

## «THE YAKUT MEDICAL JOURNAL» ISSUE MATERIALS

### ORIGINAL RESEARCHES

S.A. Chugunova, T.Ya. Nikolaeva, T.S. Egorova

### FEATURES OF ANTICOAGULATION-ASSOCIATED INTRACEREBRAL HEMATOMAS

#### ABSTRACT

Anticoagulant-associated intracerebral hemorrhage is characterized by the clinical severity and an increased risk of death. Previously published data on the anticoagulation-associated hematoma's localization are controversial. This study was provided to characterize the localization of intracerebral hematomas, associated with anticoagulant therapy, in patients with warfarin-associated and spontaneous hypertensive intracerebral hematomas.

It is found that warfarin-associated hematoma characterized by a common site in the cerebellum compared with hypertensive intracerebral hematomas.

**Keywords:** hemorrhagic stroke, intracerebral hematoma, anticoagulation therapy, warfarin.

#### INTRODUCTION

In recent years, the antithrombotic-associated hemorrhagic stroke (HS) due to changes in blood coagulation is very actual problem. It is because of the growing number of patients who are appointed by the anticoagulant and antiplatelet therapy for prevention of the thromboembolism. The anticoagulant therapy increases the risk of HS [2, 21, 22]. The anticoagulant-associated intracerebral hemorrhages (ICH) consist up to 20% of all cases of HS [10, 11, 25]. This ICH has a higher risk of hematoma expansion, subsequent clinical deterioration and death [11]. Predictors of hemorrhagic complications of anticoagulant therapy include the previous ischemic stroke history, arterial hypertension, leukoaraiosis, the initiation period of anticoagulant therapy, excessive anticoagulation, elderly age, and the concomitant use of antiplatelet agents [11, 18]. Reported data about the localization features of anticoagulant-associated ICH are controversial [5, 17, 27]. In Yakutia, studies on the clinical features of anticoagulant-associated HS have not been carried out.

**Aim of the study.** To characterize the localization of intracerebral hematomas associated with anticoagulant therapy.

#### METHODS

The retrospective study was performed in the group of HS patients consecutively admitted to the Regional Vascular Center (Yakutsk) in 2012-2014.

Criteria for inclusion in the study group:

1) patients with ICH in acute stage due to anticoagulation background (warfarin-associated ICH, valCH) with international normalized ratio (INR) > 3.0 (first group) and 2) patients with primary hypertensive spontaneous ICH (the second group). Exclusion criteria: patients with ICH due to rupture of cerebral vascular anomalies (arterial aneurysms, arteriovenous malformations, cavernous angiomas); traumatic hemorrhage; tumor hemorrhage; HS due to liver disease, blood disease, using of the antiplatelet therapy, "new anticoagulants", heparin, thrombolytic therapy. The diagnosis was confirmed by the neurological examination data, anamnesis, neuroimaging (cerebral computer tomography (CT) and / or magnetic resonance imaging of the brain (MRI)) in 100% of cases. Status of blood coagulation was estimated at INR indicator. The demographic data, INR indicators, ICH localization according to neuroimaging were analyzed in both groups. Localization of hematoma was distributed as follows: 1) supratentorial hematoma includes lateral, medial, lobar, and mixed localization; 2) cerebellar hematoma; 3) stem hematoma. The anticoagulant dosage at the ICH onset; the risk factors of thromboembolic events according CHADS<sub>2</sub> scale; risk factors of hemorrhagic complications of anticoagulant therapy according HAS-BLED scale were analyzed in the first group.

Statistical analysis was performed

using software packages STATISTICA 8. Quantitative characteristics described medians (Me) and quartile [Q1; Q3]. The comparison of the group's central parameters was performed using U-Mann-Whitney nonparametric method. Study of the interrelationship between the pairs of discrete qualitative characteristics was performed using the paired analysis of conjugation tables. In addition to Fisher's exact test, associations strength was analyzed with relative risk values (OR) and 95% confidence intervals (CI).

