Assessment of Anxiety and Depressive Symptoms in the Early Post-stroke Period

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Received: 16 Dec 2019 ♦ Accepted: 1 June 2020 ♦ Published: 31 Dec 2020


Abstract

Introduction: There is some evidence suggesting an association between cerebrovascular diseases and the development of depression on the one hand, and between depression and post-stroke recovery on the other. Post-stroke depression can occur in the early post-stroke period or in the later stages of recovery (over 9 months after the incident).

Aim: To find a connection between stroke and the development of anxiety and depression in the early period after the development of neurological deficit and to evaluate several scales for their potential usefulness in the screening of post-stroke patients for early signs of depression and anxiety.

Materials and methods: We conducted a study on the presence of depression in 117 patients, divided into 2 groups: 73 of these patients were admitted due to ischemic stroke, while the other 44 were controls matching the patients in age, sex and education status. The inclusion and exclusion criteria were defined clearly. We included patients that consented to undergo psychiatric evaluation between 24 hours and 7 days after the onset of neurological symptoms. Both groups were assessed by the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), Hospital Anxiety and Depression Scale – Depression Subscale and Combined Scale (HADS-D, HADS-T).

Results: On evaluation with HADS-D we noted the largest difference between the two groups with a very high statistical significance and a medium effect size (7.92±4.44 points vs. 4.86±4.27 points for the control group, \(p<0.001, r=-0.417\)). Anxiety and depressive symptoms were found also with MADRS and HAM-A.

Conclusions: Anxiety and depressive symptoms were found in the early post-stroke period. MADRS, HADS-D, and HAM-A are sufficiently specific and sensitive in the evaluation of post-stroke anxiety and depression.

Keywords

anxiety, depression, ischemic stroke

INTRODUCTION

Ischemic stroke is the neurological disease with the highest social impact. It ranks fifth among the causes of premature mortality and first among the causes of long-term disability in the USA.\(^1,^2\) Clinicians focus usually on the focal neurological deficit, but the neuro-psychiatric issues arising from stroke are just as important. They can be divided into 2 main groups: cognitive impairment and psychiatric symptomatology. Post-stroke cognitive impairment is widely studied in the context of vascular dementia which is the second most common cause of cognitive impairment.
worldwide. Due to the severity of the classic symptoms of stroke coupled with the fact that some of them (e.g., aphasia) tend to complicate the neuro-psychiatric assessment, affective disorders after stroke often end up neglected. In literature sources, there is evidence suggesting a connection between cerebrovascular disease and development of depression on the one hand, and between depression and post-stroke recovery on the other. According to several different studies, post-stroke depression is developed at some point during their recovery in as many as one-third of stroke survivors. Post-stroke depression according to T. Beblo and M. Driessen has some marked somatic symptoms such as weight loss, appetite loss, and lethargy compared to sleep and ideation pathology. On the other hand, Spaletta et al. focus more on the importance of vegetative symptoms and note that in post-stroke depression all DSM criteria are important.

Post-stroke depression can occur in the early post-stroke period or in the later stages of recovery (over 9 months after the incident). Early post-stroke depression is associated with some common vegetative symptoms and correlates in its severity with lesion volume. Spaletta et al. also noted more prevalent somatic depressive symptoms such as fatigue and psychomotor retardation. Early post-stroke depression has a noted positive tendency of psychic recovery mirroring neurological recovery. This does not seem to be the case in late-onset post-stroke depression.

