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Features of polymorbid pathology in patients with autoimmune bullous dermatosis

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ABSTRACT

Background. Autoimmune bullous dermatosis (ABD) is a group of inherited and acquired skin diseases, the main morphological elements of which are the bullas, developed as a result of autoantibody production directed against protein structures of the epidermis and dermo-epidermal junction, leading to epidermal detachment and blistering on the skin and mucous membranes.

The aim of the research was to analyze the detection rate and structure of polymorbid pathology in patients with autoimmune bullous dermatoses and to determine the Charlson index and 10-year survival in patients before and after prescription of glucocorticosteroid therapy.

Materials and methods. The research included retrospective and prospective stages. At the first stage, the analysis of primary medical records was carried out, and histories of 70 patients over 18 years old, before the onset of autoimmune bullous dermatosis were analyzed. Clinical and epidemiological data were taken into account, the main and concomitant diagnoses were determined in accordance with ICD X. The Charlson index was calculated for all patients, the 10-year survival rate of patients with autoimmune bullous dermatoses was determined.

Results. Polymorbid pathology was recorded in 81.4% of patients, before the onset of autoimmune bullous dermatosis. 48.6% of patients had two or more concomitant diseases. Among patients with diseases of internal organs, those with cardiovascular pathology (52.8%) occupied the first place, patients with gastroenteric pathology (41.4%) occupied the second place, patients with endocrinopathy held the third place (20.0%). The Charlson index median in patients of this group was 2.5 (1–3), the risk of fatal outcome over a 10-year period was 16.5%. Subsequently, after the onset of autoimmune bullous dermatosis, 65.7% of patients required the prescription of glucocorticosteroid therapy. Decompensation of concomitant pathology was diagnosed in 39.1% of patients, therefore they needed consultation of related specialists. The median polymorbidity index increased to 3.5 (2–5), the risk of a death increased to 34.5% ($p < 0.05$).

Conclusion. Polymorbid pathology worsens the course of autoimmune bullous dermatoses, increases the risk of disability and mortality, especially in patients receiving systemic glucocorticosteroid therapy, and therefore these patients should be under regular medical check-up not only of a dermatovenereologist, but also of related specialists.

Key words: autoimmune bullous dermatosis, polymorbidity, Charlson index, glucocorticosteroids.

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Особенности полиморбидной патологии у больных аутоиммунными буллезными дерматозами

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РЕЗЮМЕ

Цель. Изучить частоту выявления и структуру полиморбидной патологии у больных аутоиммунными буллезными дерматозами. Определить индекс полиморбидности Чарлсон и 10-летнюю выживаемость у больных до и после назначения глюкокортикостероидной терапии.

Материалы и методы. Исследование включало ретроспективный и проспективный этапы. На первом этапе проведен анализ первичной медицинской документации, 47 амбулаторных карт и 23 историй болезни больных старше 18 лет до дебюта аутоиммунного буллезного дерматоза. Учитывали клинико-эпидемиологические данные, основной и сопутствующий диагнозы устанавливали в соответствии с Международной классификацией болезней 10-го пересмотра. Всем пациентам рассчитан индекс Чарлсон, определена 10-летняя выживаемость больных аутоиммунными буллезными дерматозами.

Результаты. Полиморбидная патология до дебюта аутоиммунного буллезного дерматоза зафиксирована у 81,4% больных. У 48,6% пациентов выявлено два и более сопутствующих заболевания. Наиболее часто диагностируются заболевания сердечно-сосудистой системы (первое ранговое место – 52,8%), затем патология желудочно-кишечного тракта (второе ранговое место – 41,4%), на третьем месте – эндокринопатии (20,0%). Медиана индекса Чарлсон у больных данной группы составила 2,5 (1–3), риск летального исхода за 10-летний период 16,5%. Впоследствии 65,7% пациентам, после дебюта аутоиммунного буллезного дерматоза, потребовалось назначение системных глюкокортикостероидов. Декомпенсация сопутствующей патологии диагностирована у 39,1% пациентов. Медиана индекса полиморбидности возросла до 3,5 (2–5), риск развития летального исхода увеличился до 34,5% ($p < 0,05$).

Заключение. Полиморбидная патология ухудшает течение и прогноз аутоиммунных буллезных дерматозов, увеличивает риск инвалидизации и смертности, в особенности у пациентов, получающих системную глюкокортикостероидную терапию, в связи с чем больные должны находиться на диспансерном учете не только у врача-дерматовенеролога, но и смежных специалистов.

Ключевые слова: аутоиммунные буллезные дерматозы, полиморбидность, индекс Чарлсон, глюкокортикостероиды.