#### RESULTS

It was randomized 492 acute ICH patients, including 14 patients with valCH (first group, 2.8%) and 478 patients with spontaneous hypertensive ICH (second group, 97.2%). Demographic and clinical characteristics of both groups are presented in Table 1.

The average age of first group patients was 61.5 [57; 67] years (min – 42, max – 75). Male patients amounted 57.1% (n = 8). In the second group, the patients mean age was 59 [51; 66] years (min – 16, max – 89). The proportion of male patients was 58.2% (n = 278). The average age of the patients had no significant difference between groups ( $p = 0,305$ ).

In the first group (n = 14) before the ICH onset, the anticoagulation therapy for the thromboembolism prevention has been appointed in 10 patients with atrial fibrillation (71.4%), with the operated

### Demographic and clinical characteristics of the anticoagulant-associated intracerebral hematomas and spontaneous hypertensive intracerebral hematomas

	First group	Second group	$p^*$ , OR (95 % CI)
n	14	478	
Male gender, n (%)	8 (57,1)	278 (58,2)	
Age, years	61,5 [57; 67]	59 [51; 66]	$p = 0,305$
INR > 3, n (%)	14 (100)	-	
CHADS <sub>2</sub> and > points, n (%)	14 (100)	-	
HAS-BLED 3 and > points, n (%)	10 (71,4)	-	
Localization of hematoma:			
Supratentorial, n (%)	9 (64,3)	407 (85,1)	$p = 0,05$ ; OR = 0,314; 95 % CI: 0,093 – 1,113
Cerebellar, n (%)	4 (28,6)	33 (6,9)	$p = 0,017$ ; OR = 15,39; 95 % CI: 1,398 – 20,144
Stem, n (%)	1 (7,1)	38 (7,9)	$p = 1,00$ ; OR = 0,89; 95 % CI: 0,042 – 6,826
Hematoma volume	25,5 [6,0; 45,0]	22,3 [8,0; 80,0]	$p = 0,857$
Breakthrough blood brain ventricles, n (%)	7 (50)	150 (31,4)	$p = 0,153$

\*Two-tailed Fisher Exact Test

heart valves – 3 patients (21.4%), with a combination of atrial fibrillation and operated heart valve – 1 patient (7.1%). The heart failure was diagnosed in 12 patients (85.7%), arterial hypertension – 14 patients (100%), diabetes mellitus – 3 patients (21.4%). There were no patients aged > 75 years in the first group. Patients with previous stroke or transient ischemic attack history (TIA) consist 10 cases (71.4%). Thus, CHADS<sub>2</sub> scale score 2 and > was established in 100% cases among atrial fibrillation patients (n = 10).

In the first group, the following anticoagulant therapy's hemorrhagic complications factors were diagnosed: arterial hypertension – 100% (n = 14); acute cerebrovascular accident in history – 71.4% (n = 10); anticoagulant receiving without laboratory monitoring of INR – 42.8% (n = 6); age > 65 years – 35.7% (n = 5); concomitant use of drugs (antiplatelet agents, non-specific anti-inflammatory drugs) – 21.4% (n = 3); alcohol abuse – 14.3% (n = 2); bleeding history – 7.1% (n = 1); abnormal liver function – 7.1% (n = 1); abnormal renal function – 7.1% (n = 1). Thus, the risk of hemorrhagic complications of anticoagulant therapy according to scale HAS-BLED with 3 and > points was established in 71.4% (n = 10).

In the first group, ICH occurred due to warfarin using in 100% cases (n = 14). Patients admitted with INR > 3.0 in 14 cases (100%), including: INR from 3.0 to 5.0 – in 8 cases (57.1 %), INR > 5.0 – 6 cases (42.8%). Minimum INR rate was 3.18; maximum – 12.54. On the valCH onset warfarin dose was 5 mg and < in 13 patients (92.9%); > 5.0 mg – 1 patient (7.1%). In the second group, the INR rate was estimated < 3.0 in 100% cases (n = 478). In 2 cases (14.8%), HS combined with extracranial hemorrhages, including hematuria in 7.1% (n = 1), gastric bleeding – in 7.1 % (n = 1). In 85.7% (n = 12) only cerebral hemorrhage occurred.

