Psychosis and dementia: prodrome or risk factor?

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Key Highlights

1- Patients with early onset schizophrenia are at increased risk of developing dementia and accelerated ageing due to neurotoxicity associated with psychotic exacerbations.
2- Patients with late and very late onset schizophrenia also have increased risk of developing dementia compared to healthy controls.
3- Late onset psychosis is increasingly believed to be a prodromal sign of dementia; abnormal perception or thought content is an integrated domain of the mild behavioural impairment (MBI) construct which involves neuropsychiatric symptoms preceding dementia.
4- Although psychosis may be the least common MBI domain, it was found to be the strongest predictor of transition to dementia.
5- The definition of psychosis comorbidity in cognitive impairment has been revised in 2020 by the international psychogeriatric association (IPA) group to include mild neurocognitive disorder in addition to dementia.

Text

Dementia revolves around alterations in molecular pathways that disturb cellular functions leading to loss of synapses, inflammation, gliosis, and eventual cell death [1]. Those pathophysiological alterations cause changes in functional networks that control cognition, personality, behaviour, and sensorimotor functions, eventually impacting an individual's autonomy and activities of daily living [1]. The diagnosis of dementia should be differentiated from other mental disorders including delirium, mood disorders or schizophrenia with comorbid cognitive impairment. Medical disorders need to be ruled out such as hypothyroidism and vitamin B12 deficiency which can be responsible for reversible cognitive impairment [1].

The current trend in dementia research is to prevent the onset of the disease by targeting modifiable risk factors, or identify early signs, also known as prodromal symptoms, to implement early intervention strategies. To date, the Lancet commission has identified 12 modifiable risk factors that could theoretically account for 40% of dementia cases. They include low education level, hypertension, hearing impairment, smoking, depression, obesity, diabetes, physical inactivity, low social contact, excessive alcohol consumption, traumatic brain injury and air pollution [2]. Minor neurocognitive disorder, previously called mild cognitive impairment (MCI) has long been known as a risk factor for dementia. More recently, mild behavioural impairment (MBI) has been identified as a constellation of neuropsychiatric symptoms preceding the onset of cognitive decline [3].

The MBI criteria are shown in the table 1 below, and neuropsychiatric symptoms in MBI cover the following domains: 1) decreased motivation; 2) emotional dysregulation; 3) impulse dyscontrol; 4) social inappropriateness; and 5) abnormal perception or thought content (psychosis). Among these domains, there has been an emphasis on affective symptoms, notably depression and apathy. Psychosis has been less discussed because it has been thought to occur later in the dementia continuum, with increasing disease severity.

More recently, psychosis has been receiving more attention, whether it is a risk factor or a prodrome for dementia. In fact, the risk of developing dementia was found to be two-fold higher in patients diagnosed with schizophrenia relative to those without this diagnosis, after adjustment for other risk factors for dementia such as cardiovascular diseases. Of 100 patients diagnosed with schizophrenia 7.4 presented with dementia before the age of 80 years, compared to 5.8 of 100 persons who developed dementia not diagnosed with schizophrenia [4].

One of the hypotheses underlying this phenomenon is the neurotoxicity of dopaminergic hyperactivity (notably in those with untreated psychosis), leading to neural degeneration of brain structures that contain dopaminergic receptors [5]. Schizophrenia is also thought to lead to accelerated aging, explaining higher odds of developing dementia in this population [6]: patients with schizophrenia between 50 and 60 years old had neurocognitive assessment scores (speed and episodic verbal memory) comparable to 70- and 80-year-old healthy individuals. Early onset schizophrenia is thus recognized as both a neurodevelopmental and neurodegenerative disorder.

In addition, late and very-late onset schizophrenia (occurring after the age of 40 and 60

years, respectively) has been associated with accelerated conversion to dementia[6]. It is debated whether very-late onset schizophrenia is part of the neuropsychiatric symptoms of prodromal dementia/MBI-psychosis. In a recent systematic review, patients with very late onset schizophrenia exhibited significantly higher rates of dementia diagnosis than controls without psychosis over follow-up periods ranging from 6 months to 17.7 years. Rates of dementia ranged between 4.4% over 3 years and 44.4% over 15 years which may be attributable to the heterogeneity of studies in terms of design and assessment tools. However, no difference was found between patients with very late onset schizophrenia and aged patients with early onset schizophrenia. Among the psychosis symptoms, hallucinations emerged as the strongest risk factor for a rapid progression to dementia [7].

