RESEARCH ARTICLE

Characteristics of first ever ischemic stroke in patients with early and late poststroke epilepsy

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Background: Stroke and epilepsy are common neurological disorders. Post-stroke epilepsy (PSE) was classified early and late if seizures occurring within or after 1 week after stroke respectively. Poststroke epilepsy, could be as a complication or presenting symptoms of stroke.

Method: One hundred and twenty-two patients [66 men (54.1%) and 56 women (45.9%)] with first-ever acute ischemic stroke and developing seizures after the stroke insult were enrolled in this study. NIH Stroke Scale (NIHSS) and modified Rankin's Scale (mRS) were used to evaluate stroke severity and functional outcome respectively. EEG and radiological data, including ASPECT score, Duplex ultrasound and echocardiography were used to assess the patient.

Results: Most of the cases of stroke developed PSE after 7 days (late PSE) (76.2%) in contrast to Early PSE was found in 23.8% and about one half of the patients experienced focal seizures. There significant association between PSE and functional stroke outcome, stroke severity, presence of MCA territory infarction, cortical involvement and ASPECT score. There is no significant relationship between early and late PSE as regard smoking, hypertension, IHD, seizure semiology, etiological type stroke on of TOAST classification, presence of hemorrhagic transformation

Conclusion: Early PSE is significantly associated with severe stroke measured by NIHSS score, involvement of middle cerebral artery (MCA) territory, Alberta Stroke Program Early CT (ASPECT) score and severe functional outcome measured by mRS. While late onset epilepsy associated with atrial fibrillation (AF) and cortical involvement.

Key Words: *Post-ischemic stroke seizure; Early poststroke epilepsy; Late poststroke epilepsy; Epilepsy; Ischemic stroke*

Stroke, accounts for up to 11% of epileptic patients in western countries. Epilepsy is a common neurological disorders and characterized by an excessive discharge of certain neurons in the nervous system [1]. According to an epidemiological survey, about 0.5% of the human population is suffering from epilepsy with increased risk of death compared to the standard population [2,3]. Recently International League Against Epilepsy (ILAE) classified epilepsy according to the onset as focal with or without impaired awareness and generalized either motor or non-motor [4]. The terms ''post stroke seizures'' was defined as ''single or multiple convulsive episode/s (fit/s) after stroke and thought to be related to reversible or irreversible cerebral damage due to stroke regardless of time of onset following the stroke'' and post-stroke epilepsy as ''recurrent seizures that met the criteria for diagnosis of epilepsy [5]. The risk of PSE after stroke varies between 2% and 15% [6] and it is more common after hemorrhagic stroke than after ischemic one, except for the total anterior circulation infarctions, which may carry a higher risk of PSE than hemorrhages [7-12]. PSE is classified according to their time of onset to early and late PSE when seizures occurring within or after one week after stroke respectively [13].

Metabolic changes that occurring in the penumbral areas in the acute post-stroke phase may explain the pathophysiology of PSE namely a reduction in γ-aminobutyric acid (GABA) and an increase in glutamate (Glu) will lead to excitotoxicity, disturbance of electrolyte balance and destruction of phospholipid membranes [14-17]. In addition, the accumulation of intracellular calcium and sodium results in depolarization of the transmembrane potential which can lower the seizure threshold [8].

It was documented that atrial fibrillation (AF), lesion size, cortical involvement and a greater stroke severity are all independent susceptibility factors for PSE [14,18]. ASPECTS (Alberta Stroke Program Early CT Score) are a quantitative score that measures the extent of early ischemic changes in anterior circulation hyper acute ischemic stroke and also posterior circulation (PC-ASPECT) [19].

It is not always easy to diagnose post stroke epilepsy particularly in the elderly population due to the variety of atypical seizure presentation like acute confusional state, slowing, behavioral change, and syncope of unknown origin [5] and the most common symptoms that frequently misdiagnosed as stroke recurrence, is post-ictal paralysis or Todd's paralysis which could last up to four days [20]. Another important issue particularly in older adults is distinguishing a post-stroke seizure from other causes of acute symptomatic seizures such as central nervous system infection, electrolyte imbalance, and cardiac rhythm disturbances [5].

