Geriatric Depression: Age of Onset and Dementia

George S. Alexopoulos, Robert C. Young, and Barnett S. Meyers

Age of depression onset was studied in 183 consecutively hospitalized elderly patients with major depression. Patients with both depression and dementia had onset of depression at a significantly later age than patients with depression alone. Depressives with reversible dementia had age of onset comparable to that of depressives with irreversible dementia. These findings suggest that late-onset depression is a heterogeneous syndrome and includes a considerable number of patients who develop depression as part of a dementing illness.

Key Words: Geriatric depression, age of onset, dementia

Introduction

Differences in family history, biological measures, and clinical characteristics have been reported in patients who had their first depressive episode in late life compared to patients of similar age who had had depressive episodes since early life. Late-onset depressives appear to have a family history of depression less frequently than depressed patients with early illness onset (Mendlewicz and Baron 1991). Biological differences reported to differentiate between late- and early-onset depression include larger ventricle–brain ratio, higher plasma 4-hydroxy-3-methoxyphenylglycol (MHPG), lower platelet adrenoreceptor binding, higher platelet monoamine oxidase activity in women, and lower sedation and sleep thresholds to barbiturates in late-onset depressives (Alexopoulos 1990; Sacchetti et al 1985). Clinical differences between late- and early-onset depression include more frequent depressive relapses and greater mortality (Alexopoulos 1990).

Post (1979) advanced the hypothesis that age-related brain deterioration may predispose to late-onset depression. This view is supported by similarities between changes associated with aging and those found in depression and include evidence of brain atrophy, changes in rhythmic and neuroendocrine functions, and changes in brain neurotransmitter systems (Veith and Raskind 1988). The low frequency of familial depression in late-onset patients is consistent with a role of age-associated factors in the etiology of late-onset depression.

Another pathogenetic possibility is that late-onset depression is a heterogeneous disorder that includes a subgroup of patients who develop depression as part of a dementing illness. Dementing neurological disorders occur in approximately 12% of the geriatric population; depression occurs in 17%–50% of patients with dementing disorders (Alexopoulos and Abrams 1991), and in some cases depression may precede the onset of the dementia syndrome.

The relationship between dementia and age at onset of depressive disorders was examined in a sample of psychiatrically hospitalized geriatric depressed patients. The hypothesis was tested that depression associated with dementia has later onset than geriatric depression occurring in cognitively unimpaired elderly patients.

Method

The subjects were patients consecutively admitted to a university-based inpatient geriatric psychiatry service. They were all 60 years old or older and met criteria for major

From the Department of Psychiatry, Cornell University Medical College, White Plains, NY 10605.
Address reprint requests to George S. Alexopoulos, M.D., Department of Psychiatry, Cornell University Medical College, 21 Bloomingdale Road, White Plains, NY 10605.
Received September 19, 1992; revised April 21, 1993.

0006-3223/93/$06.00

depression. Exclusion criteria were: (1) conditions associated with dementias, i.e., parkinsonism, alcoholism, drug abuse, Huntington's chorea, space-occupying lesions, thyroid disease, vitamin B_{12} or folate deficiency, central nervous system infection, renal failure, hepatic failure, severe heart failure, and collagen disease; and (2) history of psychiatric disorders other than major depression or dementing disorders. This selection method produced a sample of patients with major depression with or without dementia.

All subjects had a medical and neurological examination and a laboratory test battery consisting of complete blood count; differential; determination of blood urea nitrogen, creatinine, and electrolytes; liver function tests; urine analysis; Venereal Disease Research Laboratory test; determination of triiodothyronine, thyroxine, and thyrotropin levels; chest radiograph; electrocardiogram; and in demented patients, assessment of serum vitamin B_{12} and folate levels. Psychiatric diagnosis was made by agreement of two geriatric psychiatrists using the Structured Clinical Interview for DSM-III-R–Patient Version (SCID-R) (Spitzer and Williams 1985) and the DSM-III-R. Age of depression onset was determined by reviewing previous medical records and interviewing the patient and an informant. During the first week after admission, depression was quantified with the 24-item Hamilton Depression Rating Scale (HDRS). This scale includes the 21 items of the original Hamilton Depression Rating Scale (Hamilton 1960) plus three additional symptoms: hopelessness, helplessness, and worthlessness. Cognitive dysfunction was assessed with the Cognitive Capacity Screening Examination (CCSE) (Jacobs et al 1977). Psychiatric evaluation and ratings with the HDRS and CCSE were repeated during the week prior to discharge from the hospital.

