Original Article

Pathological Yawning in Patients with Acute Middle Cerebral Artery Infarction: Prognostic Significance and Association with the Infarct Location

Aksoy Gündoğdu et al. Pathological Yawning in Middle Cerebral Artery Stroke

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The study has previously been presented as an e-poster at the 50. Turkish National Neurology Congress held between 21-27 November 2014 in Antalya and as an oral presentation at the II. Hippocrates Congress held between 28-30 June 2019 in İstanbul.

Background: Pathological yawning (PY) is a compulsive, frequent, repetetive yawning triggered by a specific reason besides fatigue or boredom. It may be related to iatrogenic, neurologic, psychiatric, gastrointestinal or metabolic disorders. PY could also be seen in the course of ischemic stroke.
Aims: We aimed to determine whether PY is a prognostic marker of middle cerebral artery (MCA) stroke and evaluate its relationship with the infarct location.
Study Design: Cross-sectional study
Methods: We examined 161 patients with acute middle cerebral artery stroke who were consecutively admitted to emergency department. Demographic information, stroke risk factors, stroke type according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, blood oxygen saturation, body temperature, blood pressure, heart rate, glucose levels, daytime of stroke onset, National Institutes of Health Stroke Scale (NIHSS, at admission and 24 h), modified Rankin Scale (mRS, at 3 m) and infarct locations were documented. PY was defined as ≥3 yawns/15 min. All patients were observed for 6 hours to detect PY. NIHSS>10 was determined as severe stroke. The correlation between the presence of PY and stroke severity, infarct location and the short and long term outcomes of the patients were evaluated.
Results: Sixty-nine (42.9%) patients had PY and 112 (69.6%) patients had cortical infarcts. Insular and opercular infarcts were detected in 65 (40.4%) and 54 (33.5%) patients respectively. PY was more frequently observed in patients with cortical, insular and opercular infarcts ($p<0,05$). PY was related to higher NIHSS scores. Patients with severe stroke (NIHSS≥10) presented with more PY than mild to moderate strokes ($p<0.05$).
Conclusion: PY in MCA stroke is associated with stroke severity, presence of cortical involvement, insular and opercular infarcts. However no association was found regarding long term outcome and mortality.
Keywords: Pathological yawning, middle cerebral artery infarction, anterior cerebral circulation, infarct location, prognosis

Stroke is a common neurological disease which is the major cause of disability and mortality in both genders and has an accelerating frequency due to the increase in life expectancy in adult age group. (1,2) A variety of factors influence the outcome of stroke including age, gender, stroke severity, early rehabilitation, stroke etiology, infarct location, rehabilitation, cognitive decline, aphasia, depression and comorbid diseases. (3) Being able to predict the

prognosis of stroke makes length of stay in the hospital or long-term costs manageable and may reduce the economic burden of stroke. Studies providing and comparing prognosis, survival and recurrence data in stroke allows clinicians to identify high-risk patients for stroke recurrence and stroke-related death, researchers to plan clinical trials to develop new strategies, and provide public health policy-makers with a clearer picture of the social impact of ischemic stroke.

Yawning is a very common stereotyped motor behavior which is physiologically observed in humans, other mammals and numerous animal species. (4,5) Healthy humans may yawn 0-28/day and this frequency of physiological yawning may vary according to the age, circadian rhythm, arousal, decreased attention, boredom, fatigue, hunger, satiety, before and after sleep episodes. (6,7) Former studies revealed that, paraventricular nucleus of the hypothalamus, hypocampus, reticular activating system in the brainstem, cervical spinal cord (phrenic nerve C1–4), intercostal muscles, oxytocin, acetylcholine, dopamine, glutamate, serotonin, GABA, adrenergics, ACTH, and αMSH are involved in the occurrence and the mediation of yawning. (6-8)

Cortical involvement of yawning has been defined by recent studies but not fully demonstrated yet. (5,7) Frequent, repetetive and compulsive yawning episodes are termed as excessive, abnormal or pathological. Besides the physiological factors such as fatigue, boredom or contagion, pathological yawning (PY) is found to be triggered by various cases, iatrogenic causes, and several metabolic, gastrointestinal, psychiatric, or neurological diseases. (9-12) PY has been reported in numerous neurological conditions including parkinsonism, Parkinson's disease, progressive supranuclear palsy, Huntington disease, myasthenia gravis, bulbar amyotrophic lateral sclerosis, multiple sclerosis, neuromyelitis optica spectrum disorders, migraine aura, vasovagal syncope, narcolepsy, brain tumor, encephalitis, intracranial hypertension, stroke, Chiari malformation type I, epilepsy, stress and anxiety disorders. (6,9-25)

Although PY in brainstem and anterior circulation (AC) ischemic stroke has been previously reported in the literature; to date, the exact mechanism of cortical network remains to be established by functional neuroimaging studies. Some recent studies concluded that ischemic lesions of the posterior insula and caudate nucleus induces PY. Still there is no sufficient clinical data in humans regarding PY in AC stroke and no data regarding the frequency or prognostic effect of PY on long-term prognosis and mortality rates of middle cerebral artery (MCA) strokes.

