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A Comparison between Anxious-Depressive Disorders of Stroke and Multiple Sclerosis Patients, Evaluated with Specific Twin Scales

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Abstract

Objective

High levels of depression and anxiety are usually observed in patients with stroke and multiple sclerosis. Many studies have been conducted to clarify the factors subsuming these disorders, but all these investigations have used structured clinical criteria and general psychiatric scales, not very appropriate to assess these disorders in patients with specific neurological diseases.

Methods

To overcome this problem, we constructed a Post-Stroke Depression Rating Scale and a Multiple Sclerosis Depression Rating Scale, that take specifically into account symptoms and problems observed in stroke and in multiple sclerosis patients. These scales, which are composed by sections, aiming to evaluate specific aspects of the psychological disorders of stroke and multiple sclerosis patients, were administered to 124 stroke, 94 multiple sclerosis patients and 27 patients with endogenous major depression.

Results

Quantitative and qualitative differences were found between our three pathological groups. Fourty-five stroke (37%) and 12 multiple sclerosis (13%) patients were diagnosed as showing major depression-like episodes. The analysis of scores obtained by these patients on the various sections of the Scales showed that depression is greater in endogenous major depression patients than in stroke and multiple sclerosis patients with major depression-like episodes and that different profiles are shown by the various patients groups. Depressed mood is associated with suicidal thoughts and apathy in endogenous major depression patients, whereas it is associated with a high level of anxiety and of vegetative disorders both in stroke and multiple sclerosis patients. Furthermore, depression prevails in stroke patients, whereas anxiety prevails in multiple sclerosis patients.

Conclusions

Psychological factors are on the foreground of anxious-depressive disorders observed in stroke and multiple sclerosis patients.

Keywords

Depression; Anxiety; Stroke patients; Multiple sclerosis patients; Psychological reactions

Introduction

High levels of depression and anxiety are usually observed in almost all the severe medical conditions and in particular in neurological diseases. Depression is, for instance, the psychiatric syndrome that has received most attention in individuals with cancer, where the prevalence of major depression is greater than the 5% expected for the general population [1] reaching sometimes the level of 38% [2]. Analogously, pathological anxiety is commoner in people with cancer than in those with chronic medical conditions [3]. Very similar is the situation in patients with heart disease, because depression [4] and anxiety [5] are more common and severe in patients after an acute myocardial infarction than in the general community. Analogous results are found if we pass from the general medical to the neurological diseases and in particular to the post-stroke depression, that is the most widely studied form of depression in neurological patients. According to epidemiological studies, about 30% of stroke patients develop depression, either in the early or in the late stages after stroke [6] and about 20% of hospitalized stroke patients meet the criteria for major depression [7]. A comparable high level of generalized anxiety has been observed by Astrom [8] in the 3 years following stroke. The situation does not change if we pass from stroke to multiple sclerosis (MS), because results of a recent survey via the Web Portal of the UK MS Register [9] and of a comprehensive review [10] have estimated the lifetime risk of major depression in people with MS to be as high as 50% compared to 10-15% in the general population. Furthermore, Korostil and Feinstein [11] have evaluated that the lifetime prevalence of anxiety disorders in MS patients exceeds the 35%, and high levels of anxiety have been observed in these patients by Janssens et al. [12] both in the first year after diagnosis and at a two-year follow-up. It must be acknowledged, however, that important and rather similar methodological and theoretical objections have been raised to results obtained in these different pathological areas. The methodological objection concerns the fact that in all these studies the prevalence of anxiety and depression has been determined with the Structured Clinical Interview for DSM-5 [13] diagnostic criteria, or with general psychiatric scales, such as the Hospital Anxiety and Depression Scale [14], the Hamilton Depression rating scale [15], the Hamilton Anxiety rating scale [16], the Beck Depression Inventory [17] or the Beck Anxiety Inventory [18]. Now, according to both structured clinical criteria and depression rating scales, a diagnosis of depression can be made if, in addition to a depressed mood or a loss of interest, the patient presents some of the following somatic symptoms: - loss of weight, - sleep disorders, - agitation or motor retardation, - loss of energy, - lack of concentration. But it is clear that in most of the above mentioned pathological conditions some of these symptoms, (e.g. loss of energy, sleep disorders and lack of concentration) can be due to the disease itself and not to a concomitant depression. These tools, constructed to evaluate depression or anxiety in the general population are, therefore, not appropriate to assess these disorders in patients with medical or neurological diseases.

