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A Cross-Sectional Study to Assess the Association between Major Depression and Inflammatory Markers in Patients with Acute Ischemic Stroke in North East Rajasthan

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Abstract

Increased interest in the relationship between affective disorder and long-term health consequences has generated recent examinations of depression and stroke. Observations suggest that depressive disorder is associated with abnormal physiological and immunological responses and a resultant increase in inflammatory markers. Given the high prevalence of stroke and associated costs for the community, it is important to understand the mechanisms that may impact on the outcome to achieve the best possible prognosis. The view that inflammatory factors contribute to depression is predicated on findings that circulating cytokines and other inflammatory factors are increased in depressed patients. Therefore, it has been hypothesized that inflammation could be one of the mechanisms by which depression increases risk for ischemic stroke. Our aim was to determine whether there is any relationship between major depression and tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-18, brain derived neurotrophic factor (BDNF), and neuron specific enolase (NSE) in patients with acute ischemic stroke (AIS). This study has a cross-sectional design, was carried out on patients of department of Psychiatry at tertiary care teaching hospital in north east Rajasthan. Fifty-three AIS patients admitted to the hospital within the first 24 h after stroke onset was recruited. Major depression was ascertained by means of the structured clinical interview for the diagnostic and statistical manual of mental disorders, Fifth Edition. The enzyme-linked immunosorbent assay was used to measure the serum levels of TNF-α, IL-1 β, IL-18, BDNF, and NSE at admission. A total of 54 patients with a mean age of 66.9 years were recruited. Of these patients, 17 (32.1%) had major depression. Depressive and nondepressive patients had similar demographical and clinical features. There was no significant statistical difference between depressive and nondepressive patients with AIS with respect to levels of TNF-α, IL-1 β, IL-18, BDNF, and NSE.

Keywords: Cytokine, depression, inflammation, stroke.

Introduction

Stroke is a leading cause of death and permanent disability with significant economic losses due to functional impairments. Increased interest in relationship between affective disorder and long term health consequences has generated recent examinations of depression and stroke. Depression has been associated with increased rates of diabetes mellitus, hypertension and cardiovascular disease

and this raises the possibility that a similar relation may exist for cerebrovascular disease and mortality. Several studies indicate a positive association between depression and stroke. In this study, depression was an independent risk factor for an incidence of stroke. In addition, the risk of developing stroke was 4.23 times greater in those individuals with depression. Significant psychological distress was also a predictor of fatal ischemic stroke. Previous studies suggested that, in patient groups who have depressive symptoms, stroke morbidity increases by 2.3–2.7-fold, and baseline depression was found to be an independent predictor for total incidents of stroke and fatal stroke. It has been hypothesized that inflammation could be one of the mechanisms by which depression increases risk for ischemic stroke. Inflammatory factors have been linked to ischemic stroke. The view that inflammatory factors contribute to depression was initially predicated on findings that circulating cytokines and other inflammatory factors were found to be increased in depressed patients. A number of investigative clinical studies have found individuals with depression to have higher circulating levels of cytokines, for example, interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) and IL-18. The administration of IL-1β administration after experimentally induced Ischemia increases infarct size and edema formation. TNF-α is a depression-related proinflammatory cytokine that increases in response to ischemic conditions. IL-18 can mediate delayed neuro-inflammatory processes in experimental hypoxic–ischemic brain injury. To sum up, proinflammatory cytokines increases in acute ischemic stroke (AIS); it is also increased in psychiatric patients with depression and without stroke compared to control. These studies have also shown that, in psychiatric patients with major depression and suicide victims, brain-derived neurotrophic factor (BDNF) levels are lower. neuron-specific enolase (NSE) is a glycolytic pathway enzyme, predominantly found in neuronal cells in the isoform γγ. NSE has been studied less frequently in both depressive psychiatric patients and neurological patients with AIS. One study found individuals with depression to have high levels of cerebrospinal fluid (CSF) and NSE. Wunderlich et al. suggested that the relationship between the severity of neurological deficit in patients with ischemic stroke and infarction size with NSE.

These changes in inflammatory response could be related to the presence of depression before AIS and stroke related neurological deficits can make sense in regard to morbidity and mortality. If the presence of major depression in patients just before AIS affects post stroke proinflammatory cytokines, BDNF and NSE; due to the negative effects of these biological parameters on prognosis, the diagnosis and treatment of major depression, especially in patients with high AIS risk, must be primary goal. In this study, we aim to examine these associations between these biological parameters and major depression in patients with AIS.

