Differential Diagnosis of Depressive Pseudodementia and Primary Degenerative Dementia

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One major manifestation of the complex interaction of aging and mood is the considerable overlap of symptoms in depressive and dementing disorders. Therefore, it is not surprising to clinicians that a patient with Alzheimer’s disease should be vulnerable to affective decompensation, nor that the superimposition of a depressive illness upon a fragile aging person should produce cognitive impairment. Indeed the interrelationship of depression and dementia is one of the central clinical and experimental problems of geriatric psychiatry.

Although it would be ideal to see depression and dementia in “pure culture” at a clinical level, in reality the geriatric patient with symptoms of both depression and dementia frequently presents diagnostic, therapeutic, and prognostic uncertainties. For example, Folstein and McHugh estimate that approximately 50% of elderly depressives (aged 60 or over) have cognitive deficits similar to patients with dementia of the Alzheimer type or secondary to cerebrovascular accidents.1 Roth estimates that approximately 15% of depressed patients aged 60 or over have cognitive deficits.2 Conversely, estimates of the frequency of depressive symptoms in dementia have varied from 2.7% to 25%.3 A conservative summary of existing data would show that at least 10% of elderly depressives have cognitive deficits of such severity that at first glance these patients appear to have an organic dementia.

These estimates suggest that patients with symptoms of both depression and dementia may be heterogeneous not only with respect to laboratory findings, family history, response to antidepressant chemotherapy or electroconvulsive therapy, and long-term follow-up, but also with respect to underlying pathophysiological mechanisms. The prevailing conceptualization of “depressive pseudodementia” is that it is a retrospective diagnosis based upon the reversibility of cognitive impairment through adequate treatment of depression. The experimental question is whether reversible dementia associated with depression
Elderly depressives with reversible dementia are not at increased risk for developing senile dementia of the Alzheimer type.

has a pathogenesis similar to that of depression itself, perhaps based upon age-related changes in the brain. Alternatively, some elderly depressives with cognitive impairment may in fact be in the early stages of Alzheimer’s disease (or have other types of dementia), but cognitive impairment does not become clinically evident until depression supervenes. Available follow-up studies suggest that approximately 60% of elderly depressives will recover with or without a subsequent episode, that less than 10% will die each year, and that only 1% to 2% per year will develop dementia—a rate similar to that seen in the general older population. In contrast, the death rate associated with Alzheimer’s dementia is higher; estimated by Kay to be about three times that of depressed elderly and almost four times that of normal elderly. These findings suggest that elderly depressives with reversible dementia are not at increased risk for developing senile dementia of the Alzheimer type, even though our clinical experience suggests some may be at increased risk for institutionalization.

Because of the overlap in symptoms, the heterogeneity of the group, and the potentially tragic implications of misdiagnosis, a need for objective indicators of depression and dementia clearly exists. The goal of this paper is to review currently available diagnostically procedures and, as well, describe briefly a new experimental approach, the use of EEG sleep measures, which offers promise for both clinical diagnosis and experimental elucidation of underlying pathogenetic mechanisms. What follows, therefore, is a review of clinical approaches to the differential diagnosis (including history, mental status, and neurological examination), followed by a review of recent pertinent developments in clinical laboratory approaches, and concluded with a brief overview of a new experimental approach using EEG sleep measures.

CLINICAL APPROACHES TO DIFFERENTIAL DIAGNOSIS

■ History

The differentiation of depression and dementia is difficult in the absence of an independent or corroborating history, particularly in cases of more severe illness with recent onset (eg, 6 to 9 months). Identification and management of treatable diseases are, of course, the primary objectives of the clinician. The developmental course of an affective illness can often be distinguished from that of progressive brain failure by ascertaining which symptoms occurred first: those of disturbed mood and affect (eg, loss of interest, confidence, and drive), or those of disturbed cognition (eg, impairment of memory functioning, especially with respect to new learning, and of orientation and abstracting abilities). Thus, Post has argued that in the case of affective disorder, “objective failure at work or memory disorder will become a problem only by the time that the depression has become well established,” whereas in the cerebral deteriorations of later life, “symptoms of anxiety, depression, hypochondriasis, or paranoid behavior have been foreshadowed by failure at work, episodes of disorientation, etc.” A prior history of affective episodes also suggests the possibility of a depression-related reversible dementia, but does not rule out the possibility of a superimposed irreversible dementia. A positive family history of affective (spectrum) disorder or of dementing illness may also provide a valuable, if inconclusive, clue. Finally, clinical experience suggests that a demen
tiform clinical picture of recent onset is more likely to be reversible.

