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Early Diagnosis of Delirium in Elderly Patients with Acute Stroke

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Abstract—Delirium is a common of stroke complication that aggravates the patient's prognosis. The aim of this study was to identify the groups that are at risk of developing delirium among elderly patients with acute stroke and assess the diagnostic value of the 4-A test in identifying delirium in this category of patients. In total, 73 patients were included in the study; 33 of them (45%) had the symptoms of delirium, according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). Delirious patients had more severe neurological deficit and more prominent chronic changes in the brain on CT images; they also had more frequently positive primitive reflexes and a higher erythrocyte sedimentation rate. All six patients with pneumonia were delirious. The Russian version of the 4-A test demonstrated good psychometric properties. Thus, the risk of developing delirium in elderly patients in the acute period of stroke is increased in cases of severe strokes, in the presence of chronic changes in the brain according to CT and clinical examination, and inflammatory complications. The targeted screening of patients with the indicated risk factors using tools such as 4-AT will allow delirium to be identified more efficiently and quickly in its early stages in elderly patients with acute stroke.

Keywords: stroke, delirium, elderly, 4-A test, diagnosis
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INTRODUCTION

Delirium is a transient acute neuropsychic disorder that is characterized by alterations in consciousness and global cognitive-behavioral changes [11]. Delirium can, in fact, develop in any internal and neurological disease. The occurrence rate of delirious conditions is particularly high among elderly people [11].

The mechanisms of the development of delirium has not been well studied. The majority of researchers explain the development of delirium by alterations in the neurotransmitter systems of the brain, as well as by neuroendocrine and neuroimmune changes within a pathological response to a stress. The damage to the neural pathways that are responsible for maintaining attention and other cognitive functions may be the main cause of delirium due to focal brain lesion [11]. The development of delirium aggravates the prognosis for the main disease and increases the risk of developing dementia later [1, 11].

Depending on the character of psychomotor impairment, delirium is subdivided into hyperactive, hypoactive, and mixed forms. While it is not difficult to identify the hyperactive form, the diagnosis of hypoactive delirium could be a problem. According to literature data, up to 60% of delirium cases are not diagnosed in a timely manner or remain undiagnosed [1, 11]. An early diagnosis of delirious conditions allows health care professionals to start timely treatment of the delirium and reduce its duration. An important condition for early diagnosis of delirium is targeted screening in the group of an increased risk for its development.

The diagnostics of delirium is based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV Revision (DSM-IVR) [9]. However, their application requires special training. Diagnostic scales are usually applied in routine clinical practice [11]. The assesment test (4AT) for delirium and cognitive impairment was first published in 2011 (Table 1). Its name was associated with the fact that each of four test components begins with the letter *A*: Alertness, lucidity; Abbreviated Mental Test-4 (AMT-4), which is a rapid test for intellectual capacities by Hodkinson that consists of four questions; Attention; and Acute change. This test is preferable to other tests, since it allows physicians to make preliminarily differentiation between delirium and chronic cognitive disorders [15].

According to different authors, the frequency of post-stroke delirium ranges within 2.3–66%, on average it equals 26% (95% CI 19–33%) [8]. According to our own data, signs of delirium are observed in 23% of the patients in the hyperacute period of stroke [3]. The early identification of delirium can be considered as one of the measures for improving the outcome of stroke and preventing the development of post-stroke dementia. This problem is especially actual for elderly patients, in whom subclinical forms of delirium are

Table 1. The 4A screening test for delirium and cognitive impairment (translated by M. Kutlubaev)

1.	**Alertness**
	This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating: • normal (fully alert, but not agitated, throughout the assessment), 0; • mild sleepiness for less than 10 s after waking and then normal, 0; • clearly abnormal, 4
2.	**AMT4**
	Age, date of birth, place (name of the hospital or building), current year: • without mistakes, 0; • one mistake, 1; • two mistakes, 2
3.	**Attention**
	Ask the patient to say the months of the year in backwards order starting from December: • the patient achieves 7 months or more correctly, 0; • the patient starts but scores less than 7 months or refuses to start, 1; • Untestable (the patient cannot start because they are unwell, drowsy, and inattentive), 2
4.	**Acute change or fluctuating course**
	Evidence of significant changes or fluctuation in alertness, cognition, or other mental functions (paranoia and hallucination) that began over the last 2 weeks and are still evident in the last 24 hours: • No, 0; • Yes, 4

more often observed and the frequency of dementia is higher [1, 11].