Neurophysiology of post-stroke depression

It is well documented that the main neuropathological substrate of affective disorders is dopaminergic dysfunction. In the case of depression, there are reduced levels of biogenic amines in the limbic structures of the frontal and temporal lobe, and also in the basal ganglia. Anhedonia is among the main symptoms of depression and its presence is a mandatory diagnostic criterion. This symptom can be explained by the reduced levels of dopamine in the mesolimbic cortex. Reduction of the levels of serotonin and noradrenaline in the limbic system and prefrontal cortex is pointed out as a likely reason for mood changes, and reduced noradrenergic activity in the descendent pathways, regulating pain sensitivity, is the main contributing factor for chronic pain in depressive patients. These pathways can be disturbed both directly by the ischemic lesion and also by secondary degeneration of structures outside the ischemic zone. The binding of monoamine oxidase A (MAO-A) in the prefrontal cortex, the anterior part of the cingulate gyrus and the hippocampus is increased in these patients, further corroborating the impact of monoamines in the pathophysiology of this condition. In addition, imaging of patients suffering from post-stroke depression demonstrates a reduced volume of the prefrontal cortex and the hippocampus, while at the same time there is a heightened basal activity of the ventromedial and lateral part of the prefrontal cortex and the hippocampus. Basal activity in the dorsolateral prefrontal cortex and the posterior part of the cingulate gyrus is decreased. In patients recovering from post-stroke depression, there is a noted return to the pre-stroke levels of basal activity.

AIM

To find an association between stroke and the development of anxiety and depression in the early period after development of the neurological deficit. To evaluate several scales for their potential usefulness in the screening of post-stroke patients for early signs of depression and anxiety.

MATERIALS AND METHODS

We conducted a study on the presence of depression in 117 patients, divided into 2 groups: 73 of them were admitted due to ischemic stroke, while the other 44 were controls matching the patients in age, sex, and education status. The participants for this study were recruited from the patients admitted for treatment in the Neurology Department of a multi-profile hospital.

The inclusion criteria were:
- Patients admitted due to ischemic stroke for whom the stroke is their first cerebrovascular event.
- Patients consenting to undergo psychiatric evaluation between 24 hours and 7 days after the onset of neurological symptoms.
- Participants rated between 2 and 12 points on the National Institute of Health Stroke Scale (NIHSS).
- Patients aged between 18-70 years, to avoid depression arising from the aging process.

The exclusion criteria were:
- Presence of aphasia. Patients suffering from aphasia and/or severe cognitive deficit tend to have significant issues with verbal communication and understanding the questions in specialized scales. In this study, we have excluded these patients, but there are options available that can allow their inclusion. In patients with pure motor aphasia, these difficulties can be overcome with modified visual-analog scales; however, in patients with sensory or global aphasia, a neuropsychological interview is virtually impossible. In such cases, we are forced to rely on information from other sources such as a patient’s relatives or observing non-verbal behavior. For such patients, there is the Structured Aphasia Depression Questionnaire which focuses on somatic symptoms of depression, which can be evaluated through observation. Another option is a modified version of the Hospital Depression and Anxiety Scale (HADS). This option was used by Finkelstein et al. in 1982.
  - Impaired consciousness defined as fewer than 15 points on the Glasgow Coma Scale.
  - Fewer than 26 points on the Mini-Mental State Examination (MMSE).
The presence of psychiatric disorders from the following categories as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) has been diagnosed prior to the cerebrovascular incident:

- Depressive disorders
- Anxiety disorders
- Bipolar and related disorders
- Disruptive, impulse-control, and conduct disorders
- Substance-related and addictive disorders
- Neurocognitive disorders

Evaluations used

- Psychiatric assessment for anxiety and depression via a semi-structured psychiatric interview and a battery of scales for the assessment of anxiety and depression, including the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), Hospital Anxiety and Depression Scale (HADS-D, HADS-T). The Hamilton Depression Scale was not chosen due to its relatively lower sensitivity for the severity of depression and reproducibility of the results across different evaluators. The Zung Self-Rating Depression Scale was also not chosen for this study, as we did not want to use more than one self-rated scale and we decided on the HADS which evaluates both depression and anxiety and is specifically designed for hospital settings. We decided to use only one self-rated scale for comparison and to evaluate the possible discrepancies between the two types of measuring depressive symptoms.

- MADRS is a scale developed in 1974 for the assessment of the severity of depression in patients where it has already been diagnosed. It includes 10 items, covering mood changes, internal tension, sleep changes, concentration, daytime activity, pessimism, and suicidal thoughts. This scale allows a rather precise 6-stage differentiation of the severity of each of the 10 symptoms evaluated. This scale’s main advantage is its quickness and ease of use, and its main flaw is the relatively lower sensitivity for the somatic symptoms of depression.

