eSLEEP EUROPE
October 4-6, 2023 | Virtual Congress

The association of polymorphisms of PER3 and CLOCK genes with etiology and functional outcomes in ischemic stroke (preliminary results)

L Korostovtseva[1], S Kolomeichuk[1,2], S Osipenko[1,3], U Nikishkina[1,3], M Bochkarev[1], V Zheleznyakov[1], A Vasilieva[1], M Golovkova-Kucheryavaia, [1] V Amelina[1,4], Y Sviryaev[1]

[1]Almazov National Medical Research Centre, St Petersburg; [2]Karelian Research Centre Russian Academy of Sciences, Petrozavodsk; [3]Pavlov University, St Petersburg; [4]Herzen State Pedagogical University, St Petersburg, Russian Federation

INTRODUCTION

Background. Ischemic stroke is one of the leading causes of mortality, morbidity and disability worldwide (Fig. 1, 2). There is evidence of the potential role of circadian modulation of neuroplasticity mechanisms and post-stroke neurological recovery (Fig. 3), however, the data are limited.

Objective. We assessed the ischemic stroke etiology subtypes, severity and functional outcomes (at discharge) depending on the polymorphic variants of circadian genes PER3 rs5787598 and CLOCK rs1801260.

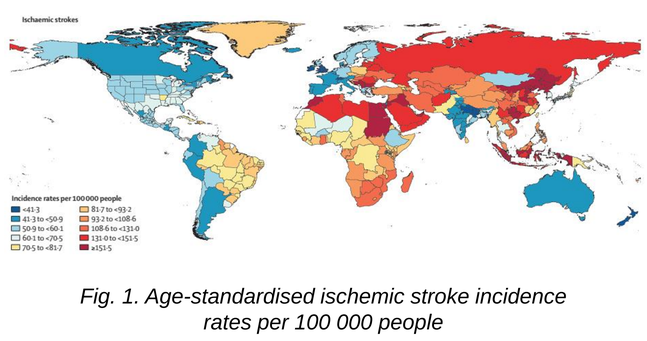


Fig. 1. Age-standardised ischemic stroke incidence rates per 100 000 people

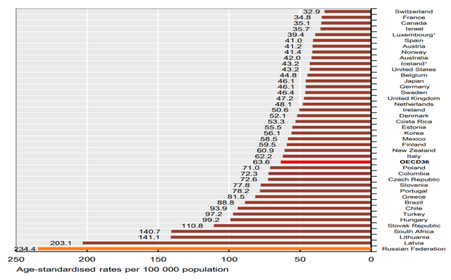


Fig. 2. Age-standardised mortality rates in stroke

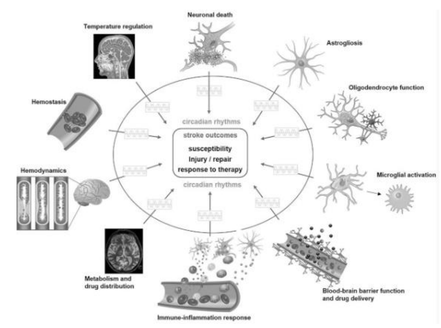
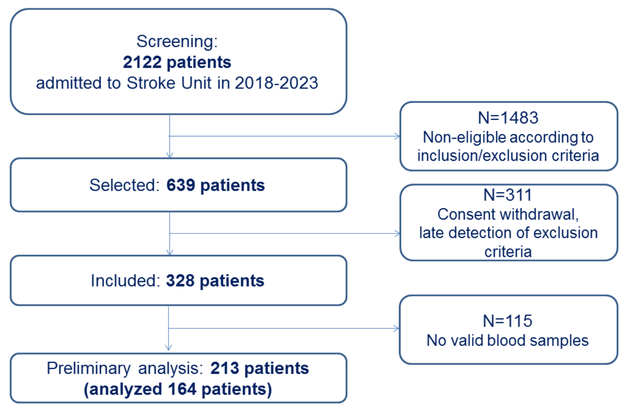


Fig. 3. Potential role of circadian system in stroke

METHODS

- A prospective, observational, cohort study.