In the first group, the ICH localization was as follows: supratentorial hematoma diagnosed in 9 patients (64.3%), cerebellar hematoma – in 4 cases (28.6%), stem hematoma – 1 case (7.1%). In the second group, supratentorial hematoma diagnosed in 407 cases (85.1%), cerebellar hematoma – in 33 cases (6.9%), stem – in 38 cases (7.9%). Comparative analysis of the hematoma locations frequencies between groups shows that the cerebellum hematoma has higher frequency in the first group (28.6% vs. 7.1%) ( $p = 0,017$ ; OR = 15.39; 95% CI: 1.398 – 20.144). The stem hematomas frequency had no significant differences between groups (7.1% vs. 7.1%).

( $p = 1.00$ ; OR = 0.89; 95% CI: 0.042 – 6.826)), as well as the supratentorial hematomas frequency (64.3% vs. 85.1% ( $p = 0.05$ ; OR = 0,314; 95% CI: 0.093 – 1.113)).

The mean hematoma volume was 25.5 cm<sup>3</sup> [6.0; 45.0] (min – 1.8; max – 150.0) in the first group. In the second group, the mean hematoma volume was 22.3 cm<sup>3</sup> [8.0; 80.0] (min – 1.0; max – 196.0). No significant differences in the hematoma's volume was found ( $p = 0.857$ ). It was diagnosed 7 cases of the blood breakthrough into the brain ventricular system in the first group (50 %), and 150 cases in the second group (31.4%). No significant difference was established between groups ( $p = 0.153$ ).

### DISCUSSION

This study is performed in the actual field of intracerebral hemorrhages due to the anticoagulant therapy. We conducted a study of the ICH localization in patients receiving anticoagulant therapy, as compared with spontaneous hypertensive ICH which is the most common type of HS. The share of primary spontaneous intracerebral hemorrhage accounts vast majority (88%) of the intracerebral hemorrhages [3, 20, 23]. Primary ICH include hematomas, which occur due to rupture of small blood vessels damaged by chronic hypertension or amyloid angiopathy.

In recent years, the antithrombotic-associated hemorrhagic stroke due to changes in blood coagulation is very actual problem. It is because of the growing number of patients who are appointed by the anticoagulant and antiplatelet therapy for prevention of the thromboembolism. Many studies have demonstrated the benefit of anticoagulation therapy compared with other methods of prevention of these complications. Thus, the effectiveness of anticoagulants for stroke prevention in patients with atrial fibrillation is much higher than the effectiveness of antiplatelet therapy (risk reduction by 64% and 22%, respectively) [14]. However, effectively reducing the risk of ischemic stroke associated with atrial fibrillation, warfarin anticoagulation increases the risk of major bleeding. Particularly, actual problem is the anticoagulation-associated hemorrhagic stroke. Using the vitamin K antagonist warfarin increases the HS risk estimated 5-10 times [22]. In study [21] investigated the HS risk factors in a group of 597 patients. It was found that warfarin is a risk factor for HS (OR = 4.63; CI 95 %: 3.17 – 6.76;  $p < 0.001$ ). Thus, using warfarin is a risk factor for both lobar (OR

= 5.23; CI 95%: 2.88 – 9.50;  $p < 0.001$ ), and nonlobar ICH (OR=4.24; CI 95%: 2.6–6.94;  $p < 0.001$ ). Using “new” anticoagulants (dabigatran and apixaban), has lower bleeding complication’s frequency compare warfarin [6, 8, 9, 15].

