Apathy and Depression Following Stroke

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ABSTRACT

Depression and apathy are the two most frequent behavioral complications of stroke. This article reviews the prevalence of these conditions in poststroke patients, as well as their clinical correlates, longitudinal course, and possible media torso A number of controlled clinical trials of the efficacy of various drugs in the treatment of poststroke depression are also reviewed.

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INTRODUCTION

Depression is the most frequently occurring behavioral problem among stroke victims. Two depressive syndromes-namely, major depression and minor (dysthymic) depression-have been reported in patients with stroke lesions. The most frequent symptoms of poststroke major depression are sadness, anxiety, tension, loss of interest and eoncentration, sleep disturbances with early moming awakening, los s of appetite with weight loss, difficulty concentrating and thinking, and thoughts of death. [1] Minor poststroke depression consists of sadness or anhedonia (ie, los s of pleasure) and at least one but fewer than fouradditional symptoms of major depression.

Marin[2] defined apathy as the absence or lack of feeling, emotion, interest, concem, and motivation. Andersson et aP[3] suggested that the main characteristics of apathy are lack of productivity, effort, structure, and initiative with cognitive symptoms, such as lack of interest, curiosity, concem, and insight into one's own situation, as well as emotional symptoms, such as emotional flattening, unaffectiveness, and lack of responsivity towards positive and negative events. They further noted that apathy may be considered as both a neuropsychiatric syndrome associated with specific aspects of brain damage and a psychological syndrome closely as soeiated with depression.

However, it has not been established whether apathy is either a single symptom or a behavioral syndrome. Moreover, there are no valid diagnostic criteria for this condition, and the extent of overlap between depression and apathy is still unclear. Marin[2] proposed diagnostic criteria for apathy based on the overt behavioral, cognitive, and emotional concomitants of goal-directed behavior. These enteria were recently adapted for patients' neurologic disorders by Starkstein.[4] (Table 1.)

PREVALENCE OF DEPRESSION AND APATHY

The prevalence of poststroke depression in acute and rehabilitation settings is about 40% to 50%, whereas the prevalence in community-based studies has been reported to range around 20% to 25%.[5] About half of these depressed patients meet the criteria for major depression, whereas the remaining half meet the criteria for minor (dysthymic) depression. In a study of 103 consecutive patients admitted to the hospital with acute cerebrovascular lesions, Robinson and colleagues[6] found that 27% met symptom criteria for major depression and 20% met symptom criteria for minor depression. Most other studies of patients hospitalized with cerebrovascular lesions in acute or rehabilitation settings have reported similar frequencies of major depression (11 % to 27%) and minor depression (20% to *40%)Y*

The frequency of depression in community settings, however, appears to be lower. Among 89 community patients examined during the first month poststroke, House and associates[9] found that II % had major depression and 12% had other types of depression. Burvill et all[O] found that 15% of 294 community patients with an acute stroke had major depression and 8% had minor depression.

Few studies have examined the prevalence of apathy in stroke patients. In a consecutiv~ series of 80 patients with acute stroke lesions, Starkstein and colleagues[11] found both apathy and depression in 9 patients (11 %), apathy alone in 9 patients (11 %), depression but no apathy in 18 patients (23%), and neither apathy nor depression in 44 patients (55%). These findings demonstrate that depressed patients are no more likely to have apathy than nondepressed patients. Another interesting finding of this study was that among depressed patients, apathy was significantly more frequent in those with major depression compared with those who had minor depression. This suggests that while major depression and apathy can occur independently, apathy is significantly associated with major but not minor depression.

Among patients with chronic stroke lesions, Marin and cowokers[12] reported a prevalence of apathy of 18% (23% in patients with right hemisphere lesions and II % in those with left hemisphere lesions). Coexistent apathy and major depression were present in only 1 of the 40 patients, suggesting that apathy and major depression may be significantly associated early after stroke but not in the chronic stage. In a recent study, Andersson et aP[3] noted apathy in 57% of stroke patients, 46% of patients with a traumatic brain injury, and 79% of patients with hypoxic brain damage due to cardiac arresto Similar to the findings by Starkstein and colleagues,[11] they found a significant overlap between apathy and depression in their group of stroke patients. ~