The aim of this work was to identify the groups that are at risk of developing delirium among elderly patients in the acute period of stroke and assess the diagnostic value of the 4A test as an express-test for the screening of this category of patients for delirium

MATERIALS AND METHODS

The patients were recruited in December of 2013 and January of 2014 at the neurovascular department of a general hospital in Ufa. All patients aged 65 and over who were admitted in their hyperacute period of stroke (the first 3 days) were included in the study. The exclusion criteria were the following: patients with subarachnoid/subdural hemorrhages without the formation of intracerebral hematoma and patients with transient ischemic attacks and impairment of consciousness as severe as sopor and coma and with significant chronic mental disorders in the past. Cerebral stroke was diagnosed in accordance with the WHO criteria [10].

A neurologist examined patients concerning the presence of signs of delirium within hours after their admission if they were admitted during a working day or on the next day if they were admitted in the evening or night time. The patients were examined twice at the interval of 12–24 hours. Delirium was diagnosed according to the DSM-IV criteria [9]. The presence of delirium was additionally assesed by the 4A test (Table 1).

The 4A test consists of four components to assess alertness (the score of 0 indicates alertness; the score of 4 means changed consciousness), self-assessment, the place and time (the score of 0–2), attention (the score of 0–2), the acuity of the change and a fluctuating course (the score of 0 is given in the absence of these signs and the score of 4 is used in their presence). Delirium was diagnosed if the patient received a score of 4 and higher (Table 1) [15].

The NIH Stroke Scale (NIHSS) was used to assess the severity of neurological deficit [14] and the modified Rankin's scale (mRS) was used to assess the degree of limitation in functional capacities [13]. The presence of primitive reflexes (snout, nasolabial, palmomental, and grasping) was registered to assess the degree of impairment in the frontal lobes [12].

All cases of stroke were subdivided into first and recurrent (anamnestically), ischemic and hemorrhagic (according to CT data) strokes, and, by vascular territories, into strokes in the left carotid, right carotid, and vertebrobasilar circulations (clinically). The CT were analyzed by an experienced neurologist. Among images the considered indicators were the localization of a acute stroke lesion, the presence of chronic foci, as well as the severity of a white matter lesions (leukoaraiosis) and cerebral atrophy. The white matter lesions were assessed in the anterior and posterior hemispheres using a four-score scale (0, no lesion; 1, mild; 2, moderate; and 3, expressed).

Cerebral atrophy was subdivided into central and cortical atrophies. Central atrophy was assessed by the width of lateral ventricles; this width indirectly reflected the degree of atrophy in subcortical structures. Cortical atrophy (atrophy of the cortex) was assessed by the degree of widening in the cortical sulci. The severity of atrophy was assessed by a four-score scale, according to the same principle as the severity of white matter lesions [6, 16]. The following biochemical indicators were recorded: the levels of creatinine (the reference values are 50–110 μmol/L), bilirubin (8–21 μmol/L), ALT (0–40 U/L), AST (0–40 U/L), and glucose (3.5–5.9 mmol/L) and the following hematological indicators: the count of erythrocytes, the mean volume of erythrocytes, the count of leukocytes, the level of hemoglobin and ESR, as well as the presence of fever (increased body temperature over 37°C), the presence of a urinary catheter, uroinfections by routine urinalysis data, and pneumonia at the moment of assessment. A patient's anamnestic data (the presence of arterial hypertension, ischemic heart disease (IHD) with and without myocardial infarction in the past, diabetes mellitus, substantial impairment in vision or hearing that require wearing glasses and a hearing device, respectively, and alcohol abuse) were based on the results of a patient's medical records and interviews of relatives. Alcohol abuse was diagnosed as a daily consumption of more than three standard alcohol doses (the equivalent of 10 g of pure ethanol).

The statistical data analysis was performed using the IBM SPSS Statistics 21 software package. Due to the use of short scales and a non-normal data distribution for the majority of parameters in the analysis, we predominantly utilized nonparametric statistics methods. The data are represented as a median and an interquartile range. Using the χ^2 parameter and the Mann–Whitney U-criterion, we compared, respectively, the binary and categorical data. A difference at $p < 0.05$ was regarded as statistically significant. To identify independent predictors for delirium in the hyperacute period of stroke, we performed a multivariate logistic regression analysis with stepwise inclusion of variables. The presence/absence of delirium was the dependent variable. The independent variables were selected from the variables whose values were statistically significantly different in patients with and without delirium by the comparative univariate data analysis. If two parameters had an significant correlation between one another (collinearity), only one parameter was included in the model at the researcher's choice.