Many studies have examined the risk factors associated with PSE in both ischemic and hemorrhagic stroke and the studies investigating the different characteristics in early and late PSE are lacking and unlike previous studies that correlated cerebral hemorrhage with post stroke epilepsy, we are focusing on the first ever ischemic stroke and the time onset of seizures with the incorporation of relatively new imaging modality like ASPECT score.

The aim of this cross sectional study is to clarify the differences between early and late post stroke, epilepsy regarding clinical characteristics and radiological findings.

PATIENTS AND METHODS

Participants

One hundred and twenty two patients [66 men (54.1%) and 56 women (45.9%)] with ischemic stroke were admitted at Neurology department Sohag University Hospital during the period from October 2017 to June 2018. Informed written (when possible) consent was obtained from the patients or relative. The study was approved by the local ethical committee in Faculty of Medicine, Sohag University in September 2017. Patients with first-ever acute ischemic stroke were enrolled, stroke diagnosed with focal neurological signs or symptoms thought to be of vascular origin that persisted for >24 h [21] and confirmed by brain computed tomography (CT) and/or magnetic resonance imaging (MRI). Those with clinical data corresponding to stroke with normal brain CT-Scan result was also considered as ischemic stroke and follow up CT and/or MRI was done. Stroke severity was measured by the NIHSS and categorized as 0-5 is considered mild stroke, 6–14 is considered moderate and 15–31 foe sever stroke [22].

Glasgow coma scale was used to assess the conscious level of the patient and was graded as mildly disturbed (GCS=13-15), moderately disturbed (GCS=9-

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12), severely disturbed (GCS ≤8) [23].

Post-stroke epilepsy was defined according to the ILAE, as a single seizure associated with an enduring condition that could cause epilepsy (for example stroke) and met the criteria of epilepsy [24]. Seizures occurring ≤7 days after the insult were classified as early PSE and seizures occurring thereafter were classified as late PSE [25]. Status epilepticus (SE) is defined as 5 minutes or more of continuous clinical and/or electrographic seizure activity, or recurrent seizure activity without recovery between seizures [26].

During the study period, no patient received IV or IA thrombolysis, apart from the usual antiplatelet treatment.

The following criteria exclude patients from this study: Patients with Transient ischemic attack (TIA), recurrent stroke, Posterior circulation vascular syndrome, Primary intracerebral hemorrhage, traumatic brain injury, brain surgery, cortical dysplasia, brain tumor, and cerebral vascular malformation. Patients with radiologic evidence of clinically silent old lacunar infarctions, periventricular Leukoaraiosis were also excluded.

Each patient was subjected to the following; full medical and neurological evaluation including age, sex and traditional stroke risk factors. High blood pressure was defined as; use of anti-hypertensive drugs or persistently elevated blood pressure (>140/90 mmHg) on admission. Diabetes mellitus was defined as; use of hypoglycemic agents or a fasting plasma glucose of >126 mg/dl (after no caloric intake for at least 8 hours) or, casual plasma glucose >200 mg/dl [27]. Functional disability was evaluated at discharge after stroke care based on the modified Rankin score (mRS) categorized as mild (mRS ≤ 1), moderate (2 ≤ mRS ≤ 3), or severe (mRS ≥ 4) [18].

METHODS

Electroencephalography (EEG)

EEG was obtained through digital equipment's with minimal duration of 20–30 minutes with placement of scalp electrodes according to international 10˜20 systems. Provocative stimuli like hyperventilation, photic stimulation were given for three minutes each. The EEG abnormalities were classified as:

(1) Non-specific abnormalities (diffused and focal polymorphic delta slowing, ipsilateral attenuation or loss of alpha and beta activities, as well as sleep spindle) [28,29]; (2) Interictal epileptiform abnormalities which generally indicate an increased potential for developing seizures, like sharp and spike waves, lateralized periodic discharges (LPDs, formerly known as periodic lateralized epileptiform discharges), bilateral independent periodic discharges (BIPD formerly known as bilateral independent periodic lateralized epileptiform discharges), generalized periodic discharges (formerly known as generalized periodic epileptiform discharges), and temporal intermittent delta activity or lateralized rhythmic delta activity [30,31]; and (3) Ictal abnormalities which may present as rhythmic evolving theta, delta or alpha activities, rhythmic spike or spike waves, and electrodecremental activities [32-34]. PLEDs were defined as repetitive periodic, focal, or hemispheric epileptiform discharges (spikes, spike and waves, poly spikes, sharp waves) usually recurring every 1 to 2 seconds [35]. EEGs with marked artifacts were excluded from this study.