Dementia was defined according to DSM III criteria and a score of 23 or less on the CCSE. Because cognitive dysfunction may subside with amelioration of affective symptomatology, dementia was categorized as reversible or irreversible after improvement of the depressive syndrome. Improvement of depression was operationally defined as a change in HDRS to a final score of less than 12. Depressed subjects who also met criteria for dementia were classified as having depression with reversible dementia if their cognitive dysfunction improved (change in CCSE score of three or more points and a final CCSE score greater than 23). Subjects with depression and dementia who remained cognitively impaired (DSM-III criteria for dementia and final CCSE lower than 24) even after improvement of depression were considered to have irreversible dementia.

Age of illness onset was determined by interviewing the subject and an informant and by reviewing all medical records. The method of the Longitudinal Interval Follow-up Evaluation (LIFE) (Kellner et al 1987) was used for assigning time parameters. According to LIFE, illness-related events are identified by their relationship to other life events that the subject and the informant can accurately recall. In order to assess the interrater reliability of this method in geriatric depressed patients, 23 subjects were rated by two trained clinical raters independently. Each rater selected his or her own informant according to the following criteria: (1) knowledge of the subject's history and (2) familiarity with the subject's relatives and friends who are able to fill gaps of the informant's knowledge. Ratings and an account of how history was obtained were presented to a panel of three senior clinical investigators by each of the two raters, and a consensus opinion was derived. Ratings were considered to be in agreement if they differed by no more than 1 month in identifying the onset or duration of an episode of illness.

Analysis of data was performed using intraclass correlation, one-way analysis of variance (ANOVA), one-way analysis of covariance (ANCOVA), post hoc *t*-test, χ^2, and logistic regression. All levels of significance are two-tailed.

Results

Interrater reliabilities of the onset of depression and the duration of depressive episodes were studied in 23 elderly subjects who had 80 affective episodes. Age of first episode onset was the most reliably identified historical element; intraclass correlation (ICC) was 0.94 in comparisons between rater 1 and rater 2, 0.94 between rater 1 and consensus, and 0.98 between rater 2 and consensus. Duration of episodes had a range of ICC from 0.68 to 0.96.

A total of 183 subjects were studied in order to test the hypothesis that depressed–demented patients have later age of depression onset than geriatric patients with depression alone. Of the 183 subjects, 77 met criteria for major depression and dementia at entry, and 106 had only major depression (Table 1). Because subjects with depression and dementia were somewhat older than patients with depression alone (Table 1), ages of onset were analyzed using ANCOVA with age as the covariate. Patients with major depression alone ($n = 77$) ($F = 5.75$, df = 2,180, $p < 0.017$) even when the effect of age was taken into consideration.

The sample was divided into late- and early-onset depression using 50 years of age as the cutoff point. Subjects with depression and dementia had a higher percentage of late-onset cases (83%) than patients with depression alone (66%) ($\chi^2 = 6.64$, df = 1, $p < 0.01$). Logistic regression showed that this difference remained significant even after adjustment for age (likelihood ratio $\chi^2 = 4.47$, df = 1, $p < 0.03$).

BIOL PSYCHIATRY
1993;34:141–145

Table 1. Age of Depression Onset in 183 Geriatric Patients With Major Depression With and Without Dementia[a]

Groups	Age (yr)	Age of onset (yr)
Depression alone (n = 106)	72.8 ± 6.6	56.0 ± 18.9
Improved (n = 82)	72.6 ± 6.6	54.7 ± 19.5
Depression and dementia (n = 77)	75.8 ± 7.2	65.1 ± 6.2
Improved (n = 51)	75.1 ± 7.0	63.5 ± 16.0
Reversible dementia (n = 30)	74.0 ± 6.6	61.8 ± 14.8
Irreversible dementia (n = 21)	76.8 ± 7.5	65.7 ± 17.6

[a]Values are mean ± SD.

After antidepressant treatment, 82 (77%) of the 106 patients with depression alone met criteria for improvement of depression (Table 1). Of the 77 patients with depression and dementia, 51 (66%) had improvement in depression, and of these 30 met criteria for reversible dementia, whereas 21 were classified as having depression with irreversible dementia (Table 1). Of the 21 patients with irreversible dementia, 13 (62%) met DSM-III-R criteria for primary degenerative dementia, 4 (19%) met criteria for multi-infarct dementia, and 4 (19%) had characteristics of both conditions. In the last four cases, the dementia syndrome had insidious onset, followed a progressive course, and there were no focal neurological symptoms and signs. However, these subjects had histories of vascular disease, such as arteriosclerotic heart disease, angina, myocardial infarction, and hypertension. Despite the vascular risk factors, these four patients did not meet DSM-III-R criteria for multi-infarct dementia, and therefore they were not considered mixed cases of primary degenerative dementia and multi-infarct dementia. Although the clinical presentation and course of illness was suggestive of primary degenerative dementia, vascular diseases might have contributed to the pathogenesis of dementia. For this reason, these cases were classified separately. There were no subjects with dementias other than primary degenerative or multi-infarct dementia because our selection criteria excluded patients with such conditions.