Materials and Methods

Study Sample

This study has a cross-sectional design, and it was conducted in department of Psychiatry at tertiary care teaching hospital in north east Rajasthan. Before starting the study approval of the ethical committee was taken and after that Informed consent was obtained after providing verbal and written information to participants or nearest relatives. Two hundred and twenty nine patients with a first episode of AIS were admitted to our hospital within the first 24 hour of stroke onset during the study period, and we excluded patients according to the exclusion criteria at baseline. Ultimately, 54 patients were included in the study. Only patients without significant clinical factors that promote inflammation were selected. The

inclusion criteria were the clinical presentation of the first-ever stroke in those age 18 years or older. Those who were admitted after 24 hour of stroke whose cause of stroke was intracerebral and subarachnoid hemorrhage; who were unconscious; who had aphasia or dysphasia; who had a brain tumor or systemic malignancy; who recently or simultaneously had acute myocardial infarction and unstable angina pectoris; who had renal dysfunction; who had symptomatic peripheral artery disease; who had a history of infection within the last month, who had acquired an infection after admission and a simultaneous diagnosis of sepsis; who had trauma or a history of surgical intervention within the last month, who had acute/ chronic inflammatory gastrointestinal disease; who had rheumatic disease and had been diagnosed with metabolic syndrome; who had been using antidepressant or other psychotropic drugs during the last month; who had anxiety disorder, schizophrenia or other psychotic disorders, bipolar disorder, or alcohol-substance abuse apart from major depression disorder were not recruited to the trial.

Stroke case ascertainment

Stroke was defined as the presence of rapidly developing focal neurological signs or symptoms of vascular origin that persisted for 24 hour. A general medical history was collected; and physical and neurological examinations, standard laboratory tests, and a 12-lead electrocardiogram were performed on all patients upon admission. The ischemic lesion and affected brain region were assessed and confirmed by both the clinical examination and computed tomography and/or brain magnetic resonance imaging during hospitalization for acute stroke. The location of the stroke was determined by radiologically findings. The stroke subtype was classified according to trial of ORG 10172 in acute stroke treatment (TOAST) criteria. Stroke severity was evaluated at admission by trained neurologists using the National Institutes of Health Stroke Scale (NIHSS).

Psychological measurement

After neurological assessments were completed, and the sociodemographic features were recorded, the patients were assessed by a psychiatrist in the same hospital. Psychiatric interviews were carried out by psychiatrists. Psychiatric disorders were screened using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Preexisting major depression in the patients was diagnosed by the same clinical structured interview.

Statistical analysis

Statistical analyses were performed with SPSS 20. For comparisons between the study groups, a t-test (for normally distributed variables) and the Mann–Whitney U test (for abnormally distributed variables) were used for continuous variables and a Chi-square test (for 3 or more × 2 variables) or Fisher's exact test (for 2 × 2 variables) for categorical variables. All significant levels were two-tailed and set at a level of 0.05.

Results

The mean age of the study sample (n = 54) was 66.90 ± 13.09 (range: 31–89) years. Of the patients, 26 (49.1%) were women, and 28 (51.85%) were men. 51 (94.44%) were living in the urban and 49 (90.74%) belonged to an ordinary income group. Hypertension 41 (75.9%), diabetes mellitus 19(35.2%), coronary artery disease 17(35.5%), and HL 15(27.8%) were the most common diseases [Table 1]. The mean hospitalization time was reported as 12.92 ± 4.85 day. The initial mean NIHSS score was reported as 6.96 ± 4.75. Serum samples were collected within a mean of 11.84 ± 2.56/hour after the onset of AIS symptoms (range = 6–18/hour).

In the depressive patient group, serum samples were collected within a mean of 11.66 ± 3.14 hour after the

beginning of AIS symptoms, whereas in the nondepressive patient group, serum samples were collected within a mean of 12.02 ± 2.58/h after the onset of AIS symptoms. The difference was not statistically significant (P = 0.587). As shown in Table 2, patients with AIS were classified as follows: 13 (24.07%) large artery disease; 13 (24.07%) cardio embolic; 8 (14.81%) small vessel disease and 19 (35.18%) unknown etiology. While 44 (81.48%) supratentorial space lesions were most commonly observed, the following were also observed: 14 (25.92%) parietal, 13 (24.07%) basal ganglion, and 10 (18.51%) temporal region lesions. Nearly 18 (33.33%) of the 54 patients in the study group were diagnosed with major depression.

Table 3 demonstrates hematologic (including complete blood count) and biochemical (metabolic panel, C-reactive protein, uric acid) parameters in the major depressive or nondepressive AIS patients. There was no significant difference between the preexisting major depressive and nondepressive AIS patients regarding sociodemographic characteristics, medical histories, mean duration between beginning of AIS symptoms and collection of serum samples, the average length of stay in the hospital, NIHSS score at admission, TOAST classification, stroke location, and hematologic and biochemical parameters. In addition, there was no significant difference between the major depressive and nondepressive AIS patients in terms of serum levels of TNF-α, IL-1 β, IL-18, BDNF, and NSE [Table 3].