Radiological data

Infarction size was evaluated by using the ASPECTS score into which ischemic stroke patients with a baseline ASPECTS >7 has a better outcome than ASPECTS ≤7 [36,37]. Those with clinical data corresponding to stroke with normal brain CT scan result were also considered as ischemic stroke, but another CT and/or MRI was done after 2 days for evaluation of hemorrhagic transformation, cortical or subcortical infarct location.

Duplex ultrasound study using 2D and M mode was performed using Siemens Acuson X700 device, Germany for all patients and transesophageal or transthoracic echocardiography (TEE/TTE) were performed when necessary for further TOAST etiological classification of stroke [38]. Radiological data were reviewed by 2 seniors neuroradiologists and doubts were discussed by consensus.

Statistical analyses

The data were analyzed by Statistical Package for the Social Sciences (SPSS 20.0, IBM Corp., Armonk, NY, USA).Chi-square was used to compare categorical variables. The independent t-test was used for continuous variables to make unfavorable comparisons of clinical characteristics. Associations were evaluated by odd ratios (OR) with 95% confidence intervals (CI). The relationship between between seizure onset after stroke and patients' characteristics was investigated using Spearman's Correlation coefficient and preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. Two-sided P-value of less than 0.05 was considered as statistically significant.

RESULTS

The mean age of our study population was 65.6 ± 10.2 years, the percentage of males and females were 54.1%, 45.9% respectively. Hypertension was found in 64.8%. Diabetes mellitus was found in about one third of our cases (34.4%), and past and current smoker were found in 41%. Regarding cardiac diseases, the most common heart disease found was IHD (39.3%), followed by AF (19.7%) (Table 1).

Most of the cases of stroke developed PSE after 7 days (late PSE) (76.2%) in contrast to early post stroke epilepsy was found in 23.8% and 48.4% of the patients experienced focal seizures.

The most prevalent stroke severity on NIHSS was moderate which was found in 58.2% and ASPECT score >7 were found in 54.1%.

The mean age of patient with early and late PSE was 67.5 ± 11.9 and 65 ± 9.6 respectively (P value 0.2).

There is no significant relationship between PSE and smoking, hypertension, IHD, seizure semiology, etiological type stroke on of TOAST classification, presence of hemorrhagic transformation (Table 2).

AF is statistically associated with late PSE [P-value=0.04; OR (95% CI)=0.2 (0.05-1.08)].

There is statistically significant difference between early and late PSE as a regard functional stroke outcome, stroke severity, presence of MCA territory infarction, cortical involvement and ASPECT score.

Table 3 showed the correlation between seizure onset after stroke and different patient's variables.

DISCUSSION

Post-stroke seizure and post-stroke epilepsy are much more common than previously thought and important causes of hospital admissions, either as a presenting feature or as a complication after a stroke [5].

Despite the high risk of PSE, there are no reliable guidelines for the management of seizures after stroke [39,40]. Most of the previous studies investigating the PSE are enrolling both hemorrhagic and ischemic stroke which include both first ever and recurrent ones. In addition, they are searching the predictors of recurrence of seizures and finally a large number of these studies are retrospective without patient evaluation, so some seizures could be missed or underdiagnosed.

We found that early PSE was reported in 23.8% of the patients while late PSE was found in 76.2%.Previous studies reported that early PSE was found in 35% of patients in contrast to late PSE which is present in 90% [41].

In this work we found that the most of the prevalent vascular risk factors is hypertension (64.8%) then diabetes mellitus (34.4%) finally AF (19.7%) which is only risk factor that is statistically associated with late PSE (p-Value=0.04) a finding, confirmed by previous study, which is conducted on a large number of Korean patients admitted to Ewha Woman's University Hospital [18]. In contrast to another study which failed to find this relation as they enrolled all cases of stroke including cerebral hemorrahges [42]. In patients with post stroke epilepsy we found that the percentage of early and late PSE was 23.8% and 76.2% respectively which is in agreement to the results obtained by other study who documented that the percentage of early PSE was 38.7% while that of the late PSE was 61.2% [18].