Predictors of hemorrhagic complications of anticoagulant therapy include previous ischemic stroke history, arterial hypertension, leukoaraiosis, the initiation period of anticoagulant therapy, excessive anticoagulation, elderly age, and the concomitant use of antiplatelet agents [11, 18]. In addition, carriers of some variants of *CYP2C9* gene and *VKORC1* gene have increased sensitivity to warfarin [18]. In study [1], conducted in stroke patients in Yakutia, has been shown that carriers of *CYP2C9* and *VKORC1* genotypes, determining the increased sensitivity to warfarin, accounted for 40% of the patients. Elderly age increases the risk of bleeding, particularly the risk of HS [4]. In our study, the mean age of the patients of the first group was higher (61.5 years) compare to the patients of the second group (59 years), but these differences were not significant ( $p = 0.305$ ).

According to our data, the anticoagulation administration in first group patients was expedient because of the fact that warfarin was administered to patients with operated heart valves and atrial fibrillation, and CHADS<sub>2</sub> scale score equal to 2 and >points estimated in 100% cases. On the other hand, the risk of bleeding complications according to HAS-BLED scale with 3 points and >was in 71.4%. This indicates that it was performed no control of modifiable hemorrhagic complication’s risk factors in the first group. Thus, according to the our data, 42.8% of patients did not conducted laboratory INR monitoring; in 21.4% had the concomitant use of warfarin and antiplatelet or non-specific anti-inflammatory drugs, in 14.3% cases had alcohol abuse. The INR monitoring absence is the anticoagulant-associated ICH risk factor [11].

Anticoagulant-associated intracerebral hemorrhage constitutes up to 20% of all cases of hemorrhagic stroke [10, 11, 25]. The vaICH’s small proportion in our study (2.8%), compared to other studies data, is probably due to the fact that number of patients constantly receiving anticoagulant therapy for prevention thromboembolism currently is not large in Yakutia. Another possible explanation for this phenomenon is that the INR rate has not reached the “therapeutic” level in the majority cases. Thus,

it is necessary to continue to examine the association between the receiving anticoagulant therapy and hemorrhagic intracranial complications rates and cardioembolic stroke rates. The proportion of patients receiving warfarin and have recommended INR levels is not quite high according to study [19]. Thus, according to the study [19] conducted in the United States population, among 5210 patients with atrial fibrillation treated with warfarin only 59% had an INR rate between from 2.0 to 3.0, while the share of those who have this rate above were 17%, below – 10%.

Currently, only few research data on the clinical features of the anticoagulation-associated ICH have been published. Compared with other types of HS, it is characterized by an increased risk of hematoma expansion, as well as a greater risk of the subsequent clinical deterioration and death [11, 12]. Data on the anticoagulation-associated ICH’s localization features are controversial. According to different authors, the anticoagulation due to anticoagulant therapy promotes stem, cerebellar, lobar, thalamic localization of hematomas [5, 17, 27]. According to study [15] conducted in a cohort of 18,113 patients with atrial fibrillation, there were 154 intracerebral hemorrhages for 2 years, including 46% of intracerebral hemorrhage, 45% of subdural hematoma and 8% of subarachnoid hemorrhage. In the study [5] the risk factors of cerebellar hemorrhage were analyzed. This hematoma localization was diagnosed in 38 cases (12%) in the group of consecutively admitted 327 patients. In 75% cases the cerebellar hematoma occurred in patients with INR rate > 2.5 ( $p < 0.0001$ ). Using warfarin with an INR rate > 2.5 and an increase in blood glucose levels at admission were independently associated with cerebellar hematoma localization, in comparison with the hematomas at other sites. In addition, ischemic stroke history ( $p = 0.002$ ) and heart disease ( $p = 0.018$ ) were more common in patients with cerebellar hematomas as compared with patients with hematomas at other sites. The authors concluded that warfarin therapy with an INR > 2.5 is associated with the cerebellar hematoma localization.

