Neuroendocrine, Cognitive and Structural Imaging Characteristics of Women on Longterm Sickleave with Job Stress–Induced Depression

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Background: *A recent increase in long-term sick leave (LTSL) in Sweden affects mostly women in the public sector. Depression-related diagnoses account for most of the increase, and work-related stress has been implicated.*

Methods: *We examined dexamethasone/corticotropin-releasing hormone (dex/CRH) test responses, magnetic resonance imaging measures of prefrontocortical and hippocampal volumes, and cognitive performance in 29 female subjects fulfilling three core criteria: 1) LTSL>90 days; 2) unipolar depression or maladaptive stress reaction with depressed mood; 3) job-related stress given as a reason for disability. This group was compared with 28 healthy matched controls.*

Results: *The cortisol response to CRH differed markedly between the two groups (p = .002), with a dampened response in patients. This difference remained after removing subjects on antidepressant drugs (p = .006) or smokers (p = .003). Neither hippocampal nor prefrontocortical volumes differed. Performance on hippocampus-dependent declarative memory tests did not differ between groups, but the LTSL group had impaired working memory.*

Conclusions: *Our most salient finding is an attenuated dex-CRH response in patients on LTSL due to job-stress related depression. This is opposite to what has been described in major depression. It remains to be established whether this impairment is the end result of prolonged stress exposure, or a pre-existing susceptibility factor.*

Sweden has experienced a dramatic increase in long-term sick-leave (LTSL), mainly accounted for by psychiatric diagnoses. The largest increase of LTSL has occurred in the public sector. The underlying causes and potential commonalities that would prompt a study of LTSL as a syndrome in its own right are presently unclear. There are, however, several indications that a study focusing on this growing population is of considerable interest. Thus, the increase in LTSL is largely accounted for by diagnoses of depression, anxiety and maladaptive stress reactions, while the prevalence of psychotic disorders and substance abuse has not increased as a cause for LTSL. The most overrepresented group on LTSL are workers in the health and human services (HHS) sector. Women constitute a majority of the workforce in this sector, and the largest increase in LTSL has been among women, accounting for two thirds of total Swedish LTSL. The Swedish HHS sector has experienced repeated reorganizations and downsizing during the last decade, providing a plausible cause for increased social stress in the work place, and leading to suggestions that this may have contributed to the increase in LTSL. Taken together, these observations suggest that the increase in LTSL may reflect a range of responses to an increased load of social stress. Furthermore, LTSL per se carries with it significant consequences related to altered life style, decreased social interaction, and loss of income.

Although depressive syndromes and maladaptive stress reactions account for the recently observed increase in LTSL, the underlying statistics are based on insurance databases of clinical diagnoses. This is a potential source of error. However, using validated, structured face-to-face interviews, SCID I and SCID II (First et al 1997a, 1997b) on a sample of 200 private employees on LTSL, we found that about 80% of the participants indeed met diagnostic criteria for major depressive disorder while, for example, personality or substance disorders were rare. Subjectively, 45% of subjects attributed their illness to prolonged job stress, 41% to job stress in combination with factors in their private life and 11% to factors in their private life only (Rylander et al, unpublished data). Participants described a characteristic course, with symptoms gradually evolving over time, initial symptoms of aches and pains, palpitations, fatigue, and irritability. A majority reported pronounced memory and concentration problems. This clinical presentation has also been reported in relation to other chronic stressors (McEwen 2000).

The hypothalamic-pituitary-adrenal (HPA) axis is a key mechanism linking life events and disease. Its activation is an adaptive mechanism in the short term, primarily aimed at coping with acute physical challenges. In contrast, its chronic activation caused by complex psychological demands imposes an "allostatic load." This refers to the wear and tear caused by the demand to maintain regulatory stability at abnormal levels of activation. Depression, decreased hippocampal volume and impaired cognitive function have perhaps attracted the most interest among potential consequences of allostatic load, and may be interrelated through a dysregulation of the HPA axis leading to chronic hypercortisolemia (Holsboer 2000; McEwen 2000).

Early studies of depressive illness described non-suppression of cortisol secretion in the dexamethasone suppression test, DST. It has subsequently become clear that the relation between HPA axis dysfunction and depression is more complex, and hypercortisolism is only seen in approximately half of depressed patients, yielding an only 25% overall sensitivity for the DST (Strohle and Holsboer 2003). Despite this, there is broad agreement that HPA axis dysfunction is of central importance in

depression (Holsboer 2000; Nemeroff and Owens 2002). To more precisely probe the dynamic status of the HPA axis, an improved challenge test has been developed, in which corticotropin-releasing hormone (CRH) stimulation is given after dexamethasone pre-treatment (the combined Dex-CRH test). This test is thought to have a 80–90% sensitivity for detecting depression (Heuser et al 1994).

