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REVIEW

Late-Onset Psychosis; Is It Real?

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The nature of late-onset psychosis in the absence of a dementia or secondary to organic dysfunctions in the fifth decade of life and beyond is contentious and unresolved. Different terminologies, diagnostic criteria and age cut-offs have been applied to late-onset psychosis, which have stymied clinicians and researchers. No official diagnostic designation for patients with late-onset psychosis is included in the current psychiatric diagnostic system (Diagnostic and Statistical Manual of Mental Disorders-V, International Classification of Diseases-10). The validity of this diagnostic exclusion has been questioned. Despite these problems, a relatively consistent clinical picture has reported. However, many questions remain regarding the underlying etiology, pathophysiological mechanisms, treatment and prognosis. Whether late-onset psychosis is distinct from schizophrenia and whether it might be a harbinger of dementia are unclear. Recent studies have suggested an underlying biological pathophysiology of late-onset psychosis.

Key Words   late-onset psychosis, dementia, nosocology, schizophrenia.

INTRODUCTION

Korea, like other nations, is experiencing a demographic transition featuring the rapid expansion of the proportion of aged persons. Elderly-related mental health issues are gaining prominence. Late-onset psychosis, which has been a well-recognized but poorly-understood phenomenon, has emerged as an important issue in geriatrics. It is unclear whether this psychosis occurs for the first time at this later stage of life in the absence of organic brain dysfunction is a manifestation of schizophrenia in older age (i.e., variant or subtype of schizophrenia) or represents a disorder that is distinct from typical schizophrenia. For patients who develop psychosis in later life, the arbitrary and inconsistent use of terminology, each with different age cut-offs (i.e., 40, 45, or 60 years), have complicated the understanding of the issue and patient treatment.

The current diagnostic confusion originated from historical differences in the nosocological approach that have continued to influence current psychiatric classification systems. Various terms have been used to designate primary late-onset psychosis. These include paranoia, presenile delusional insanity, late-onset schizophrenia, late paraphrenia, delusional disorder, paranoid psychosis, late-onset schizophrenia disorders and very-late-onset schizophrenia-like psychosis.[1-7] Despite the varying landscape of terminology, these phenomena present a rather consistent clinical picture. Similarities have been found between late-onset psychosis and early-onset psychosis in terms of the social isolation, associated depressive symptoms and certain neuroimaging findings. But, notable differences between early- and late-onset psychosis exist.

Terminological/diagnostic confusion and uncertainty will continue because the cause and underlying pathophysiological mechanisms of psychosis regardless of age-onset are still unknown. Proposed diagnostic criteria had been not clearly outlined, which has led to ongoing inconsistency and confusion about how the criteria should be applied clinically and in research studies.[8-10] Moreover, whether distinguishing schizo-

phrenia and delusional disorder in patients with late-onset psychosis does actually have any validity or usefulness is unclear.[5,6] Considering the relative absence of thought disorganization, catatonia and negative symptoms in patients with late-onset psychosis,[8,11-15] differentiating schizophrenia from delusional disorder is rather arbitrary. The clinical usefulness of this differentiation may be questioned.

The lack of nosocological clarity has spurred recent studies to adopt a combined diagnosis, such as schizophrenia with delusional disorder,[8,9] schizophreniform disorder,[9] schizoaffective disorder[9,10] and nonspecific psychotic disorder[9] under the umbrella terms of late-onset schizophrenia and/or very-late-onset schizophrenia-like psychosis.

The present review addresses late-onset psychosis. Due to historical and on-going terminological confusion, we have maintained the terms primarily employed by each author to designate diagnosis, with the exception of groups of studies in which a range of diagnoses (e.g., late paraphrenia, schizophrenia, delusional disorder) are summarized together. In the latter case, late-onset psychosis is used for the sake of brevity.

