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ORIGINAL ARTICLE

The Influence of Gender and Laterality of Lesion on Severity of Post-Stroke Depressive Symptoms

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ABSTRACT

Introduction. This prospective study evaluates the effects of gender and stroke lateralization-related differences on the severity of depressive symptoms.

Materials and Methods. A total of eighty right-handed patients (20-80 years of age) were enrolled prospectively. These individuals were in the subacute phase of their first, single unilateral stroke. Thirty-five (44%) were women. The majority of patients (74%) had cerebral infarcts, and 26% had an intracerebral hemorrhage. The Beck Depression Inventory (BDI) edition 2, was used to assess the severity of depressive symptoms. (A cutoff point of 14 or higher was applied to distinguish patients with depressive symptoms).

Results. At discharge from rehabilitation, the BDI-II identified depressive symptomatology in 33% of patients (n=26 patients). Although the frequency of depressive symptoms was similar in both sexes, we identified significant differences in the frequencies of post-stroke depressive symptoms between men and women with different localization of stroke. Females with poststroke depressive symptomatology were more likely to have a cortical lesion, whereas males with poststroke depressive symptomatology were more likely to have a subcortical lesion. We also noted that women had significantly more severe depressive symptoms (higher mean BDI-II scores) than men. In addition, the severity of depressive symptoms was related to the laterality of lesion in men but not in women. Men with left-sided stroke had significantly more severe depressive symptoms than men with right-sided stroke.

Conclusion. Our paper emphasizes the association of gender and laterality of lesion with the severity of post-stroke depressive symptoms.

KEY WORDS

Gender, stroke, lateralization, depressive symptoms.

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Common behavioral and cognitive sequalae of stroke include depression, psychosis, anxiety and personality changes among others.[1,2] The prevalence of post-stroke depression (PSD) is reported to range from less than 30% to more than 50%, depending on methodological differences between studies and especially on the criteria for depression and the period over which depression is assessed.[2,3]Neither the causes nor the mechanisms of PSD are well understood. The higher prevalence of mood symptoms in stroke survivors, as compared with orthopedic patients with the same degree of functional disability, argues against PSD as a purely psychological reaction.[4] PSD likely has a multifactorial etiology with both reactive and organic components. The evidence in humans suggests that injury of specific brain areas with hemispheric and anterior-posterior asymmetries increases the risk of developing PSD.

Robinson et al in a series of articles emphasized that left-sided stroke may be associated with a higher incidence of depression,[5,6] although some investigators were unable to replicate these results.[3] It has been suggested that the strength and direction of experienced emotions should be evaluated within the context of asymmetrical activation of left-frontal (dominance) versus right-frontal (submis-

sion) brain regions.[7] More recently, changes of noradrenergic, serotonergic, and dopaminergic pathways, and neurotransmitter receptor sensitivity have been implicated in the pathogenesis of PSD. The question of much higher lifetime prevalence of major depressive disorders in women compared to men, including stroke survivors, remains unanswered.[8,9] However, numerous gender-related differences in neuroanatomy and neurochemistry are documented. It appears that males and females recruit different brain regions during emotion recognition of happy or sad facial expression.[10] A wealth of preclinical and clinical evidence indicates gender-related differences in serotonin (5-hydroxytryptamine, 5-HT) neurotransmission.[11] Serotonin has been implicated in the pathology of mood disorders, sleep and eating disorders and schizophrenia.

It is important to emphasize that patients with improved depression perceived their recovery as significantly greater than those with continued depression; they also felt that their physical condition and social participation had improved in contrast to those with less improvement in depression.[12]

This prospective study was designed to evaluate the severity of depressive symptoms related to gender- and stroke lateralization in patients after their first, single unilateral stroke.

Materials and Methods

All patients in the subacute phase of stroke admitted to the rehabilitation clinic "Dr M. Zotović" in Belgrade, during a 3-year period were registered prospectively and considered for inclusion for this study. The mean time period from the onset of illness to admission into the study was 91.7 days. During the acute phase of stroke the patients were hospitalized at neurology departments in several hospitals, where the diagnosis of stroke was based on history, clinical examination and neuroradiological findings obtained by head computed tomography (CT) or magnetic resonance imaging (MRI).