Inclusion criteria	Exclusion criteria
• admission within 24 h after symptom onset • age 18-805years • ischemic stroke (MRI or CT scans) • signed informed consent	• loss of consciousness • primary hemorrhagic stroke • need for intubation or O_2 supply >2 l/min • unstable or life threatening condition • congestive heart failure (EF≤45% or III-IV NYHA class) • known psychiatric diseases • known progressive neurological diseases • concomitant benzodiazepine medication • drug or alcohol abuse • pregnancy • disability to participate in the study • non-valid sleep study • CPAP treatment before stroke or initiation of CPAP treatment after stroke onset



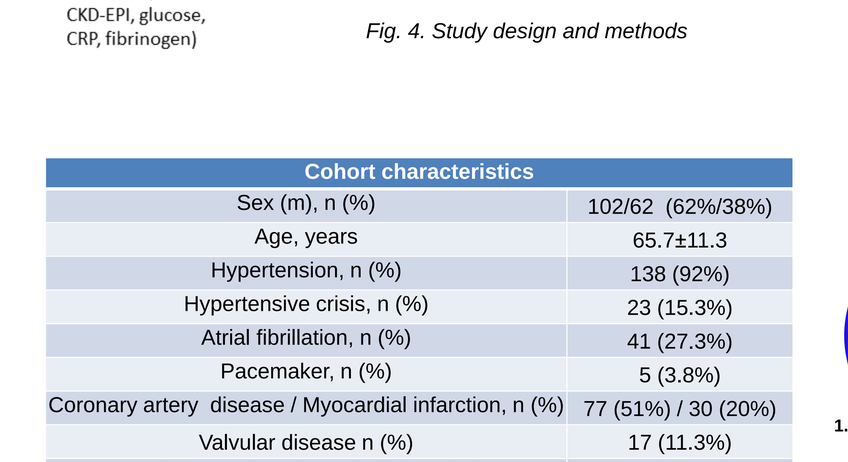


Fig. 4. Study design and methods

Statistical analysis: Kolmogorov-Smirnov test; frequency analysis (Chi-square test and Fisher's exact (independent samples), McNemar test (related samples), comparison of continuous variables (Mann-Whitney for 2 groups, Kruskall-Wallis for >2 groups), ANOVA or Wilcoxon test (for the related samples), Correlation Spearman analysis, Kaplan-Mayer analysis, Cox-regression analysis, the ROC-curve analysis. IBM SPSS Statistics v.26.0

RESULTS

Cohort characteristics	
Sex (m), n (%)	102/62 (62%/38%)
Age, years	65.7±11.3
Hypertension, n (%)	138 (92%)
Hypertensive crisis, n (%)	23 (15.3%)
Atrial fibrillation, n (%)	41 (27.3%)
Pacemaker, n (%)	5 (3.8%)
Coronary artery disease / Myocardial infarction, n (%)	77 (51%) / 30 (20%)
Valvular disease n (%)	17 (11.3%)
Pulmonary thromboembolism, n (%)	2 (1.3%)
Other CVD (myxoma, patent foramen ovale)	6 (4%)
Diabetes mellitus, n (%)	36 (24%)
Obesity, n (%)	40 (26.7%)
Dyslipidemia, n (%)	83 (55.3%)
Chronic obstructive pulmonary disease, n (%)	13 (8.7%)
Previous stroke or TIA, n (%)	46 (30.7%)
Trombolytic therapy, n (%)	22 (13.4%)
Thrombaspiration/Thromextraction, n (%)	37 (22.6%)

C homozygotes CLOCK had higher rate of coronary artery disease: 13 (81%) in CC versus 61 (47%) in TT+TC (χ^2 =6,57, p=0,015). There was no difference between PER3 genotypes.

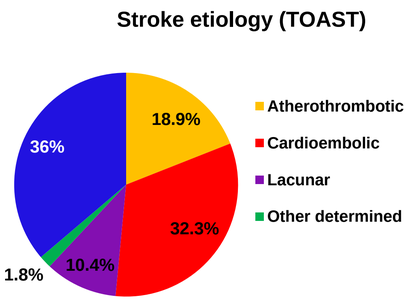
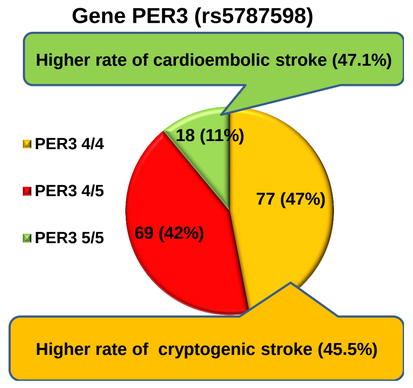