HISTORY OF LATE-ONSET PSYCHOTIC DISORDER

Development in early adulthood is considered a cardinal characteristic of early-onset psychosis (i.e., schizophrenia). Historically, the literature on late-onset psychosis dates back over a century. Then, Kraepelin[16] coined the term "dementia praecox" for an illness with a progressive mental decline (dementia) and as a way of distinguishing it from disorders arising in late-life (praecox). According to Kraepelin, the non-affective primary psychosis could be classified into three main groups according to their phenomenology and different longitudinal courses: dementia praecox (now referred to as schizophrenia), paraphrenia (for patients with symptomology similar to dementia praecox, but with predominantly paranoid features and lateonset), and paranoia (for patients with paranoid delusions manifesting in mid-to-late life without the other symptoms of dementia praecox, now referred to as delusional disorder).[17] A few years after Kraepelin's description, Mayer[18] discarded this classification system based on a follow-up study of Kraepelin's original patient sample. Only one-third of Kraepelin's patients retained their initial clinical characteristics, with the diagnosis having changed for the rest. Subsequently, many studies have lead to an evolving concept regarding psychosis presenting in mid-to-late adulthood. One of the most controversial issues has been whether later-onset psychosis should be classified as a distinct subtype of schizophrenia, or whether it represents a distinct disease from schizophrenia, such as a neu-

rodegenerative process.

A form of psychosis occurring in mid-to-late life was described as "involutional psychotic reaction" in Diagnostic and Statistical Manual of Mental Disorders-I (DSM-I) and "involutional paranoid state (involutional paraphrenia)" in DSM-II. DSM-I and -II recognized that psychosis could develope for the first time in mid-to-late life, but consensus was not reached as to whether sub-groups should be designated within this age category.[19,20] In the DSM-III, a diagnosis of schizophrenia was not permitted if psychosis occurred after the age of 45 years.[21] DSM-III-R eliminated this age restriction and allowed a diagnosis of schizophrenia at any age, but included a specifier of 'late-onset' for onset after the age of 45 years.[22] Later editions of the DSM have not included age-related criteria or specifiers.[23,24]

The diagnosis of late-onset psychosis is different in the International Classification of Diseases (ICD). The most recent version (ICD-10, World Health Organization 2007) included "paraphrenia (late)", but only as a term and not as a diagnosis under the diagnosis of delusional disorder. In 1998, an international conference including a panel of experts of the International Late-Onset Schizophrenia Group claimed that psychosis with the onset between the ages of 40 and 60 years should be classified as a subtype of schizophrenia and recommended this group as a "late-onset schizophrenia".[3] The panel at this conference also claimed that schizophrenia-like symptoms arising after 60 years are more likely to have a different underlying pathology (i.e., degenerative rather than neurodevelopmental). The name very-late-onset-schizophrenia-like-psychosis was recommended to describe such patients.[10,25] Despite this proposed age cut-off, the categorization by specific age at onset is not evidence based.[1] As well, the diagnostic criteria proposed by the International Late-Onset Schizophrenia Group were not clearly outlined,[1] which has led to variable use of this term.[9,10,26,27] Subsequent studies directly comparing these proposed age categories on clinical and epidemiological aspects were equivocal.[9]

In the current psychiatric diagnostic systems (DSM-V, ICD-10), schizophrenia and delusional disorder is only diagnostically allowed, and age-specific diagnostic terms are not included in DSM-V[24] or ICD-10.[28]

EPIDEMIOLOGY

There have been few well-designed studies of the prevalence and incidence of late-onset psychosis, due to the difficulties in case selection and the non-specific symptoms associated with aging. This field has been further complicated by the inconsistent diagnosis for late-onset psychosis or which simply have an exclusion for a particular diagnosis at a certain age. In spite of these problems, late-onset psychosis can be distinguished from

early-onset psychosis for many of the features, as Kraepelin described over 100 years ago.

Incidence and prevalence

In an early extensive review of patients with schizophrenia, 13%, 7%, and 3% had an illness onset over 40 years, 50 years, and 60 years, respectively.[29] A subsequent study reported a similar prevalence of patients with schizophrenia or paranoid psychosis, after 40-years-of-age.[30] A study involving a large community population reported an incidence of schizophrenia in subjects over 45-years-of-age of 12.6 per 100000 population per year.[31] A retrospective review of a geriatric psychiatry inpatient admission with schizophrenia reported that 3.3% had an illness after 40-years-of-age.[32] In a more recent study, the cumulative incidence of first-onset psychotic symptoms was 4.8% in subjects aged 70−90 years and 19.8% in surviving to age 85.[33] Although different study inclusion criteria of late-onset psychosis made interpretation of these studies difficult, these findings suggest that late-onset psychosis is not uncommon.