In our series the stroke patients presented with focal onset (48.4%) which including focal and focal to bilateral tonic clonic seizures, generalized motor seizures (37.7%) and status epilepticus (13.9%) with seizure recurrence in 40.2% which is similar to Kim et al. [18] who found that partial seizures were reported in 45.1,, while generalized seizures were reported in 54.9, with no cases reported to have status epileptic. Berge's et al. [43] who reported that partial seizures were found in 63.5% of the patients, generalized seizures in 36.5%, while status epilepticus was observed in 19.4%, and this slight difference in percentages to those of our study as they enrolled both cerebral infarction and hemorrhage in their series [44]. Most of the previous studies documented that the most prevalent seizure type of post stroke epilepsy were focal one. Stefanidou et al. [43] found that 72% of PSE were focal onset seizures, among them 22% (4 of 18) with evolution on bilateral convulsion and 28% (7 of 25) of PSE were generalized onset seizures. While

TABLE 1

Baseline characteristic of stroke patients with PSE.

	Frequency	Percent
Age	65.6±10.2	
Sex		
Male	66	54.1
Female	56	45.9
Smoking		
Non smoker	72	59.0
current smoker	31	25.4
past smoker	19	15.6
Hypertension	79	64.8
Systolic Blood Pressure	142.6±23.9	
Diastolic Blood Pressure	87.1±12.3	
Diabetes Mellitus	42	34.4
Ischemic heart disease	48	39.3
Atrial fibrillation	24	19.7
Seizure onset		
Early PSE <7 days	29	23.8
Late PSE >7 days	93	76.2
Seizure semiology		
Focal	59	48.4
Generalized	46	37.7
Status epilepticus	17	13.9
EEG		
Normal	2	1.6
Non-specific abnormalities		
Generalized slowing	20	16.4
Regional slowing	22	18.0
Interictal epileptiform abnormalities		
Generalized epileptic discharge	31	25.4
Focal epileptic discharge	42	34.4
PLEDs	5	4.1
Functional stroke outcome (mRS		
Mild disability	9	7.4
Moderate disability	50	41.0
Severe disability	63	51.6
Stroke severity by NIHSS		
Mild	1	9.0
Moderate	71	58.2
Severe	40	32.8
Etiological stroke classification (TOAST)		
Large artery	46	37.7
Cardio embolism	19	15.6
Small vessel occlusion	57	46.7
Large artery atherosclerosis	49	40.2
MCA infarction territory	43	35.2
Cortical involvement	58	47.5
Hemorrhagic transformation	20	16.4
ASPECT score		
>7	66	54.1
≤7	56	45.9

ASPECT: Alberta Stroke Program Early CT Score.
MCA: Middle cerebral artery.
mRS: modified Rankin scale.
NIHSS: National Institutes of Health Stroke Scale.
PLEDs: periodic lateralized epileptiform discharges.
TOAST: Trial of Org 10172 in Acute Stroke Treatment.

TABLE 2

Stroke characteristics in early and late post stroke epilepsy.