We hypothesised that PY may be an practical and easy detectable predictive phenomenon of outcome after acute ischemic stroke. In this study, we aimed to determine whether PY is a prognostic marker of MCA stroke and evaluate its relationship with the patient demographics, clinical parameters infarct location and outcome of the patients.

Material and Methods

In this observational, cross-sectional study, we assessed 161 acute middle cerebral artery stroke patients in one-year period who were consecutively admitted to the Emergency Department and referred to our Neurology Stroke Unit within 24 hours of stroke onset. All of the patients were over 18 years old, and only acute ischemic stroke patients included to the study. Exclusion criteria were seizures, hypoglycemia, hypoxia, fever (>38°C), usage of anesthetic agents and acute or history of posterior circulation stroke.

Demographic information, stroke risk factors, stroke type, daytime of stroke, blood oxygen saturation, body temperature, blood pressure, heart rate, glucose, receiving intravenous thrombolytic therapy and neurological and functional outcome and mortality status of the patients were documented. Stroke risk factors including hypertension, hyperlipidemia, atrial fibrillation (AF), patent foramen ovale (PFO), diabetes mellitus, angina pectoris, coronary artery disease, peripheral artery disease, metabolic syndrome and tobacco use were registered. A previous history of stroke or transient ischemic attacks (TIA) were recorded. The usage of the statins, antihypertensive (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium-channel blockers), anticoagulant, antiplatelet, antiparkinsonian, antidepressant drugs and the patients received intravenous trombolytic therapy were noted. Routine haematological and biochemical peripheral blood analyses were obtained on admission. Daytime of stroke attacks between 00:00 and 06:00 were recorded as "increased sleepiness". Clinical severity at baseline and 24 hours after symptom onset were assessed prospectively by using the NIHSS. The patients with NIHSS≥10 were considered to have severe neurological deficits. The mRS was used to assess neurological and functional outcome at 24 hours and 3 months after stroke. The prognosis was stratified according to the mRS at 3 months: very favorable outcome- score: 0-1; favorable outcome- score: 0-2; unfavorable outcome- score: 3-6. Cranial Computed tomography (CT) and Magnetic Resonance Imaging (MRI) were performed in all patients. Hemispheric side, cortical, subcortical, frontal, temporal, parietal, insular and opercular infarcts were recorded. All of the patients underwent carotid doppler ultrasonography, 12- lead electrocardiography, transthoracic echocardiography, transesophageal echocardiography, 24-hour holter monitoring, CT/MR angiography and DSA whenever indicated. Stroke type was determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial criteria. (26)

All of the patients were observed by the neurologists for 6 hours after admission for the presence of PY. According to the criteria for abnormal yawning of Singer et al. (24), the counts of >3 yawns/15 minutes was determined as the cut-off number for PY. All findings of the patients are compared between two groups as follows: Patients with PY and without PY.

This study was approved by the local ethics committee. Statistical analysis of our study was performed by using SPSS program (Statistical package for social sciences, 24.0 windows; SPSS Inc., Chicago, IL, USA). A post-hoc power analysis of this study was performed on GPower program considering an alpha error of 0.05, a medium effect size (0.3), the power of our study was calculated as 85% and a total sample size of 160 patients was found to be sufficient. Student's t-test was used for the comparison of two independent groups with normally distributed data and Mann Whitney U was used to test for the abnormally distributed data. Categorical data were presented as frequency of occurence and were analyzed by Pearson's chi-square and two ratio tests. Continuous data presented as means ± Standard deviation. A value of $p<0.05$ was accepted as the level of significance.

Results

Among 161 patients, 81 patients were male (51.3%) and 80 patients were female (49.7%). The mean age of the patients was 67.3±10.9 (range, 18 to 85) years and 69 (42.9%) of 161 patients revealed PY. Table 1 gives the demographics and clinical characteristics of the patients. No significant relationship were found regarding age, sex, increased sleepiness, glucose levels, leukocyte count (p=0.722, 0.82, 0.516, 0.715 and 0.401, respectively) and vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, valvular heart disease, AF, metabolic syndrome, tobacco use, history of previous stroke) except from the history of previous TIA between the patients with PY and those without PY (p=0.299, 0.504, 0.184, 0.265, 0.665, 0.857, 0.844, 0.061, 0.890 and 0.908, respectively).

