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COMORBIDITY PROFILE IN CHRONIC BRAIN ISCHEMIA ON THE BACKGROUND OF MULTIFOCAL ATHEROSCLEROSIS

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Ключевые слова: *хроническая ишемия мозга, факторы риска, коморбидность, индекс коморбидности Charlson модифицированный*

Abstract. Comorbidity profile in chronic brain ischemia on the background of multifocal atherosclerosis. Dzyak L.A., Rosytska O.A. *Aim to evaluate the comorbidity profile in patients with chronic cerebral ischemia on the background of multifocal atherosclerosis. The study included 137 patients aged 40 to 84 years with chronic cerebral ischemia (CCI) on the background of multifocal atherosclerosis, which were divided into three clinical groups depending on the localization of vascular lesions by stenosing atherosclerosis. The co-morbidity profile and severity were evaluated using the Charlson's index in modification of R.A. Deyo (1992). In CCI patients, regardless of the combination of vascular basins affected by atherosclerosis, a severe degree of comorbidity prevailed - the Charlson's comorbidity index (IC) was predominantly > 5 points (84.7% of cases). In the analysis of IC in age categories, depending on the combination of atherosclerotic lesions of the vascular basins, it was found that comorbidity of severe degree (IC>5) was predominantly represented by patients of the older age group (60-74 years), and comorbidity of moderate severity (IC≤5) – patients of middle age group (45-59 years). A median difference of 3 points in assessing the mean value of age-matched comorbidity index showed that age, as a non-modifiable risk factor, in 1/3 cases determines the comorbidity index, which depends on the number of vascular basins affected by atherosclerosis. In 2/3 of the cases it is a modified comorbid pathology. Assessment of IC in clinical groups, taking into account the nature of the disease course (p <0.05), showed a correlation between the number of atherosclerosis affected by vascular basins, the severity of the clinical course of CCI and the severity of comorbidity. The severity of comorbidity, as measured by the Charlson's index modified by R.A. Deyo, depends on age and determines the nature of the atherosclerotic lesion, as well as the severity of the clinical course of CCI. Assessing the profile and severity of comorbidity makes it possible to influence the nature of the development and course of brain ischemia, which is caused by systemic atherosclerotic lesions of the vascular system.*

Реферат. Профіль коморбідності при хронічній ішемії мозку на фоні мультифокального атеросклерозу. Дзяк Л.А., Росицька О.А. *Мета дослідження – оцінити профіль коморбідності у хворих з хронічною ішемією мозку на тлі мультифокального атеросклерозу. У дослідження включено 137 хворих у віці від 40 до 84 років з хронічною ішемією мозку (ХІМ) на тлі мультифокального атеросклерозу, які були розподілені на три клінічні групи залежно від локалізації ураження судинних басейнів стенозуючим атеросклерозом. Проводилась оцінка профілю коморбідності і ступеня її тяжкості за допомогою індексу Charlson у модифікації R.A. Deyo (1992 г.). У хворих з ХІМ незалежно від поєднання уражених атеросклерозом судинних басейнів переважав тяжкий ступінь коморбідності - індекс коморбідності (ІК) Charlson становив переважно> 5 балів (84,7% випадків). При аналізі ІК у вікових категоріях залежно від поєднання атеросклеротичного ураження судинних басейнів встановлено, що коморбідність тяжкого ступеня (ІК> 5) була представлена переважно особами старшої вікової групи (60-74 роки), а коморбідність середнього ступеня тяжкості (ІК ≤5) - особами середньої вікової групи (45-59 років). Різниця медіани на 3 бали при оцінці середнього значення індексу коморбідності з урахуванням віку показала, що вік, як фактор ризику, що не модифікується, в 1/3 випадків визначає індекс коморбідності, який залежить від кількості судинних басейнів, уражених атеросклерозом. У 2/3 же випадків - це коморбідна патологія, яка модифікується. Оцінка ІК у клінічних групах з урахуванням характеру перебігу захворювання достовірно (p <0,05) показала залежність між кількістю уражених атеросклерозом судинних басейнів, тяжкістю клінічного перебігу ХИМ і ступенем тяжкості коморбідності. Ступінь тяжкості коморбідності, що оцінюється за індексом Charlson у модифікації R.A. Deyo, залежить від віку і визначає характер атеросклеротичного ураження, а також тякість клінічного перебігу ХИМ. Оцінка профілю та тяжкості коморбідності дає можливість впливати на характер розвитку і перебіг ішемії мозку, яка зумовлена системним атеросклеротичним ураженням судинної системи.*

