Late-Onset Schizophrenia and Very-Late-Onset Schizophrenia-Like Psychosis: An International Consensus

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Objective: Although schizophrenia is generally regarded as an illness with onset in late adolescence or early adult life, a sizeable minority of patients first become ill in middle or old age. Inconsistencies in diagnostic systems and nomenclature, coupled with a tendency among most schizophrenia researchers to ascribe late-onset psychoses to organic factors, have led to such cases occupying an ambiguous position in relation to schizophrenia. Through systematic review of the literature and publication of a consensus statement from an international group of experts in the field, this article aims to clarify the positions of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis. **Method:** The authors conducted a MEDLINE literature review and developed a consensus statement summarizing the findings from 2 days of debate and discussion by members of the International Late-Onset Schizophrenia Group. **Results:** The group achieved consensus on diagnosis, nomenclature, treatment guidelines, and future research directions. **Conclusions:** In terms of epidemiology, symptom profile, and identified pathophysiologies, the diagnoses of late-onset schizophrenia (illness onset after 40 years of age) and very-late-onset schizophrenia-like psychosis (onset after 60 years) have face validity and clinical utility. General adoption of these categories will foster systematic investigation of such patients.

(Am J Psychiatry 2000; 157:172–178)

LITERATURE REVIEW

Historical Development of Concepts

Studies of late-onset schizophrenia began with Manfred Bleuler (1), who personally examined 126 patients whose illness began after the age of 40 years. These late-onset cases constituted 15% of the schizophrenia patients he examined; 4% of the patients had an onset after 60. About 50% of the patients with late-onset schizophrenia had symptoms that were indistinguishable from those seen in schizophrenic patients with the more typical younger age at onset. Bleuler's age cutoff of 40 years influenced the German literature (2). Subsequent reports in the English literature used either 55 or 60 years of age as the dividing line (3, 4) and adopted the term "late paraphrenia" to both distinguish the illness from chronic schizophrenia and emphasize its clinical similarities with the condition described by Kraepelin (5). This was an unfortunate choice, however, since Kraepelin had never regarded late age at onset as a feature of paraphrenia. Moreover, the concept of paraphrenia—experiencing hallucinations and delusions without deterioration or disturbance of affective response, thus distinguishing the disorder from dementia praecox—had been discredited (6). Driven by the early emergence in Europe of geriatric psychiatry as a distinct subspecialty, as well as the apparent syndromic coherence of late paraphrenia, including female preponderance (4, 7, 8), abnormal premorbid personality and social functioning (4, 9, 10), and deafness (4, 7, 11–13), the late paraphrenia concept was readily adopted and included in ICD-9.

In the United States, the inclusion within DSM-III-R of a separate category for patients whose illness emerged after age 45 was largely in reaction to the unsatisfactory upper limit for age at onset that had hitherto prevailed for a diagnosis of schizophrenia (14,

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The consensus meeting was supported by an unrestricted educational grant from Janssen Pharmaceuticals. A published abstract of the Consensus Statement of the International Late-Onset Schizophrenia Group can be found in Late-Onset Schizophrenia (Howard R, Rabins PV, Castle DJ [eds]. Petersfield, U.K., Wrightson Biomedical, 1999).

15). With what represented unprecedented transatlantic agreement (in late-onset schizophrenia terms), neither ICD-10 nor DSM-IV contained separate codeable diagnoses for late-onset schizophrenia. The current "official" view would seem to be that all cases that satisfy diagnostic criteria for schizophrenia, regardless of onset age, fall into the same illness category. Ghosts of the earlier diagnoses remain, however. DSM-IV mentions that cases of schizophrenia with onset after age 45, while similar to early-onset cases, are associated with a higher ratio of women, better occupational and marital histories, more paranoid delusions and hallucinations, and less disorganization and negative symptoms. The presence of sensory deficits is also mentioned among those with the "oldest age at onset" (over 60).