In study [27] was the group of 404 consecutively hospitalized ICH patients, including 69 patients with warfarin. Patients receiving warfarin had a large hematoma volume (median 23.9 vs. 14.2 mL,  $p = 0.046$ ). In the cases with an INR ratio > 3.0 the stem hematomas frequen-

cy was higher in compare to cases with INR ratio within the therapeutic range (6.1% vs. 24.0%;  $p = 0.005$ ). Thus, it was concluded that the patients with warfarin-associated ICH have tend to localize stem hematoma. 484 acute intracerebral hemorrhage cases admitted within 7 days after stroke onset analyzed in a study [17]. Among them, there were 116 patients receiving the antithrombotic therapy before onset, including 38 patients with warfarin, 70 patients – antiplatelet therapy, 8 patients – both drugs simultaneously. Antithrombotic therapy was an independent risk factor for cerebellar hemorrhage (OR = 3.66, 95% CI: 1.31 – 10.18), lobar hemorrhage (OR = 2.27, 95% CI: 1.12 – 4.57), and thalamic hemorrhage (OR = 2.20, 95% CI: 1.06 – 4.54) compared to putamenal hemorrhage.

In our study, we divided the ICH into three subgroups: supratentorial hematomas, which included the medial, lateral, lobar and mixed hematomas localized in the cerebral hemispheres; stem hematoma and bruising of the cerebellum. The vaICH localization frequency was compared with the most common HS form – spontaneous intracerebral hematomas. Most of primary spontaneous ICH localized in the basal ganglia and the thalamus (70%), 13% – in the stem, 10% – in different brain lobes, 9% – in the cerebellum [24]. In our study, the incidence of cerebellar hematoma was significantly higher in patients receiving warfarin compared to patients with hypertensive hematomas ( $p = 0.017$ ; OR = 15.39; 95% CI: 1.398 – 20.144). These findings are consistent with those in study [5], in which it was found that the warfarin-associated hematomas occur in cerebellum more often than compare to another ICH. In addition, this trend has also been established in patients with hypocoagulation as in our study.

Our study has limitations. In the studied group, there are a few cases of warfarin-associated ICH ( $n = 14$ ), what is probably due to the small proportion of this ICH in the HS structure in Yakutia. In addition, the study doesn’t include ICH associated with other anticoagulant therapy. Further studies on the anticoagulant-associated ICH are needed. Finding features of vaICH localization are interesting due to the fact that high frequency of cerebellar hematomas due to hypocoagulation is likely to be caused by poorly understood pathophysiological mechanisms of hemorrhagic stroke.

## CONCLUSION

Thus, our data suggest that intra-

cerebral hematomas caused by anticoagulant therapy, are characterized by a common site in the cerebellum, in comparison with hypertensive hematomas ( $p = 0.017$ ; OR = 15.39; 95% CI: 1.398 – 20.144). In the group of anticoagulant receiving patients, the hemorrhagic stroke occurred in cases with high risk of hemorrhagic complications of anticoagulant therapy according HAS-BLED scale with score 3 and >in 71.4% cases. Further study on the associations between the using of various types of antithrombotic therapy and hemorrhagic stroke risk is needed in Yakutia.