The validity of the 4A-test was evaluated by parameters of the specificity, sensitivity, and positive and negative prognostic value; the ROC-analysis included the calculation of the area under the curve (AUC). The indicated parameters were calculated for both the results of the entire test and its individual components. The psychometric properties of the test were evaluated by its internal consistency as judged by the Cronbach α-coefficient [5]. The study was approved by the local ethics committee of the Bashkir State Medical University.

RESULTS AND DISCUSSION

Based on our criteria, we selected 73 subjects for our study from 132 patients who were admitted to the hospital during our recruitment period. The majority of the patients had ischemic stroke (94%). The demographic and clinical data of patients with the characteristics of their strokes, as well as the laboratory and CT-data, are presented in Table 2.

Delirium according to the DSM-IV criteria was diagnosed in 33 (45%) of 73 patients. Another 9 patients (12%) had only some delirium symptoms, which corresponded to subdelirium, or a possible manifestation of mild delirium or its prodromal phase [1].

Risk Factors of Delirium Development

Table 2 shows that the patients with delirium were older than the patients without it and had more severe neurological deficit by the NIHSS and limitations in their functional abilities according to the mRS. Delirium was more frequently observed in left hemispheric strokes. According to the brain CT data, the patients with delirium showed foci of past strokes more frequently, leukoaraiosis in the anterior parts of cerebral hemispheres and cortical atrophy were more severe. Delirium was more frequently observed in patients with strokes in the left carotid terriotory and less frequently in the right carotid and vertebrobasilar territories. The laboratory studies showed that the ESR and ALT levels increased in delirium. Delirium was observed in all patients with post-stroke pneumonia and in 40% of patients with urinary catheters at the moment of assessment. Patients with delirium more frequently had positive primitive reflexes (snout,