- HAM-A is among the first scales developed for the evaluation of anxiety and has proven itself over 60 years of clinical practice and clinical trials. It consists of 14 units, covering the psychic and somatic symptoms of anxiety. Each unit is scored between 0 and 4 points and the maximum cumulative score is 56. A score under 17 points is interpreted as none to mild anxiety, 18-24 is mild to moderate and 25-30 is a moderate-to-high level of anxiety. A score of over 30 indicates severe anxiety.

- HADS is a scale for the evaluation of depression and anxiety, specifically developed for use in a hospital setting. It is a self-rating scale consisting of 14 questions covering the main symptoms of depression and anxiety. In certain cases, only part of the scale concerning one of the conditions is used, usually to focus on a higher degree of specificity in diagnosing the particular disorder. This is exactly the case in the current study. This scale is remarkably quick and easy to use and is an excellent choice for screening purposes. It focuses more on the psychic symptoms of depression as opposed to the somatic and unlike MADRS gives significant importance to anhedonia.

Statistical analysis

For statistical processing of the data gathered, we used IBM SPSS Statistics 21.0. We set the cut-off value for statistical significance to reject the null hypothesis at p<0.05. We used Mann-Whitney’s U-test to test the hypothesis of significant difference between the two results of the two unconnected groups, assuming all criteria for the correct usage of this method have been fulfilled. We also calculated the effect size by Rank-Biserial correlation (RBC). We utilized Pearson’s correlation analysis to measure a linear correlation between two numeric values.

RESULTS

Demographic characteristics: the patients’ mean age was 63.5±10.9 years and distribution of education status, consistent with the national average. We enrolled 46 male and 71 female patients. The control group was age-, sex-, and education-level-matched.

<table>
<thead>
<tr>
<th>Table 1. Descriptive statistics comparison between the control and stroke group</th>
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<tbody>
<tr>
<td>MADRS</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>IQR</td>
</tr>
</tbody>
</table>

*IQR – interquartile range
Table 2. Results of the control and stroke groups compared by Mann-Whitney test

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>VS-MPR</th>
<th>Rank-Biserial Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS 0.005 ††</td>
<td>13.055</td>
<td>-0.308</td>
<td></td>
</tr>
<tr>
<td>HAM-A 0.020†</td>
<td>4.642</td>
<td>-0.257</td>
<td></td>
</tr>
<tr>
<td>HADS-D &lt;0.001†††</td>
<td>261.711</td>
<td>-0.417</td>
<td></td>
</tr>
<tr>
<td>HADS-T 0.089</td>
<td>1.704</td>
<td>-0.187</td>
<td></td>
</tr>
</tbody>
</table>

* VS-MPR: Vovk-Sellke maximum p-ratio: Based on a two-sided p-value, the maximum possible odds in favour of H₁ over H₀ equals 1/(-e^p log(p)) for p ≤ 0.37 (Sellke, Bayarri, & Berger, 2001).

Note: For the Mann-Whitney U-test, the effect size is given by the rank biserial correlation. † p < 0.05, †† p < 0.01, ††† p < 0.001

Table 3. Correlation analysis of the connection between patient age and results on the tests used

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>MADRS</th>
<th>HAM-A</th>
<th>HADS-D</th>
<th>HADS-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson's r</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>p-value</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pearson's r</td>
<td>0.203†</td>
<td>—</td>
<td>—</td>
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<tr>
<td>p-value</td>
<td>0.028</td>
<td>—</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Pearson's r</td>
<td>0.164</td>
<td>0.707†††</td>
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</tr>
<tr>
<td>p-value</td>
<td>0.077</td>
<td>&lt;0.001</td>
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<tr>
<td>Pearson's r</td>
<td>0.268††</td>
<td>0.522†††</td>
<td>0.454††</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>p-value</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pearson's r</td>
<td>-0.031</td>
<td>0.404†††</td>
<td>0.495†††</td>
<td>0.581†††</td>
<td>—</td>
</tr>
<tr>
<td>p-value</td>
<td>0.740</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
</tbody>
</table>

† p < 0.05, †† p < 0.01, ††† p < 0.001

In the results of testing with MADRS, there was a significant difference between the patient and control group (median=17 points with IQR=10 vs. median=12 points with IQR=16.5 for the control group, p=0.005 RBC=-0.308) (Tables 1, 2; Fig. 1).