The theoretical problem concerns the fact that, even if the multi-factorial nature of these disorders is generally acknowledged, the prevalence of biological or psychological determinants remains controversial. The nature of the putative biological determinants

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obviously differs according to the disease condition. Thus, both in individuals with cancer and in those with MS it has been hypothesized that part of the depression may be directly caused by activation of the immune system (e.g. [19]) or by pro-inflammatory cytokines, which act on the brain causing behavioural symptoms of sickness and depression (e.g. [20]). On the other hand, several authors have stressed the importance of brain lesions and of their localization in the pathophysiology of depression and anxiety observed both in stroke patients (e.g. [21-24]) and in MS patients (e.g. [25,26]). Other authors, however (e.g. [27-31]) have considered depression and anxiety observed in stroke and MS patients as reactive manifestations to cognitive and functional impairments, rather than a direct result of damage to specific brain regions. In addition to these methodological and theoretical controversies, Schramke et al. [32] have shown that administration of a structured clinical interview and of various rating scales for anxiety and depression result in different estimates of incidence and severity of post-stroke depression and anxiety. They have, therefore, suggested that these scales are sensitive to distress rather than specific for identifying depressive and anxiety disorders in stroke patients.

In order to overcome this problem, we constructed in recent years a Post-Stroke Depression Rating Scale [27] and a Multiple Sclerosis Depression Rating Scale [33], that take specifically into account symptoms and problems usually observed in stroke and respectively in MS patients. These scales are composed by sections, aiming to evaluate specific aspects of the emotional, affective and vegetative disorders of stroke and MS patients and allow obtaining symptomatological profiles for each pathological group. Furthermore, in many sections an effort is made to distinguish biological (unmotivated) from psychological (motivated) aspects of the anxious- depressive disorders.

The scope of the present research consisted in matching the symptomatological profiles shown by groups of stroke and MS patients and by a group of subjects affected by an endogenous form of major depression. Two were the aims of this comparison: (1) to see if the symptomatological profiles of post-stroke and MS patients classified as major depression-like (MDL) episodes (on the basis of DSM-5 criteria) are similar or different from those of patients affected by an endogenous form of major depression; (2) to check if differences could also be found between the symptomatological profiles of stroke and, respectively, of MS patients, because the differences existing between these two diseases from the epidemiological and clinical point of view should provoke a different pattern of psychological and psycho-social reactions.

Methods

Subjects

The study population consisted of consecutive series of 124 stroke patients and 94 patients with multiple sclerosis, admitted at the neurological ward of the Policlinico Gemelli (Catholic University) in Rome and of 27 patients, admitted at the psychiatric ward of the Ospedale Santo Spirito (Rome) with a diagnosis of endogenous major depression.

Stroke patients were included in the study if they met the following criteria: (1) suffered from a single hemispheric stroke; (2) age between 35 and 75 years; (3) time since onset of the stroke between 2 weeks and 6 months; (4) no history of previous stroke, previous depressive episodes or significant psychiatric disorder; (5) absence of dementia or language disorders severe enough to preclude a verbal interview.

Multiple sclerosis patients were included in the study if they met the following criteria: (1) should fulfill revised MacDonald's criteria [34]; (2) minimum disease duration of 5 years; (3) educational level between 8 and 18 years; (4) stable phase of the disease and absence of new T2 or gadolinium enhancing lesions on the MRI; (5) no acute relapse or intensive steroid treatment during the preceding 3 months; (6) no psychiatric disturbances prior to the inclusion in the study. The 94 subjects enrolled in the study, included 61 patients affected by relapsing-remitting, 29 by secondary-progressive and 4 by primary-progressive multiple sclerosis. If patients with stroke or multiple sclerosis had been treated with antidepressants, this treatment was discontinued at least two weeks before the psychiatric assessment. The study was approved by the local Ethical Committee and the patients signed regularly informed consent before being enrolled in the study.

Procedures

The psychiatric assessment was conducted by two of the authors (DQ and CM), who were blind with respect to results of the CT scan or MRI data in the case of stroke or MS patients and to the physical disability level, scored using the Barthel Index [35] in the case of stroke patients and the Expanded Disability Status Scale [36] in the case of MS patients. The examination was always performed in the late morning, to minimize the possible influence of diurnal mood variations. The examination included, in addition to the Structured Clinical Interview for DSM-5 that was used to evaluate presence and clinical type of depression, the following depression and anxiety scales: (a) the Post-Stroke Depression Rating Scale (PSDRS) in the case of stroke patients; (b) the Multiple Sclerosis Depression Rating Scale (MSDRS) in the case of MS patients. The Structured Clinical Interview was conducted first in a private room, lasted about half an hour and preceded the administration of the depression and anxiety scales.