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CL/N/CAL CORRELATES OF DEPRESS/ON AND APATHY

The extent of the association between poststroke depression and deficits in activiti es of daily living (ADL) has been a debated issue. Among acute stroke patients, most studies have found only a weak albeit significant correlation between depression and deficits in ADL (ie, more severe deficits in ADL correlated with more severe depression).51t was difficult to determine whether the,functional impairment produced depression or depression influenced the severity of functional impairment, but there is evidence that depression adversely affects poststroke recovery in ADL. Parikh and associatesl3 found that 2 years after an acute stroke, patients with in-hospital poststroke depression had a significantly poorer recovery in ADL than nondepressed stroke patients with a similar severity of in-hospital deficits. Herrmann et ap4 reported significant correlations between depression and both functional outcome and handicap at 3 months and at 1 year after stroke, and Ramasubbu and coworkersl5 reported that depression, older age, poor prestroke physical activity, and prestroke disturbances in sexual functioning were all associated with more severe deficits in ADL after stroke.

Several studies have reported that patients with major depression after left hemisphere lesions had more severe cognitive deficits than nondepressed stroke patients.16 These cognitive deficits were observed in a variety of neuropsychological domains, including orientation, language, visuoconstructional ability, and executive motor functions. On the other hand, no significant differences in cognitive tasks were reported between depressed and nondepressed patients with right hemisphere lesions. In a longitudinal study, Downhill and Robinson17 found that in the acute stage, poststroke patients with major depression after left hemisphere strokes had significantly lower Mini-Mental State Exam scores than nondepressed patients; this association persisted for up to 1 year after stroke.

Poststroke depression also has been reported to be significantly associated with increased mortality. Morris and colleagueslS reported that patients with poststroke depression were 3.4 times more likely to have died during a 10-year follow-up period than nondepressed patients, and Everson and coworkersl9 reported a similar significant

relationship between depressive symptoms and a higher stroke mortality.

Initial studies by Robinson et apo and Starkstein et aP found a significant association between major depression and stroke lesions in both cortical and subcortical regions of the left hemisphere-primarily, the lateral frontal cortex and the basal ganglia. In a study that included a consecutive series of 193 patients participating in the Stroke Data Bank, Morris and colleagues22 found a significant association between depression and smallleft hemisphere lesions. Although these findings were replicated by independent laboratories,S,23 other authors had different results9,24; methodological aspects may account for these discrepancies.

Another interesting finding from the studies by Robinson et apo and Starkstein et aFI was a significant correlation between depression scores and the distance of the lesion fram the frontal pole for both left cortical and left subcorticallesions (ie, the more anterior the lesion, the more severe the depression), suggesting that lesion location along the anterior-posterior brain axis is an important variable in the severity of depression following stroke. Longitudinal studies have found that proximity of the les ion to the frontal pole is strongly associated with severity of depression during the first 6 months poststroke but not after this time period, suggesting that the mechanism of poststroke depression is a dynamic one that changes over time.25,26

The clinical correlates of apathy in patients with stroke have been rarely examined. In their study on poststroke apathy, Starkstein and colleaguesll reported that apathetic patients were older and had a greater degree of physical and cognitive impairment than stroke patients without apathy. Okada and associates27 assessed a series of 40 acute or chronic stroke patients for the presence of apathy, depression, and cognitive deficits. They found that most of their patients with mild dementia were also apathetic (77%). AIso, there were significant correlations between severe apathy and poor scores on tests assessing verbal fluency.

Andersson et aP assessed psychological reactivity in patients with either stroke lesions, traumatic brain injury, or cerebral hypoxia, using recordings of heart rate and electrodermal activity during an activation cognitive task. They found a significant inverse association between apathy and heart

rate reactivity, but no significant association between electrodennal activity and severity of apathy. They suggested that heart rate hypore-activity in response to mental stress may be the autonomic expression of the lack of interest, disengagement, and reduced emotional responsivity of apathetic patients.

Several studies have examined the association between apathy and les ion s in specific brain regions. Bogousslavsky et ap8 reported apathy in patients with bilaterallesions to ventrolateral and dorsomedial thalamic nuelei. Helgason and associates29 found a higher frequency of apathy in patients with lesions to the anterior choroidal artery territory, which ineludes the posterior limb of the internal capsule as well as the adjacent globus pallidus. Starkstein and colleaguesll reported that four of six patients with apathy had lesions involving the posterior limb of the internal capsule compared with one of eight patients with neither apathy nor depression. Andersson et aP found a higher prevalence of apathy in patients with either subcortical (79%) or right hemisphere (69%) lesions compared with patients with left hemisphere damage (28%).

Okada and colleagues27 examined the association between apathy and specific changes in regional cerebral blood flow using single photon emission computed tomography in a sample of 40 patients with stroke lesions. The main finding was that patients with apathy had significantly lower cerebral blood flow in the right dorsolateral frontal and anterior temporal regions, as well as in the left premotor and anterior temporal regions compared with patients without apathy.