Risk factors

Family history, sensory deficits, premorbid personality disorder, social isolation, neuropsychological abnormalities and female gender are possible risk factors for late-onset psychosis.

Most of the family studies of patients with late-onset psychosis suffer from methodological flaws.[34] Yet, the consensus is that relatives of patients with late-onset psychosis have a lower risk for schizophrenia than the relatives of patients with early-onset schizophrenia patients, but greater than that of the general population.[35] The prior studies did not conclusively determine whether age of onset is genetically determined, in part because not all patients at risk for late-onset psychosis live long enough to develop psychotic symptoms. However, identification of family history in older patients may be not easier than in those who are younger for several reasons that include recall difficulty and different intensity of the stigma of psychiatric illness.

Many studies have reported an excess of visual and auditory sensory impairments in patients with late-onset schizophrenia. Both deficits may constitute a risk factor.[3,4] However, these studies had serious methodological problems, including ascertainment bias, unsystematic measurement of sensory impairment and lack of appropriate controls.[36] One case-control study designed to overcome these limitations showed that only uncorrected sensory deficits were over-represented in late-onset cases. Thus, associations between sensory impairment and late-onset psychosis are not simple and the interpretation of cause-effect is complicated. Furthermore, there is no consistent association between particular modalities of sensory loss and specific psychotic symptom.

Premorbid personality traits, such as reclusiveness, hostility and paranoia have been reported in patients with late-onset psychosis.[34] However, the data most often involve retrospective assessment without a formal diagnosis of psychiatric symptoms. A study that utilized subject- and informant-informed scales of personality traits, such as being odd, eccentric, suspicious and detached, showed no such difference.[37] Of interest, most patients with late-onset psychosis had a good premorbid work life and tended to participate in social activities, in contrast to patients with early-onset psychosis. Social isolation is common among older persons and even more so among those with late-onset psychosis who are over 60-years-of-age, although it is not easy to determine whether this is the cause or a result.[38] Social isolation may partly reflect a premorbid personality, and may partly be a consequence of suspiciousness, which is a symptom of this disease. Sensory deficit might also contribute to social isolation.

The risk of early-onset schizophrenia is a slightly predominant in men, while risk of late-onset schizophrenia is more common in women than in men.[34] Odds ratios of female-to-male in late-onset psychosis range from 2.2:1 to 22.5:1. Even considering that women live longer than men, this female predominance appears more than expected. This might imply that the brains of men and women show sex-specific susceptibility of primary psychosis according to age.[34] This female dominance in the late-onset psychosis has been a consistent finding,[2,3,8,10,11,14,17,30,31,39-43] and is not due to a potential social covariate like marital status, role-expectations, help-seeking behaviors and premorbid adjustment.[44] It is conceivable that estrogen is protective and its withdrawal in mid-life following menopause creates the milieu to develop late-onset psychosis.[45]

PHENOMENOLOGY

Although both patients with early- and late-onset psychosis commonly suffer from schizophrenia-related psychopathology (i.e., positive and negative symptoms), numerous studies of late-onset psychosis have supported Kraepelin's original description (1904) of this phenomenon. For example, patients with late-onset psychosis are very unlikely to present negative symptoms of schizophrenia, and display less formal thought disorder. The relative absence of formal thought disorder rates ranges from 1.4%[14] to 26.9%,[37] which are significantly lower compared to subjects with early-onset illness.[12,30,37,46,47] Affective blunting or flattening, which are cardinal symptoms of schizophrenia,[48] is not as prominent in patients with late-onset psychosis.[11,13-15,49]

Patients with late-onset psychosis have significantly fewer negative symptoms of alogia/mutism[15] and avolition/apathy.[13]

The overall assessed severity of negative symptoms in patients with late-onset psychosis compared to old patients with early-onset psychosis,[8,37] though other studies reported no significant difference.[10,46] Especially, when psychosis develops after the age of 60 years, formal thought disorder and negative symptoms are very rare.[39,47]

Studies about the prevalence of patients with catatonia have been equivocal, with both lower (2.2% versus 8%)[12] and similar (5.6% versus 4.5%)[11] rates reported between late-onset and age-matched early-onset psychosis groups. Interestingly, when psychosis onset occurs in patients over 60-years-of-age compared to those under 25-years-of-age, catatonia manifestation is markedly different (0% versus 12%, respectively).[14]

