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REVIEW

Late-onset schizophrenia: from Manfred Bleuler to the present

Ana Dias-Amaral[1,2], Maria João Peixoto[1], Alzira Silva[1,2], and Rui Coelho[1,2]

Abstract

Background: For Bleuler, late-onset schizophrenia (LOS) was characterized by onset after age 40, symptoms similar to the classic form and absence of signs of organic brain disease. We aim to describe the current aetiology, diagnosis and treatment of LOS, emphasizing the differences between LOS and classic schizophrenia.

Methods: Non-systematic review of original articles and systematic reviews regarding late-onset schizophrenia aetiology, diagnosis and treatment indexed to Pubmed, ISI – Web of Knowledge, Scopus and EBSCO published between January 1980 and December 2017, using the MeSH query: schizophrenia AND late onset disorders. Altogether, 62 articles were deemed relevant by two independent reviewers and included in the final selection.

Results: 23% of the cases of schizophrenia have late- (> 40 years) or very late-onset (> 60 years), with higher incidence in females. Genetic factors, menopause, sensory deficits, vascular and neurodegenerative lesions, and age *per se* are risk factors. Higher educational levels and marital rates and greater cognitive reserve stand out. Well systematized persecutory and jealousy delusions and auditory hallucinations are common. On the contrary, negative symptoms are uncommon. Cognitive functions are well preserved in the first year, but high rates of dementia are described after five-year follow-up. Due to the protective effect of oestrogen, LOS appears to have a worse prognosis in postmenopausal women. Despite the anti-psychotic drugs available, most patients remain symptomatic.

Conclusion: There is a significant overlap between early-onset schizophrenia and LOS/very-late onset schizophrenia-like psychosis (VLOSLP), but there are important differences mainly regarding risk factors and symptoms that cannot be overlooked. Seventy-five years after the first description, it is necessary to better define LOS/VLOSLP as a debate identity.

Keywords: Schizophrenia, Psychosis, Late-onset.

[1]Psychiatry and Mental Health Clinic, Centro Hospitalar de São João, Porto, Portugal

[2]Department of Clinical Neurosciences and Mental Health, Faculty of Medicine of the University of Porto, Porto, Portugal

Correspondence: Ana Dias-Amaral
Clínica de Psiquiatria e Saúde Mental, Centro Hospitalar de São João
Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
E-mail address: anasdamaral@gmail.com

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Introduction

Emil Kraepelin's dementia praecox had youth onset as a core characteristic. Later, Kraepelin himself noticed that the clinical picture was not restricted to adolescence or young adulthood. The term paraphrenia was used to describe a condition that partially overlapped with dementia praecox, but where affect and volition were less affected [1]. This condition was further divided into four different entities: *paraphrenia systematica*, *expansiva*, *confabulans* and *phantastica* (**Table 1**).

Eugen Bleuler also observed a small number of patients with a similar clinical picture but with symptom onset in middle or late life. In 1943, his son, Manfred Bleuler, described an entity called "*spätschizophrenie*" (late-onset schizophrenia) whose features were: a) onset after 40 years of age, b) symptoms resembling schizophrenia with youth or early-adulthood onset and c) absence of amnestic syndrome or signs of organic brain disease. Although symptoms were similar to schizophrenia, he noticed blunted affect and formal thought disorder were less common, suggesting a milder clinical picture [1].

Terminology has always been confusing and the problem re-emerged in 1952 when Roth and Morrisey used the expression late-paraphrenia to describe patients with schizophrenia onset after 60 years of age [2]. The name choice was somehow unfortunate, as late-paraphrenia was never intended to mean the same as Kraepelin's paraphrenia.

Although late-onset schizophrenia descriptions were known since Kraepelin, this entity was largely ignored, mainly by American psychiatrists. In 1980, the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) criteria for schizophrenia diagnosis precluded it when symptom onset occurred after 45 years of age [3]. This definition was largely contested [4], and age at onset as an exclusion criterion was deleted from the DSM-III revised edition (DSM-III-R), in 1987 [3].

In 2000, the International Late-Onset Schizophrenia Group defined late-onset schizophrenia (LOS) as occurring after 40 years of age and very-late-onset schizophrenia-like psychosis (VLOSLP) when symptoms appeared after 60 years of age [5]. Controversy still remains, but current evidence suggests both LOS and VLOSLP might be schizophrenia subtypes [6].