LONGITUDINAL EVOLUTION OF DEPRESSION AND APATHY

The longitudinal course of poststroke depression has been investigated by several researchers. Some studies have suggested that depressive symptoms largely remit over time, whereas others suggest a remarkably chronic course.5 Robinson and associates3O reported that 60% of patients with major depression at the initia! evaluation were still depressed 1 year after stroke, but none of the patients had major depression at the 2-year evaluation. However, 60% of patients with dysthymia in the hospital were still depressed at the 2-year evaluation.

Other authors ha ve found that most patients with minor depression were not depressed 3 to 6 months after the stroke.

Morris et aF found that among a group of 99 patients in a stroke rehabilitation hospital, those with major depression had a duration of depression of 40 weeks, whereas those with adjustment disorders (minor depression) had a duration of depression of only 12 weeks. Astrom and colleagues26 showed that eight of 14 stroke patients (57%) with acute onset major depression had recovered within 1 year after stroke, but among the six patients who were still depressed, only one had recovered by the 3-year follow-up. Starkstein et aPI demonstrated that lesion location may influence the duration of poststroke depression, since patients with subcortical (primarily basal ganglia) and cerebellar/brain stem lesions recovered significantly faster from depression than patients with corticallesions.

To our knowledge, there are no longitudinal studies of apathy in stroke patients. Marin and coworkers32 reported on four patients who developed apathy in the acute stage after a cerebrovascular accident and were still apathetic 9 months later, suggesting that apathy may constitute a pervasive behavioral change in stroke victims.

MECHANISMS OF DEPRESSION AND APATHY

Dysfunction of biogenic amine systems may play an important role in the mechanism of poststroke depression. Mayberg and associates33 found that right hemisphere stroke lesions produced a significantly higher ratio of ipsilateral-to-contralateral spiperone binding (primarily to serotonin receptors) in uninjured parietal and temporal cortices compared with similar left hemisphere strokes. On the other hand, patients with left hemisphere strokes showed a significant inverse correlation between the amount of spiperone binding in the left temporal cortex and depression scores (ie, higher depression scores were significantly correlated with lower spiperone binding). These findings suggest that a greater depletion of biogenic amines in patients with left hemisphere lesions may lead to left temporallobe dysfunction and ultimately result in depression.

Further evidence of serotonergic dysfunction as a mediator of poststroke depression was provided in a pilot study by Breyer and colleagues,34 who showed that depressed stroke patients had a significantly lower concentration of 5-hydroxyindoleacetic acid (a

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serotonin metabolite) in the cerebrospinal fluid than nondepressed patients with comparable strokes or controls without strokes.

Several studies have demonstrated a high frequency of apathy after lesions involving the globus pallidus and the adjacent internal capsule.ll,29 The ansa lenticularis is one of the main internal pallidal outputs, ending in the pedunculopontine nucleus after going through the posterior limb of the internal capsule.35 In cats and rodents, the ansa lenticularis is localized within the mesencephalic locomotor region and sends monosynaptic projections to motoneurons in the anterior horno The ansa lenticularis may have a prominent role in goal-oriented behavior,36 and dysfunction of this system may explain the presence of apathy in patients with lesions of the posterior limb of the internal capsule. The frequent association between major depression and apathy may result from lesions to the ventral striatum, producing disruption of biogenic amine pathways and damage to the contiguous posterior limb of the internal capsule, which may in turn produce dysfunction of goal-motivationallocomotor systems.

Other mechanisms of apathy after focal brain lesions have also been proposed. Heilman et ap7 suggested that apathetic and indifferent behaviors after right hemisphere stroke lesions may result from dysfunction of corticolimbic-reticular systems important for attention and arousal. In addition, Cummings38 as well as Okada and associates27

proposed that poststroke apathy may result from dysfunction of the anterior cingulate and frontal areas, including dysfunction in the connections of these regions with the basal ganglia and thalamus.