The number of patients suffering from several diseases increases every year [1]. Comorbidity is the coexistence of two and / or more syndromes or diseases in one patient, pathogenetically interacting with each other or coinciding in time. Both conditions are the result of a single pathological process, and the differences in their course are due to the influence of external behavioral factors [3].

Comorbidity not only acts as a global medical problem and determines an individual prognosis for each patient (functionality, duration and quality of life, disability and mortality), but also has large-scale social consequences at the population level. Especially it affects the determination of the diagnostic and therapeutic approach for patient management [4]. Often, it is comorbid lesions that worsen the course of the underlying disease and / or lead to chronicity, cause disability and premature death of the working population. The presence of comorbid diseases significantly worsens the course of each disease separately [1]

Most patients, especially the elderly and senile, have a combined pathology: damage to the brain, cardiovascular system and kidneys, as well as metabolic syndrome. On average, examination of elderly and senile patients reveals from 4 to 8 leading diseases. With age, there is an increase in the number of patients with coronary heart disease, arterial hypertension (and their complications - myocardial infarction and heart failure), chronic

kidney disease, diabetes mellitus (and its complications - primarily diabetic nephropathy, retinopathy and polyneuropathy), anemic syndrome. Each of the diseases is an independent risk factor for death in elderly patients. It has been established that risk factors for cerebrovascular diseases are simultaneously risk factors for cardiovascular diseases. The development and progression of cerebrovascular diseases, as well as cardiovascular diseases, is closely associated with modifiable risk factors (smoking, unhealthy diet, physical inactivity, psychosocial factors, hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome, microalbuminuria, hyperhomocysteinemia, endothelial dysfunction and other factors (age, gender, adverse heredity) [5].

It was found that multidimensional indices, including the degree of severity (measured by functional constraint) for assessing comorbidity, correlate well with health outcomes, including quality of life and mortality. However, there are much fewer studies evaluating the severity or functional limitation of comorbidity [9, 11. For example, comorbidity prevents rehabilitation after a stroke [10], increases the number of complications after surgery, and increases the likelihood of falls in the elderly. Thus, the effect of comorbidity on the clinical manifestations, diagnosis, prognosis and treatment of many diseases is multifaceted and individual [2]. High comorbidity is an independent predictor of poor prognosis for survival [8] and can lead to mortality not associated with the underlying disease [11].

The possibility of the development and progression of cerebrovascular diseases, including chronic cerebral ischemia, increases with an increase in the number of compatibility and severity of behavioral factors and comorbid conditions. Comorbidity and potentially interacting vascular risk factors associated with the prevalence of atherosclerosis, which determine its heterogeneity, occupy an important place in the study of chronic brain ischemia. In domestic literature, such studies are not adequately covered, which determines the relevance of this work.

The purpose of the study: to evaluate the profile of comorbidity in patients with chronic brain ischemia on the background of multifocal atherosclerosis.

MATERIALS AND METHODS OF RESEARCH

The study included 137 patients aged 40 to 84 years, with multifocal vascular lesions. Of these, 107 (78.1%) patients are male and 30 (21.9%) are female. The average age of patients was (63.6±0,8) years.

Depending on the location of the lesion of vascular beds with stenosing atherosclerosis, all patients were divided into three clinical groups: I group – 30 (21.9%) patients with vascular lesions of the brain, heart and lower extremities; II group – 87 (63.5%) patients with vascular lesions of the brain and heart; III group – 20 (14.6%) patients with vascular lesions of the brain and lower extremities. The distribution of patients depending on the course of chronic cerebral ischemia (CCI) were as follows: CCI no episodes of acute ischemia of the disease in anamnesis (23 patients), CCI with TIA in anamnesis (15 patients), CCI with a single cerebral infarction in the anamnesis (59 patients), with repeated infarcts of the brain in history (40 patients).