On admission to rehabilitation, all patients were assessed by clinical and neurological examinations and neuropsychological and language testing. The severity of the initial stroke was measured by the National Institutes of Health Stroke Scale (NIHSS) score, which is a widely used and validated tool for assessment of stroke severity.[13] According to CT and/or MRI findings, the patients were classified based on localization of the cerebral lesion in the right hemisphere (RH) or left hemisphere (LH) as well as in the cortex or subcortex.

Inclusion criteria were: the first-ever single unilateral stroke, both genders, age 20-80 years, CT or MRI examination performed in the acute hospital phase of stroke and right-handedness (defined by the Clinical test of hand dominance, Kimura & Vanderwolf, 1970). Exclusion criteria were: history of previous stroke, bilateral or multiple cerebral lesions caused by stroke, history of previous psychiatric illness, severe post-stroke cognitive impairment, severe post-stroke aphasia and presence of chronic disabling conditions. None of the selected patients were treated with antidepressant medication or any drug with depression as a known side effect.

The rehabilitation plan was designed by the same physiatrist for all patients; it included physical therapy, occupational therapy, and if necessary, speech therapy. The rehabilitation program was performed 5 days per week over 6-8 consecutive weeks. All patients included in this study completed the rehabilitation program. After receiving a detailed study description, participants provided informed consent to a research protocol, which was carried out in accordance the principles of the Declaration of Helsinki (1964).

At the time of discharge, on average 5.5 months after stroke onset (range 3.5-6 months), we evaluated the severity of PSD. The patients completed the 21-item Beck Depression Inventory, edition 2 (BDI-II), which is a screening instrument designed to assess the severity of depression, not whether a patient meets diagnostic criteria for that disorder.[14] The inventory contains 21 items and identifies symptoms and attitudes associated with depression. The respondent must recall, based on the previous two weeks, the relevance of each statement relating to the following: sadness, pessimism, sense of failure, loss of pleasure, guilt, expectation of punishment, dislike of self, self accusation, suicidal ideation, episodes of crying, irritability, social withdrawal, indecisiveness, worthlessness, loss of energy, insomnia, irritability, loss of appetite, preoccupation, fatigue, and loss of interest in sex. A BDI-II cutoff point of 14 or higher was applied to distinguish the patients with a depressive symptomatology in the clinical range from those with less severe symptomatology.

Statistical analysis. Characteristics of the participants are described by mean and standard deviation (SD) for continuous variables and by frequency and percentage for categorical variables. A difference in mean values of BDI-II or NIHSS scores between two groups of patients was determined by Student t-test. The chi square test was used to assess differences in categorical variables between men and women. Probability values <0.05 were considered significant.

Results

A total of eighty right-handed patients (mean age 55.4 years, SD = 10.6 years, range 20-80 years) in the subacute phase of their first-ever single unilateral stroke were enrolled prospectively. Thirty-five (44%) were female, and 45 (56%) were male. There was no significant difference in mean ages between men and women (55.1 and 55.6, respectively).

Fifty-seven % of females (20 of 35), and 45% of males (20 of 45) had a stroke in the LH, whereas 43 % of females (15 of 35) and 55% of males (25 of 45) had a stroke in the RH. Further, 57 % of females (20 of 35), and 40 % (18 of 45) of males had a stroke localized cortically, whereas 43 % of females (15 of 35) and 60 % of males (27 of 45) had a subcortical stroke. Prior to the initiation of rehabilitation the mean NIHSS score was similar for both men (6.51) and women (6.57) (Table 1).