Patients with late-onset psychosis are more likely have certain symptoms including well organized and persecutory delusions,[12,49] and certain types of hallucinations including visual, tactile, and accusatory or abusive auditory hallucinations[49,50] with a running commentary.[12] One recent study found that among those with delusions, patients with late-onset psychosis have greater belief conviction and poorer insight.[51] Much higher rate of these partition delusions in patients with late-onset psychosis was also reported.[12,49,52]

Auditory hallucinations are also highly prevalent in patients with late-onset psychosis.[47] Third-person and abusive auditory hallucinations are reported more often in patients with late-onset psychosis than in young early-onset patients.[14,47] Partition delusions, in which people, animals, materials or radiation are believed to be capable of passing through a physical structure like a wall or ceiling that would normally constitute a impassable barrier appear to be quite characteristic symptoms of late-onset psychosis.[11,52] A wider range of perceptual misperceptions or hallucinations may be more prevalent in patients with late-onset psychosis,[9] although another study did not consistently report these differences.[37] In keeping with Kraepelin's original description, patients with late-onset psychosis may be more likely to present paranoid symptoms compared to age-matched early-onset schizophrenia patients,[13] although no such difference was evident in a recent publication with a larger sample size.[10] The overall severity of positive symptoms is thought to be less in late-onset patients compared to age-matched early-onset patients,[10] although previous smaller studies found no significant difference.[13,37,46] The presence or severity of depressive symptoms between late-onset and age-matched[8,10] or young[6,15] early-onset psychotic disorder patients showed no significant differences.

Thus, though these two entities share some clinical aspects, these phenomenological differences suggest that the difference of the two entities are not merely a consequence of the aging process itself, but may be due to different pathophysiology.

COGNITION

Patients with early- and late-onset psychosis are cognitively impaired compared to age-matched controls.[10,13,53,54] However, findings regarding detailed cognitive deficits have varied, with one study reporting that late-onset psychosis is associated with less severe cognitive deficits[2] and others reporting no differences.[10,13]

A meta-analysis of the relationship between onset-age and cognition in schizophrenia[55] reported that cognitive functions including arithmetic, processing speed, vocabulary and Wisconsin card sorting were relatively preserved in late-onset schizophrenia compared with early onset schizophrenia. However, late-onset patients had relatively greater impaired on auditory and visual attention, fluency and visuospatial construction. This pattern of neurocognitive impairment was the opposite of the pattern seen in patients with youth-onset (before 20-years-of-age) and those with early-onset (20−39-years-of-age) schizophrenia.[55] From these studies, it seems that patients with late-onset schizophrenia are particularly impaired in auditory and visual attention aspects, whereas their processing speed (measured by digit symbol coding) is relatively spared when compared to patients with early-onset schizophrenia. Cross-sectional studies comparing late-onset patients to similarly aged patients with early-onset schizophrenia showed similar neuropsychological impairment between the groups.[13,54] A more recent much larger sample sized study reported better cognitive function of processing speed, abstraction/cognitive flexibility and verbal memory in patients with late-onset schizophrenia compared to age-matched patients with early-onset schizophrenia. However, considering the duration of illness, only processing speed and perceptual organization remained significant differences.[10] Impairment of processing speed in patients with early-onset psychosis compared to patients with late-onset psychosis regardless of age or chronicity of illness has been consistently reported.[10,55]

With the possible exception of chronically institutionalized elderly patients who appear to have increased rates of dementia, the level of cognitive impairment tends to be stable over time.[56] A gradual cognitive decline with age parallels the decline seen in the general population in processing speed, executive function and episodic memory with a relative preservation of crystallized verbal knowledge.[57] However, it is not clear whether this pattern also applies to the very late-onset psychotic group (i.e., psychotic symptom onset in those over 60-years-of-age), in light of recent studies demonstrating an association with dementia. Further study is needed to better elucidate the relationship between later-onset psychosis and ageing, underlying disease mechanisms, chronicity of illness, effects of med-

ication and other factors, such as cerebrovascular disease, to the development of cognitive deficits and their pattern over time in late-onset psychosis.