TREATMENT OF DEPRESSION AND APATHY

Three controlled studies have demonstrated that poststroke depression may be effectively treated with antidepressant drugs. Lipsey and colleagues39 examined the efficacy of nortriptyline in a randomized, double-blind, placebo-controlled study. The initial dose was 20 mg daily for the first week, which was increased to 50 mg daily for weeks 2 and 3, 75 mg daily for week 4, and 100 mg daily for weeks 5 and 6. Patients taking nortriptyline showed significant improvements in depression scores compared with the placebo group. The most frequent side effects were dry mouth and constipation, and three patients had to discontinue nortriptyline because of delirium, drowsiness, and agitation. Contraindications to the use of tricyclic antidepressants include heart block or severe conduction abnormalities, myocardial infarction within the past 6 months, significant prostatism, narrow-angle glaucoma, and medications that may adversely interact with this type of antidepressant. Improvement in depression scores was dose related.

In a study comparing trazodone vs placebo, Reding et al40 found that depressed stroke patients who had a positive dexamethasone suppression test had greater improvements in ADL than patients on placebo. Trazodone was started at a dose of 50 mg daily, and then increased by 50 mg every 3 days until a total dose of 200 mg daily was achieved. The sedation produced by trazodone may limit its usefulness in stroke patients.

Two studies have examined the efficacy of selective serotonin reuptake inhibitors in poststroke depression. Andersen and associates41 examined the efficacy of citalopram in a 6-week, double-blind, placebo-controlled study that included a series of 66 patients, Patients on citalopram showed a significant mood improvement compared with the placebo group, and the only si de effects of citalopram were transient increases in astheni a, lassitude, and fatigability during the first week of treatment.

In a recent study, Robinson and colleagues compared nortriptyline and fluoxetine with

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TABLE 1. **DIAGNOSTIC CRITERIA FOR APATHY**

A. Lack of motivation relative to the patient's previous leve! of functioning or the standards of his or her age and culture as indicated either by subjective account or observation by others.

B. Presence of at least one symptom belonging to each of the following three domains:
- Diminished goal-directed behavior
  - Lack of effort
  - Dependency on others to structure activity
- Diminished goal-directed cognition
  - Lack of interest in leaming new things or in new experiences
  - Lack of concem about one's personal problems
- Diminished concomitants of goal-directed behavior
  - Unchanging affect
  - Lack of responsivity to positive or negative events

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to diminished level of consciousness or the direct physiologic effects of a substance (eg, a drug of abuse or a medication).

placebo in the treatment of and recovery from physical and cognitive impairments following stroke in a 12-week treatment study that included 104 patients with acute stroke (unpublished data, 1999). Nortriptyline was started at a dose of 25 mg daily and gradually increased to 100 mg daily, whereas fluoxetine was started at 10 mg daily and gradually increased to 40 mg daily. The main finding was that nortriptyline produced a significantly higher response rate than fluoxetine or placebo in treating poststroke depression, with response rates of 77%, 14%, and 31 %, respectively. Nortriptyline also produced significant improvements in ADL and anxiety symptoms compared with both fluoxetine and placebo. However, neither nortriptyline, fluoxetine, nor placebo produced significant improvements in social functioning or cognitive deficits.

To our knowledge, no controlled pharmacologic studies of apathy in stroke patients have been performed. Marin et al32 treated a series of four stroke patients who met criteria for apathy with a variety of psychopharmacological agents. They suggested the use of direct dopamine receptor agonists (eg, bromocriptine) for patients with basal ganglia and frontal lobe lesions, whereas patients with multiple infarcts may obtain greater benefit from either stimulant drugs (eg, methylphenidate and dextroamphetamine) or indirect dopamine drugs (eg, amantadine and bupropion). In the case of patients with both apathy and depression, the authors suggested the use of antidepressants with a more stimulant profile (eg, bupropion or tranylcypromine), and stimulant medication (eg, methylphenidate or dextroamphetamine) for residual symptoms of motivationalloss, such as lack of energy, lack of drive, or lack of initiative.

CONCLUSIONS

Depression is one of the most common behavioral manifestations of stroke lesions. About 40% of patients with acute strokes and 20% of stroke patients living in the community may show either major or minor (dys

thymic) depression. Poststroke depression is significantly related to more severe cognitive deficits, less recovery in ADL, and left anterior cortical or subcorticallesions. Controlled drug trials have demonstrated the efficacy of nortriptyline and citalopram in the treatment of poststroke depression.

Apathy is another frequent complication of stroke. About 10% of patients with stroke lesions may show apathy as the single behavioral change, whereas another 10% may show comorbid apathy and depression. Apathy after stroke is significantly associated with older age, more severe cognitive deficits, lesions to subcortical structures (such as the posterior limb of the internal capsule), and frontotemporal hypoperfusion. There are no controlled studies of the usefulness of psychoactive drugs in apathy, but stimulants and dopaminergic agonists have been reported to produce someimprovement. ∼

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