The usage of the statins, antihypertensive (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium-channel blockers), anticoagulant, antiplatelet, antiparkinsonian, antidepressant drugs and the patients received intravenous trombolytic therapy were recorded. Only one patient was using dopamin agonist medication for Parkinson disease. However, no PY was observed in this patient. For, excluding antiparkinsonian drugs, there was no significant relationship found between the usage of these drugs and PY (p=0.648, 0.776, 0.147, 0.111, 0.773, 0.738, 0.427 and 0.642, respectively).

Patients with PY presented with a higher NIHSS score compared with patients without PY (p=0.019). Patients with severe stroke (NIHSS≥10) presented with more PY than mild to moderate stroke (NIHSS<10) (p=0.004). PY is related to higher baseline NIHSS scores representing clinically severe patients (NIHSS≥10). A total of 32 (19.8%) patients died during follow-up period. The clinical outcome (very favourable, favourable and unfavourable) and mortality rates of the patients showed no significant relationship with the occurrence of PY. Clinical severity and outcome of the patients were summarized in Table 2.

Hemispheric side of the infarcts or subcortical infarcts revealed no significant relationship with the PY (p=0.237 and 0.772). However, PY was observed more frequently in patients with cortical, insular and opercular infarcts (p=0.015, 0.046 and 0.008, respectively). Table 3 gives the neuroimaging findings (Cerebral MRI and CT) of the patients.

Discussion

This observational study investigates whether PY affects the clinical outcome and mortality of the patients with acute MCA stroke. We hypothesised that certain infarct locations in the AC system may facilitate PY and the presence of PY may be considered as a prognostic factor of MCA strokes. Among our cohort of 161 patients, PY was observed in 69 (42.9%) patients and likely to occur in patients with higher NIHSS scores. The equal distribution of gender is a strong aspect of our study. We found PY to be related with cortical involvement, insular and opercular infarcts. Our study revealed that, PY is a common phenomenon among patients with MCA stroke and seems to be associated with stroke severity. However, no relationship was found regarding its effect on long term outcome or mortality rates of the patients.

The evidence of former case reports and studies suggests that PY occurs frequently in the course of many neurological diseases. (6,9-25) A limited number studies have been reported PY in acute ischemic stroke. (9,23,24) Bauer et al. stated that, the patients with locked-in syndrome can elicit yawning movements involuntarily despite the total paralysis of the volunteer bulbar muscles. (27) Cattaneo et al. published a case report of two patients with brainstem stroke who were presented with PY. (9)

To date, only 2 studies have provided data concerning PY in AC stroke. The pivot study of Singer et al. revealed that PY can be a sign of AC lesions. They observed PY in 7 patients with AC strokes in MCA territory and hypothesized that PY occurs due to supratentorial lesions releasing the hypothalamic PVN from neocortical control mechanisms and increasing activity of hippocampus and periamygdalar regions. (24) A more recent study of Krestel et al. investigated PY in 10 patients with acute AC stroke. Infarct regions and volumes of the patients were evaluated

using MRI lesion maps, diffusion weighted (DWI) and apparent diffusion coefficient (ADC) images. Intensity of the infarcts were found to be correlated with the period of abnormal yawning They proposed that insular and caudate nucleus infarcts are responsible for PY. (25)

The use of dopaminergic D2 agonists, imipramine, selective serotonin reuptake inhibitor (SSRI) agents, morphine withdrawal, valproate overdose and oestrogen substitution may induce PY. Anesthetic agents are leading drowsiness and loss of consciousness. (28) None of our patients were using these agents. Intravenous thrombolytic therapy has a positive impact on prognosis. However, we found no significant relationship between the patients who received thrombolytic therapy and the occurrence of PY.

It has been noted that PY is primarily triggered by low vigilance. However, PY can be seen even there is no change in consciousness level during stroke attacks. This may be as a result of the increased intracranial pressure secondary to stroke or the damage of the particular cortico-subcortical circuits and the disruption of the connections between the reticular formation that regulates alertness in the brain stem. As the clinical severity of stroke increases, PY is observed more frequently. (5-7) Krestel et al. found a significant correlation between the period of PY and stroke severity. (25) Factors such as low vigilance, increased brain temperature, intracranial hypertension, deterioration of homeostasis and damage of more neuroanatomical structures including cortico-subcortical circuits may be the possible causes of PY. (5-7)

This study has several limitations. First of all, during observation period we could not video-record the patients. Thus, the duration or the distinctive features of yawning attacks could not be measured quantitatively. Moreover, despite the cut-off yawning count for PY (≥3/15 min) was determined after two previous studies (24,25), physiological yawning may also occur at the same frequency. And finally sleepiness scale tests could not be performed to the aphasic or clinically severe patients. This situation has led us insufficient data regarding increased sleepiness or drowsiness of the patients.