LONGITUDINAL COURSE

Due to historical inconsistency in diagnostic criteria for late-onset psychosis and a notable dearth of well-designed studies for long-term course of late-onset psychosis, the longitudinal course of late-onset psychosis remains unclear. There are several practical problems in following and evaluating this group. Firstly, comorbid medical illnesses may confound evaluation of disease course and treatment response. Secondly, sensory and cognitive deficits may restrict access to neuropsychiatric functions and can make complying with therapy difficult. Finally, social isolation may make medical follow-up difficult.

In a study with a 14−21 month follow-up of 65 patients with paranoid symptoms that developed after age 50 who were receiving antipsychotics, one-third remained symptom free, just over one-third had symptoms for varying periods and the remaining approximately one-third had persistent psychotic symptoms.[4] In a retrospective chart review study, three-quarters of patients with late-onset paranoid psychosis were discharged home after their initial admission, while the rest went to a nursing home. However, only one-quarter of patients were remitted and the remainder had residual psychiatric symptoms for an average 10-year follow-up or at death.[58] Another study found that half of the patients were continuously medicated with antipsychotics, with 60% having resolution of the initial psychotic symptoms after an average of 3.7 years follow-up.[59] Yet another study used Danish case register data to compare the 10-year prognosis of schizophrenia before 40-years-of-age with schizophrenia evident between 40- and 60-years-of-age. The patients with schizophrenia between ages 40 and 60 years had a significantly lower mean number of hospital admissions, shorter hospital stay and longer time prior to hospital readmission compared to patients with schizophrenia before age 40. Late-onset female patients tended to have a poorer prognosis (i.e., spent more stays in hospital) than late-onset male patients, whereas a poorer course was observed for early-onset male patients.[30]

With respect to mortality, patients with late-onset schizophrenia were reportedly no more likely to have died at the 120-month follow-up than patients with late-life major depression disorder, but had significantly lower mortality than patients with dementia and organic psychosis.[56] Recently, a 2−3-fold higher mortality was reported in late-onset psychotic patients compared to healthy controls,[17,60,61] although such a difference was not found in earlier studies.[32,56] However, most long-term outcomes studies of late-onset psychosis have been hampered by their retrospective nature, small sample size and reliance mainly on case register data. With these caveats, it appears that patients with late-onset psychosis may have a comparatively better course than early-onset psychosis with regard to hospitalization, despite persistent psychosis.

NEUROIMAGING

Computed tomography and magnetic resonance imaging (MRI) studies for early-onset psychosis and late-onset psychosis have revealed tissue loss of certain brain regions, including the medial temporal lobe, anterior temporal gyri, and frontal lobe.[62-64]

MRI of late-onset psychosis has revealed greater cortical atrophy compared to age- and gender-matched healthy controls.[65] The temporal lobes, which are thought to be related to thought disorganization, auditory hallucinations and cognitive impairments in schizophrenia, were smaller than controls in the same study. This may affect the related substructures of the hippocampus-amygdala complex, superior temporal gyrus and planum temporale.[64] Other MRI studies examining the temporal lobe in patients with late-onset psychosis have been inconsistent, reporting smaller volumes[65-67] and no differences[68,69] compared to age-matched healthy controls. No difference compared to age-matched controls in late-onset psychosis was reported for the frontal lobe[67-69] and the size of the caudate and lenticular nuclei or the thalamus.[68,69]

Most studies comparing late-onset psychosis with age-matched early-onset psychosis found no significant differences. As well, no differences between these groups were reported in the size of the lateral and third ventricles,[67,69,70] temporal lobe,[67,69,70] frontal lobe,[67,69] cerebellum[67] and corpus callosum,[71] with no reported differences in cortical atrophy.[67,70,72] One of the latter studies reported significantly greater ventricular enlargement and cortical atrophy in early-onset paranoid schizophrenia compared to age-matched late-onset paranoid psychosis cases.[72] Another of these studies documented greater mid-parietal atrophy in late-onset schizophrenia compared to early-onset counterparts.[67] Enlarged thalamus compared to age matched early-onset schizophrenia patients that was described could reflect a relatively decreased size rather than enlargement itself in early-onset illness.[69]