Table 1. Frequencies of post-stroke depressive symptomatology in men and women with different localization of stroke (Chi square test = 14.197; DF = 3; p<0.01)

Stroke localization	Frequency (n)
Women (n = 12 with depressive symptoms)	
RH cortically	33 % (4 of 12)
LH cortically	50 % (6 of 12)
RH subcortically	0 % (0 of 12)
LH subcortically	17 % (2 of 12)
Men (n = 14 with depressive symptoms)	
RH cortically	14 % (2 of 14)
LH cortically	0 % (0 of 14)
RH subcortically	29 % (4 of 12)
LH subcortically	57 % (8 of 14)

Abbreviations: RH = right hemisphere, LH = left hemisphere

Frequency and severity of post-stroke depressive symptomatology

At discharge from rehabilitation, the BDI-II identified depressive symptomatology in 33% of patients (26 of 80) where the cutoff point of 14 or higher was applied. The frequency of depressive symptoms in the clinical range was 32% in males (14 of 45) and 34% in females (12 of 35). There was no significant difference between these frequencies (Chi square test = 0.09; DF = 1; p>0.05). However, we identified a significant (p<0.01) difference in the frequencies of post-stroke depressive symptoms between men and women with different localizations of stroke (Chi square test = 14.197; DF = 3; p<0.01). Females with poststroke depressive symptomatology were more likely to have a cortical lesion (83%, 10 of 12 patients), whereas males with poststroke depressive symptomatology were more likely to have a subcortical lesion (86%, 12 of 14 patients, Table 1).

We also found that women had significantly (p<0.01) more severe depressive symptoms (higher mean BDI-II score) than men. The severity of depression was dependent on stroke lateralization in males, but not in females. Men with left-sided stroke had significantly (p<0.01) more severe depressive symptoms (higher mean BDI-II score) than men with right-sided stroke (Table 2).

Discussion

The frequency of depressive symptoms (33%) in our study is comparable to the prevalence of PSD reported in previous clinical trials. The prevalence of PSD ranges from less than 30% to more than 50%, depending on the methodological differences between studies, specifically the criteria for depression and the period over which depression is assessed.[2,3]

Bearing in mind that previous clinical trials indicate that recognized risk factors for post-stroke depression include stroke severity and disability, it is important to note that prior to initiation of rehabilitation we noted no gender-related difference in the severity of clinical stroke. However, we found that women with a first-ever single unilateral stroke had significantly more severe depressive symptoms than men. Furthermore, the severity of symptoms was related to the laterality of lesion in men, but not in women. Men with left-sided stroke had significantly more severe depressive symptoms than men with right-sided stroke. Our results concur with previous studies that demonstrated a greater prevalence of post-stroke depressive symptoms in women than in men. However, all of these results remain inconclusive because the question of much higher lifetime prevalence of major depressive disorders in women remains unanswered.[9]

Gender-related differences in neuroanatomy and neurochemistry have drawn increasing interest over the past

Table 2. Differences in mean values of BDI-II scores between men and women, as well as between men or women with right-sided or left-sided stroke

	Men/Women (n = 45) (n = 35)	Men RH/Men LH (n = 25) (n = 20)	Women RH/Women LH (n =15) (n=20)
BDI-II Mean (SD)	10.14 (7.30)/13.25 (8.35)	8.96 (6.92)/11.60 (7.51)	12.47 (7.97)/13.85 (8.74)
T	4.568 (DF =78)	3.198 (DF =43)	1.211 (DF =33)
P	<0.01	<0.01	>0.05

Abbreviations: BDI = Beck Depression Inventory, SD = standard deviation, RH = right hemisphere, LH = left hemisphere.

decades, including differences in the size of brain nuclei, regional concentrations of neuroregulators, pharmacological response and behavior.[9,12] Men synthesize 5-HT significantly faster than women,[15] whereas 5-HT transporters are selectively decreased in an age-specific manner in depressed women, but not in depressed men.[10] Also, gender-specific differences are apparent in brain regions involved in regulating negative or positive emotions.[11,16,17] Numerous clinical measurements on functional cerebral asymmetries indicate that women are less lateralized than men for a variety of cerebral functions. The facial recognition of emotion is distributed more bilaterally in females compared to males, whereas studies of transient mood induction triggered by viewing emotional pictures registered more neural activities in the bilateral superior temporal gyri and cerebellar vermis in females who viewed negative emotional pictures than in male viewers.[18-20] Furthermore, reports on gender-specific differences in hemispheric recruitment suggest that men are right-hemisphere dominant, while the female pattern indicates dominance of the left hemisphere.[21] Importantly, functional cerebral asymmetries likely fluctuate across the menstrual cycle as a result of estrogen and/or progesterone-related modulation of inter-hemispheric inhibition.[22]