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INTRODUCTION

Autoimmune bullous dermatosis (ABD) is a group of hereditary and acquired skin diseases that is formed as a result of the production of autoantibodies to various structures of the dermoepidermal compound, leading to epidermal detachment and blistering [1, 2]. The most severe ABD leading to permanent disability, as well as mortality, include acantholytic pemphigus, Lever's bullous pemphigoid, Dühring's herpetiform dermatitis, and acquired and congenital epidermolysis bullosa [3, 4].

Currently, mortality in ABD remains at a high level and varies from 15.0% to 30.0% despite pathogenetic treatment with systemic glucocorticosteroids

(GCS) and immunosuppressants [5, 6]. The prognosis of the disease also depends on polymorbidity. Researchers point out that ABD is often associated with diabetes, hypothyroidism, and inflammatory bowel disease, and an increased risk of stroke is observed in patients of this group [7, 8]. The presence of polymorbid pathology leads to a deterioration in the condition of ABD patients, an uncontrolled course of concomitant diseases and their resistance to basic therapy, a decrease in life quality, adherence of patients to drug therapy, and increased rates of patient disability and mortality [9].

Most studies of domestic and foreign scientists come down to identifying the most common diseases in ABD patients and do not include an assessment of the diagnosed polymorbidity severity, which is relevant, as it will enable to predict the course of both ABD and concomitant pathology, as well as to determine the death risk.

The aim of the research is to study the detection frequency and structure of polymorbid pathology in patients with autoimmune bullous dermatoses, to determine the Charlson polymorbidity index and 10-year survival in patients before and after glucocorticosteroid therapy.

MATERIALS AND METHODS

The study included retrospective and prospective stages. At the first stage, the analysis of primary medical documentation was carried out: 47 ambulatory medical records and 23 patient charts of subjects older than 18 years before the onset of autoimmune bullous dermatosis. Clinical and epidemiological data were taken into account. The main and concomitant diagnoses were established in accordance with the International Classification of Diseases, 10th Revision (ICD-10). Polymorbidity was registered by the number of nosologies in one patient. To assess somatic pathology, the Charlson index was determined. The overall score is the total of each patient's comorbid conditions (weighted according to severity and age) and points for each decade of life if a patient exceeded the age of 40.

The diseases assessed by calculating the Charlson index include cardiovascular diseases, dementia, chronic lung diseases, connective tissue diseases, peptic ulcer disease, liver damage, diabetes mellitus, kidney disease, liver disease, malignant neoplasms, and acquired immunodeficiency syndrome. Depending on the severity of concomitant diseases, the number of accrued points may be equal to 1, 2, 3 and 6.

With the help of the Charlson index, 10-year survival of patients with autoimmune bullous dermatoses was predicted. At the second stage, a clinical and instrumental examination of this group of patients was carried out, after the debut of autoimmune bullous dermatosis and the prescription of basic therapy. Statistical processing of the obtained data was carried out using the Excel 2000 and Statistica 13 packages. The median, upper and lower quartiles were calculated *Me* (Q_1–Q_3), nonparametric statistical methods (χ^2) with continuity correction were used. The level of statistical significance of the differences was considered at $p < 0.05$.

RESULTS

According to the retrospective analysis of primary medical documentation of 70 patients with autoimmune bullous dermatoses (ABD), 81.4% (57/70) of them had polymorbid pathology diagnosed before the debut of bullous dermatosis. The median age in the group of men with ABD was 49 years (interquartile range (IQR): 41.5–63.0 years), and in the group of women it was 56 years (IQR: 45.0–67.5). In 48.6% (34/70) patients, two or more concomitant diseases were detected.

Moreover, in the structure of the internal organs pathology, diseases of the cardiovascular system were diagnosed in 52.8% (37/70) patients, pathology of the gastrointestinal tract was registered in 41.4% (29/70) patients, endocrinopathies were observed in 20.0 % (14/70) patients, diseases of the musculoskeletal system were found in 15.7% (11/70) of ADB patients (Table). Patients also had diseases such as bronchial asthma, renal cell cancer, colon adenocarcinoma, senile cataract.