In HAM-A results there was also a significant difference between the results of the two groups with a medium effect size (median=25 points with IQR=14 vs. median=17 points with IQR=17 for the control group, p=0.002, RBC=-0.257) (Tables 1, 2; Fig. 1).

Evaluating with HADS-D, we noted the largest difference between the two groups with a very high statistical significance and a medium effect size (median=7 points with IQR=5 vs. median=3.5 points with IQR=5.25 for the control group; p<0.001, RBC=-0.417) (Tables 1, 2; Fig. 1).

In HADS-T, there was not a significant difference between the scores of the two groups (median=6 points with IQR=5 vs. median=5 points with IQR=4.5 for the control group, p=0.09, RBC=-0.187) (Tables 1, 2; Fig. 1).

Using linear correlation analysis, we found a positive correlation between patients' age and MADRS score (r=0.202, p=0.028) and HADS-D score (r=0.267, p=0.003). On the other hand, such a correlation is not present for the HAM-A and HADS-T results (Table 3).

DISCUSSION

Using MADRS as an evaluation tool, only one of the stroke patients was scored as asymptomatic (≤6). In 1998 Hüwel et al. used the same scale to evaluate patients in the first days after an ischemic stroke. They reported that in the acute phase 55% of all stroke patients showed symptoms of at least a minor depressive episode. They also reported a less pronounced connection between depressive symptoms and the patient's age. They did not find any connection between depression and lesion location, lesion volume, and cognitive deficit. Their data on the frequency of depression in stroke patients as scored with MADRS and also the connection between age and depression is confirmed by the results of the current study, and the results in our cohort are even more strongly in favour of the thesis that there is a marked link between stroke and depression. When evaluated with HAM-A there is greater variability in the results, however, the tendency of stroke patients having a smaller variability and a prevalence of the psychiatric disorder is still notable. On HADS-D testing there is the largest and most statistically significant difference, where the values for the stroke group are mostly borderline or pathological, while the control group's scores are mostly within the norm. This demonstrated that HADS-D, as a scale specialized for the evaluation of depression in a hospital setting, is the most appropriate scale to use for post-stroke depression and its use as a screening method should be strongly considered, to prevent the negative impact of affective disorders on post-stroke recovery. This is the scale that Lincoln et al. used in 1999 in their study of the rehabilitation needs of stroke patients. They report that 1 month after stroke 13% of patients had depressive symptoms, defined by them as a HADS score >10. The results of our current study are similar with 25% of the stroke patients having a HADS score...
The higher percentage of depressive patients can be explained by the fact that we have performed our evaluations at an earlier stage of the post-stroke recovery.35

Another approach to evaluating early post-stroke depression was used by Åström et al. in 1993. They examined a cohort of 98 stroke patients, no more than 7 days after their incident, whom they examined during their hospital treatment (days 4 and 10, and on discharge) and then followed-up on their status for 3 years. The evaluation was performed via a psychiatric interview for the diagnosis of depression by the DSM-3 criteria. On discharge, 25% fulfilled the criteria for a major depressive episode. At three months, the number of depressed patients rose to 31%. After one year, the percentage of depressed patients fell to 16%, at the second year it remained practically unchanged (19%, with 16 patients dropping out) and after three years, the percentage once again rose to 29%, but when the dropping out of another 8 patients was taken into account the difference couldn’t reach significance (p=0.102). Similarly to our study, they evaluated the potential depression in the early post-stroke period, however their lack of success in proving a significant correlation further demonstrates the need for a different battery of scales and evaluations.36 By comparison, our study manages to prove a significant difference by u-test in the depression scales used.

In 2016, Jørgensen et al.37 conducted a large-scale study for the development of depression among patients with a first-time hospitalization for stroke. The study included 15 243 stroke patients and a reference population of 160236 matched for age, sex, and municipality. The presence of depression was defined by hospital discharge diagnoses or antidepressant medication use. Among the stroke patients, 34346 experienced depression within 2 years of stroke, with 17690 it was within the first 3 months after stroke. By comparison, among the control group, 11330 had depression within 2 years of study entry with 2449 developing depression within the first 3 months. These results are similar to ours in demonstrating a notable difference in the incidence of depression after surviving a stroke. Defining depression by discharge diagnosis and medical prescription is a significantly slower method, albeit one that ensures the least number of misdiagnosed patients. Since our study focuses on the early assessment and screening for post-stroke depression, a quicker method was needed, hence the use of the scales described.