In the year 2000, Jeste and Finkel developed the first definition of psychosis including delusions and hallucinations, in the context of clinically diagnosed AD. Given the increasingly recognized association between psychosis in the prodromal phase of AD (at the stage of mild cognitive impairment) with incident dementia, the definition of psychosis was revised in 2020 by the International Psychogeriatric Association (IPA) to include psychosis symptoms at the stage of minor neurocognitive disorders (MCI) in addition to dementia, as shown in the figure 1 below [8]. There is emerging data indicating that individuals with MBI represent a group at considerable risk of cognitive decline, and of the MBI domains, psychosis seems to be less frequent but associated with the highest risk of cognitive decline [9]. Research with large samples involving biomarkers is required to further elucidate the association between psychosis and different subtypes of dementia. Early identification of individuals with psychosis as an index for manifestation of neurodegeneration could potentially offer a window for prevention in individuals at risk for dementia.

Changes in behavior or personality observed by patient or informant or clinician, starting later in life (age ≥ 50) and persisting at least intermittently for ≥ 6 months. These represent clear change from the person's usual behaviour or personality (motivation, affective dyregulation, impulse dyscontrol, social inappropriateness, **abnormal perception or thought content**)
Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas: interpersonal relationships; other aspects of social functioning, ability to perform in the workplace

The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance
Although co-morbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder (e.g. generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication.
The patient does not meet criteria for a dementia syndrome (e.g., Alzheimer's dementia, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia).
Mild Cognitive Impairment (MCI) can be concurrently diagnosed with Mild Behavioral Impairment.

Table 1: Mild Behavioural Impairment (MBI) criteria as defined by the International Society to Advance Alzheimer's Research and Treatment (ISTAART) [3].

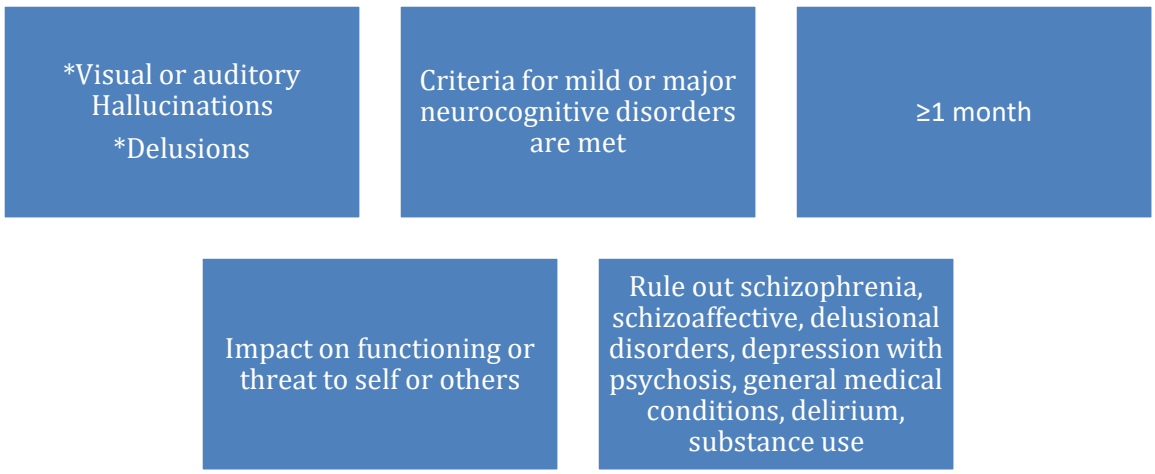

Figure 1: Revised Criteria for Psychosis for mild and major neurocognitive disorders [10]

*Psychotic symptoms have not been present continuously since prior to the onset of cognitive impairment.

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