Neurological status was assessed with the identification of leading clinical symptoms and the establishment of a form of cerebral circulation disorder. The nature of vascular lesions was refined by ultrasound Doppler ultrasound of the extra- and intracranial arteries on the device HP SONOS-1000 HP made by Hewlett Packard (USA), as well as selective cerebral angiography (according to indications). Structural lesions and their extent were determined using a brain MRI on the apparatus of “General Electric” (USA).

Assessment of the comorbidity profile was performed using the Charlson’s index in the modification of R.A. Deyo (1992) [10,11], which is a point system for estimating age, presence and number of comorbid diseases and allows to determine the severity of comorbidity: moderate – Charlson’s comorbidity index ≤5 and severe – Charlson’s 5 comorbidity index (Table 1).

Statistical analysis of the obtained data was performed using the licensed program Statistica v.6.1® (StatSoft, USA) (serial number AGAR909E415822FA). Mean values are presented as arithmetic mean with standard error (M±m) in cases of normal distribution law (Shapiro-Wilk test) or as median and quartile – Me (25-75%) in other cases. When comparing the relative indicators Fisher's two-way exact test (FTWET), was used for medium – the Mann-Whitney test.

RESULTS AND DISCUSSIONS

The analysis of the comorbid profile of patients with CCI in clinical groups showed heterogeneity of risk factors and concomitant diseases that contribute to the development and progression of vascular damage to the brain (Table 2).

It was found that hypertension in 92.7% of cases and ischemic heart disease in 85.4% of cases predominanted among pathogenetically related comorbid diseases. In 22.6% of cases, patients with gastrointestinal tract pathology were identified, which we attributed to pathogenetically unrelated comorbid diseases. However, the term "pathogenetically unrelated diseases" is very conditional, given the concept of uniform behavioral factors that can lead to the development of atherosclerotic lesions of the

vascular system and ischemic events. In the presented study, among the behavioral modifiable risk factors, the leading ones were identified: eating disorders (94.9%), physical inactivity (63.5%) and smoking (57.7%), and an unmodifiable factor – age (60 years and older – 66.4%)

Table 1

The presence of comorbid pathology and its score in the calculation of the Charlson comorbidity index in the modification of R.A. Deyo

Disease	Points
Myocardial infarction	1
Angina / heart failure	1
Hypertension	1
Peripheral artery disease	1
CVD or transient cerebral circulation disorders	1
Disorders of cerebral circulation with hemiplegia	2
Chronic lung diseases	1
Diabetes	1
Targeted diabetes mellitus	2
Moderate or severe kidney damage	2
Moderate liver damage	2
Severe liver damage	3
Disease of thyroid gland	1
Connective tissue disease	1
Gastric ulcer	1
Dementia	1
Tumor without metastases (lymphoma, leukemia)	2
Depression	1
Skin cancer	2
Malignant tumors with metastases	6
AIDS (disease)	6
+ 1 point added for every 10 years of life after 40	

Considering the large number of combinations of comorbid diseases in patients with CCI, we evaluated the severity of comorbidity in selected clinical groups (Table 3).

Table 2

The prevalence of comorbid conditions and risk factors in patients with CCI in clinical groups