It is noteworthy that among 37 patients with cardiovascular pathology, all ABD patients showed arterial hypertension. Moreover, every second patient had stage 2 or stage 3 of high blood pressure. In 56.7% (21/37) of patients with arterial hypertension, target organs were affected (left ventricular hypertrophy, atherosclerotic plaques of the magistral vessels, creatinine clearance <60 ml/min), and in 35.1% (13/37) associated clinical conditions (ACC) were identified. Among patients with ACCs, 29.7% (11/37) patients with pathology of the cardiovascular system demonstrated coronary heart disease, 8.1% (3/37) patients had a history of myocardial infarction, 24.3% (9/37) patients were diagnosed with chronic heart failure, and 5.4% (2/37) patients had chronic renal failure. Atherogenic dyslipidemia

was reported in 13.5% (5/37) patients with ABD. It should be noted that two of the three patients with previously established arterial hypertension subsequently required the prescription of high daily doses of systemic glucocorticosteroids due to the onset of ABD.

Table

The comorbidity structure in patients with autoimmune bullous dermatosis, *n* = 70

№	Chapter of the ICD-10	Total	
		n	%
1	Chapter IX. Diseases of the circulatory system	37	52.8
2	Chapter XI. Diseases of the digestive system	29	41.4
3	Chapter IV. Endocrine, nutritional and metabolic diseases	14	20.0
4	Chapter XIII. Diseases of the musculoskeletal system and connective tissue	11	15.7
5	Chapter XIV. Diseases of the genitourinary system	7	10.0
6	Chapter VII. Diseases of the eye and adnexa	7	10.0
7	Chapter X. Diseases of the respiratory system	5	7.1
8	Chapter II. Neoplasms	4	5.8
9	Chapter V. Mental and behavioural disorders	2	2.8
10	Chapter VI. Diseases of the nervous system	1	1.4
	Total number of patients with pathology of internal organs	57	81.4

Note. The total number of observations exceeds 100.0% due to the presence of several pathological conditions in one person.

In the structure of the gastrointestinal tract (GIT) diseases, in 65.5% (19/29) of ABD patients with gastrointestinal pathology, endoscopic signs of gastritis were diagnosed, every third patient suffered from chronic cholecystitis and / or chronic pancreatitis. 10.3% (3/29) patients had a history of gastric ulcer. It should be noted that only two ABD patients with gastrointestinal complaints had a history of esophagogastroduodenoscopy. In one case, esophagitis was diagnosed, in another, erosion was found throughout the organ, which was regarded as a manifestation of erosive esophagitis. However, these manifestations regressed after the use of systemic glucocorticosteroids prescribed due to the debut of ABD. One patient had an esophageal stricture of unknown etiology.

In 72.7% (8/11) ABD patients with pathology of the musculoskeletal system, first detected or previously established osteoporosis and osteopenia were observed. It should be noted that therapy in these patients, before inclusion in the study, consisted of taking NSAIDs and calcium preparations.

Among endocrinopathies, 57.1% (8/14) ABD patients were diagnosed with type 2 diabetes mellitus, this pathology was detected before taking systemic glucocorticosteroids. And 28.5% (4/14) patients were diagnosed with autoimmune thyroiditis.

Pathology of the visual organs was detected in seven patients with ABD, patients with senile cataract occupy the first rank place, and every second patient required surgical treatment. Two patients were diagnosed with conjunctivitis and blepharitis.

Diseases of other organs and systems, such as bronchial asthma, chronic pyelonephritis, sensory polyneuropathy, iron deficiency anemia, were found in isolated cases. It should be noted that 4 out of 70 ABD patients were diagnosed with a malignant neoplasm, which could be a trigger factor in the development of paraneoplastic pemphigus and Lever's bullous pemphigoid.

The Charlson polymorbidity index was calculated for all patients with ABD. The median Charlson index in patients with ABD was 2.5 (1–3), the risk of death over a 10-year period is 16.5%. No gender differences were observed when comparing the Charlson index. A high proportion of patients with arterial hypertension, chronic heart failure, type 2 diabetes mellitus, gastric and duodenal ulcer was found. None of the ABD patients reported diseases included in the calculation of the Charlson index: peripheral vascular damage, transient cerebrovascular accident, collagenosis, liver cirrhosis without portal hypertension, acute cerebrovascular accident with hemiplegia or paraplegia, acute and chronic lymphoid or myeloid leukemia, lymphomas, cirrhosis of the liver with portal hypertension, acquired immunodeficiency syndrome.

Six concomitant diseases were registered in one man with Lever's bullous pemphigoid before the onset of ABD, including renal cell carcinoma of the right

kidney, coronary heart disease: post-infarction cardiosclerosis (2007), voltage angina pectoris (II functional class), hypertension (III stage, risk 4), chronic heart failure (II functional class), type 2 diabetes mellitus, cataract, and benign prostatic hyperplasia. The Charlson index was 8 and the risk of death was more than 79.0% (Figure).