Whether late onset psychotic disorder is associated with white matter hyperintensities (WMH) compared to age-matched early onset psychosis is unclear, with data being equivocal. In one study, the late-onset schizophrenia group had more hyperintensities in the periventricular area and thalamus than early-onset schizophrenia, even considering the younger age of the

early onset group.[67] Similarly, compared to age-matched early-onset patients who were similar in education and cerebrovascular risk factors, patients with late-onset showed a significant increment of WMH in the periventricular and deep white matter regions.[72] Abnormal white matter integrity in the left parietal lobe and right posterior cingulum in late-onset schizophrenia patients compared with age matched controls was also reported, although these abnormalities and symptomology were not associated.[73] On the other hand, another study did not report significant differences in the presence of WMH between late-onset and early-onset groups matched for age, gender, and education.[69]

More research is required to determine whether there are specific structural abnormalities in specific brain area and differences in the patterns of white matter alterations between patients with early onset psychosis and late-onset psychosis, and how this alteration relates to specific symptomatology.

BIOCHEMICAL FINDINGS

Case-control studies have provided increasing evidence that patients with schizophrenia have elevated plasma levels of inflammatory markers.[74] These findings suggest the involvement of inflammation in the pathogenesis of schizophrenia. A recent prospective study demonstrated the association of C-reactive protein (CRP) measured on average of 7−8 years before hospitalization with schizophrenia or schizophrenia-like psychosis, with a 6−11-fold increased risk of late- and very-late-onset schizophrenia in the general population.[75] CRP is one of the most commonly used inflammation markers. The biological mechanism linking CRP and schizophrenia is not fully understood. There are two possible hypotheses. Firstly, given the observation that subjects with severe infections and autoimmune diseases have persistent or acutely elevated levels of inflammatory biomarkers including CRP, so this marker may reflect these neuro-inflammatory processes. Secondly, CRP per se could damage the blood-brain barrier, as has been demonstrated in an animal model.[76] Such a disruption might lead to increased permeability for proinflammatory cytokines and/or autoantibodies. The evidence suggests that late-onset psychosis could be associated with early certain inflammatory process and delayed neuronal modulations.

NEUROPATHOLOGICAL FINDINGS

Several studies reported that pathologies of Alzheimer's disease[77-79] and Lewy body dementia[78] were not significantly associated in patients with late-onset psychosis. Other than these studies, the available pathological data regarding late-onset psy-

choses are limited.

Increased neurofibrillary tangles was reported in schizophrenia patients with an onset occurring after 40-years-of-age compared to normal controls, although the extent of the tangles was insufficient to meet the pathological diagnosis of Alzheimer's disease.[80] In late-onset schizophrenia patients, these neurofibrillary tangles were predominantly distributed in the entorhinal region, transentorhinal cortex and subiculum of the anterior hippocampus. Patients with late-onset psychosis can often display mild to moderate neurofibrillary tangles in the limbic region[80] but there are few pyramidal neurons in the hippocampus.[78,80] Amyloid plaques are sparse, with no significant cell loss compared to controls. These pathological findings are compatible with neurofibrillary tangle-predominant form of senile dementia,[81] which is associated with slowly progressive cognitive decline resulting in dementia in extreme old age. However, due to methodological limitations (retrospective study design, lack of exclusion criteria and potential confounder of age), this finding should be confirmed.

Recently, four-repeat tauopathies were reported in late-onset psychosis patients, especially after 65-years-of-age. The study demonstrated that late-onset schizophrenia and delusional disorders have heterogeneous neurodegenerative backgrounds, including tauopathies.[66] Further clinicopathological studies should be done to provide more precise prognostic information to families based on biological findings and to develop therapeutic strategies.

GENETIC STUDIES

Family history is present in 10−15% of patients with early-onset and late-onset schizophrenia.[17] A 32 base-pair deletion allele in the C-C chemokine receptor type 5 (CCR5) was found with greater frequency in psychotic patients with first admission after the age of 40 compared to those with earlier first admission.[82] CCR5 is a protein on the surface of leukocytes that regulates the immune system and serves as a co-receptor for retrovirus. The protein is also involved in various normal functions in the brain, including neurodevelopment, intercellular communication and neuronal survival.[83] In prenatal life or early childhood, this might have a significant effect on the brain development.[84] The retroviral hypothesis of schizophrenia posits that cytokine disturbances induced by prenatal exposure to common viruses may be associated with the development of schizophrenia.[85,86] Therefore, the deletion allele could hypothetically result in impaired clearing of viral infections, leading to neuronal damage and development of late-onset schizophrenia.