Comorbid conditions and risk factors	Number of patients examined							
	I group (n=30)		II group (n=87)		III group (n=20)		Total in the general group (n=137)	
	n	%	n	%	n	%	n	%
1. Pathogenetically related								
Hypertension	28	93.3	81	93.1	18	90	127	96.7
IHD, including	30	100 p_{III}	87	100 p_{III}	-	- $p_{I,II}$	117	85.4
- IM	10	33.3 p_{III}	18	20.7 p_{III}	-	- $p_{I,II}$	28	20.4
Diabetes mellitus	13	43.3 p_{II}	12	13.8 $p_{I,III}$	8	40 p_{II}	33	24.1
Coronary artery disease (CAD)	28	93.3 p_{II}	-	- $p_{I,III}$	18	90 p_{II}	46	33.6
2. Pathogenetically unrelated								
Diseases of the pulmonary system	6	20	8	9.2	-	-	14	10.2
Disease of thyroid gland	5	16.7	5	5.7	-	-	10	7.3
Gastrointestinal diseases	8	26.7	16	18.4	7	35	31	22.6
Diseases of the urogenital system	9	30 $p_{II,III}$	10	11.5 p_{I}	-	- p_{I}	19	13.9
3. Vascular risk factors								
Smoking	17	56.7	49	56.3	13	65	79	57.7
Eating disorders	29	96.6	83	95.4	18	90	130	94.9
Hypodynamia	25	83.3 p_{II}	49	56.3 p_{I}	13	65	87	63.5
Chronic stress	15	50	33	37.9 p_{III}	14	70 p_{II}	62	45.2
Alcohol abuse	4	13.3	9	10.3	3	15	16	11.7
Age.years								
25-44	-	-	2	2.3	-	-	2	1.5
45-59	5	16.7 p_{III}	30	34.5	9	45 p_{I}	44	32.1
60-74	19	63.3	48	55.2	8	40	75	54.7
75-90	6	20	7	8.0	3	15	16	11.7

Note. pI, pII, pIII – $p< 0,05$ compared to the corresponding group I, II, III according to Fisher test.

Table 3

Characteristics of the degree of comorbidity in patients with CCI in clinical groups

The degree of severity of comorbidity	Number of examined patients							
	I group (n=30)		II group (n=87)		III group (n=20)		Total in the general group (n=137)	
	n	%	n	%	n	%	n	%
Moderate degree of comorbidity (CI ≤5)	-	- $p_{II,III}$	17	19.5 p_I	4	20 p_I	21	15.3
Severe degree of comorbidity (CI > 5)	30	100 $p_{II,III}$	70	80.5 p_I	16	80 p_I	116	84.7

Note. pI, pII, pIII – p< 0,05 compared to the corresponding group I, II, III according to Fisher test.

The analysis of the comorbidity profile in the selected clinical groups showed the heterogeneity of its severity associated with number of vascular basins affected by atherosclerosis. It was found that in patients with CCI, regardless of the combination of vascular beds affected by atherosclerosis, a severe degree of comorbidity prevailed – Charlson's comorbidity index (CI) was predominantly> 5 points (84.7% of cases). Thus, if in the first clinical group with combined atherosclerotic lesions of the vessels of the brain, heart and lower extremities, a severe degree of comorbidity was observed in 100% of cases, then in the II and III groups it was 80.5% and 80.0%, respectively (p<0.05 compared with group I), and a moderate degree of comorbidity in these groups was 19.5% and 20.0% of cases, respectively.

It was found that the severity of comorbidity, which means an increase in the number of comorbid conditions, affects not only the number of vascular basins affected by atherosclerosis, but also the nature (severity) of clinical manifestations of vascular brain lesions in patients with CCI (Table 4). Thus, if patients with a history of TIA had a severe degree of comorbidity – 66.7% of cases, then in patients with a history of stroke, it was already 79.7% of cases, and in patients with a history of relapses – 90% of cases.

To clarify the factors that determine the severity of comorbidity in clinical groups the comorbidity index was evaluated, taking into account age categories (Table 5).

In the analysis of the comorbidity index (IC) in age categories in selected clinical groups depending on a combination of the atherosclerotic lesion of the vascular beds it was established that severe comorbidity (IC>5) was represented mainly by the older age group (60-74 years) and comorbidity of moderate severity (IC≤5) – middle-age group (45-59 years). In individuals aged over 75 years only severe comorbidity was established (IC>5).

Table 4

Characteristics of the degree of comorbidity severity in patients with CCI, taking into account the nature of the disease

The degree of severity of comorbidity	Number of examined patients									
	CCI without Acute Brain Disorders (n=23) (1)		CCI with TIA (n=15) (2)		CCI with ischemic stroke (3) (n=59)		CCI with recurrent stroke (1) (n=40)		Total in the general group (n=137)	
	n	%	n	%	n	%	n	%	n	%
Moderate degree of comorbidity (CI ≤5)	-	- $p_{2,3}$	5	33.3 p_1	12	20.3 p_1	4	10.0	21	15.3
Severe degree of comorbidity (CI > 5)	23	100 $p_{2,3}$	10	66.7 p_1	47	79.7 p_1	36	90.0	116	84.7

Note. p1, p2, p3, p4 – p< 0,05 compared to the corresponding group I, II, III, IV according to Fisher test.

