ORIGINAL ARTICLE

CONTENTS

Prevalence and structure of pain syndrome in patients with stroke and Covid-19

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ABSTRACT

Aim: To investigate the prevalence and characteristics of pain syndrome in patients with ischemic stroke against the background of COVID-19 over a 3-month period.

Materials and Methods: A total of 34 patients with laboratory-confirmed COVID-19 and ischemic stroke were examined during the acute phase. Pain syndrome onset was studied within 3 months of stroke development, focusing on musculoskeletal pain, central post-stroke neuropathic pain, shoulder pain, and headache. Pain intensity was measured using the Visual Analog Scale and the DN4 questionnaire was applied to determine neuropathic pain.

Results: Pain syndrome developed in 75% of patients. Musculoskeletal pain (58.38%) and headache (54.2%) were the most common. More than half of patients experienced a combination of pain types, with musculoskeletal pain and headache frequently co-occurring in one-third of cases. Moderate pain syndrome was the most common (48.7%). Headache positively correlated with COVID-19 severity ($r = 0.486$, $p = 0.005$), and shoulder pain positively correlated with stroke severity ($r = 0.517$, $p = 0.002$).

Conclusions: Identifying the prevalence, structure, and severity of pain syndrome in combined ischemic stroke and COVID-19 cases highlights the importance of timely recognition and management. Effective intervention can prevent pain syndrome chronification, improve functional recovery, and enhance patients' quality of life.

KEY WORDS: stroke, COVID-19, headache, central post-stroke pain, shoulder pain

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INTRODUCTION

Stroke is a leading cause of disability and mortality worldwide. Pain syndrome (PS) after stroke significantly contributes to disability and reduced quality of life, alongside symptoms such as paresis-paralysis, speech impairment, and sensory disturbances [1]. The prevalence of post-stroke pain ranges from 19% to 74% [2, 3], with chronic pain observed in 45–65% of patients, 70% of whom experience it daily. PS is one of the most common complications post-stroke, along with depression, falls, and urinary tract infections [2, 4–6]. Risk factors for PS include female gender, advanced age, depression, spastic paresis, and lesion localization in the brainstem or thalamus [7].

The COVID-19 pandemic has added new challenges, infecting over 676 million people and causing more than 6.8 million deaths globally [8]. Neurological manifestations in COVID-19, including myalgia, joint pain, headaches (HA), and neuropathic pain, are reported both in the acute phase and post-acute period [9]. These symptoms result from systemic inflammation, direct neuropathic mechanisms, or complications of infection and treatment [10].

COVID-19 also increases the risk of stroke, with an incidence twice as high compared to non-COVID-19 patients and an approximate rate of 5% [12, 13]. Stroke in the context of COVID-19 is associated with greater severity, higher mortality [14], younger age, and more comorbidities such as diabetes and obesity [15],], as well as a higher prevalence of undetermined pathogenic subtypes [16].

However, data on the prevalence and characteristics of PS in combined stroke and symptomatic SARS-CoV-2 infection remain scarce. The overlap of these conditions may enhance pain intensity, increase neuropathic pain prevalence, and create unique variants of requiring further study. Understanding these aspects is critical for improving diagnostics, treatment, and rehabilitation, thereby enhancing quality of life and reducing societal burdens.

AIM

To investigate the prevalence and characteristics of pain syndrome (PS) in patients with ischemic stroke against the background of COVID-19 over a 3-month period.

MATERIALS AND METHODS

We examined 32 patients with ischemic stroke (IS) and laboratory-confirmed COVID-19 (PCR test), who were hospitalized at Kyiv City Clinical Hospitals No.1 from April 2020 to November 2021.The clinical severity of COVID-19 was assessed based on symptoms, physical examination, laboratory test results, and findings from instrumental diagnostic methods [17]. Inclusion criteria were:mild to moderate COVID-19 severity, ability to establish contact with the patient to assess and characterize PS. The diagnosis of IS was based on clinical neurological examination and neuroimaging results, including spiral computed tomography (sCT) or magnetic resonance imaging (MRI). The National Institutes of Health Stroke Scale (NIHSS) was used to assess stroke severity, spasticity was evaluated using the Modified Ashworth Scale (MAS) [18]. Assessment of spasticity involved flexion and extension movements around the joints of the upper limb (shoulder, elbow, wrist, and fingers) and lower limb (hip, knee, and ankle) in a resting state. The study was conducted in accordance with the Helsinki Declaration of Ethics [19]. We assessed the development of PS following a stroke, starting from hospitalization and up to 12 weeks after the acute infection. The following variants of PS were distinguished: Shoulder pain (SP) on the paretic side, headache (HA), musculoskeletal pain (MSP), central (neuropathic) post-stroke pain (CPSP).