## REFERENCES

1. Chugunova S.A. Nikolaeva T.Ya. Danilova A.L. [et al.]. Polimorfizmy genov VKORC1 i CYP2C9, vliyayushhih na chuvstvitel'nost' k antikoagulyantnoj terapii, u bol'nyh s ostrymi narushenijami mozgovogo krovoobrashhenija [The gene polymorphism of CYP2C9 and VKORC1, affect the sensitivity to anticoagulant therapy in patients with acute ischemic stroke]. *Jakutskij medicinskij zhurnal* [Yakut Medical Journal], V. 2 (46), 2014, P. 64 – 67.
2. Skvortsova V.I. Krylov V.V. Gemoragicheskij insult: prakt. rukovodstvo [A hemorrhagic stroke: practical guide] ed. V. I. Skvortsova, V.V.Krylov, Moscow: "GEOTAR-Media", 2005, 155 p.
3. Toole J.F. Sosudistye zabolevaniya golovnogo mozga: ruk.dlja vrachej; per. s angl. [Cerebrovascular disease: practical guide; trans. from English]. ed. E.I.Gusev, A.B. Hecht. 6th ed, Moscow: "GEOTAR-Media", 2007, 608 p.
4. Age and the Risk of Warfarin Associated Hemorrhage: The Anticoagulation and Risk Factors in Atrial Fibrillation Study / M. C. Fang, A.S. Go, E.M. Hylek [et al.] // *J Am Geriatr Soc.* - 2006. - V. 54 (8). - P.1231-1236. /// Doi: 10.1111 / j.15325415.2006.00828.
5. Antithrombotic therapy and predilection for cerebellar hemorrhage / K. Toyoda, Y. Okada, S. Ibayashi [et al.] // *Cerebrovasc Dis.* - 2007. - V. 23 (2-3). - P. 109 – 116.
6. Apixaban versus warfarin in patients with atrial fibrillation / C.B. Granger, J.H. Alexander, J.J. McMurray [et al.] // *N Engl J Med.* - 2011. - V.365. - P.981 – 992.
7. Bleeding complications of oral anticoagulant treatment: An inception cohort, prospective collaborative study (ISCOAT) / G. Palareti, N. Leali, S. Coccheri [et al.] // *Lancet.* - 1996. - V. 348. - P.423 – 428.
8. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials / C.T. Ruff, R.P. Giugliano, E. Braunwald [et al.] // *Lancet.* - 2014. - V. 383. - P. 955 – 962.
9. Dabigatran versus warfarin in patients with atrial fibrillation / S. J. Connolly, M. D. Ezekowitz, S.Yusuf [et al.] // *N Engl J Med.* - 2009. - V. 361. - P.1139 – 1151.
10. Effect of warfarin on intracranial hemorrhage incidence and fatal outcomes / D. M. Witt, T. Delatea, E. M. Hylek [et al.] // *Thrombosis Research.* - 2013. - V.132. - P. 770 – 775.
11. Flaherty M.L. Anticoagulant-associated intracerebral hemorrhage / M.L. Flaherty // *Semin Neurol.* - 2010. - V. 30 (5). - P. 565– 572. /// doi: 10.1055 / s-0030-1268866.
12. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage / J. C. Hemphill, S. M. Greenberg, C.S. Anderson [et al.] // *Stroke.* - 2015. - V. 46. - P. 2032 – 2060.
13. Hart R.G. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas [Text] / R.G. Hart, S.B. Tonarelli, L.A. Pearce // *Stroke.* - 2005. - V. 36 (7). - P. 1588 – 1593.
14. Hart R.G. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation / R.G. Hart, L.A. Pearce, M.I. Aguilar // *Ann. Intern Med.* - 2007. - V.146 (12). - P.857 – 867.
15. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial / R.G. Hart, H.C. Diener, S. Yang [et al.] // *Stroke.* - 2012. - V. 43 (6). - P. 1511-1517. /// Doi: 10.1161 / STROKEAHA.112.650614.
16. Landefeld C.S. Major bleeding in outpatients treated with warfarin: Incidence and prediction by factors known at the start of outpatient therapy / C.S. Landefeld, L. Goldman // *Am J Med.* - 1989. - V.87. - P.144 – 152.
17. Location of acute brain hemorrhage in patients undergoing antithrombotic therapy / R. Itabashi, M. Yasaka, T. Kuwashiro [et al.] // *J Neurol Sci.* - 2009. - V. 280 (1-2). - P. 87 – 89. /// doi: 10.1016 / j.jns.2009.02.304.
18. Meschia J.F. Advances in genetics in 2010 / J.F. Meschia // *Stroke.* - 2011. - V.42. - P. 285 – 287.
19. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry / S.D. Pokorney, D.N. Simon, L. Thomas [et al.] // *Am Heart J.* - 2015. - V. 170 (1). - P.141– 148. // doi: 10.1016 / j.ahj.2015.03.017
20. Qureshi A. I. Spontaneous intracerebral hemorrhage [Text] / A. I. Qureshi, S. Tuhim S, J. P. Broderick [et al.] // *New England Journal of Medicine.* - 2001. - Vol. 344. - P. 1450 – 1460.
21. Risk factors for intracerebral hemorrhage differ according to hemorrhage location / S.R. Martini, M.L. Flaherty, W.M. Brown [et al.] // *Neurology.* - 2012. - V.79 (23). - P. 2275 – 2282. /// doi: 10.1212 / WNL.0b013e318276896f
22. Steiner T. Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions / T. Steiner, J. Rosand, M. Diringer // *Stroke.* - 2006. - V. 37 (1). - P.256 – 262.
23. Stroke: Pathophysiology, Diagnosis and Management / Ed. H. J. M. Barnett, J. P. Mohr, B. M. Stein, F. M. Yatsu. Second Edition. - New York, «Churchill Livingstone»: 1992. - 1270 p.
24. The Harvard Cooperative Stroke Registry: a prospective registry [Text] / J. P. Mohr [et al.] L. R. Caplan, J. W. Melski [et al.] // *Neurology.* - 1978. - Vol. 28. - P. 754.
25. The increasing incidence of anticoagulant-associated intracerebral hemorrhage [Text] / M.L. Flaherty, B. Kissela, D. Woo [et al.] // *Neurology.* - 2007. - V. 68 (2). - P. 116-121.
26. The risk for and severity of bleeding complications in elderly patients treated with warfarin [Text] / S.D. Fihn, C.M. Callahan, D.C. Martin [et al.] // *Ann Intern Med.* - 1996. - V.124. - P. 970 – 979.
27. Warfarin-associated intracerebral hemorrhage: volume, anticoagulation intensity and location [Text] / M. Ma, A. Meretoja, L. Churilov [et al.] // *J Neurol Sci.* - 2013. - V. 332 (1-2). - P.75 – 79. /// doi: 10.1016 / j.jns.2013.06.020.