Figure. Patient A., 63 year, Lever's bullous pemphigoid

It should be noted that after the onset of ABD, 65.7% (46/70) of patients required the prescription of pathogenetic therapy, namely systemic glucocorticosteroid therapy. Patients with acantholytic pemphigus, bullous pemphigoid Lever, acquired bullous epidermolysis were treated with medium and high daily doses of glucocorticosteroids. During treatment, 39.1% (18/46) of patients receiving systemic glucocorticosteroid therapy were diagnosed with decompensation of concomitant pathology.

In 29,7% (11/37) patients with diseases of the cardiovascular system, there was a lack of correction of arterial hypertension of varying degrees. Of these, nine patients reported an increase in blood pressure, requiring correction of antihypertensive therapy by a cardiologist.

Decompensation of type 2 diabetes mellitus was diagnosed in every second patient with previously established endocrinopathy (7/14), so all patients needed an endocrinologist's consultation with a view to adjusting the dose of sugar-lowering drugs.

After the prescription of systemic glucocorticosteroid therapy for patients with ABD, the Charlson index was re-calculated. The Charlson index median in 65.7% (46/70) of patients with ABD treated with glucocorticosteroid therapy was 3.5 (2–5), which reliably indicates an increased risk of death to 34.5% ($p < 0.05$) in a comparative analysis. It should be noted that in this group of patients, the polymorbidity index increased by one, and the risk of death increased by 18.0%, compared with indicators before the debut of ABD and the prescription of glucocorticosteroid therapy.

DISCUSSION

Despite the low prevalence of ABD, according to domestic and foreign researchers, mortality reaches 30.0%, which is due to both the disease severity and the development of complications during treatment [10, 11]. In this regard, patients with ABD should be kept at the dispensary of a dermatovenerologist throughout their lives [12].

In the last decade, doctors and scientists all over the world report the effect of polymorbid pathology on the clinical course of the disease, quality of life, treatment effectiveness of the underlying disease and its prognosis, noting that the more concomitant diseases the patient has, the worse the patient's quality of life and the higher the risk of death are [13, 14]. Foreign authors point out that the most common concomitant diseases in patients with ABD were cardiovascular, infectious and autoimmune diseases, metabolic disorders, while mortality in these patients was significantly higher than in patients of the same age without ABD [15]. According to the results of the study, polymorbid pathology was detected in 81.4% of patients, while more than two concomitant diseases were found in 48.6% of patients.

M. Pishgahi and N. Namazi (2018) evaluated the risk of developing atrial fibrillation in ABD patients. The authors note that mortality among bullous dermatoses patients with diseases of the cardiovascular system, such as coronary heart disease and arrhythmia, is higher than in the population. Scientists report a high risk of developing atrial arrhythmias in patients with

acantholytic pemphigus, while the risk is increased in patients taking high doses of glucocorticosteroids [16, 17].

We obtained similar data, however, the study revealed high comorbidity in patients with ABD with arterial hypertension and type 2 diabetes mellitus, which is due to the drug therapy of the underlying disease – prolonged use of oral glucocorticosteroids. At the same time, it should be noted that diabetes, after the prescription of high-dose glucocorticosteroid therapy, develops a more severe course and needs early prevention.

Most foreign studies come down to assessing the incidence of concomitant diseases in patients with ABD without assessing the polymorbidity index and taking into account the severity of the comorbid disease diagnosed by them [18, 19]. The study was the first to conduct a comprehensive examination of patients with ABD with the determination of the Charlson index, which is the "gold standard" in various types of studies to assess polymorbidity. With its help, you can predict the risk of death, as well as personify a follow-up plan for patients receiving long-term high-dose glucocorticosteroid therapy.

CONCLUSION

Polymorbid pathology was detected in 81.4% of patients before the debut of ABD. The most common pathologies were hypertension, pathology of the gastrointestinal tract, type 2 diabetes mellitus and osteoporosis. After the debut of ABD and the prescription of systemic glucocorticosteroid therapy, decompensation of somatic pathology was observed in 39.1% of patients. The presence of polymorbid pathology is a negative predictive factor that increases the risk of death, as evidenced by the high Charlson index. Thus, ABD patients receiving systemic glucocorticosteroid therapy need to be registered at the dispensary, not only by a dermatovenereologist, but also by related specialists.

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Authors contribution

Ufimtseva M.A., Bochkarev Yu.M. – dermatology consultation, editing of the article. Izmozherova N.V. – polymorbid pathology consultation, editing of the article. Gurkovskaya E.P. – conduction of the clinical study, preparation of the article.

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