The post-stroke depression rating scale: The PSDRS is a rating scale completed and scored by a professional (neurologist, psychologist or psychiatrist) examiner, following a semistructured patient interview. The scale is composed of 10 sections, each of which aims to evaluate a specific aspect of the emotional, affective and vegetative disorders of stroke patients. The 10 sections take into account the following different components of the anxious-depressive disorders of patients with PSD: (1) depressed mood; (2) feelings of guilt; (3) thoughts of death and/or suicide; (4) vegetative (sleep and appetite) disorders; (5) apathy and loss of interest; (6) anxiety (psychic and somatic anxiety; psychomotor agitation); (7) catastrophic reactions; (8) hyperemotionalism; (9) anhedonia (i.e. an inability to enjoy pleasant experiences); (10) diurnal mood variations.

For each section (with the exception of the last one), scores range between 0 (corresponding to a normal state) and 5 points (corresponding to severe disturbance). In section 10 (diurnal mood variations), scores range between a negative pole (-2), corresponding to an "unmotivated" prevalence of depression in the early morning and a positive pole (+2) corresponding to a "motivated" prevalence of depression during situations stressing handicaps and disabilities. This section was introduced to evaluate if the occurrence of depressive disorders in PSD patients are mainly due to biological, disease-related factors or to psychological and psycho-social factors. Furthermore, to better distinguish biological (unmotivated) from psychological (motivated) depressive disorders, in sections 1, 2 and 3, patients are requested to say if their bad mood, guilt feelings and thought of death are related to aspects of their actual condition or are independent from them.

The multiple sclerosis depression rating scale: The MSDRS draws its general structure from the PSDRS, but has been widely revised to accommodate the specific clinical aspects of anxious-depressive disorders observed in MS patients. For instance, the section (7) of the PSDRS (catastrophic reactions) has been changed with a less specific section (emotional reactivity) and the section (9) anhedonia has been deleted. Apart these differences, the general structure and the sections concerning: (1) depressed mood; (2) feelings of guilt; (3) thoughts of death and/or suicide; (4) vegetative (sleep and appetite) disorders; (5) apathy and loss of interest; (6) anxiety (psychic and somatic anxiety; psychomotor agitation); (8) hyperemotionalism and (10) (diurnal mood variations) are almost identical in the two scales.

Information about validity and reliability of PSDRS and MSDRS can be found respectively in [27] and [33]. The sum of scores obtained on sections 1 to 9 of the PSDRS were considered as the 'global PSDRS score' and allowed to evaluate with a score ranging between 0 and 45 points prevalence and severity of the anxious-depressive disorders of stroke patients. On the other hand, the sum of scores obtained on sections 1 to 8 of the MSDRS were considered as the 'global MSDRS score' and allowed to evaluate with a score ranging between 0 and 40 points prevalence and severity of the anxious-depressive disorders of multiple sclerosis patients. In the present research, these global scores were not used, because our attention was mainly focused on the symptomatological profiles, which could allow us to see: (1) if the profiles of post-stroke and MS patients classified as major depression-like (MDL) episodes (on the basis of DSM-5 criteria) are similar or different from those of patients affected by an endogenous form of major depression; (2) if differences could also be found between the profiles of stroke and of MS patients, because the differences existing between these two diseases from the epidemiological and clinical point of view should provoke a different pattern of psychological and psycho-social reactions.

Assessment of presence and type of depression in stroke and MS patients: The DSM-5 [13] criteria for mood disturbance after a general physical state disorder were used to categorize stroke and MS patients according to presence and type of depression. More precisely, a distinction was made between patients with mood disorders with depressive manifestations (MDDM) that do not satisfy DSM criteria for major depression and patients with major depression-like (MDL) episodes that satisfy DSM criteria for major depression. A diagnosis of 'depression with major depression-like episodes' (MDL) was made, within the depressed patients, when 1 core symptom (depressed mood or loss of interest) was present in association with at least 5 associated symptoms, whereas a diagnosis of 'mood disorder associated with a general medical condition with depressive manifestations' (MDDM) was made when 1 core symptom was present with more than 2 and less than 5 associated symptoms, according to DSM-5 criteria. However, since the aim of the present research consisted in matching the symptomatological profiles of patients with severe depressive disorders, only the profiles of MED patients and of stroke and MS patients presenting a MDL episode were considered in the present study.