Table 1: Sociodemographic data and medical history of the patients

Sociodemographic data		**Patient with AIS (n=36)**	**Patient with AIS and MD (n=18)**	**P**
Age, mean±SD		65.25±13.98	67.47±11.20	0.569
Gender, n (%)	Male	19 (52.8)	9 (50)	0.773
	female	17 (47.2)	9(50)	0.773
Domicile, n (%)	Rural	2 (5.6)	0 (0)	1.376
	Urban	34(94.4)	17(100)	1.376
Income status, n (%)	High income	2 (5.6)	3 (16.66)	0.585
	Ordinary income	34 (94.4)	15(83.34)	0.585
Medical history, n (%)	HTN	27 (75)	14 (77.8)	1.000
	DM	11 (30.6)	8 (44.4)	0.358
	CAD	11 (30.6)	6 (33.3)	0.760

	HL	9 (25)	6 (33.3)	0.520
	CHF	4 (11.1)	2 (11.1)	1.000
	AF	5 (13.9)	6 (33.3)	0.143
	HVD	2 (5.6)	3 (16.6)	0.313
	SMOKING	11 (30.6)	2 (11.1)	0.813
	Anticoagulant use	0 (0)	2 (11.1)	0.099
	Antihypertensive use	23 (63.9)	12 (66.6)	0.760
	OAD use	8 (22.2)	3 (16.6)	1.000
	Insulin use	7 (19.4)	5 (27.8)	0.490

AIS – Acute ischemic stroke; HT – Hypertension; DM – Diabetes mellitus; CAD – Coronary artery disease; HL- Hyperlipidemia; CHF – Chronic heart failure; AF – Atrial fibrillation; HVD – Heart valve disease; OAD – Oral antidiabetic; MD – Major depressive;; SD – Standard deviation

Table 2: Etiological classification and stroke location of the patients

		Patient with AIS (n=36)	**Patient with AIS and MD (n=18)**	**P**
TOAST classification, n (%)	Large artery	9 (25)	4 (22.2)	1.000
	Cardio-embolism	5(13.9)	8 (44.4)	0.016
	Small vessel disease	6 (16.7)	2 (11.1)	0.408
	Other cause	1 (2.8)	0 (0)	1.000
	Unknown	15 (41.7)	4 (22.2)	0.235
Stroke location	Supratentorial	29 (80.6)	15(83.3)	0.701

	İnfratentorial	7 (19.4)	2 (11.1)	0.701
	Frontal	6 (16.7)	3 (16.6)	1.000
	Temporal	8 (22.2)	2 (11.1)	0.471
	Parietal	10 (27.8)	4 (22.2)	1.000
	Occipital	4 (11.1)	2 (11.1)	1.000
	Cerebellar	5 (13.9)	1 (5.5)	0.651
	Thalamus	3 (8.3)	0 (0)	0.543
	Basal Ganglion	7 (19.4)	6 (33.3)	0.306
	Brain stem	2 (5.6)	2 (11.1)	0.585

TOAST – Trial of ORG 10172 in acute stroke treatment; AIS – Acute ischemic stroke; MD – Major depressive

Table 3: Biological parameters of the patients

Biological parameters (mean±SD)	**Patient with AIS (n=36)**	**Patient with AIS and MD (n=18)**	**P**
Blood glucose level	149.18±66.26	123.24±37.52	0.365
Urea	40.58±15.38	40.88±16.12	0.951
Creatine	0.27±0.43	0.41±0.50	0.334
Hemoglobin	13.62±2.14	12.8±2.17	0.752
WBC	8374.33±2084.31	8476.47±2036.70	0.235
C-reactive protein	4.47±3.30	4.88±3.88	0.692
Uric acid	5.36±1.75	5.29±1.74	0.898
TNFα pg/ml	34.55±40.44	35.75±36.91	0.856
IL1βpg/ml	3.69±4.58	3.37±1.86	0.760
IL-18-pg/ml	164.42±86.04	211.71±164.97	0.197

NSE-ng/ml	6.18±6.27	4.57±2.71	0.320
BDNF-pg/ml	728.39±501.90	751.35±642.86	0.892

WBC – White blood cells; TNF-alfa – Tumor necrosis factor-alpha; IL – Interleukin; NSE – Neuron specific enolase; BDNF – Brain derived neurotrophic factor; AIS – Acute ischemic stroke; MD – Major depressive; SD – Standard deviation

Discussion

As far as we know, our trial is the first study in which the relationship between major depression in patients with AIS and proinflammatory cytokines (TNF-α, IL-1 β, and IL-18), BDNF, and NSE has been investigated. In previous studies, most commonly the relationship between these biological parameters and aforementioned diseases in patient groups diagnosed with AIS, major depression and poststroke depression. In our sample, we determined that there is no significant relationship between major depression and basal proinflammatory cytokines (TNF-α, IL-1 β, and IL-18), BDNF and NSE. It is known that in studies concerning acute ischemia, an increase in proinflammatory cytokines and NSE serum levels were linearly related with infarction size, edema formation and severity of neurological deficits, whereas decreased BDNF serum levels were linearly related to increased stroke risk. On the other hand, studies conducted with individuals with depression revealed an increase in levels of proinflammatory cytokines and a decrease in BDNF levels.