Table 5

Characteristics of the comorbidity index in clinical groups by age

The degree of severity of comorbidity	Number of examined patients							
	I group (n=30)		II group (n=87)		III group (n=20)		Total in the general group (n=137)	
	n	%	n	%	n	%	n	%
Comorbidity Index ≤5 (Moderate Comorbidity)	-	- $p_{II,III}$	17	19.5 p_I	4	20 p_I	21	15.3
25-44 years	-	-	1	1.1	-	-	1	0.7
45-59 years	-	- $p_{II,III}$	13	14.9 p_I	4	20 p_I	17	12.4
60-74 years	-	-	3	3.5	-	-	3	2.2
75-90 years	-	-	-	-	-	-	-	-
Comorbidity index> 5 (Severe degree of comorbidity)	30	100 $p_{II,III}$	70	80.5 p_I	16	80 p_I	116	84.7
25-44 years	-	-	1	1.1	-	-	1	0.7
45-59 years	5	16.7	17	19.5	5	25	27	19.7
60-74 years	19	63.3	45	51.7	8	40	72	52.6
75-90 years	6	20.0	7	8.1	3	15	16	11.7

Note. pI, pII, pIII – p< 0,05 compared to the corresponding group I, II, III according to Fisher test.

Assessment of IC in clinical groups, taking into account the nature of the disease (Table 6) (p<0,05), showed a relationship between the number of vascular pools affected by atherosclerosis, the severity of the clinical course of CCI and the severity of comorbidity. Thus, at atherosclerotic lesions of the vessels of all three basins (brain, heart and lower extremities), the highest values of the mean IC value (10 points) were established. That is, patients in the first clinical group with atherosclerotic lesions of the vessels of the brain, heart and lower extremities had the highest number of the ones with a greater number of comorbid conditions than in the second and third clinical groups with the damage of two basins - vessels of the brain and heart and vessels of brain and lower extremities, respectively.

Table 6

The average value of the comorbidity index in clinical groups, taking into account the nature of CCI course

Clinical groups	The average value of the index of comorbidity in points, Me (25-75%)				
	CCI without Acute Brain Disorders (n=23)	CCI with TIA (n=15)	CCI with ischemic stroke (n=59)	CCI with recurrent stroke (n=40)	Total (n=137)
Clinical group I (n = 30)	10.0 (8.0-10.5)	9.5 (6.0-13.0)	8.0 (6.0-10.0)	8.0 (7.0-10.0)	8.0 (7.0-10.0)
Clinical group II (n = 87)	7.0 (6.0-8.0)*	7.0 (5.0-8.0)	6.5 (5.5-9.0)	7.0 (6.0-9.0)	7.0 (6.0-9.0)
Clinical group III (n = 20)	6.5 (6.0-7.0)*	5.5 (4.0-7.0)	6.5 (5.5-7.5)	7.5 (7.0-9.0)	7.0 (6.0-7.5)

Note. * - p <0.05 compared with group I.

To assess the effect of modifiable and non-modifiable risk factors on the severity of comorbidity, an analysis of the Charlson comorbidity index in R.A. Deyo excluding age estimates (Table 7).

Table 7

Characteristics of the comorbidity index without taking into account age in clinical groups, taking into account age categories

The degree of severity of comorbidity	Number of examined patients							
	I group (n=30)		II group (n=87)		III group (n=20)		Total in the general group (n=137)	
	n	%	n	%	n	%	n	%
Comorbidity Index ≤5 (Moderate Comorbidity)	12	40.0 $p_{II,III}$	57	65.5 p_I	15	75.0 p_I	84	61.3
25-44 years	-	-	1	1.1	-	-	1	0.7
45-59 years	-	- $p_{II,III}$	21	24.1 p_I	8	40.0 p_I	29	21.1
60-74 years	12	40.0	30	34.5	6	30.0	48	35.0
75-90 years	-	-	5	5.7	1	5.0	6	4.4
Comorbidity index> 5 (Severe degree of comorbidity)	18	60.0 $p_{II,III}$	30	34.5 p_I	5	25.0 p_I	53	38.7
25-44 years	-	-	1	1.1	-	-	1	0.7
45-59 years	5	16.7	9	10.3	1	5.0	15	11.0
60-74 years	7	23.3	18	20.7	2	10.0	27	19.7
75-90 years	6	20.0 p_{II}	2	2.3 p_I	2	10.0	10	7.3

Note. pI, pII, pIII – p< 0,05 compared to the corresponding group I, II, III according to Fisher point test.