The presence and characteristics of PS (type and intensity) were determined through interviews and questionnaires conducted during hospitalization or via telephone interviews. To diagnose CPSP, the classification of central neuropathic pain and the DN4 questionnaire (Douleur Neuropathique 4) were applied [20]. A positive response to 4 out of 10 items on the DN4 questionnaire indicated the presence of central post-stroke neuropathic pain.

The pain was evaluated quantitatively using the Visual Analog Scale (VAS, 0–10 cm) and categorized using the Numeric Rating Scale (NRS): 1–3 points: mild pain, 4–6 points: moderate pain, 7–10 points: severe pain. In cases of combined pain types, VAS scores were assessed separately for each type of pain.

Statistical analysis was performed using IBM SPSS Statistics 22. Descriptive statistics were calculated, and normality was tested with the Chi-square test. Data with normal distribution were presented as the mean (M) ± standard deviation (SD) and analyzed using the paired or independent Student's t-test. Non-normally distributed data were analyzed with the Wilcoxon signed-rank test or the Mann-Whitney U test. Relative values were compared using Pearson's χ^2 test or the one-sample χ^2 test. Correlation analysis employed Pearson or Spearman coefficients, with significance set at $p < 0.05$.

RESULTS

The mean age was 71.6 years, with a male-to-female ratio of 53.3% to 43.8%. The mean NIHSS score for stroke severity was 11.5, corresponding to a moderate severity level. The most common stroke subtype was atherothrombotic (40.6%). Vascular lesions were predominantly localized in the carotid arterial system (50.0%). The majority of patients experienced a mild course of COVID-19 (78.1%), while 21.9% had a moderate course (Table 1).

Among the 32 examined patients with stroke and COVID-19, PS was detected in 24 patients (75.0%). In 7 patients PS was observed during hospitalization, in 17 patients PS developed within 3 months from disease onset during ongoing symptomatic COVID-19.

In more than half of patients with PS (46.9 %) large artery involvement was identified.

Among patients with PS in 11 patients (45.8%) the stroke occurred in the carotid arterial system, in 10 patients (41.7%) the infarction focus was localized in structures supplied by the vertebrobasilar arterial system. In 3 patients (12.5%) both vascular territories were affected (Table 2).

There were no significant differences in the distribution of pathogenetic subtypes between patients with and without PS. Additionally, no differences were found in the prevalence of different subtypes among patients with PS in cases of combined stroke and COVID-19. There was also no difference in the prevalence of PS depending on the clinical severity of COVID-19: among patients with a mild course, PS was observed in 18 (72.0%), and with a moderate course – in 6 (85.7%), $p = 0.459$. The analysis of patients with ischemic stroke by the structure of PS is presented in (Table 3).

The data indicate that the most common type of pain disorder was MSP, observed in 14 patients, which accounted for 58.3% of patients with PS and 43.8% of all examined patients. Patients reported pain in the neck and shoulder girdle (6 patients), lower back and sacral region pain was noted by 3 patients,1 patient reported pain in the lower legs. In 4 patients, the PS had a multiple nature, simultaneously affecting several anatomical regions.

HA was the second most common cause of PS, occurring in more than half of patients with PS (54.2%) and in 40.6% of all examined patients. In 2 patients, the HA was described as bilateral, localized in the temporo-parietal and occipital regions, resembling vascular pain associated with elevated blood pressure. In 3 patients, the HA was migraine-like. For the remaining patients, the HA resembled daily tension-type HA and developed on days 4–6 after the stroke, in the absence of any preexisting HA complaints.

Shoulder pain (SP), observed in a quarter of patients, was associated with various factors: subluxation of the shoulder joint (due to spasticity and restricted range of motion),tissue contracture around the shoulder caused by prolonged immobilized positioning, features of adhesive capsulitis. SP in 4 patients was combined with spastic hemiparesis in the right limbs (3–4 on the MAS scale). In another 3 cases, it was associated with central monoparesis without significant spasticity (2 points on the MAS scale). At the same time, the frequency of pain types such as HA, SP, and MSP did not show any statistical differences (all $p > 0.05$).

CPSP was found in 2 patients associated with lesions in the lenticulo-capsular region, in 1 patient - with a lesion in the lateral medulla, in 1 patient with a lesion in the pons, in 1 patient, with a lesion in the parietal cortex. CPSP occurred significantly less frequently than HA, $p = 0.026$ and MSP, $p = 0.014$ (Table 4).

It was shown that in more than half of cases (58.3%), patients reported a combination of two types of pain that developed after a stroke. In one patient, three pain syndromes occurred simultaneously (Table 5).