Classification into irreversible or reversible dementia was made after improvement of depression. For this reason, these groups were compared with the nondemented depressives who met criteria for improvement of depression. One-way ANOVA showed differences in the distribution of age of onset among subjects with depression alone (n = 82), depression with irreversible dementia (n = 21), and depression with reversible dementia (n = 30), (F = 4.48, df = 2,129, $p < 0.01$) (Figure 1). Post hoc t-test showed that depressives with irreversible dementia had onset of first depressive episode at a later age than patients with depression alone (t = 2.36, df = 101, $p < 0.03$). Similarly, there was a trend toward later age of illness onset in depressives with reversible dementia compared to subjects with depression alone (t = 1.81, df = 110, $p < 0.07$). Age of depression onset was statistically indistinguishable in depressives with reversible and irreversible dementia (t = 0.86, df = 49, $p < 0.40$).

Subjects who improved after antidepressant treatment (n = 133) were classified as late- or early-onset cases using 50 years of age as the dividing point. There were significant differences in the distribution of late-onset depression cases among subjects with depression and irreversible dementia (81%), depression and reversible dementia (83%), and depression alone (60%) (χ^2 = 6.77, df = 2, $p < 0.03$). Logistic regression showed that a trend toward differences in the distribution of late-onset subjects remained in the three groups even after adjustment for age (likelihood ratio χ^2 = 5.71, df = 2, $p < 0.057$).

Discussion

The main finding of this study is the association between dementia and major depression of late onset. On a clinical level, this finding raises the question whether late onset of depression is a risk factor for development of dementia in elderly depressed patients. Longitudinal studies of cognitively intact geriatric depressives suggest that these patients have a rather low rate of dementia development on follow-up (Murphy 1983; Balldwin and Jolley 1986). However, a considerable number of elderly depressives present cognitive dysfunction and may be at high risk for development of irreversible dementia (Emery and Oxman 1992). Further research using a detailed neuropsychological assessment and a longitudinal design may examine whether late depression onset can help identify those cognitively impaired depressives who will proceed to develop irreversible dementia.

Elderly depressives with reversible dementia had onset of depression at an age similar to that of patients with irreversible dementia. Increasing evidence suggests that depression with an initially reversible dementia often follows a course of gradual cognitive deterioration, with irreversible dementia as the end result (Kral and Emery 1989; Alexopoulos et al in press). In addition, depressives with reversible dementia have elevated platelet monoamine oxidase activity similar to that of depressed Alzheimer's patients and higher than that of nondemented elderly depressives (Alexopoulos et al 1987). The association between reversible dementia and late-onset depression further supports the view that biological changes associated with dementing disorders may be the pathogenetic back-