Another study assessed the presence of dopamine D2 recep-

tor gene polymorphisms in 157 patients with schizophrenia and 250 control participants. The rs2734829 gene variant was associated with schizophrenia and with later age of onset.[87] Further large-scale studies will be required to replicate these findings and to fully understand their meaning. For now, the evidence suggests that there may be different genetic backgrounds influencing susceptibility between early-onset psychosis and late-onset psychosis, and that specific genes may be associated with the age of onset.

TREATMENT

Antipsychotics are a widely-used treatment. However, most of the supporting randomized controlled trials were conducted on early-onset psychosis. Trial-based evidence to guide the use of antipsychotics in late-onset psychosis remains sparse. From a review of previous open studies dating back to 1966, approximately half of patients with late-onset psychosis achieved full remission of symptoms when treated with antipsychotics.[1] Another study including a various care settings and a wide range of antipsychotics preparations reported a much lower full response rate of 26%.[88] Depot administration was strongly associated with a positive treatment response, but the presence of hallucinations or first-rank symptoms, age or age of onset, level of patient care and antipsychotic dosage were not significantly associated with positive treatment response.[88] Even when matched for age, it has been consistently reported that patients with late-onset psychosis require lower doses of antipsychotics compared to patients with early-onset.[8,10,46,89] The short-term benefit of risperidone and olanzapine for treatment of psychotic symptoms in middle-aged and older adults has been supported in multiple double-blind trials.[90-93] Single, short-term trials of aripiprazole and paloperidone have suggested beneficial effects.[94] However, a Cochrane Review conducted in 2012 regarding the use of antipsychotics in late-onset schizophrenia[95] found only one study meeting the review's inclusion criteria and acceptable quality. This was an eight-week randomized trial of risperidone and olanzapine in 44 patients with late-onset schizophrenia. The symptom outcome measure, the Brief Psychiatric Rating Scale, was similarly decreased with both drugs.[96]

In summary, there is a notable dearth of well-qualified studies. To date, a substantial proportion of patients with late-onset psychosis have achieved positive, if not full, remission using relatively low doses of antipsychotic medications. However, due to the paucity of well-controlled randomized prospective studies, further studies are needed to understand the efficacy and tolerability of antipsychotics and preparations, as well as treatment response in regards to duration, relapse and chronicity.

IS LATE-ONSET PSYCHOSIS A PRODROMAL SYMPTOM OF DEMENTIA?

In early-onset schizophrenia, with the minor exception of chronically institutionalized patients, a greater than age-expected cognitive decline and conversion to clinical dementia was not found.[55] Whether late-onset psychosis might be a prodrome to dementia is one of the most controversial issues. Those in favor argue that late-onset psychosis is a neurodegenerative disorder. On the other hand, early-onset psychosis is basically a neurodevelopmental disorder. However, as previously described, diagnostic confusion and methodological limitation of studies, including neuropsychological tests (i.e., how to exclude patients with dementia in this group), makes this issue difficult. A certain cutoff Mini-Mental State Examination (MMSE) score or similar neuropsychological test score for inclusion used in many studies have not been strictly comparable. Some studies excluded patients only on the basis of a clinical diagnosis of dementia,[58,60,61,97] while another study did not use any specific exclusion criteria regarding cognitive status.[46] Considering the lack of standardized and validated study design, it is not surprising that cognitive cut-off scores adopted in study populations varied from a MMSE score of 17.6[46] to 28.21.[98] How patients are initially recruited and excluded with respect to cognition is not an easy task. According to this inclusion criterion of late-onset psychosis, patients with latent cognitive impairment may be recruited in the study populations.