■ Mental Status Findings

There is some consensus among geriatricians that “near-miss” answers are more likely to be associated with organic mental syndromes of an irreversible type, whereas “don’t know” answers are more characteristic of the negativistic and possibly depressed patient. Affective lability and incontinence are also more characteristic of demen
tiform, rather than affective, illness. In a study with a now widely used bedside instrument, the Mini-Mental State Examination, Folstein and collaborators have found that patients with reversible dementia syndrome of depression frequently score 22 or 23 out of a possible 30 points; patients with established dementia, on the other hand, typically score less than 22, suggesting more severe and usually irreversible cognitive deficits. Of course, patients in the early stages of dementia frequently score higher than 22, indicating that degree of cognitive impairment does not necessarily imply either reversibility or irreversibility.

Data suggest that the cognitive deficits seen in elderly depressives are characterized by impairment in attention, orientation, and memory (referred to by Caine as a pattern of “subcortical dementia”), in contrast to “cortical” deficits of dyspraxia and dysphasia attributable to Alzheimer’s and other “organic” dementias). The “cortical-subcortical” distinction may not, however, prove to be tenable, particularly in the case of Alzheimer’s disease. Gainotti et al compared patients with Alzheimer’s disease, multi-infarct dementia, normal pressure hydrocephalus, Parkinson’s disease, Huntington’s disease, and depression on eight neuropsychological measures. The Alzheimer patients performed consistently more poorly than did other patients with greater impairment on tests of memory and
There is no consensus of whether coexisting cognitive impairment and depression are usually precursory to a progressive dementing illness.
Dementia syndrome of depression is usually associated with a normal EEG and CT scan.

The technique of studying grey matter/white matter discrimination has been found to correlate significantly with estimates of cognitive functioning in patients with Alzheimer's disease. Normative data are still needed, however, to define and, perhaps, reduce the overlap between the CT image of demented and nondemented individuals. As in neuropsychological research, longitudinal use of these techniques in the same patient, rather than single, cross-sectional use, may also prove to be a powerful aid to diagnosis.

The combined use of several laboratory examinations in differential diagnosis and prediction of treatment response has recently been proposed. A retrospective study by Grunhaus and colleagues suggests a profile for the diagnosis of patients with depressive pseudodementia. Specifically, patients with cognitive impairment, dysphoric mood, abnormal response to the Dexamethasone Suppression Test (DST) and normal CT scan tend to have depressive pseudodementia and respond to "adequate" antidepressant treatment ("adequate" is defined as six or more ECT treatments or a tricyclic antidepressant trial with therapeutic blood levels for at least three weeks). Thus, six of seven patients with abnormal DST results and adequate treatment improved significantly as evidenced by changes in both Hamilton depression scores and dementia ratings. Three patients whose cognitive impairment recovered fully, as measured by decreases in dementia ratings, all had normal CT scans and abnormal DST results; whereas patients whose dementia improved only partially (n=4) or not at all (n=4) tended to have abnormal CT scans.

From the combined use of clinical elements (mood and cognitive changes) and routine laboratory studies (CT scan and DST), the authors hypothesized the existence of three groups of patients who show a pattern of differential response to somatic antidepressant therapy. In the "true" pseudodementia group (dysphoric mood, dementia symptoms, abnormal DST, and normal CT), symptoms of depression and cognitive impairment should improve with adequate antidepressant therapy. In a second group of patients with both depression and dementia of the Alzheimer type (abnormal DST and normal CT), antidepressant treatment should be associated with normalization of the mood disorder and possible partial recovery of cognitive deficits. The third group of patients having a predominantly demientiform clinical picture and few depressive symptoms (normal DST, abnormal CT) should show little response to antidepressant treatment and, indeed, may show enhanced vulnerability to the psychotoxic effects of such treatment. Although promising, the diagnostic approach suggested by this study should be viewed with caution, since the sample size is modest and the specificity of the DST to depression is questionable.