It was determined that the most common combination of two pain variants was MSP and HA, observed in 8 patients (33.3%). The mean pain score on the VAS was 4.7 ± 1.7 points (range: 2–8 points), with no significant differences depending on the type of pain, all $p > 0.05$ (Table 6).

Among all presentations of pain syndrome and its combinations (40 variants), moderate PS was the most common, occurring in 47,5% of cases.

An assessment of pain intensity depending on the type of PS revealed certain features (Table 7).

Thus, MSP belonged to the «mild and moderate» categories with the number of mild cases exceeding moderate ones by more than 1.5 times. HA of moderate intensity occurred more frequently than other gradations – 2.5 times more often than mild pain and 4 times more often than severe pain. Among patients with CPSP 80% reported moderate and severe pain. Shoulder pain, associated with spasticity, was characterized as moderate in 50% of cases.

Correlation analysis revealed significant associations: between HA and COVID-19 severity ($r = 0.486$, $p = 0.005$), between stroke severity (NIHSS score) and SP($r = 0.517$, $p = 0.002$).

Table 1. General characteristics of patients (n=32)

Characteristic	Indicator
Age (years), M±SD	71.6 ± 4.5
- Male n (%)	18 (53.3)
- Female n (%)	14 (43.8)
Stroke severity (NIHSS), M±SD	11.5 ± 2.7
Stroke subtype, n (%)	
- Atherothrombotic	13 (40.6)
- Atrial fibrillation	9 (28.1)
- Lacunar infarcts	7 (21.9)
- Undetermined mechanism	3 (9.4)
Vascular localization	
- Carotid arterial system	16 (50.0)
- Vertebrobasilar arterial system	13 (40.6)
- Both localization	3 (9.4)
COVID-19 course; n (%):	
Mild:	25 (78.1)
Moderate:	7 (21.9)
Pain syndrome; n (%):	24 (75)

DISCUSSION

Among hospitalized patients with COVID-19, ischemic stroke occurred in 1.1–4.7% of cases with a cumulative prevalence of 2% [21].

This urges researchers to devote serious attention to studying the pathophysiological and clinical aspects of

Table 2. Prevalence of pain syndrome depending on stroke subtype and vascular localization

Indicator	Proportion of subtype and vascular localization in PS, n (%)		Prevalence of PS within each subtype/vascular localization		
	n=24	P	n=32	n (%)	P
Stroke subtype					
Atherothrombotic	9 (37.5)	0.228	13	9 (69.2)	0.848
Cardioembolic	7 (29.2)	9	7 (77.8)		
Lacunar	6 (25.0)	7	6 (85.7)		
Undetermined	2 (8.3)	3	2 (66.7)		
Vascular localization					
Carotid	11 (45.8)	0.093	16	11 (68.8)	0.507
Vertebrobasilar	10 (41.7)		13	10 (76.9)	
Both localization	3 (12.5)		3	3 (100.0)	

Table 3. Distribution of patients with IS and COVID-19 by type of PS

Type of pain syndrome	Absolute (n)	% of Total patients (n=32)	% of Patients with PS (n=24)
CPSP	5	15.6	20.8
Headache	13	40.6	54.2
Shoulder Pain	8	25.0	33.3
Musculoskeletal Pain	14	43.8	58.3

Table 4. Pain syndrome comparison: statistical significance (p-values)

Pain syndrome comparison	p-value
CPSP vs Headache	0.026
CPSP vs MSP	0.014
Headache vs SP	>0.05
Headache vs MSP	>0.05
Shoulder Pain vs MSP	>0.05

this comorbidity. Our study focuses on the prevalence and features of PS in stroke patients with COVID-19 and, to our knowledge, is the first to address this issue in such a direction. Our interest in this practically unexplored topic can be explained by the fact that PS in COVID-19 alone is a prominent and quite persistent element. The overall prevalence of pain reported after COVID-19 was 34.2%, which is higher than for any other symptoms and exceeds post-influenza pain (24.0%) [26]. According to FAIR Health data, which includes more than 34 billion private medical records, persistent pain was reported in 5.1% of COVID-19 patients and was identified as one of the five most common symptoms lasting 30 days or more after the initial diagnosis [23].

Among the patients we examined with combined IS and COVID-19, PS developed in 75% of cases, which exceeds the rates reported in the literature for the stroke population before the pandemic [4, 6, 24]. One of the most common types of pain in the structure of post-stroke pain is HA, and this is also true for the neurological manifestations of COVID-19 in the absence of stroke. The overall prevalence of HA in hospitalized COVID-19 patients ranges from 11% to 34% [25], while data from Carvalho LCLS et al. [26] showed that it persisted after the acute phase of COVID-19 in 52% of patients.