Clinical Features

Although one of his diagnostic criteria for late-onset schizophrenia had been a symptom profile similar to that of earlier-onset schizophrenia, Bleuler (1) did report some differences. Just over 50% had "paraphrenia-like, depressive-anxious catatonic or confused agitated" symptoms. The rest had symptoms similar to those of earlier-onset patients, but with less affective flattening and a more favorable prognosis. Subsequent researchers have also been struck by similarities between the symptoms of early- and late-onset schizophrenia (15, 16–28). Late-onset patients, however, are more likely than their earlier-onset counterparts to complain of visual, tactile, and olfactory hallucinations (18, 20, 21); persecutory delusions (21, 29); partition delusions (7, 21, 30); and third-person, running commentary, and accusatory or abusive auditory hallucinations (29, 31); they are less likely to display formal thought disorder (21, 29), affective flattening, or blunting (21, 25, 29). When onset of psychosis is after age 60, formal thought disorder and negative symptoms are very rare (8, 32).

Epidemiology

Some diagnostic criteria for schizophrenia exclude late-onset cases, and since many incidence and prevalence studies of psychotic disorders did not include patients older than 60 (27, 28, 33, 34), data for this group are scarce. The point prevalence of paranoid ideation in the general elderly population has been estimated to be 4%–6% (35–37), but most of these patients will have dementia. The proportion of schizophrenia patients whose illness first emerged after the age of 40 has been estimated to be 23.5% (22), and the 1-year prevalence rate of schizophrenia in individuals between ages 45 and 64 is 0.6% (38). For individuals over 65 years of age, community prevalence estimates for schizophrenia range from 0.1% to 0.5% (39–42). From a register of contacts with psychiatric services (41), incidence rates of 12.6 per 100,000 population per year have been reported for cases of DSM-III-R-defined schizophrenia with first onset after 44 years. First admission data for patients over the age of 60 suggest that the annual incidence of schizophrenia-like psychosis increases by 11% with each 5-year increase in age (43).

Risk Factors

Later onset of schizophrenia among women and overrepresentation of women among late-onset cases are robust findings (7, 8, 15, 32, 42, 44–49) that are not readily explicable in terms of sex differences in care-seeking and societal role expectations (50, 51) or in delay between symptom emergence and service contact (52). It is conceivable that aging-associated psychosocial factors such as retirement, financial difficulties, bereavement, deaths of peers, or physical disability may contribute to the precipitation of the symptoms of schizophrenia in later life. The role of these factors has not, however, been studied systematically in late-onset patients.

Most of the reported family studies that involved patients with late-onset schizophrenia suffer from methodological shortcomings (53), but there is good evidence that the relatives of very-late-onset patients have a lower morbid risk for schizophrenia than the relatives of early-onset schizophrenia patients (21, 54). Although the classical descriptions of very-late-onset patients stressed the high prevalence of sensory deficits, particularly longstanding conductive deafness (4, 9, 12, 13), these seem to be less strongly associated with onset after 40 years and may reflect paranoid patients' reluctance to seek corrective measures or their inability to get correction of these deficits because of problems with the health care system for mentally ill older adults (26). Premorbid educational, occupational, and psychosocial functioning is less impaired in late-onset than early-onset schizophrenia (25, 55), although many late-onset patients are reported to have had premorbid schizoid or paranoid personality traits that fell short of currently accepted diagnostic criteria for personality disorders (4, 9, 10, 21, 25).

Brain Imaging

As seen in early-onset cases, computed tomography (56–60) and magnetic resonance imaging (MRI) (61–65) studies have reported nonspecific structural changes (e.g., higher ventricle-to-brain ratio and third ventricle volume) in patients with late-onset schizophrenia than in appropriate age-matched comparison subjects. Focal structural abnormalities such as volume reductions of the left temporal lobe (66) or superior temporal gyrus (61) again mirror changes reported in younger patients. Thalamic volume in one series of late-onset patients, although not significantly different from unaffected subjects, has been reported to be larger than that seen in early-onset patients (64). Focal cerebrovascular abnormalities—in the form of actual infarcts (67, 68) or areas of high signal intensity seen on T_2-weighted MRI (67, 69–74)—have been reported in very-late-onset patients. However, studies that carefully screened to eliminate organic cerebral disorder

(62, 64, 75, 76) have not revealed an excess of such abnormalities when compared with comparison subjects. In functional imaging studies, regions of hypoperfusion in frontal and temporal areas (72), left posterior frontal and bilateral inferior temporal (77), and bilateral frontal and temporal lobes (78) have been reported. Neuroreceptor studies that used positron emission tomography (PET) and single photon emission computed tomography (SPECT) have shown both an increase (61) and no increase (79) in D_2 receptor density in late-onset patients in relation to that of comparison subjects. In an event-related potential study, late-onset schizophrenia patients had a significantly later peak latency of the N400 congruity effect than did normal subjects (80), a finding similar to that reported in younger patients with schizophrenia (81).