## The authors:

1. Chugunova Sargylana A. – PhD, docent of Department of Neurology and Psychiatry, North-Eastern Federal university named after M.K. Ammosov, Yakutsk;

Address: 93 A, Petr Alekseev street, Yakutsk, 677005, Russia, Phone/fax: +7(4112) 43-27-40

E-mail: [sargyc@mail.ru](mailto:sargyc@mail.ru);

2. Nikolayeva Tatiana Ya. – MD, professor, Head of Department of Neurology and Psychiatry, North-Eastern Federal University named after M.K. Ammosov, Yakutsk

Address: 36, Kulakovskiy street,  
Yakutsk, 677007, Russia, Phone/fax:  
+7(4112) 49-67-00

E-mail: [tyanic@mail.ru](mailto:tyanic@mail.ru);

3. Egorova Tuiyara S. -

neurologist, ordinator of Department of  
internal medicine and general practice  
(family medicine), North-Eastern Federal  
University named after M.K. Ammosov,  
Yakutsk, Address: 36, Kulakovskiy street,

Yakutsk, 677007, Russia, Phone/fax:  
+7(4112) 49-67-00

E-mail: [labyrinth\\_of\\_december@mail.ru](mailto:labyrinth_of_december@mail.ru).

D.V. Kroshka, A.A. Dolgalev, E.A. Bragin

## TIME AND GRAPHIC PARAMETERS OF MASTICATORY MOVEMENTS OF SUBJECTS WITH TEMPOROMANDIBULAR JOINT AND MASTICATORY MUSCLES DYSFUNCTION