Table 5. Distribution of patients with IS and COVID-19 by combination of pain types (n=24)

Pain syndrome	CPSP	Headache	Shoulder Pain	Musculoskeletal Pain
CPSP	-	0 (0.0%)	3 (12.5%)	1 (2.4%)
Headache	0 (0.0%)	-	2 (8.3%)	8 (33.3%)
Shoulder Pain	3 (12.5%)	2 (8.3%)	-	3 (12.5%)
Musculoskeletal Pain	1 (2.4%)	8 (33.3%)	3 (12.5%)	-

Table 6. Pain score on VAS by pain syndrome type

Pavin syndrome	N	M ± SD	Min–Max
CPSP	5	5.4 ± 2.1	3 – 8
Headache	13	4.9 ± 1.5	3 – 8
Shoulder Pain	8	5.3 ± 1.8	3 – 8
Musculoskeletal Pain	14	3.9 ± 1.5	2 – 6

Table 7. Distribution of patients by pain intensity gradations on the VAS Scale depending on PS type

Pain syndrome	Pain intensity						Total	
	Mild		Moderate		Severe			
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
CPSP	1	20.0	2	40.0	2	40.0	5	100
Headache	3	23.1	8	61.5	2	15.4	13	100
Shoulder Pain	2	25.0	4	50.0	2	25.0	8	100
Musculoskeletal Pain	9	64.3	5	35.7	0	0.0	14	100

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According to the latest meta-analysis, HA after stroke in patients without signs of COVID-19 occurs with a prevalence of 6–44%, is predominantly characterized as tension-type HA, and is associated with stroke in the posterior circulatory territory and with the female gender [30]. Our results showed the presence of HA in more than half of patients with PS (54.2%), which was higher than in cases of isolated COVID-19 infection during the same period and exceeded the prevalence of this symptom in the "stroke without COVID-19" group. Unlike Harriott A.M. et al. [27], we did not find a difference in the prevalence of HA depending on the affected vascular territory. At the same time, we identified a moderate, positive, and statistically significant correlation between the prevalence of HA and the severity of COVID-19, which aligns with the findings of these researchers.

SP after stroke is a common phenomenon, with a reported prevalence ranging from 22% to 47% [28]. In cases of stroke combined with COVID-19, our data revealed SP in 25% of all patients examined and in one-third of those with pain syndrome. Thus, the prevalence of this syndrome did not differ significantly from that in the "non-COVID" stroke group. However, we observed a correlation with stroke severity, rather than with the clinical severity of COVID-19.

MSP are frequently observed in COVID-19 during both the acute and subacute periods. According to a systematic review and meta-analysis [21], their prevalence was 92.3% during hospitalization, 72.7% after 2 weeks, and 56.3% after 1 month.

In patients with IS and COVID-19, our data showed MSP in 58.3% of patients. This frequency was more than 4 times higher than the frequency of MSP reported in stroke patients without COVID-19 by Cherenko T.M. [6]. However, other studies [29] report a significantly higher frequency of MSP, though 30.9% of cases were identified as having a local nociceptive nature.

In isolated studies [30], it has been reported that stroke can potentially cause prolonged neuropathic pain in 7–8% of patients after COVID-19 within 1 year (without specifying central or peripheral neuropathic pain). In our study, the prevalence of central post-stroke neuropathic pain (CPSP) in the "COVID-19 + stroke" group was over 20% within 12 weeks. This higher rate, compared to stroke without COVID-19, likely reflects the synergistic effect of the underlying pathophysiological mechanisms.

The study has certain limitations, as our conclusions do not cover cases of combined stroke and COVID-19 with a severe clinical course, nor was the prevalence of pain syndromes during the long COVID investigated. At the same time, these aspects require further research to optimize approaches to pain syndrome management.

CONCLUSIONS

Thus, acute and subacute PS in patients with COVID-19 and stroke represents a significant medical issue, affecting 75% of such patients within 12 weeks of the disease. In the spectrum of pain disorders, the most common were MSP (58.3%) and HA (54.2%), while SP was observed in 33% of cases. Notably, CPSP was recorded with a high prevalence of 20.8%. In more than half of the cases, PS involved a combination of two pain types: MSP and HA were observed in one-third of patients. Moderate pain was the most frequent, occurring in 48.7% of cases, while severe pain was recorded in 15.4%.

Thus, PS links two global medical challenges through common clinical intersections. Identifying the specific prevalence , structure, and severity of PS in the combination of ischemic stroke and COVID-19 will help focus attention on its timely recognition and management. This will enable the prevention of pain chronicity, improve functional recovery after stroke, and enhance patients' quality of life.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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