In our study we had expected that in patients with major depression who experienced AIS, compared to nondepressive patients who experienced AIS the serum levels of proinflammatory cytokines would be much higher and BDNF levels would be much lower. However the results from our sample indicate that, even if the presence of major depression in patients affects these parameters, whether just before AIS or not, this effect disappears within hours after AIS. The insufficient of studies concerning the relationship between NSE and depression makes it hard to clearly our results about NSE. However, a similar interpretation could be possible for NSE too.

It has been reported that increased levels of proinflammatory cytokines and decreased serum levels of BDNF exacerbate neurological deficit and increase mortality using worsening of prognosis by effecting functional recovery. Studies have also shown that the relationship between depressive symptoms and increased stroke risk increases ischemic stroke-related morbidity and mortality. Therefore, although we had posited that proinflammatory cytokines and BDNF mediate the negative effect of major depression in patients with AIS to probable prognosis, our results do not support this hypothesis.

Among the possible causes for results not in accordance with our expectations, the first place goes to proinflammatory cytokines (TNF-α, IL-1 β, IL-18) and BDNF. Before we conducted the study, our expectations were shaped because of results obtained from previous studies conducted with psychiatric patients with major depression. Most of these studies were conducted in adolescent and middle-age groups. However, there was a scarcity of relevant studies and limited data available regarding older psychiatric patients with depression. Therefore, the reason that these parameters to be irrelevant for depressive and nondepressive patient groups right after AIS could be specific to this patient group. Second, given

the strict exclusion criteria of our study and NIHSS of patients at admission, it can be observed that the study group is composed of patients with strokes of low and moderate severity. Therefore, we can say that our findings show relevance for patients with strokes with low and moderate severity, rather than patients with strokes with of high severity. Third, we collected the serum samples of the patients within 24 h after the initiation of AIS symptoms. Therefore, even though our aforementioned parameters were affected before AIS in patients with major depression, hours after AIS, they had come to be at similar levels as in nondepressive patients.

We found no study examining the association between preexisting major depression and specific brain regions in AIS in the literature. In studies up to now, even some data that supported the relationship between post stroke depression and specific stroke region, was concluded that the likelihood of a relationship between post stroke depression and a specific stroke region being a major risk factor was weak. On the other hand, some authors stated that, in patient groups where patients were divided as depressive and nondepressive by investigation for diagnosis of post stroke depression, mean hospitalization times were similar. In our sample, preexisting depression was not associated with hospital stay and specific stroke location in AIS. We think this situation may be related to the patient group comprising our sample.

When the results of our study are interpreted some limitations should be taken into consideration. First the study has a relatively small sample size. The strictness of the exclusion criteria of the study led to expulsion of a majority of recruited patients. In addition, in the presence of these exclusion criteria, we think it will be very difficult to study aforementioned biological parameters by recruiting large patients numbers from a single center. Second, the study has a cross sectional but not a prospective observational design. As noted above in our patients group, we collected serum sample within hours after AIS. Ideally studying the relevant biological parameters before AIS by following up patients with major depression who do not have any disease that can cause any neuro-inflammatory response could provide more reliable data. However, the prospective of following up depressive patients who are not receiving antidepressant treatment and being able to collect serum samples just before AIS are quite difficult both ethically and methodologically. In addition, ensuring that post-AIS mean serum sample collecting time is similar for the depressive and nondepressive patients in our study would partially compensate for this limitation.

Regardless of all these limitations, a diagnosis of major depression just before AIS using a psychiatric interview devices structured by a psychiatrist and the expulsion of patients diagnosed with psychiatric disorders other than major depression are powerful parts of our study. In addition, we evaluated current depression, not a preexisting one. Diagnosis of current major depression shows the relationship between depression and relevant parameters just before AIS, compared to preexisting major depression. This is powerful part of our study.

Conclusion

Regardless of limitations, our study results show that, in patients with major depression, an experience of AIS has no effect on proinflammatory cytokines (TNF-α, IL-1 β, IL-18), BDNF, and NSE in acute ischemic stroke patients. For obtaining clearer data and clearer interpretations, controlled studies that are cross-sectional and multi-centered with a large sample are needed.

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Conflict of interest:- There are no conflicts of interest.

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