An analysis of hospital records determined that a quarter of the late-onset paranoid psychosis patients were re-administered over a 48-month follow-up, with the clinical diagnosis changed to dementia in one-third of the re-administered patients.[58] The authors opined that this was due to the development of new independent cognitive symptoms rather than changing previous diagnosis. Using a retrospective chart review of the patient's clinical status and neuropsychological test score, another study also reported that 35% of patients of new late paraphrenia patients progressed to dementia within three years.[41] Change of the diagnosis to dementia was associated with initially lower performance on orientation, memory and general knowledge, with no other differences in the characteristics at presentation between the two groups. These findings suggest that such subjects may already have a prodomal stage of mild cognitive impairment. One study documented no difference in the performance of community-dwelling patients with late-onset psychosis on the MMSE or Mattis Dementia Rating Scale over time compared to age-matched early-onset patients and normal controls for a 1−2 year follow-up period. A cognitive change follow-up study in late-onset schizophrenia patients

reported no significant change from baseline to 1 year follow-up on the MMSE or more detailed cognitive tests like the Cambridge Cognitive Examination in patients with an onset age exceeding 50 years.[97] However, this study included patients with initial mean scores consistent with mild cognitive impairment/dementia (e.g., mean MMSE=21). This low initial mean score likely reflected the possibility that cognitive impairment may have already occurred based on the mean duration of illness of 6.69 years.

A study featuring a 5-year follow-up reported on clinical outcomes in 27 late-onset schizophrenia patients (50-years-of-age or older) and 34 healthy controls. The patient group tended to be institutionalized at an earlier age (79 years versus 86 years) and showed a greater decline in cognitive functions (e.g., Clinical Dementia Scale, MMSE) and activities of daily living scores. Nine of 19 patient group progressed to dementia at 5 years including Alzheimer's disease (n=5), vascular dementia (n=1), and unknown type of dementia (n=3), compared to none of the 24 controls. A post-hoc analysis revealed a trend, where those with a diagnosis changed to dementia having a lower socioeconomic status, older age at baseline, longer illness duration, poorer performance in activities of daily living and instrumental activities of daily living and MMSE at baseline, higher ventricle-to brain ratio and more WMH on MRI.[99] High hazard ratio (3.5) to dementia was also reported in those who presented with first primary psychotic symptoms at an age exceeding 70 years compared to those did not develop psychotic symptoms over the 20-year follow-up period. Hallucinations, particularly of the visual type, were significantly associated with the development of dementia at a mean interval of 5.0 years.[33]

In Danish register data study, patients with late-onset schizophrenia (first-contact over age 40) and very-late-onset schizophrenia (first contact over age 60) were both 3-times more likely to develop dementia than patients with osteoarthritis, and twice more likely to develop dementia than a gender- and age-matched sample of the general population over a median follow-up period of 3−4 years.[61] Another study, based on the same registry approach, showed that patients with very-late-onset delusional disorder were 8-times more likely to develop dementia (15.2% versus 2.1%) compared to those with osteoarthritis over a median follow-up period of approximately 2 and 4 years, respectively.[60] Compared to age-, gender-, and calendar-matched general population, very-late-onset delusional disorder were 5-times more likely to develop dementia. Interestingly, the diagnosis of dementia was high within the first 6 months after initial diagnosis of delusional disorder, which may reflect the obscuration of underlying dementia by the delusions. However, even after a 12-month follow-up, female and male patients with delusional disorder were still 4- to 8-times more likely, respectively, to develop dementia. These findings suggest that primary psychosis occurring after the age of 60 years may be associated with the process of dementia. However, studies were limited by a lack of available treatment information, social confounders, educational level and other demographic variables that may have contributed to the development of dementia. Studies with a long follow-up have suggested an increased rate of dementia for late-onset psychosis compared to normal controls. However, whether late-onset psychosis is only a triggering factor or is actually a prodromal form of dementia is unresolved. Further large-scale longitudinal or biological marker studies should be done to address these relationships.

CONCLUSIONS

Although the pathophysiology of later-onset psychosis remains unclear, recent findings are helping clarify the picture. Although late-onset psychosis shares most fundamental demographic and core clinical characteristics with early-onset psychosis, late-onset psychosis also differs from early-onset psychosis in aspects that include sex distribution, lower average severity of positive symptoms, low negative symptoms and lower average antipsychotic dose requirement. New neuroimaging and molecular studies have identified possible underlying biology of late-onset psychosis, which support the concept of late-onset psychosis as a distinct identity from early-onset psychosis. One possibility is that late-onset psychosis, especially very late onset schizophrenia-like symptoms, may be a prodrome of dementia. Well-designed prospective studies for treatment in patients with late-onset psychosis are needed to develop treatment guidelines.

Conflicts of Interest

The authors have no financial conflicts of interest.

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