Neuropsychological Impairments

Studies of neuropsychological function in early-onset schizophrenia patients who have grown old have reported both deterioration (82, 83) and stability or improvement (84, 85). Such patients do not have an excess of those neuropathological abnormalities found in neurodegenerative disorders (86, 87). Although a precise characterization of the cognitive abnormality that accompanies schizophrenia is still awaited, young patients seem to be impaired on most cognitive tasks (88–91). Late-onset schizophrenia patients (like earlier-onset patients) perform significantly less well than comparison subjects on measures of executive functions, learning, motor skills, and verbal ability, but they are relatively less impaired on the Wisconsin Card Sorting Test and the learning score from the California Verbal Learning Test (25). In patients whose illness emerges after the age of 60, a similar pattern of impairment is seen, with widespread functional deficits (57, 71, 92) that are quantitatively and qualitatively different, since the patients' learning capacity is preserved, from those seen in patients with dementia.

Response to Treatment

Few controlled trials of the use of typical antipsychotic medications in these patients have been reported. In open studies, 48%–61% (9, 15, 21, 93–96) of patients show full remission of psychotic symptoms with treatment, although poor compliance may render treatment in the community less successful (97). In four North American clinical centers, 192 mg of chlorpromazine equivalents was the mean daily dose prescribed to late-onset patients (22), which is about 40% of the amount given to young patients at the same centers and about 150% of the dose given in the United Kingdom to patients with illness onset after the age of 60 (97). The newer atypical antipsychotics appear to be well tolerated, since they have less potential for producing extrapyramidal side effects and tardive dyskinesias (98–101). The atypical antipsychotics do have some side effects of their own and also do not produce complete remission of all the symptoms of schizophrenia in most patients. Psychosocial and behavioral approaches, which include cognitive behavior therapy and social skills training, are important adjuncts to pharmacological therapy for patients with schizophrenia, although their role in the management of patients with late-onset schizophrenia remains to be investigated.

THE INTERNATIONAL LATE-ONSET SCHIZOPHRENIA GROUP CONSENSUS CONFERENCE

Participants. The International Late-Onset Schizophrenia Group comprised 17 representatives of basic science and clinical schizophrenia research and academic and clinical geriatric psychiatry centers. Membership was based on publication of papers in the area of late-onset schizophrenia and international recognition for schizophrenia research, as well as the aim of the group to be international with representation from all the continents (although we were unable to identify an African representative). The group met for 2 days in July 1998.

Evidence. Individual group members presented reviews of the published data on the epidemiology, phenomenology, pathophysiology, etiology, and treatment of late-onset schizophrenia together with the current diagnostic position of these psychoses in each of their countries. The group discussed the published evidence and drew on their individual professional experience.

Consensus process. Each conference presenter prepared a manuscript on his or her respective topic based on the literature review and discussion at the consensus conference. The authors of this article then wrote a draft of the consensus statement and circulated it to all conference participants for their comments. The draft was revised after the authors took into account other participants' comments. This article reflects the statement that has been approved by all participants of the International Late-Onset Schizophrenia Group.

CONSENSUS STATEMENT OF THE INTERNATIONAL LATE-ONSET SCHIZOPHRENIA GROUP

Schizophrenia, whether of early or late onset, from childhood to old age, is fundamentally heterogeneous and presumably consists of a group of related illnesses. In order to better understand the pathophysiology and etiology of the schizophrenias, to overcome difficulties associated with a lack of consistency in diagnostic criteria and nomenclature, and to develop multicenter studies of late-onset schizophrenia, an international consensus has been articulated with respect to specific definitions and current research questions. We believe that there is sufficient evidence to justify recognition of two illness classifications: late-onset (onset after the age of 40 years) schizophrenia and a very-late-onset (onset after 60) schizophrenia-like psychosis.