Evidence suggests that the injury of specific brain areas in humans increases the risk of developing PSD. In particular, the occurrence of PSD has been linked to injuries of the left anterior frontal lobe and left caudate nucleus, as well as bilateral injuries of the anterior frontal and temporal lobes and caudate nuclei.[6,23] Astrom et al. found that a left-sided lesion was the most important predictor of immediate depression; the occurrence of major depression in left-sided lesions was 10 times greater than in lesions in the right hemisphere.[24] Some other authors have been unable to replicate this association of lesion location and PSD.[3]

A wealth of preclinical and clinical evidence supports the concept of functional cerebral asymmetries for neurotransmitter systems, including neurotransmitter levels, reuptake transporters and receptors, and the effects of drugs that act on these neurotransmitter systems. Two decades ago Mayberg et al. reported right-left asymmetry in functioning of serotonin in healthy normal subjects and stroke patients.[25] Later Fitzgerald suggested that 5-HT preferentially activates the right hemisphere through some unknown mechanism.[26] Postmortem binding studies done with brain tissue from mentally normal humans and the tricyclic antidepressant imipramine (which binds with high affinity to the 5-HT reuptake transporter) indicated higher binding values in the orbitofrontal cortex (connected by the efferent projections with the serotonergic raphe nuclei) of the right hemisphere than in the left hemisphere.[27,28]

If men are more lateralized than women for a variety of cerebral functions,[18-20] if the male pattern of dominance is characterized by the right hemisphere,[21] and if there is serotonergic predominance in the right hemisphere, [26] this might explain why we found more severe depressive symptoms in men with left-sided lesions.

We recognize that our study has limitations. The sample size is small, and the stroke patients participating in the study cannot be considered a random sample. We assessed the severity of depressive symptoms, but not the presence of a diagnosis of depression. For all these reasons, the results of this study cannot be generalized to the entire population of unselected stroke survivors. Despite these shortcomings, our paper emphasizes the association of gender and laterality of lesion with the severity of post-stroke depressive symptoms. The nature of this complex association requires further investigation with a larger number of patients and tools for examining neurotransmitter systems.

Financial disclosure
I declare that I have no conflicts of interest.

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Uticaj pola i lateralizacije lezije na težinu postapoplektične depresivnosti

APSTRAKT

Uvod. Cilj ove prospektivne studije bio je da se utvrdi postojanje razlika u težini postapoplektične depresivnosti u zavisnosti od pola i lateralizacije lezije.

Materijal i metode. Uključeno je ukupno 80 desnorukih bolesnika u subakutnoj fazi prvog unilateralnog moždanog udara, starosti 20-80 godina. Od ukupnog broja bolesnika 35 (44%) su bile žene. Prema kategoriji moždanog udara, 59 (74%) bolesnika je imalo cerebralnu ishemiju, a 21 (26%) intracerebralnu hemoragiju. Kao instrument istraživanja je korišćena Bekova skala za procenu depresivnosti-II (upotrebljen je granični skor 14).

Rezultati. Po završetku rehabilitacije, registrovana je postapoplektična depresivnost u 33% (n=26) bolesnika. Iako je učestalost postapoplektične depresivnosti bila približno jednaka kod oba pola, registrovana je značajna razlika u učestalosti postapoplektične depresivnosti između polova sa različitom lokalizacijom moždanog udara. Žene sa utvrđenom depresivnom simptomatologijom su značajno češće imale leziju korteksa, dok su muškarci sa utvrđenom depresivnom simptomatologijom značajno češće imali leziju subkorteksa. Pokazano je da žene ispoljavaju značajno težu simptomatologiju postapoplektične depresije (više srednje vrednosti BDI-II skora) u odnosu na muškarce. Takođe, registrovana je statistički značajna razlika u težini depresivne simptomatologije u zavisnosti od lateralizacije lezije kod muškaraca, ali ne i kod žena.

Zaključak. Rezultati ove studije ukazuju na značaj pola i lateralizacije lezije na težinu postapoplektične depresivne simptomatologije.

KLJUČNE REČI

Pol, moždani udar, lateralizacia, depresivni simptomi.