Methods

We have led a non-systematic review of original articles and systematic reviews regarding late-onset schizophrenia aetiology, diagnosis and treatment (including its former classification) indexed to Pubmed, ISI – Web of Knowledge, Scopus and EBSCO published between January 1980 and December 2017, using the MeSH query: *schizophrenia* AND *late onset disorders*, which resulted in 448 articles, after exclusion of duplicate records. Inclusion criteria comprised current evidence regarding biological and social factors contributing to the aetiology, clinical picture, treatment and prognosis of late-onset schizophrenia. Papers discussing other late-onset entities were excluded. Altogether, 62 articles discussing aetiology, diagnosis and treatment of late-onset schizophrenia were deemed relevant by two reviewers independently and were included in the final selection.

Results

Epidemiology

It is estimated that 23% (15.4-32.0%) of schizophrenia cases have a late onset, with a mean age at onset of 60.7 years-old [7]. Global incidence is estimated to be 7.5 per 100,000 person-years [8]. However, these patients are not frequently seen in hospitals maybe due to their pre-morbid personalities and functioning. In many cases, they have always been seen as eccentric, isolated and odd. After delusions and hallucinations onset, their lack of social life prevents others to become aware of the disease [9]. Late-onset schizophrenia also seems to have a more benign course, allowing treatment in outpatient clinics [10]. In the United States of America, for example, these patients are rarely seen in public hospitals, and are more frequently seen in private facilities, probably because their working years allowed them to benefit from health insurance [10].

Table 1. The four paraphrenia types according to Kraepelin.

Paraphrenia type	Characteristics
Systematica	Insidious onset between 30 and 40 years-old and in a lesser degree 40-50 years-old. Marked persecutory delusions. Later, exaltation, delusions of reference and auditory hallucinations. Personality is preserved. More common in men.
Expansiva	Onset between 30 and 50 years-old. Megalomania and exalted mood, with hallucinations. Later, delusions become disorganized. Loss of critical judgment, hypobulia, incoherence and blunted affect. Personality is preserved. More common in women.
Confabulans	Onset between 20 and 50 years-old. Persecutory delusions, exalted mood, false memories and megalomania. Auditory hallucinations can be present. Later, patients become irritable or indifferent. Men and women are affected equally.
Phantastica	One-quarter of cases arise after 40 years-old. Disorganized delusions, including of persecutory type. Auditory hallucinations and false memories. Indifferent or exalted mood. Disorganized speech, with neologisms. Patients can become violent. More frequent in men.

In a British study from 2010, 9.5% (12 out of 126) of patients older than 65 years with first episode psychosis treated in a clinic in a seven-year time range were diagnosed with schizophrenia. The remaining 89.5% were diagnosed with delusional disorder (15.1%), acute and transient psychotic disorders (6.3%), bipolar affective disorder (5.6%), psychotic depression (24.6%), and other conditions [11].

An excess of women when late-onset schizophrenia is discussed has been widely reported [12]. After 40 years of age, male-to-female incidence ratio is about 3:5, but ranges from 1:3 to 2:45 in very late-onset schizophrenia-like psychosis [9]. It has been hypothesized that the higher incidence in women may be related to the anti-dopaminergic properties of oestrogens, whose protection against psychosis ceases after menopause [9].

Genetic and epigenetic risk factors

Genetics seems to be a weaker risk factor for late-onset schizophrenia than for the classic presentation [13]. A 32-base pair deletion in chemokine receptor CCR5 may delay the age of onset [14]. Dopa descarboxylase may also modulate age of onset, mainly in males [15]. Dopamine receptor D2 (DRD2) polymorphisms have been widely discussed regarding schizophrenia vulnerability. DRD2 polymorphisms have also been found in patients with late-onset disease and may predict age at onset [16]. Interestingly, family history of schizophrenic disorder is rare (2.9%) in patients diagnosed with LOS or VLOSLP, but the burden of affective disorders in other family members can be important [17]. Globally, the risk of family incidence is lower than in early-onset disease [5]. However, finding affected relatives can be quite difficult, as disease manifests later in life, and older family members can be already deceased [1].

Unlike what has been described for the early-onset illness, obstetric complications and developmental issues are not common in LOS and VLOSLP [17].

Menopause seems to be a risk factor for psychosis, as oestrogen modulates dopaminergic neurotransmission [18], namely the sensitivity of central DRD2 [19], possibly contributing to the delayed schizophrenia presentation in women [20]. The hypothesized milder course in young women and more severe in older ones may be related with the ceasing of oestrogen protective effect [19].

Putative low-grade systemic inflammation translated by elevated serum levels of C-Reactive Protein (CRP), has been associated with a 6- to 11-fold increased risk of LOS and VLOSLP [21, 22].

Regarding VLOSLP, sensory impairing is an important risk factor: over 30% have hearing loss, 20% have vision loss and 12% have both [17]. Interestingly, the effect of hearing loss as a risk factor only becomes apparent when it occurs after language acquisition, not before [1]. Evidence suggests older psychiatric patients have suboptimal correction of their deficits [23].