Analysis of the characteristics of comorbidity severity without taking into account age showed a decrease in its severity in the selected clinical groups (Table 7). So, if age was taken into account when assessing IC, then in the I clinical group only a severe degree of comorbidity was established, and if age was not taken into account, then in this group a moderate degree of comorbidity was established, and severe – in only 60% of cases. These data confirm the concept of the effect of age on comorbidity severity and on the number of vascular basins affected by atherosclerosis in patients with CCI.

Table 8

The average value of the comorbidity index without taking into account age in the clinical groups, taking into account the nature CCI

Clinical groups	The average value of the index of comorbidity in points, Me (25-75%)				
	CCI without Acute Brain Disorders (n=23)	CCI with TIA (n=15)	CCI with ischemic stroke (n=59)	CCI with recurrent stroke (n=40)	Total (n=137)
Clinical group I (n=30)	7.0 (5.5-7.5)	7.5 (6.0-9.0)	5.0 (4.0-7.0)	7.0 (4.0-8.0)	7.0 (5.0-8.0)
Clinical group II (n=87)	4.0 (3.0-6.0)*	4.0 (3.0-5.0)	5.0 (3.0-6.0)	5.0 (3.0-7.0)	4.0 (3.0-6.0)
Clinical group III (n=20)	4.0 (4.0-4.0) *	4.0 (3.0-5.0)	4.5 (3.0-5.0)	6.0 (5.0-6.5)	4.5 (3.5-5.5)

Note. * - p <0.05 separately from group I.

The same pattern was observed when assessing the average IC value without taking into account age. There was a decrease in the severity profile of comorbidity in the subjects when comparing these indicators with a group of people where the age of the patients was taken into account (Table 6, 8). So in clinical group I with CCI without acute ischemic episodes in history, a decrease in these indicators was noted by 30%, with CCI with TIA in history – by 21%, with CCI with one stroke in history – by 37.5% and by 12.5% – with CCI with a history of repeated strokes. The same trend persisted in the second and third clinical groups with a different nature of CCI course.

Median difference of 3 points when assessing the average value of the comorbidity index taking into account age showed that age, as an unmodifiable risk factor, in 1/3 of the cases determines the comorbidity index, which depends on the number of vascular basins affected by atherosclerosis. In 2/3 of the cases, this is a modifiable comorbid pathology (hypertension, diabetes mellitus, coronary heart disease and lower extremities, heart failure, and others), which can be controlled, compensated, and affect the nature of chronic cerebral ischemia course.

Thus, the assessment of the comorbid profile of patients with chronic cerebral ischemia on the background of multifocal atherosclerosis showed a significant effect of modifiable and unmodifiable factors not only on the development, but also on the nature and severity of the disease course. Determining the degree of comorbidity, the sequence of occurrence or progression of comorbid diseases, both pathogenetically related and unrelated, which may depend directly or indirectly on certain age groups in patients with CCI, will allow more effective primary and / or secondary preventive measures for this disease.

CONCLUSIONS

1. It was noted that the severity of comorbidity, as assessed by the Charlson's index in the modification of R.A. Deyo, depends on age and determines the nature of the atherosclerotic lesion, as well as the severity of the clinical course of CCI.

2. It was found that the profile of comorbidity in patients with chronic cerebral ischemia on the background of multifocal atherosclerosis in 1/3 of the cases was not a modifiable factor (age), but in 2/3 of the cases – modifiable factors.

3. Assessment of the profile and severity of comorbidity makes it possible to influence the nature of the development and course of cerebral ischemia, which is caused by systemic atherosclerotic lesions of the vascular system.

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