The Case for Heterogeneity With Increased Onset Age

Schizophrenia-like psychoses, which cannot be attributed either to an affective disorder or focal or progressive structural brain abnormality, can arise at any time in the life cycle between childhood and old age. The expression of such psychotic symptoms shows greatest variation when onset age is at both extremes of life. Since the etiologies and the distinctive pathophysiologies of schizophrenia are at present unknown, variations in epidemiology, symptomatology, pathophysiology, and treatment response with age at onset can help to provide important clues to causative risk factors.

Epidemiology. Female sex is associated with later age at onset. Incidence curves for men and women are different, and some preliminary data suggest three adult peaks that correspond to early adult life, middle age, and old age (42, 43, 102). Very-late-onset cases may arise in the context of sensory impairment and social isolation (4).

Symptomatology. Early- and late-onset cases are more similar than different in terms of symptoms (especially positive symptoms) (21, 26, 29). The only study of a large representative sample found almost no differences up to age 60 (27), but in clinical samples, extreme old age at onset is associated with a low prevalence of formal thought disorder and affective blunting and a higher prevalence of visual hallucinations (8, 15, 28, 29). Differences in symptom profiles with onset across the age span do not necessarily imply differences in pathophysiology or etiology; they could represent cohort differences or age-associated central nervous system differences independent of the illness. Alternatively, similar symptoms could arise from different etiopathological processes.

Pathophysiology. There is no evidence that a progressive dementing disorder is associated with onset in middle or old age. Regardless of onset age, schizophrenia is associated with a generalized cognitive impairment relative to age-matched unaffected subjects (25, 91). No difference in type of cognitive deficits has been found between early- versus late-onset cases. Later onset of schizophrenia is, however, associated with somewhat milder cognitive deficits, especially in the areas of learning and abstraction/cognitive flexibility (25). Brain imaging findings are essentially similar regardless of onset age (61, 63, 65). In the late-onset group, no excess of focal structural abnormalities, such as areas of MRI signal hyperintensity within white matter, have been reported (75, 76). This contrasts with the finding that white matter hyperintensities are more prevalent in patients with late-onset affective disorders than in age-matched comparison subjects (103).

Etiology. Familial aggregation of schizophrenia is more common in earlier and middle-age onset than in very-late-onset cases (26, 54). There is no satisfactory evidence that later age at onset of these disorders breeds true. Some studies suggest familial loading for affective disorders in patients with later-onset schizophrenia. The prevalence of a family history of Alzheimer's disease, vascular dementia, dementia with Lewy bodies, or apolipoprotein E genotype is not higher in later-onset cases (104).

Age at Onset Cutoff Points

The available data suggest that categorization by specific age at onset ranges is relatively arbitrary. Although consensus was achieved, members of the group could not reach unanimity on either the presence of age cutoffs or where they should be set. There was general agreement that cutoffs have clinical utility and act to stimulate research effort. Epidemiological evidence is strongest for a cutoff at age 60 to define the very-late-onset group. Some clinical studies support another cutoff at age 40, although epidemiological data suggest that this age point may be too high for the middle-age onset group (102).

Nomenclature

After much discussion, a consensus was reached that cases in which onset occurs between age 40 and 60 be called late-onset schizophrenia and that cases in which onset occurs after the age of 60 should be called very-late-onset schizophrenia-like psychosis. The purpose of this nomenclature is to clarify the position of these patients and to stimulate more research, rather than to put a closure on this issue.

Assessment and Treatment

Regardless of age at onset, psychiatric and medical examinations and available investigative procedures should always be obtained to exclude identifiable etiologies. If available, brain imaging should be obtained in cases of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis. The presence of sensory impairments and social isolation should be ascertained and appropriate remedial action taken if found. The place of nonpharmacological treatments has not been adequately investigated but access to these therapies should not be prejudiced by age. Psychological management may reduce distress associated with psychotic symptoms and facilitate a therapeutic relationship, within which commencement and compliance with medication can occur.