### ABSTRACT

Chewing is the one of the most important functions of the human stomatognathic system. We have done the research of the volunteers with in the period from 2014 till 2015 years with an aim of receiving information about the parameters of chewing with signs of pathological changes in the temporomandibular joint (TMJ), which are characterized for patients with TMJ and masticatory muscles disfunction syndrome. Registration of the chewing moves on the habitual and non-habitual sides of chewing was made by using electronic gnathograph Jaw tracker 3D (Bioresearch, USA) and software BioPAK 7.2. by the standard method as recommended by the equipment manufacturer. As a result of this work was identified time and graphical parameters of chewing moves, which are characterized for subjects with pathological changes in the TMJ. Comparative analysis of the time parameters of chewing moves on the habitual and non-habitual sides of chewing with using Wilcoxon signed rank criterions allowed to determine: the absence of significant differences in the average duration of the opening mouth phase ( $Z = -1,6$ ;  $p = 0,11$ ), an average duration of the occlusion phase of dentition ( $Z = -1,5$ ;  $p = 0,139$ ), average duration of the closing mouth phase ( $Z = -1,4$ ;  $p = 0,173$ ), average duration of the one masticatory cycle ( $Z = -1,7$ ;  $p = 0,086$ ), variability of the duration of the opening mouth phase ( $Z = -1,4$ ;  $p = 0,155$ ), variability of the average duration of the occlusion phase of dentition ( $Z = -0,9$ ;  $p = 0,342$ ), variability of the duration of the closing mouth phase ( $Z = -1,4$ ;  $p = 0,155$ ), variability of the duration of the one masticatory cycle ( $Z = -0,5$ ;  $p = 0,635$ ). When the patient chewing on the habitual and non-habitual sides of chewing, there were found the absence of significant differences between variability of the duration of the opening mouth phase and the variability of the duration of the closing mouth phase ( $Z = -1,4$ ;  $p = 0,155$  for the habitual side,  $Z = -1,8$ ;  $p = 0,086$  for non-habitual side), the variability of the duration of the closing mouth phase and variability of the duration of the occlusion phase of dentition ( $Z = -0,3$ ;  $p = 0,767$  for the habitual side,  $Z = -1$ ;  $p = 0,314$  for non-habitual side).

**Keywords:** temporomandibular joint disfunction syndrome, masticacigraphy, electronic gnathography, masticatory cycle.

### INTRODUCTION

The role of chewing in the process of digestion determines the value of this function for the existence of the body [1]. The researching of this function received considerable attention of the foreign researchers [5, 10]. There are some different ways of chewing researching. They are: the analysis of parameters of moves of the lower jaw [2], the analysis of the bio potentials of chewing muscles [4], chewing tests, connected with the measuring of the chewed particles of food [11].

In many sources the great attention devoted to the analysis of parameters of moves of the lower jaw in the process of chewing [6, 7, 8]. According to the opinion of the specialists using of such method of researching allows to receive information about the functional condition of the chewing muscles, occlusion and the articulation of the dentition, the TMJ [12].

The analysis of the parameters of chewing of the patients with temporomandibular joint and the chewing

muscles dysfunction syndrome (TMD syndrome) represents a great science interest. This occurs because the information, received in a result of using this method of searching, can allow to detect the level of severity formed pathological and functional changes in the masticatory organ, and also determine the degree of involvement of the main elements of system in a disease pathogenesis [9].

An aim of our researching was receiving information about the parameters of chewing, which is characterized to the patients with TMD.

#### *Objectives of the study:*

1. To determine the time and graphic parameters of the masticatory movements of the subjects with TMD.
2. To determine the influence of the side of chewing to the time and graphic parameters of chewing moves of subjects with TMD.

### MATERIALS AND METHODS

In the period from 2014 to 2015 was done the survey of 52 volunteers aged from 18 to 46 years old. The criteria for participation in the researching were:

age from 18 years old, a wish to participate in a research and informed consent to participate in it. The criteria for non-participation in the researching was: age till 18 years old, the presence of large extent defects on the dentition or total loss of teeth of a volunteer at the treatment time, bone defects of the upper and / or lower jaw, exacerbation of existing chronic somatic diseases, mental or other disorder determining the incapacity of a volunteer, finding a volunteer at the time of treatment in the active phase of orthodontic treatment, treatment due to the presence of tumors, post-myocardial infarction or cerebral stroke in the history of treatment in the previous half of year, carrying out surgery on the TMJ in the anamnesis, unwillingness of a volunteer to take part in the researching and the absence of informed consent to participate in the researching.

On the basis of the survey (by the "Hamburg" reducing scheme) and collection information to the anamnesis, 45 volunteers were included in the researching. Among included people were