The hippocampus is involved in acquisition of declarative memory, and in the regulation of endocrine stress responses. It is rich in glucocorticoid receptors involved in feedback inhibition of the HPA axis, and lesions to this structure lead to elevated resting as well as stress-induced glucocorticoid levels. Glucocorticoids in turn increase hippocampal susceptibility to a wide range of insults. Decreased hippocampal volume has been reported in three conditions which involve stress exposure and/or pathological HPA axis activation, and where also impaired memory function is a common symptom: major depression, post-traumatic stress disorder (PTSD) and Cushing's disease (Bremner et al 1993, 1995, 2000; Sheline et al 1999, 2003; Starkman et al 1992, 2001). Hypercortisolism is present in about 50% of depressed subjects, and is an invariable component of Cushing's disease. In Cushing's disease tumor extirpation has led to normalization of glucocorticoid levels and also to increased hippocampal volumes (Starkman et al 1999). In depression, hippocampal volume reduction has been reported after multiple depressive episodes, but not in first-episode patients (MacQueen et al 2003). Furthermore, a correlation between duration of untreated depressions and hippocampal atrophy was found in female depressed subjects (Sheline et al 1999, 2003). Together, these findings indicate that hippocampal volume loss and by extension potentially also accompanying cognitive impairment may be the result rather than the cause of depression.

Here, we investigated women employed in the HHS sector, recruited on the basis of three core criteria: 1) presence of LTSL with a duration of >90 days; 2) a diagnosis of depression or maladaptive stress syndrome with depressed mood; 3) self-report of job stress as a factor significantly contributing to the disability. This selection was aimed at recruiting a group representative of the factors that account for the recent increase in LTSL, where these three phenomena coincide. To obtain insights into the processes leading to this phenomenon, we evaluated whether this group shows altered HPA-axis function, if their hypothesized chronic stress exposure is reflected in decreased hippocampal volumes, if subjectively reported cognitive impairment would be detected by cognitive tests, and if so whether a relation would exist between hippocampal volume loss and cognitive symptoms. Our primary hypothesis was that the cortisol response would be exaggerated, as previously described in major depression; the secondary hypothesis was that this might be accompanied by structural and cognitive impairments characteristic of a chronic hypercortisolemic state.

Methods and Materials

Subjects and Overall Design

The study was approved by the Karolinska Human Subject Ethics Committee North (Dnr. 01/373). All subjects gave their written informed consent.

Participation Criteria. Participants were subject to the following criteria: Inclusion: female gender; 40–55 years of age; employed in the health care sector or as a teacher, child caretaker, psychologist or social worker in Stockholm; working ≥ 30 h/week for ≥ 3 years in their profession before becoming

ill or being included as controls; right handed; learned Swedish in childhood; Exclusion: any ongoing daily medication except estrogen or contraceptives; in the patient group, antidepressants were also allowed, but a subgroup analysis was carried out for antidepressant medication-free subjects; past or present serious medical condition such as neurological, endocrine or psychotic disease; history of head injury with loss of consciousness for a minimum of 10 minutes; hazardous alcohol consumption, as defined by a score of >6 points on the Alcohol Use Disorders Identification Test (Saunders et al 1993); self-reported illicit drug use.

Additional Criteria for the Patient Group. Inclusion: on full-time sick-leave 3–8 months, major depression or adjustment disorder with depressed mood according to DSM IV; factors related to work reported as the main problem on axis IV and present for >6 months.

Additional Criterion for Controls. Exclusion: any past or present psychiatric diagnosis.

Recruitment Process. Details of the patient recruitment procedures are given in Supplement 1. Ultimately, 44 women underwent a diagnostic interview, after which 11 were excluded while two chose not to participate. Following initial inclusion, two of the 31 remaining patients had pathological findings on the MRI brain scan (intrasellar cyst and intrasellar mass, respectively), leaving 29 patients for the data analysis. The characteristics of this sample are given in Tables 1 and 2. The age of this group was 47.3 ± 4.8 (mean ± SD) and mean days on sick leave when contacted were 168.4 ± 33.2, very similar to the 115 subjects that we failed to reach or who declined either contact or participation (age: 46.1 ± 4.1; mean days on sick leave 167.4 ± 33.0).

Controls were recruited through advertising at workplaces in the human services sector in Stockholm county. The ad text and details of recruitment procedure are given in Supplement 1. Seven hundred fifty subjects responded to the ad and were informed and screened by telephone. Ultimately 210 persons were selected as potential controls, to be matched for hormonal

Table 1. Descriptive Characteristics of the Patient and Control Samples

	Patients (n = 29)	Controls (n = 28)	p-Value
Age, years	47.8 ± 4.9	47.6 ± 4.2	.92
Hight, cm	167.4 ± 6.1	167.5 ± 5.3	.95
Weight, kg	71.0 ± 12.2	66.8 ± 9.9	.16
Current nicotine use	10	7	.56
Hormonal phase			
Premenopause	17	15	.79
Perimenopause	2	3	.67
Postmenopause + oestrogen	4	5	.73
Postmenopause − oestrogen	6	5	1.00
Education			
1–9 years	6	3	.47
10–12 years	8	9	.78
>12 years	15	16	.79
Family situation			
Single household	5	4	1.00
Single + children living at home	3	4	.71
Partner + children living at home	13	15	.60
Partner − children living at home	8	5	.53

No differences were found for a number of potentially confounding variables which were analysed. Continuous variables are given as mean ± SD, with corresponding p-values generated using two-tailed t-test. Count variables are given as absolute frequencies, and compared using Fishers Exact Test.