Fig. 5. Stroke subtypes by TOAST classification



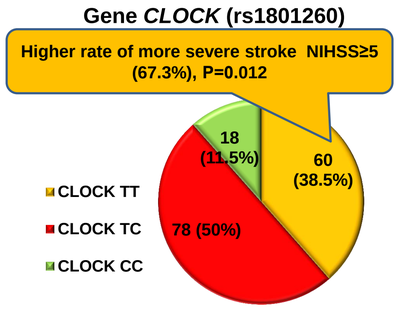


Fig. 6. Distribution of clock genes genotypes (corresponds to the rates in Central and Eastern Europe)

T allele homozygotes of CLOCK rs1801260 gene showed higher neurologic deficit at admission based on NIHSS score: TT 6 (0;31), TC 4 (0; 25); CC 4.5 (1;19) score (p=0.034).

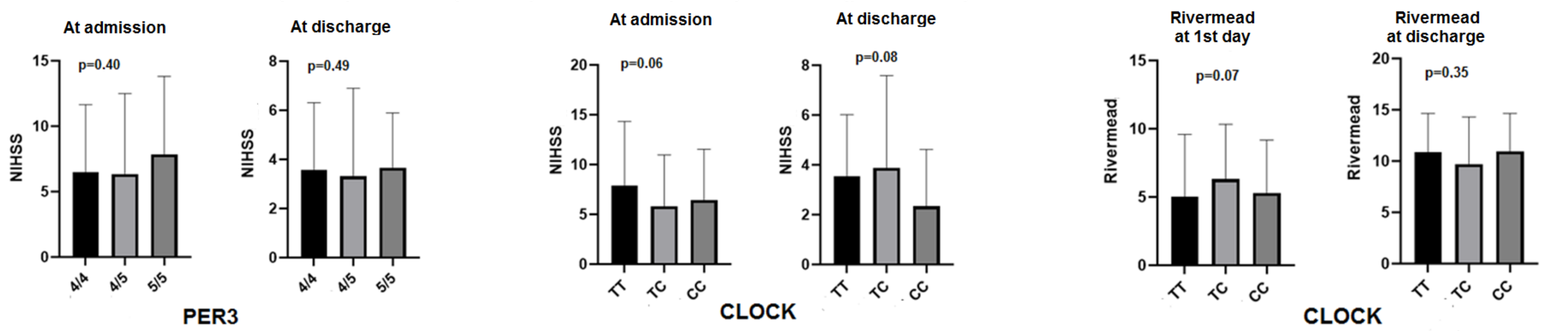


Fig. 7. Association between PER3 and CLOCK genes polymorphic variants and stroke functional outcomes

The NIHSS at discharge and functional outcomes at discharge did not differ in the carriers of three different CLOCK rs1801260 gene alleles (TT, TC and CC). However, CC homozygotes showed lower NIHSS at discharge compared to T allele carriers (TT+TC) (p=0.027). There were no differences in stroke severity or functional outcomes at discharge between patients with different PER3 genotypes (p>0.05 for all measures).

CONCLUSION

- PER3 rs5787598 polymorphisms are associated with the pathogenic ischemic stroke subtypes: 4/4 homozygotes have higher rate of cryptogenic stroke, while 6/6 homozygotes have higher rate of cardioembolic stroke. There is no such association for the genotypes of CLOCK rs1801260.
- C allele of CLOCK rs1801260 gene is associated with the more favourable functional outcomes (NIHSS at discharge), and might have neuroprotective effect. There is no such association for PER 3 variants.
- In general, circadian genes might modulate the severity of stroke, however, their role for post-stroke recovery needs further investigation.

REFERENCES

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021 Oct;20(10):795-820. doi: 10.1016/S1474-4422(21)00252-0
2. Gottlieb E, Landau E, Baxter H, Werden E, Howard ME, Brodtmann A. The bidirectional impact of sleep and circadian rhythm dysfunction in human ischaemic stroke: A systematic review. Sleep Med Rev. 2019 Jun;45:54-69. doi: 10.1016/j.smrv.2019.03.003
3. Lo EH, Albers GW, Dichgans M et al. Circadian Biology and Stroke. Stroke. 2021 Jun;52(6):2180-2190. doi: 10.1161/STROKEAHA.120.031742

ACKNOWLEDGEMENTS AND CONTACTS

The work is supported by the grant of the Russian Scientific Foundation #21–75–10173.

Contacts: lyudmila_korosto@mail.ru, korostovtseva_ls@almazovcentre.ru (Dr. Lyudmila Korostovtseva)

https://esleepeurope.eu/