Table 2. Characteristics of patients and their strokes

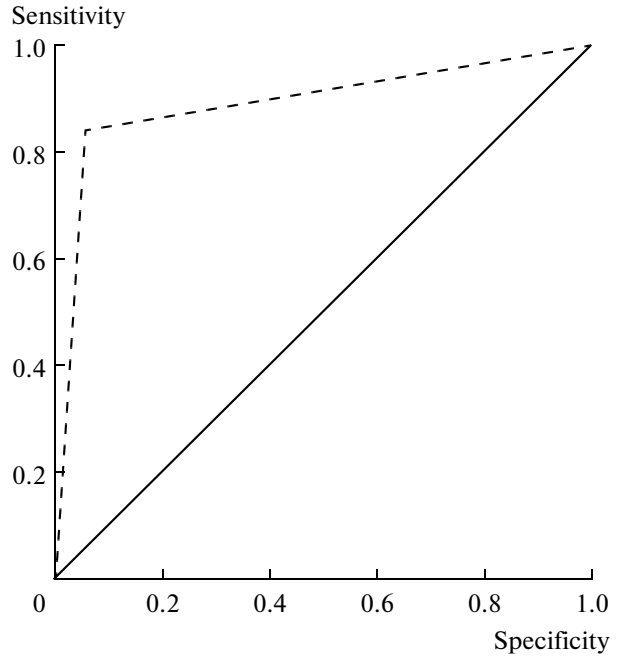
Parameter	Total indicator	Patients with delirium	Patients without delirium	*p*
Demographic data and characteristics of strokes				
Age, years	74 (69.5–78)	75 (71.5–82.5)	73 (67–76)	0.048
Gender (m/f)	21/52	12/21	9/31	0.2
Severity of stroke by the NIHSS, scores	10 (6–13.75)	13 (8.5–13)	8.5 (4–10)	0.0001
Degree of disability by the mRs, scores	4 (3–5)	4.5 (4–5)	3 (2.25–4)	0.0001
Right/left carotid/vertebrobasilar territories of stroke, %	58/25/17	22/18/5	36/7/12	0.027
CT data				
The presence of old foci on CT (yes/no)	63.4/36.6	51.5/48.5	74/26	0.05
Anterior leukoaraiosis, scores	1 (0–1)	1 (1–2)	0 (0–1)	0.002
Posterior leukoaraiosis, scores	1 (0–1)	1 (0–1)	1 (0.25–1)	0.073
Cortical atrophy, scores	1 (1–2)	2 (1–2)	1 (1–2)	0.007
Central atrophy, scores	1 (1–2)	1 (1–1)	1 (1–2)	0.07
Laboratory data				
Erythrocytes, $\times 10^{12}$	4.3 (4–4.8)	4.1 (3.9–4.5)	4.4 (4–4.8)	0.4
Hemoglobin, g/L	131.5 (120–144)	128.5 (106–142)	133 (120–144)	0.3
Mean corpuscular volume, femtoliter (fL)	86.9 (83.3–89.3)	87.2 (82.6–88.4)	86.4 (83.1–90.4)	0.6
Leukocytes, $\times 10^{9}$	7.7 (6.1–9.3)	8.1 (6–10.1)	7.6 (6.1–8.6)	0.2
ESR, mm/h	8.5 (5–15.75)	13 (8–20.5)	8 (5–13)	0.003
ALT, U/L	30 (18.3–40)	34.5 (27.7–42)	25.5 (17–39)	0.007
ACT, U/L	32 (23–40)	36 (26.8–40.8)	30 (23–40)	0.065
Bilirubin, mmol/L	10.7 (7.4–17.2)	10.7 (7.4–17.3)	9.8 (6.8–16.7)	0.6
Creatinine, mmol/L	119 (106–133)	119.5 (101.8–132.3)	118.5 (109–132.3)	0.3
Glucose, mmol/L	6.1 (5.4–7.6)	6.5 (5.1–8)	6 (5.4–6.9)	0.2
Oral automatism reflexes and stroke-related complications				
Snout reflex, %	23.6	40	10	0.002
Nasolabial reflex, %	4.1	9.1	0	0.051
Palmomental reflex, %	15	30	2.5	0.001
Grasping reflex, %	1.4	0	2.5	0.3
Fever, %	26	33	20	0.3
Urinary catheter, %	25	39.4	12.5	0.01
Pneumonia, %	9.6	9.6	0	0.003
Uroinfection, %	56	60	53	0.6
Total number of complications per patient	1 (0–2)	1 (1–2)	1 (0–1)	0.006
Anamnestic data				
Arterial hypertension, %	98.6	97	100	0.3
IHD without myocardial infarction in anamnesis, %	42.5	45	39	0.6
IHD with myocardial infarction in anamnesis, %	15	24	7.5	0.047
Vision loss, %	15	9	20	0.2
Hearing loss, %	22	20	24	0.7
Diabetes mellitus, %	32	39	25	0.2
Alcohol abuse, %	20.5	39.4	5	0.0001

Table 3. Results of logistic regression analysis

Variable	β-Coefficient	Standard error	*p*
Severity of stroke by the NIHSS	0.189	0.082	0.021
Anterior leukoaraiosis	–1.023	0.514	0.046
Complications	0.032	0.352	0.927
Age	0.051	0.054	0.348
Palmomental reflex	2.343	1.265	0.064
Territory	0.838	0.438	0.056
Constant $R^2 = 0.489$ (48.9%)	–6.726	3.975	0.001

nasolabial, and palmomental), and myocardial infarction and alcohol abuse were more frequently registered in their anamneses.

A logistic regression analysis was performed for the elderly patients to identify independent predictors for the development of post-stroke delirium. The model included the following parameters: the severity of stroke according to the NIHSS, severity of white matter lesions in the anterior parts of hemispheres, ESR, the total number of complications, and the presence of palmomental reflex. The severity of stroke according to the NIHSS ($\beta = 1.023$; $p = 0.046$) and the severity of leukoaraiosis in the anterior parts of the hemispheres ($\beta = 0.189$; $p = 0.021$) were independent predictors for delirium development in the acute period of stroke in the elderly patients (Table 3). This statistical model explained 49% of the delirium variability in elderly patients in the acute period of stroke.



ROC-curve reflecting the diagnostic value of the 4A test, if the diagnosis of delirium established according to the DSM-IV criteria was accepted as the "gold standard"; area under curve, 0.89.

The Psychometric Properties of the 4A Test

The Russian version of the 4A test (M.A. Kutlubaev's translation) was also employed in parallel with the DSM-IV criteria for the diagnosis of delirium. The 4A test specificity (the capacity of the test to correctly identify patients without delirium) was 86% and its sensitivity (the test's capacity to correctly identify patients with delirium) was 93%. The prognostic value of a positive result (the presence of delirium) according to the 4A test was 86%, the prognostic value of negative result (the absence of delirium) was 85.6%. The AUC indicator that was used for the assessment of the clinical significance of the test was 0.89 (figure). The interval of 0.8–0.9 corresponds to a very good quality of a questionnaire. The diagnostic values of the individual components of the test are presented in Table 4.