It is hypothesized that psychosocial factors such as bereavement, retirement or financial struggle may trigger psychotic symptoms in vulnerable individuals, although more studies are required to confirm these findings [5].

Brain degenerative processes, such as vascular lesions, might have a role on symptom onset [19, 24]. Actually, Pearlson et al. hypothesize aging is a risk factor itself, as it might lead to neuronal loss and vascular degenerative processes, which may trigger the disease [25].

Pre-morbid personality

As cited by Dubertret, classic studies found that abnormal personality traits were found in up to 80% of these patients [20]. Paranoid and schizoid personality traits are especially frequent [1]. Passive-aggressive traits are also found, possibly contributing to feelings of resentfulness and misunderstanding by others [26]. However, only 15% of patients diagnosed with late-onset schizophrenia show poor working performance, unlike half of early-onset patients. Two-thirds of the former are or were married [9].

An interesting study which reports patients' self-experiences describes feelings of inferiority, rejection or victimization [27].

Some authors argue that a high pre-morbid cognitive reserve may lead to onset delay. That way, the disease would only manifest when some kind of neurodegeneration threshold was crossed [28].

Clinical picture

Patients' superior educational levels and marriage rates suggest they are able to play their social and family roles early in life [29-31]. Typical early adulthood tasks as parental emancipation, financial autonomy or marriage are hard to fulfil for a patient with schizophrenia, due to cognitive defects and blunted affect and volition. On the contrary, later in life, these tasks have already been accomplished [19].

Persecutory delusions are the most frequent, followed closely by the jealousy type [32]. These are usually well-structured, organized and elaborated [9, 33]. Persecutory delusions may arise from impaired facial recognition [34] and misinterpretation of others' intentions [35]. As mentioned by Phillips, these patients tend to "jump to conclusions" [34]. Even so, Theory of Mind, "the ability to attribute mental states (thoughts, feelings, beliefs and intentions) to others in order to explain, predict and manipulate behaviour", is not as compromised as it is in early-onset patients [36]. In the Indian population, delusions of influence were reported in two-thirds of patients, unlike the majority of studies [30]. Although no possible explanation is presented by the authors, we have noticed the population mean age in this study is lower compared to other similar studies.

Auditory hallucinations [37], such as third-person hallucinations and accusatory or abusive voices [17], are also prominent, unlike formal thought disorder [37], passivity phenomena, thought echo, withdrawal, insertion or broadcasting or negative symptoms [9, 17, 33]. When negative symptoms occur, they are more severe in women[38]. They tend to occur for a longer period in LOS in women

before first admission [39]. Other types of hallucinations, as somatic (17%) or olfactory (10%), are also common [17]. Some authors argue visual impairment may predispose to visual hallucinations [23], but others state that there is no apparent relationship between a specific sensory impairment and the type of hallucination [17].

Cognitive function is significantly less impaired in LOS than early-onset schizophrenia, namely regarding learning tasks and abstraction [31]. Memory impairment is also less evident. Besides, performance in episodic and working memory tasks and the presence of hallucinations are negatively correlated [40]. However, a study comparing cognitive deficits in LOS versus early-onset schizophrenia, concluded that 80-93.3% versus 70.6-76.5% of patients, respectively, had cognitive impairment, mostly in executive functions [24]. Results were replicated later [41]. Although at one-year follow-up cognitive functions (orientation, attention, concentration, memory, calculation, language, and praxis) were preserved [42, 43], five years later, dementia rates as measured by screening tests were higher and many patients were already institutionalized [44]. Accordingly, Brodaty suggests LOS predicts dementia in half of the cases [44]. Progressive cognitive decline seems to be related with stress-related accelerated brain aging rather than a neurodegenerative pathology [45].

Neuroimaging findings and cerebral microstructure anomalies

Brain volume global reduction (2%) and reduced volumes for entorhinal cortex, anterior superior temporal gyrus (25-30%), amygdala and left hippocampus have been reported in magnetic resonance imaging (MRI) studies [37]. Cerebellar atrophy has also been found [29]. The prominent anterior superior temporal gyrus atrophy may be related with auditory hallucinations [37]. These findings are similar to the ones in early-onset schizophrenia. Corpus callosum volume is also reduced [46]. Whether volume reduction starts late in life or is present since early life but only becomes symptomatic later is still matter of debate [37]. Larger thalami [47] and increased volume of cerebral ventricles, namely the third ventricle, have also been reported in LOS [20, 46].

Lower blood perfusion in frontal and bitemporal regions was described in LOS [46]. Vascular lesions, as showed by T2-weighted MRI white matter hyperintensities, in temporoparietal, occipital [46] and frontal [48] regions and thalamus [49] have been found in VLOSLP more frequently than in early-onset disease. Moreover, periventricular hyperintensities seem to be associated with memory, executive function and verbal intelligence quotient impairment [49].