Results

Prevalence of depression in stroke and MS patients

On the basis of the above mentioned criteria, 32 (25.8%) stroke patients were classified as non-depressed, 47 (37.9%) as presenting a MDDM and 45 (36.3%) as presenting a MDL episode. Analogously, 44 (49%) MS patients were classified as non-depressed, 37 (39.3%) as presenting a MDDM and 13 (13.8%) as presenting a MDL episode. Both the overall prevalence of depression and the prevalence of patients with major depression-like episodes were greater in stroke than in MS patients with a $p<0.001$

Comparison between the symptomatological profiles of post-stroke and ms patients classified as 'depression with major depression-like episodes' (MDL) and those of patients affected by an endogenous form of major depression EMD

Table 1 reports the mean scores obtained on the common sections of the PSDRS and the MSDRS by our patients with multiple sclerosis (MS), or stroke, classified as 'depression with major depression-like episodes' (MDL) and our 27 patients with a diagnosis of EMD.

To check the significance of differences observed among the various groups and across the scale sections, a two-way ANOVA, in which Patients and Scale Section were the main factors, was undertaken. Multiple 't' tests with Bonferroni corrections were used for post-hoc comparisons. Highly significant effects for Patients groups, ($F=12.34$, $p<0.001$) Scale section ($F=53.57$, $p<0.001$) and Interaction ($F=8.65$, $p<0.001$) were obtained. The difference among the patients' groups (reported in Table 1) was due to the fact that patients with EMD obtained the highest and MS MDL patients the lowest scores on most scales sections. The interaction was due to the following main differences among the patients groups: (1) in the 'Depressed mood' section patients with EMD obtained significantly higher scores than stroke patients with MDL ($t=3.12$, $p<0.01$), who, in turn, scored significantly higher than MS MDL patients ($t=2.97$, $p<0.01$). Differences in the same direction were also obtained in the 'Suicide' section, where patients with EMD obtained significantly higher scores than both stroke patients with MDL ($t=3.91$, $p<0.001$) and MS MDL patients ($t=4.14$, $p<0.001$) and in the 'Diurnal variations'. In this section, scores obtained by patients with EMD were significantly different from those obtained by stroke ($t=3.57$, $p<0.001$) and by MS MDL patients ($t=2.96$, $p<0.01$), because in EMD patients depression tended to prevail in the early morning, whereas in stroke and in MS MDL patients it tended to prevail during situations stressing handicaps and disabilities. EMD patients also obtained the highest scores in the 'Apathy' and in the 'Guilt Feelings' sections. However in the 'Apathy' section only MS-MDL patients obtained significantly lower scores than EMD patients ($t=2.88$, $p<0.01$) and stroke patients with MDL ($t=2.71$, $p<0.01$) and in the 'Guilt Feelings' section no significant difference was found between patients with EMD and the other two pathological groups. (2) In the 'Anxiety' section, on the contrary, the highest scores were obtained by stroke patients and by MS patients. The difference between these groups was not significant, whereas marginally significant was the difference between stroke patients with MDL and patients with EMD ($t=2.03$, $p<0.05$). Furthermore, stroke patients with MDL also obtained the highest scores in the 'Hyperemotionalism' and the 'Vegetative disorders' scales, but only in the first case the difference reached the level of statistical significance with EMD ('t'=3.06, $p<0.01$) and with MS-MDL ($t=2.01$, $p<0.05$), whereas in the second case no significant difference was observed. The differences within the same group between different sections of the PSDRS and of the MSDRS were substantially limited to the fact that MS patients obtained non-significantly higher scores in the 'Anxiety' section, than in the 'Depressed mood' section (Supplementary).

Discussion

Results of the present research showed that: (1) both in stroke and in MS patients the prevalence of major depression was greater than

Table 1: Mean scores and standard deviations obtained on the various sections of the PSDRS and the MSDRS by patients belonging to the various diagnostic groups classified as 'depression with major depression-like episodes' or as endogenous major depression.