	Early N=29	Late N=93	P-Value	OR (95% CI)
Age (mean ±SD)	67.55±11.9	65.09±9.6	0.25	
Sex			0.76	1.1(0.4-2.6)
Male	15 (51.7%)	51 (54.8%)		
Female	14 (48.3%)	42 (45.2%)		
Smoking			0.68	
Non smoker	16 (55.2%)	56 (60.2%)		
Current smoker	7 (24.1%)	24 (25.8%)		
Past smoker	6 (20.7%)	13 (14.0%)		
Hypertension	19 (65.5%)	60 (64.5%)	0.92	1(0.4-2.5)
Systolic blood pressure (mean ±SD)	146.5±27.1	141.4±22.8	0.31	
Diastolic blood pressure (mean ±SD)	89.3±13.8	86.4±11.8	0.27	
Diabetes mellitus (DM)	8 (27.6%)	34 (36.6%)	0.37	0.6(0.2-1.6)
Ischemic heart disease (IHD)	8 (27.6%)	40 (43.0%)	0.13	0.5(0.2-1.2)
Atrial fibrillation (AF)	2 (6.9%)	22 (23.7%)	0.04	0.2(0.05-1.08)
Seizure semiology			0.48	
Focal	13 (44.8%)	46 (49.5%)		
Generalized	10 (34.5%)	36 (38.7%)		
Status epilepticus	6 (20.7%)	11 (11.8%)		
Seizure recurrence	8 (27.6%)	41 (44.1%)	0.11	0.4(0.1-1.2)
EEG			0.17	
Normal	1 (3.4%)	1 (1.1%)		
Non-specific abnormalities				
Generalized slowing	6 (20.7%)	14 (15.1%)		
Regional slowing	6 (20.7%)	16 (17.2%)		
Interictal epileptiform abnormalities				
Generalized epileptic discharge	2 (6.9%)	29 (31.2%)		
Focal epileptic discharge	12 (41.4%)	30 (32.3%)		
PLEDs	2 (6.9%)	3 (3.2%)		
Functional stroke outcome (mRS)				
Mild disability	1 (3.4%)	8 (8.6%)		
Moderate disability	4 (13.8%)	46 (49.5%)		
Severe disability	24 (82.8%)	39 (41.9%)	0.001	
Stroke severity by NIHSS				
Mild	1 (3.4%)	10 (10.8%)		
Moderate	12 (41.4%)	59 (63.4%)		
Severe	16 (55.2%)	24 (25.8%)	0.011	
Etiological stroke classification (TOAST)			0.22	
Large artery	14 (48.3%)	32 (34.4%)		
Cardio embolism	2 (6.9%)	17 (18.3%)		
Small vessel occlusion	13 (44.8%)	44 (47.3%)		
Large artery atherosclerosis	12 (41.4%)	37 (39.8%)	0.87	1 (0.45-2.49)
MCA infarction territory	16 (55.2%)	27 (29.0%)	0.01	3 (1.2-7)
Cortical involvement	8 (27.6%)	50 (53.8%)	0.01	0.3(0.1-0.8)
Hemorrhagic transformation	4 (13.8%)	16 (17.2%)	0.66	0.7(0.2-2.5)
ASPECT score				2.8(1.2-6.8)
>7	10 (34.5%)	56 (60.2%)		
≤7	19 (65.5%)	37 (39.8%)	0.015	

ASPECT: Alberta Stroke Program Early CT Score
EEG: Electroencephalography
MCA: Middle cerebral artery
mRS: modified Rankin scale
NIHSS: National Institutes of Health Stroke Scale
PLEDs: Periodic lateralized epileptiform discharges
TOAST: Trial of Org 10172 in Acute Stroke Treatment

TABLE 3

Spearman's Correlation between seizure onset after stroke and patient characteristics.

	Correlation Coefficient	P value
Age	0.089	0.329
DM	-0.080	0.379
Ischemic heart disease	-0.134	0.140
Atrial fibrillation (AF)	-0.179	0.048
Seizure semiology	0.069	0.448
EEG	0.007	0.941
mRS	0.051	0.579
NIHSS	0.266	0.003
TOAST	-0.072	0.432
Large artery atherosclerosis	0.014	0.880
MCA territory infarction	0.233	0.010
Cortical involvement	-0.223	0.013
Hemorrhagic transformation	-0.039	0.668
ASPECT score	0.220	0.015

ASPECT=Alberta Stroke Program Early CT Score
EEG=electroencephalography
mRS=modified Rankin scale
NIHSS=National Institutes of Health Stroke Scale
TOAST=Trial of Org 10172 in Acute Stroke Treatment

in a population-based study, Bryndziar et al. [43] found that 66% of PSE were focal (partial) onset seizures, with or without secondary generalisation. Thirty-four percent of PSE were generalized onset seizures, and 11.4% of PSE developed into status epilepticus (SE). In contrast to one study with a limited number of patients, which documented that generalized seizure was the most common seizure (56%) followed by focal seizures in 36% of patients [45].

Regarding the degree of disability, we found that patients with severe disability was 63 (51.6%), moderate disability in 50 (41%) and mild disability only in 6 (7.4%). Also the percentage of severe disability in patients with early and late PSE was 82.8% and 41.9%, respectively (P value=0.001). These results are in line with the fact that the more severe stroke the more probability to develop early PSE as documented by a meta-analysis study [46]. In contrast to a Korean study who reported that sever disability was 54.2%, moderate disability in 12.5% and mild disability only in 33.3% without significant difference between early and late PSE [18] and this difference may explained by 2 reasons, first they reviewed the patients' medical records retrospectively, so functional disability could have been underdiagnosed in some patients study second they enrolled the recurrent stroke in their series.