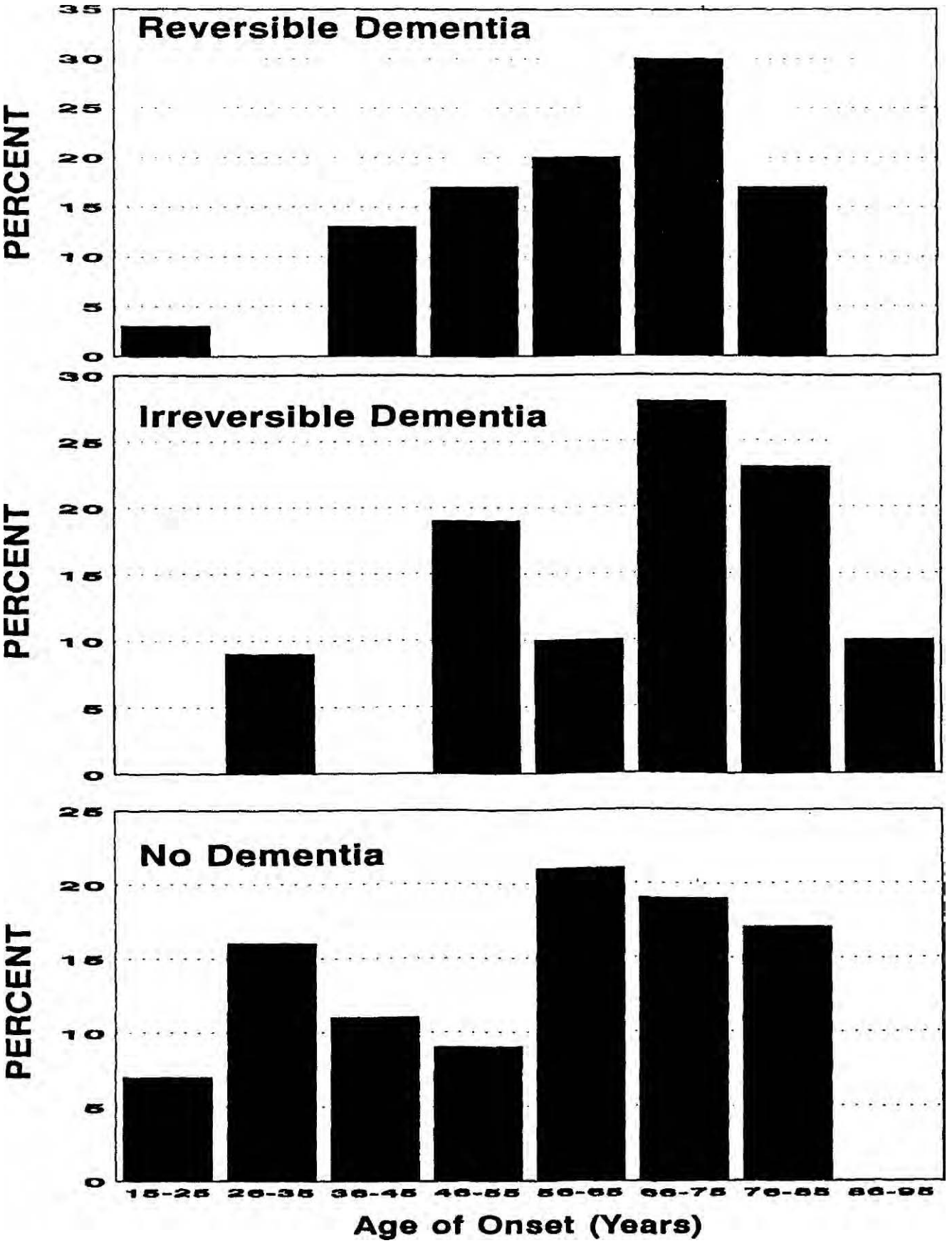

Figure 1. Age of depression onset in 183 geriatric patients with major depression.

ground in a considerable number of late-onset depressives who have not yet developed irreversible dementia.

This study was conducted in a population of hospitalized elderly patients with major depression. Therefore, the findings may not be relevant to younger depressives in whom the prevalence of dementia is low. Also, given the clinical and biological heterogeneity of depression, these findings cannot be generalized to milder geriatric depressions.

This study was supported by NIMH grants R01 MH-42819, T32 MH-19132, T01 MH-19596, and by the Xerox Foundation.

References

Alexopoulos GS (1990): Clinical and biological findings in late-onset depression. In Tassman A, Goldfinger SM, Kaufman CA (eds), *Review of Psychiatry*, Vol. 9. Washington, DC: American Psychiatric Press.

Alexopoulos GS, Abrams RC (1991): Depression in Alzheimer's disease. *Psychiatr Clin North Am* 14:327–340.

Alexopoulos GS, Young RC, Lieberman KW, Shamoian CA (1987): Platelet MAO activity in geriatric patients with depression and dementia. *Am J Psychiatry* 144:1480–1483.

Alexopoulos GS, Meyers BS, Young RC, Mattis S, Kakuma T (in press): The course of geriatric depression with reversible dementia. *Am J Psychiatry*.

Balldwin RC, Jolley DJ (1986): The prognosis of depression in old age. *Br J Psychiatry* 149:574–583.

Emery VA, Oxman TE (1992): Update on the dementia spectrum of depression. *Am J Psychiatry* 149:305–317.

Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.

Jacobs J, Bernhard M, Delgado A, Strain J (1977): Screening for organic mental syndromes in the medically ill. *Ann Intern Med* 86:40–46.

Kellner MB, Lavori PW, Friedman B, et al (1987): The longitudinal interval follow-up evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. *Arch Gen Psychiatry* 44:540–548.

Kral VA, Emery OB (1989): Long-term follow-up of depressive pseudodementia of the aged. *Can J Psychiatry* 34:445–446.

Mendlewicz J, Baron M (1991): Morbidity risks in subtypes of unipolar depressive illness. Differences between early- and late-onset forms. *Br J Psychiatry* 134:463–466.

Murphy E (1983):The prognosis of depression in old age. *Br J Psychiatry* 142:111–119.

Post F (1979): Dementia, depression and pseudodementia. In Benson DF, Blumer D (eds), *Psychiatric Aspects of Neurologic Disease*. Seminars in Psychiatry series. New York: Grune and Stratton, pp 99–120.

Sacchetti E, Conte C, Pennati A, Vita A, Alciati A, Cazzullo CL (1985): Platelet alpha$_2$-adrenoreceptors in major depression: Relationship with urinary 4-hydroxy-3-methoxyphenylglycol and age at onset. *J Psychiatr Res* 9:579–586.

Spitzer RL, Williams JBW (1985): *Structured Clinical Interview for DSM-III-R, Patient Version*. New York: Biometrics Research Department, New York State Psychiatric Institute.

Veith RC, Raskind MA (1988): The neurobiology of aging: Does it predispose to depression? *Neurobio Aging* 9:101–117.