	MS		Post-stroke		EMD							
Scale section	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**MS *vs* Post-stroke**		**MS *vs* EMD**		**Post-stroke *vs* EMD**	
							t	p	t	p	t	p
Mood	2.365	0.968	3.347	0.953	4.259	0 .944	2.97	<0.01	n.s.	n.s.	3.12	<0.01
Guilt feelings	1.182	0.995	1.108	1.110	1.740	1.195	n.s.	n.s.	4.14	<0.001	3.91	<0.001
Suicide	0.364	0.940	1.869	1.454	3.407	1.748	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Vegetative disorders	2.000	0.988	2.663	1.120	2.518	1.104	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Apathy	1.182	1.251	2.293	1.227	2.537	1.159	2.71	<0.01	2.88	<0.01	-	-
Anxiety	2.939	1.076	3.184	0.979	2.500	0.854	n.s.	n.s.	n.s.	n.s.	2.03	<0.05
Hyeremotionalism	1.758	0.671	2.684	1.488	0.963	1.125	2.01	<0.05	n.s.	n.s.	3.06	<0.01
Diurnal variations	+0.424	0.562	+0.934	1.123	-0.703	1.030	n.s.	n.s.	2.96	<0.01	3.57	<0.001

the 5% expected for the general population [1]; (2) the prevalence of patients with major depression-like episodes was greater in stroke than in MS patients; (3) significant differences existed between the severity and the symptomatical profiles of post-stroke and MS patients and those of patients affected by EMD.

Furthermore, depressed mood was associated with a high level of anxiety and of vegetative disorders both in post-stroke and MS patients, whereas depressed mood was associated with suicidal thoughts and with apathy in EMD patients. The different nature of depression observed in post-stroke and MS patients, in comparison with that of EMD patients was confirmed by the study of diurnal mood variations, because in EMD patients depression tended to prevail in the early morning, whereas in stroke and in MS MDL patients it tended to prevail during situations stressing handicaps and disabilities [27,33]. Taken together, these data suggest, in agreement with the hypothesis that have motivated the present research, that, even if the multi-factorial nature of anxious-depressive disorders observed post-stroke and in MS patients is not disputed (e.g. [21-26], [37,38]), psychological and psychosocial problems raised by these diseases are probably on the foreground (e.g. [27-31], [39-41]). In a systematic review of the influence that psychological factors can have on health-related quality of life after stroke, van Mierlo et al. [30] have stressed the importance of these factors , whereas Laures-Gore and Defife [42] have shown that in developing post-stroke depression the subjective perception of stress may be more critical than the objective neurological deficit. These claims are quite consistent with the qualitative aspects of the profiles shown by patients classified as MDL post-stroke and in MS. In stroke patients the most challenging problems are the sequelae of an event (the stroke) which has produced in the mature age a loss of functions (such as fluent language or subtle motor functions) which can play a very important role in the representation that the patient can have of himself and of his future [42,43]. The corresponding psychological reactions can consist of depression, apathy, anxiety [42-45] and hyperemotionalism. On the other hand, in MS patients the most challenging aspects of the disease are its unpredictable relapses in various functional domains from a relatively young age, with consequences that can affect working, social and affective aspects of life [40,41]. The corresponding emotional reactions are expected to consist of anxiety (even more than of depression) and of emotional and vegetative disorders [46].

Therefore, even if the occurrence of depression has often been associated to neuronal damage in the left frontal lobe in post-stroke depression [7,21-24] and to lesions in frontal and temporal lobes in depressed MS patients [25,26], several papers have stressed the psychological nature of variables predicting depression both in stroke and in MS patients. Recent studies conducted in stroke patients have shown that perceived stress and depression are strongly related in stroke patients [42] and that psychological factors such as self-efficacy and social support predict the emergence of depressive symptoms in the acute phase after stroke [45]. Other studies have reported that subjects affected by MS are more prone to depression in case of negative attitudes toward the disease [31,46-48] and that the variables more strongly predicting depression severity in MS are the subjects' perception about his/her general and mental health status, and social functioning [47,49]. Taken together, these data and results of our study support the hypothesis that the subjective interpretation of the disease's consequences is one of the main factors in determining depression and anxiety both in stroke and in MS patients. If this claim is correct, a psychological intervention, which addresses patients' illness representations, may assist these subjects in their adjustment to the loss of functions in stroke patients and to unpredictable course of their disease in MS patients.

As for the strength and weakness of the present study, we think that the greater strength consists in the use of two twin scales, specifically taylored on the clinical characteristics of stroke and MS patients (instead of general depression and anxiety scales, such as [14-18]), to evaluate and match the anxious-depressive disorders of stroke and MS patients. On the other hand, the major weakness probably consists of the relatively low number of subjects included in the MS MDL patients. However, the fact of having evidenced significant similarities and differences among the three samples of EMD, post-stroke and MS MDL patients suggests that the advantage provided by the specificity of the scales used probably allowed to compensate the disadvantage resulting from the relatively low number of MS patients investigated.

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