Further studies measuring the neurotransmitter and neurohormone levels released during PY attacks in acute stroke or using improved neuroradiological tools such as tractography are required to discover the exact pathophysiological mechanism and neural pathways responsible for PY. The causative factors that triggers PY in acute stroke, involving cortical brain areas and clinical significance of PY still remains to be clarified.

To the best of our knowledge, the present study is the first one analyzing the clinical and radiologic findings of PY in acute MCA stroke with larger human cohort including findings regarding long-term outcome and mortality rates of the patients with PY. Consistent with the existing evidence, our study revealed that cortical involvement, opercular and insular infarcts trigger PY. Supporting statistically, we established the clinical significance of PY and could evaluate its prognostic role in MCA stroke. Notwithstanding its connection with the clinical severity, PY reveals no significant predictive value for clinical outcome of patients with MCA stroke.

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Table 1. Demographics and clinical characteristics of the patients

	Patients with PY (n=69)	Patients without PY (n=92)	*P* value
Age, mean (SD), y	68 (62; 77.5)	70 (61.25; 75)	.722
Sex (male), n (%)	34 (49.3%)	47 (51.1%)	.822
Body mass index (BMI)	26.6 (24.3;31.85)	27.3 (24.37;31.17)	.061
Glucose at baseline, mean (SD), (mg/dL)	126.8 (103.7;168.5)	123.5 (106.6;159.9)	.714
Leukocytes at baseline (1/mm^3)	8270 (6960;10120)	8300 (6445;10330)	.807
Sleepiness	9 (13%)	9 (9.8%)	.516
Time symptom to emergency room (dk)	135 (68.5;232)	145 (88.5;286)	.300
Risk Factors, n (%)			
Tobacco use	30 (43.5%)	39 (42.4%)	.890
Metabolic syndrome	38 (55.1%)	37 (40.2%)	.061
Diabetes mellitus	26 (37.7%)	30 (32.6%)	.504
Hypertension	51 (73.9%)	61 (66.3%)	.299
Hyperlipidemia	10 (14.5%)	21 (22.8%)	.184
Coronary artery disease	26 (37.7%)	26 (29.3%)	.265
Heart failure	17 (24.6%)	20 (21.7%)	.665
Atrial fibrillation	22 (31.9%)	28 (30.4%)	.844
Previous transcient ischemic attack (TIA)	15 (21.7%)	8 (8.7%)	.019

Table 2. Clinical severity and outcome of the patients.

	Patients with PY (n=69)	Patients without PY (n=92)	*P* value
Clinical Severity			
Baseline NIHSS, median (interquartile range) NIHSS at 24h.	14 (9;19) 10	9.5 (6;16) 8	**.019** .141
Severe stroke (NIHSS≥10), n (%)	46 (66.7%)	40 (43.5%)	**.004**
Outcome, n (%) Very favorable outcome at 3 m. (mRS:0-1)	31 (44.9%)	47 (51.1%)	.439
Favorable outcome at 3 m. (mRS:0-2)	35 (50.7%)	52 (56.5%)	.465
Unfavorable outcome at 3 m. (mRS:3-6)	34 (49.3%)	40 (43.5%)	.465
Mortality at 3 m.	16 (23.2%)	16 (17.4%)	.362
Recurrent stroke	7 (10.1%)	5 (5.4%)	.260

Table 3. Neuroimaging findings of the patients

	Patients with PY (n=69)	**Patients without PY (n=92)**	***P* value**
Infarct location, n (%)			
Hemispheric side (right)	38 (55.1%)	42 (45.7%)	.237
Subcortical	45 (65.2%)	62 (67.4%)	.772
Cortical	55 (79.7%)	57 (61.9%)	**.015**
Frontal	30 (43.4%)	35 (38%)	.487
Parietal	43 (62.3%)	51 (55.4%)	.381
Temporal	18 (26%)	22 (23.9%)	.752
Insular	34 (52.3%)	31 (47.7%)	**.046**
Opercular	31 (57.4%)	23 (42.6%)	**.008**
Old infarction	28 (40.6%)	30 (32.6%)	.297