% of patients. The least frequent combinations were those involving the skeletal system, cardiovascular system (CVS), eyes, and skin (16.7%), as well as the skeletal system, eyes, joints, and CVS, and skeletal system, joints, eyes, CVS, and auricles (13.3%).

In the comparison group, the patterns of UCTD markers were notably different. The most common combination was between the skeletal system and eyes, seen in 15 patients (50.0%). A combination of joints and the skeletal system was found in eleven patients (36.7%). Additionally, a combination of the skeletal system, eyes, and auricles was detected in six patients (20.0%), while a combination of bones, eyes, and skin was observed in 5 patients (16.7%). Other combinations appeared much less frequently.

In the first group, the distribution of patients based on the number of affected systems was as follows: 6.7% had abnormalities in three systems, 26.7% in 4 systems, 43.3% in 5 systems, and 23.3% in all six systems. No patients had visceral stigmas and phenotypic in just 2 systems.

In contrast, among the patients in the comparison group, 10.0% had lesions in two systems, 43.3% in three

systems, 36.7% in four systems, and 10.0% in five systems. None of the patients in this group exhibited lesions across all six systems. These findings suggest that patients with UCTD had a significantly higher number of affected systems.

Moreover, all the patients with UCTD in our study exhibited various microanomalies in the connective tissue of the feet and hands. Previous studies [10, 14-16] have noted that skeletal system abnormalities, including the asthenic constitution, chest deformities, flat feet, postural issues, joint hypermobility, "gothic palate" and positive wrist symptoms were commonly observed phenotypic markers. The discrepancy can likely be attributed to the fact that those studies primarily focused on mixed groups or patients without coronary heart disease (CHD).

In our study, ocular anomalies and ear microanomalies were the second most frequent findings in patients with UCTD. These results align with previous research [10], which reported a high prevalence of radial-lacunar iris type among patients. Moreover, studies have also shown that individuals with coronary heart disease (CHD) tend to exhibit several phenotypic markers of UCTD, such as multiple dental caries and diastema in the upper jaw [14]. In contrast, other studies [15, 17] found increased skin elasticity in only 1.47% of UCTD patients with mitral valve prolapse. In our cohort, this particular stigma was observed in a small proportion—3.3%—of patients in the first group.

Recent studies from the past decade indicate a significant correlation between the number of dysplasia-related phenotypic markers and the frequency of internal organ anomalies, particularly those involving the cardiovascular system [10, 18].

In our study, fewer patients exhibited visceral markers of dysembryogenesis compared to phenotypic ones—only 13 women (43.3%) in the first group. Between the visceral markers in the first group, the most frequently observed were varicose veins in the lower extremities, easy bruising from minor injuries, and gastroesophageal reflux disease. Notably, varicose veins in the lower extremities were significantly more common in the first group compared to the comparison group ($P < 0.05$). The prevalence of varicose veins in patients with minor structural heart abnormalities alongside UCTD, as reported in various studies, ranges from 4.8% to 12.9% [10, 15, 16, 19, 20]. But, here in this study, the occurrence was much higher—33.3% of patients with mitral insufficiency and UCTD, likely due to the mixed-gender cohorts in earlier research.

Therefore, phenotypic and visceral dysplastic markers such as radial-lacunar iris, diagonal earlobe folds, blue sclera, varicose veins in the lower extremities, and easy bruising from minor trauma could serve as important prognostic indicators for a more complicated course of congenital heart disease.

Conclusion

The findings of this study underscore the importance of comprehensive evaluation for patients having acute Q-MI on the background of UCTD. This evaluation should include not only standard diagnostic methods but also the identification of phenotypic and visceral markers of UCTD. Such an approach will facilitate the prediction of potential complications in congenital heart disease (CHD) among patients having UCTD and help inform the development of new, targeted therapeutic strategies, potentially incorporating genetic-level considerations, for this patient group.

Furthermore, the study highlights the need for further research to explore the underlying mechanisms linking UCTD and the progression of CHD. Understanding the specific phenotypic and visceral markers that predict adverse outcomes could lead to more personalized treatment plans. By identifying these markers early in the disease process, clinicians may be able to intervene sooner, potentially improving patient prognosis and reducing the risk of complications. Continued exploration into the genetic factors that contribute to both UCTD and CHD could provide valuable insights for the development of more effective, tailored therapies.

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