Most of our series experience moderate stroke severity on the NIHSS (58.2%) with is statistically significant to early PSE (P-value 0.011). Arntz, et al. [43] concluded that PSE is common in stroke patients with high NIHSS score. Many previous studies also reported that stroke severity among the independent risk factors of PSE [42,47,48] and the severity of the initial neurologic deficit could be a clinical predictor for seizures after ischemic stroke [8,49,50]. As patients presenting with greater neurologic impairment tend to have larger strokes that involve wider cortical areas. A meta-analysis concluded that the early seizure onset is strongly associated with a higher NIHSS score [46].

We found a normal EEG pattern in 1.6% of the patients, generalized slowing in 16.4%, regional slowing in 18%, generalized epileptic discharges in 25.4%, focal epileptic discharges in 34.4% and lastly PLEDS to 4.1% without significant association between theses EEG results and PSE and these results were confirmed by previous studies [18,44]. One study significantly correlated the interictal epileptiform activity (IEA) in the first EEG and prediction of post stroke epilepsy [51].

Middle cerebral artery territory infarction was present in 35.2% of the total number of patients with 55.2% in early and 29% in late PSE with (P value=0.01) which is different from the results obtained by Kim et al. [18] who reported that vascular territory distribution of lesion was concentrated in the middle cerebral artery (MCA) territory in both groups (47.9% vs. 69.7%). However, there was no statistical significance in the vascular distribution between early and late PSE.

Cortical involvement was present in 47.5% of the total number of patients with 27.6% in early and 53.8 in late PSE with P value=0.014 which is in agreement with previous studies which reported that cortical involvement were significantly more present in late PSE (P value=0.002) compared to those in early PSE [18]. Browne et al. [48] reported that cortical damage is a predictor of post-stroke seizures. Also previous studies documented that cortical location is among the most reliable risk factors for post stroke seizures [8] and post stroke seizures were more likely to develop in patients with larger lesions involving multiple lobes of the brain than in those with single lobar involvement [52].

ASPECT score ≤7 was present in 45.9% of the total number of patients with 65.5% in early and 39.8% in late PSE (P value=0.015). Bentes et al. [51] reported that ASPECTS score can independently predict post ischemic stroke unprovoked seizures.

Like Kim et al. [18] we found that there is significant correlation between PSE and age, sex, smoking, seizure semiology, EEG finding, stoke subtype on TOAST classification, presence of large artery atherosclerosis, hemorrhagic transformation or functional stroke disability on mRS.

There are different mechanisms have been proposed to explain the post stroke seizures, according to their proximity to the onset of brain ischemia. Early seizures occur immediately after a stroke, and are thought to be consequences of regional metabolic dysfunction with the accumulation of intracellular calcium and sodium may result in depolarization of the transmembrane potential and other calcium mediated effects; these local ionic shifts may lower the seizure threshold [6,8,53]. The ischemic penumbra, a region of viable tissue adjacent to the infarcted core in ischemic stroke, contains electrically irritable tissue that may be a focus for seizure activity [49]. Late seizures occur when the brain is predisposed to seizures and persistent changes in neuronal excitability occur. These changes are maintained by replacement of healthy cell parenchyma by neuroglia and immune cells [6,49] with formation of gliotic scarring which has been implicated as the nidus for late-onset seizures [8].

CONCLUSION

This study has some restriction one is we did not follow up the patient to see recurrence rate second continuous EEG monitoring was not done to observe the effect of antiepileptic drugs on EEG and unmask nonconvulsive seizures. Further large, prospective studies are needed to answer many issues regarding post stroke seizures. Inspite of these limitations, the present study has shown that our results make a new contribution to the field because they clarify different patient characteristics in early and late PSE with the addition of NIHSS to measure stroke severity and ASPECT score to estimate the infarction size.

In conclusion, the present study is among the few subjects that exhibit the comparison between early and late PSE with the use of NIHSS and ASPECT scores for stroke severity and infarction volume respectively.

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