The internal consistency of the questionnaire by the Cronbach α-coefficient was 0.8. The psychometric properties of the questionnaire are considered appropriate at the Cronbach α-coefficient values within the 0.7–1 range (1 is the maximum value) [5].

The results of our study demonstrated a high frequency of post-stroke delirium in elderly patients, viz., 45%, which is twice as high as our data that were obtained when investigating patients with acute stroke without age-related limitations [3].

According to the obtained data, the following signs in elderly patients in the acute period of cerebral stroke can be attributed to the groups that are at risk of developing delirium: severe neurological deficit according to the NIHSS, the presence of foci of previous strokes and chronic CT brain changes, increased ESR, pneumonia development, a need in urinary catheter, the presence of primitive reflexes, the fact of myocardial infarction and alcohol abuse in the past. According to the results of logistic regression analysis, the severity of stroke, and the severity of anterior leukoaraiosis were independent predictors for the development of delirium in the acute period of stroke in the elderly. This statistical model explained half of the cases of the development of delirium in the elderly in the acute period of cerebral stroke.

All of the established factors that predispose a patient to the development of delirium in the acute period of stroke can conventionally be divided into three groups. The first group corresponds to the factors that are associated with the stroke itself: the sever-

Table 4. The diagnostic values of the individual components of the 4A test

Factor	Score	Sensitivity, %	Specificity, %	PVP, %	PVN, %	AUC
Alertness	4	51.4	92.5	85	69.7	0.76
Orientation	≥1	84.8	80	73.7	88.9	0.8
Attention	≥1	93.8	75	75.5	93.75	0.85
Acute change/fluctuating course	4	72	90	86	80	0.83

PVP, prognostic value of positive result; PVN, prognostic value of negative result; AUC, area under the curve.

ity of neurological deficit according to the NIHSS, the severity of functional limitations according to the mRS, and the vascular territory. This group can include the cases with the presence of urinary catheters, which are placed, as a rule, in severe strokes. The mentioned factors predispose a patient to the development of delirium, probably due to the severe pathological stress-response to brain lesions and the development of neurological deficit. The latter, in turn, leads to the development of disturbances in the hypothalamo–pituitary–adrenal system and the development of aseptic inflammation. The second group includes the factors that are associated with chronic brain changes: an elderly age, the severity of leukoaraiosis in the anterior parts of the hemispheres, the severity of cortical atrophy, the presence of foci of previous strokes, positive primitive reflexes, and alcohol abuse in anamneses. Chronic brain impairment leads to the disconnection of interneuronal pathways and probably decreases the compensatory reserves of the CNS in the conditions of acute stress. The same can be said about myocardial infarction in anamnesis, which was considered as a marker of severe atherosclerosis, including cerebral vessels. The third group is stroke-related infectious inflammatory complications, pneumonia and accelerated ESR. The latter increase the risk of developing a post-stroke delirium due to increased production of anti-inflammatory cytokins that toxically affect the brain [2].

Apart from the knowledge about groups that are at risk of developing delirium, physicians need to have a rapid psychometric tool for the diagnosis of delirium at their disposal that can be used in parallel with a routine examination. The 4A test is a tool of this kind. Our study has demonstrated that the Russian version of the test has good psychometric properties and high clinic significance. The application of this test takes a few minutes and no special training is required.

The treatment of delirium is poorly developed thus far and consists of measures for care and the use of neuroleptics [1, 11]. The study on the efficiency of acetylcholinesterase inhibitors and melatonin in the treatment of delirium is at the stage of trials [1, 4]. The prevention of delirium, or so-called prehabilitation, was initially developed for patients who are awaiting surgeries for hip replacement [7]. It includes the control of oxygenation, water balance, pain, as well as avoiding polypragmasia. The use of delirium prevention measures will be justifiable among patients who are in risk groups.

Thus, the risk of developing delirium in elderly patients with acute stroke is the highest among patients with severe strokes, pronounced chronic brain changes, and infectious–inflammatory complications. It is this group of patients that needs the screening for delirium with tools, such as the 4A test. This will allow physicians to diagnose delirium in elderly patients with acute cerebral stroke at early stages and to take timely measures to cope with it.

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