Stroke patients demonstrate a particularly large difference with the control group in the two depression scales. The fact that the difference between the two groups is notably more pronounced in HADS-D evaluation points to two main tendencies. The first one is that in self-rating scales patients tend to score themselves more negatively than when evaluated by a specialist. The other one is that HADS-D focuses to a greater degree on motor retardation and anhedonia compared to MADRS and practically excludes ideation pathology such as suicidal tendencies. This is in line with what was reported by Beblo8 and Spalletta9.

CONCLUSIONS

MADRS, HADS-D, and HAM-A are sufficiently specific and sensitive in the evaluation of post-stroke anxiety and depression. Each of them has its own set of advantages. When it comes to the early post-stroke period the
best choice out of them is HADS, which is a self-rated scale, evaluating both types of symptoms in a quick and easy-to-use way. At the same time, its depression subscale HADS-D focuses on symptoms like motor retardation and anhedonia which are shown to be of particular importance in post-stroke depression. A major flaw of this scale that can be pointed out is its relatively lower specificity, due to a possible conflation of depressive symptoms and neurologic deficit from the stroke itself. Despite these drawbacks, this quick and sensitive method is an excellent choice for screening, after which diagnosis can be further established by a neuropsychiatric interview and additional rating scales, among them the classic MADRS scale. Diagnosing post-stroke depression and anxiety is of great importance to the overall recovery of these patients and some of them end up having to be referred to a psychiatrist for long-term treatment.

Funding
The authors have no funding to report.

Conflict of Interests
The authors declare that no competing interests exist.

REFERENCES

Оценка тревожных и депрессивных симптомов в раннем постинсультном периоде

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Дата получения: 16 декабря 2019 ♦ Дата приемки: 1 июня 2020 ♦ Дата публикации: 31 декабря 2020


Резюме

Введение: Есть данные, свидетельствующие о связи между цереброваскулярными заболеваниями и развитием депрессии, с одной стороны, и между депрессией и восстановлением после инсульта, с другой. Постинсультная депрессия может возникнуть в раннем постинсультном периоде или на более поздних стадиях выздоровления (более 9 месяцев после наступления).

Цель: Установить связь между инсультом и развитием тревоги и депрессии в раннем периоде после развития неврологического дефицита и оценить несколько шкал с точки зрения их потенциальной пользы при исследовании пациентов после инсульта на предмет ранних признаков депрессии и тревоги.

Материалы и методы: Мы провели исследование наличия депрессии у 117 пациентов, разделённых на две группы: 73 из них были госпитализированы с ишемическим инсультом, а остальные 44 составляли контрольную группу, соответствуя пациентам по возрасту, полу и образовательному статусу. Критерии включения и исключения были чётко определены. Мы включили пациентов, которые согласились пройти психиатрическое обследование между 24 часами и 7 днями после появления неврологических симптомов. Обе группы оценивались по шкале депрессии Монтгомери-Асберга (MADRS), шкале тревоги Гамильтона (HAM-A), больничной шкале тревожности и депрессии – шкале депрессии и комбинированной шкале (HADS-D, HADS-T).

Результаты: При оценке с помощью HADS-D мы заметили большую разницу между двумя группами с очень высокой статистической значимостью и средней величиной эффекта (7,92 ± 4,44 балла против 4,86 ± 4,27 балла для контрольной группы, р <0.001, г = -0.417). Симптомы беспокойства и депрессии также были обнаружены при применении MADRS и HAM-A.

Заключение: В раннем постинсультном периоде обнаружены симптомы тревоги и депрессии. MADRS, HADS-D и HAM-A достаточно специфичны и чувствительны для оценки тревожности и депрессии после инсульта.

Ключевые слова
тревога, депрессия, ишемический инсульт