Antipsychotic drugs are a mainstay of therapy. Drug treatment should be started at very low doses and increases in dose should be made slowly. Typical late-onset patients will respond to dose amounts that are about one-quarter to one-half those given to early-onset patients. Very-late-onset cases may respond to dose amounts as low as one-tenth of those used in young adults. Use of depot medication at very low doses may be successful in ensuring compliance. With the exception of clozapine, whose use is problematic in older patients, the atypical antipsychotic agents are clearly advantageous in the treatment of late-onset patients

because of the reduced likelihood of extrapyramidal symptoms and tardive dyskinesias for which elderly patients are at higher risk.

Future Directions

Epidemiology. Epidemiologic studies should use standardized criteria but should have no criterion that excludes a diagnosis of schizophrenia based on late age at onset. When comparisons are made by age at onset, first-onset episodes should be clearly defined. Because cases of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis are uncommon, multicenter studies are necessary. Long-term follow-up studies can provide valuable information and test the hypothesis that patients tend to a have a similar course regardless of age at onset. Both risk and protective factors should be sought.

Symptomatology. Because late-onset schizophrenia has a higher proportion of women than early-onset illness and gender interacts with symptom variables such as emotional expressiveness and social activity, it is important to control for gender when comparing the prevalence of symptoms by age at onset. Comparison of symptoms of idiopathic cases of schizophrenia with symptoms of cases secondary to known causes at a range of onset ages would be fruitful.

Pathophysiology. Specific cognitive models should be tested in patients with onset in childhood, young adulthood, middle age, and old age to establish whether identified cognitive abnormalities are truly similar across the age-at-onset span. Cognitive tests, which are increasingly sophisticated and allow for fine distinctions of performance, should be used in combination with functional brain imaging in order to test hypotheses of differential neurocircuitry involvement. In very-late-onset cases, the possible role of sensory impairment should be further explored.

Etiology. Brain imaging studies that involve adequate numbers of subjects and that use SPECT, PET, and functional MRI should be conducted with patients across the age-at-onset span. Diffusion tensor imaging has promise as a technique to examine white matter structure. Testing models of disconnection and misconnection across a wide range of onset ages should be considered. The role of estrogen withdrawal should be further explored (105), as should genetic, viral, birth injury, and degeneration-related factors. Large existing data sets should be explored with reference to late- and very-late-onset groups.

Treatment. Appropriately designed clinical trials of pharmacological and psychological treatments are required. SPECT and PET receptor occupancy studies that compare early- and late-onset cases would be valuable for understanding drug action and treatment response. Multisite studies of combined pharmacological and psychosocial/behavioral management approaches—with meaningful outcome measures such as quality of life and activities of daily living functioning—are warranted.

DISCUSSION

Schizophrenia continues to be an illness of mysterious causation that usually strikes in adolescence or early adulthood but may uncommonly affect children or express itself for the first time in middle or late life. Both developmental and degenerative processes that affect specific brain circuitry have been implicated. Intensive study of late- and very-late-onset cases may ultimately shed light on etiology.

ACKNOWLEDGMENTS

This study was completed with the participation of the investigators of the International Late-Onset Schizophrenia Group: Kirsten Abelskov (Aarhus University, Denmark); Osvaldo Almeida (Santa Casa de São Paulo, Brazil); Nancy Andreasen (University of Iowa Hospitals and Clinics, Iowa City); David Castle (University of Western Australia, Perth); Jean-Pierre Clement (CHS Esquirol, Lomoges, France); Robert Howard (Institute of Psychiatry, London); Dilip V. Jeste (University of California at San Diego/San Diego VA Medical Center); Shitij Kapur (Clarke Institute of Psychiatry, Toronto); David Kay (University of Newcastle, U.K.); Sudhir Khandelwal (BP Koirala Institute, Dharan, Nepal); Luis Aguera Ortiz (12th of October University Hospital, Madrid); Godfrey Pearlson (Johns Hopkins Hospital, Baltimore); Peter V. Rabins (Johns Hopkins Hospital, Baltimore); Anita Riecher-Rossler (University Psychiatric Clinic, Basel, Switzerland); Mary V. Seeman (Centre for Addiction and Mental Health, Clarke Division, Toronto); Philip Seeman (University of Toronto); and Nori Takei (University School of Medicine, Hamamatsu, Japan).

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