Brain MRI and positron emission tomography (PET)-scan studies have revealed increased D2 receptors density in these patients. Actually, young men have a higher density of D2 receptors, but with aging, they lose them faster than women do, leaving women with a relative excess [25]. This may partially explain the higher incidence of LOS and VLOSLP in women.

In late-onset disease, findings suggest hippocampus degeneration by apoptosis, resulting in neuronal dysfunction and loss [50].

Tauopathy, restricted to the limbic system, and glial neurofibrillary tangles, along dorsal temporal horn, seem to be more evident in LOS than in early-onset or controls. These changes may remain silent until the accumulation of brain microlesions triggers schizophreniform symptoms [51]. Besides, impaired myelinisation, fibre organization and disrupted neuropil morphology in white matter was observed in frontal and bilateral temporal regions of these patients [47]. Integrity loss in these two regions has been reported in schizophrenia [46].

Treatment

A Cochrane Review was conducted aiming to found good-quality clinical trials regarding anti-psychotic treatment specifically in LOS, but none was found, highlighting the need for research in this age group. This review suggests psychiatrists should take clinical factors and personal experience into account when prescribing [52].

Response rates are usually good to all antipsychotics [53]. Response rates to risperidone (1-3mg daily), olanzapine (5-12.5mg daily) and aripiprazole (7.5-15mg daily) are good. No change in symptoms severity was observed with quetiapine 100mg daily [54]. Response rates to risperidone may occur in up to 71.4% of patients [29].

However, age-related pharmacodynamic changes have to be taken into account because they lead to enhanced sensitivity to neuroleptics and, obviously, to higher rates of adverse effects. Classic neuroleptics should be avoided, as the elderly are particularly sensitive to its adverse effects [55], due to nigro-striatal system degeneration [56]—up to 60% of patients manifest tardive dyskinesia after 3-year treatment [55].

In elder patients, especially sensitive to extrapiramidal symptoms, carefully monitored low-dose clozapine might be useful. Accordingly, neuroleptic doses should be started at 25% of the recommended adult dose and maintenance dose should not be higher than 50% of the recommended adult dose [53]. These doses are frequently sufficient to obtain response [57]. Long-standing delusional state seems to predict a poorer response to treatment, although the key factor in predicting success is compliance to treatment [53].

In a small size sample, amisulpride monotherapy (50-200 mg/day) was used successfully, with good response rates and non-significant adverse effects in VLOSLP [58].

Interestingly, in menopausal women, anti-psychotic doses have to be higher in order to obtain the same response rates [59]. Transdermal oestrogen seems to improve the response to anti-psychotic drugs in women [18, 59, 60]. It may be useful in men, too, but this requires further studies [59].

Despite the anti-psychotic drug used, inpatients seem to have higher response rates (76.9%) than outpatients

(37.5%) [54], possibly due to improved drug compliance.

Psychosocial and behavioural approaches, such as cognitive behaviour therapy and social skills training, are important adjuncts to pharmacological treatment [5].

Outcome

As oestrogens seem to play a protective role, early-onset schizophrenia in women has usually a milder course. More severe symptoms and worse prognosis occur when the disease first manifests after their protective role ceases in menopause. On the contrary, in men, the most severe cases occur earlier in life, with late-onset characterized by a milder course [19, 38].

After schizophrenia onset, these patients' social status declines, yet they do better than their early-onset counterparts, considering the capacity to have financial independency [61].

Better social and family support can be an important factor that may explain their better prognosis [19]. They do not lose their jobs, as they are usually retired, and after long marriages, they rarely divorce [61]. Cultural beliefs about the patients care also influence their outcome. In oriental societies, for example, family feels compelled to take care of their relatives at home [57].

However, although the prognosis is somewhat better than in early-onset schizophrenia, most patients remain symptomatic [62]. Besides, as already mentioned, a great number of patients develop dementia after one year follow-up [38].

Patients with VLOSLP are at higher risk of death than early-onset patients after adjusting for age [63].

Final considerations

Early-onset schizophrenia, LOS and VLOSLP show sufficient overlap to be considered under the same diagnostic category. However, there are important differences mainly regarding risk factors and symptoms, namely the absence of negative symptoms, that cannot be overlooked. Altogether, we consider that there are enough differences to justify, at least, a specific schizophrenia subtype, under the umbrella term "psychotic-spectrum disorders".

Abbreviations

DSM-III: Diagnostic and Statistical Manual of Mental Disorders, third edition; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition, revised edition; LOS: Late-onset schizophrenia; VLOSLP: Very-late-onset schizophrenia-like psychosis

Competing interests

The authors declare that there are no conflicts of interests.

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