Cerebral blood flow (CBF) studies have not yet been tested as a way of differentiating depression and dementia, although preliminary data indicate that this method might hold promise. Reduction of cerebral blood flow has been observed in dementia, and this reduction correlates with the severity of cognitive impairment. Thus, in the early stages of Alzheimer's disease, a reduction in cerebral blood flow in the frontal and temporal areas is...
seen. CBF may be decreased in depression as well, particularly in the left hemisphere.24 Much more work is needed, however, to elucidate differential blood flow patterns in patients with different types of depression (eg, endogenous, nonendogenous), during acute phases of illness and remission (to elucidate state-trait markers), and during conditions of pharmacologic challenge as well as without such probes.

For example, since cholinergic hypersensitivity may be responsible for some subtypes of affective disorders (as evidenced, for example, by the cholinergic REM induction test25 or the differential sensitivity of some affective disorder patients to the dysphoric effects of cholinergic compounds26), it might be of direct relevance to the pathophysiology of depression and depressive pseudodementia to determine whether there are differential effects of arecoline or phystostigmine infusion on cerebral blood flow in patients with depression, dementia, or both. However, the use of pharmacologic probes should not be limited to cholinergic agonists; the effects of adrenergic and serotonergic system manipulation on CBF and other measures (eg, tryptophan or clonidine challenge) might also be tested.

AN EXPERIMENTAL APPROACH USING EEG SLEEP DATA

Sleep disturbance is a prominent and disabling feature of late-life depressive and dementing illnesses.27 The severity of sleep fragmentation, particularly sleep continuity disturbance and early morning awakening, is highly correlated with the overall severity of depression and increasing age, and is most marked in delusional depressives. In dementia of the Alzheimer type, as the illness progresses in severity, the normal circadian rhythm of sleep/wake activity is disrupted and replaced by an arrhythmic, polyphasic pattern of multiple episodes of sleeping and waking.28 So-called “sundowning” and daytime naps develop as part of this pattern.

Our previous studies have suggested that elderly depressed patients develop somewhat different sleep physiological alterations from those that characterized probable dementia of the Alzheimer type.27 Thus, in older depressed patients, the percent of REM sleep is higher, the first REM sleep period is longer, the density of phasic rapid eye movements is greater, and the length of the first NREM sleep period (ie, REM latency) is shorter, relative to both age-matched healthy controls and Alzheimer’s patients. The latter show a gradual but progressive loss of phasic activity, both of rapid eye movements in dream sleep and of spindles and K-complexes in NREM sleep. Also, in dementia, the amount of slow wave sleep and the number of delta waves gradually diminish, whereas in depression a temporal redistribution of delta activity occurs, as evidenced by shifting of EEG slow waves from the short first NREM period to the longer second NREM period.

During the past four years, our laboratory has performed sleep studies on over 200 elderly patients and normal controls. Using EEG sleep data from this extensive sample, we recently performed discriminant function analyses of sleep alterations in nondemented (“pure”) depressed and nondemented (“pure”) demented patients.29 Overall, 80% of patients were correctly identified (P<0.001). Four measures contrib-
cognitive impairment resolve with adequate antidepressant therapy. Of course, the definition of “adequate therapy” is problematic, in part because the ability of elderly depressives to tolerate antidepressant treatment is limited (that is, a patient may show evidence of peripheral or central toxicity to medication before a therapeutic blood level is achieved).

The need for retrospective confirmation of the depressive pseudodementia diagnosis has implications for further research in this area. Retrospectively proven cases should be compared with elderly depressives without cognitive impairment with respect to dependent variables in several domains (neurophysiological, neuropharmacological, metabolic, and chro-nobiological) under conditions of challenge with nonpharmacologic and pharmacologic probes following measurement of basal endogenous activity. The use of such a retrospective strategy will have direct bearing on whether the pathogenesis of depressive pseudodementia is similar to that of depression without dementia. In addition, the predictive validity of various biological correlates of depressive pseudodementia needs to be ascertained in prospective studies of response to antidepressant therapy and of life events, and diagnostic stability.

REFERENCES

The important diagnostic issue is to distinguish reversible dementia of depression from depressive symptoms associated with Alzheimer's disease.

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