Asian Journal of Psychiatry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Review

Do schizophrenia patients age early?

Venkataram Shivakumar [a,b,*], Sunil V. Kalmady [a,b], Ganesan Venkatasubramanian [a,b], Vasanthapuram Ravi [c], Bangalore N. Gangadhar [a]

[a] The Schizophrenia Clinic, Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India
[b] Translational Psychiatry Laboratory, Cognitive Neurobiology Division, Neurobiology Research Centre, National Institute of Mental Health & Neurosciences, Bangalore, India
[c] Department of Neurovirology, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India

ARTICLE INFO

Article history:
Received 1 November 2013
Received in revised form 17 February 2014
Accepted 22 February 2014
Available online xxx

Keywords:
Aging
IL-6
Oxidative stress
P300
Schizophrenia
Telomere
Vitamin-D

ABSTRACT

The etiopathogenesis of schizophrenia is poorly understood. Within the proposed "neurodegeneration paradigm", observations have been put forth for "accelerated aging" in this disorder. This proposition is largely based on the neuroscience research that demonstrates progressive changes in brain as well as other systemic abnormalities supportive of faster aging process in patients with this disorder. In this review, we have summarized the literature related to the concept of early aging in schizophrenia. These studies include P300 abnormalities & visual motion discrimination, neuroimaging findings, telomere dynamics as well as neuropathology of related brain regions. We also propose a role of vitamin D, neuroimmunological changes and elevated oxidative stress as well as mitochondrial dysfunction in addition to the above factors with 'vitamin-D deficiency' as the central paradox. Put together, the evidence supporting early aging in schizophrenia is compelling and this requires further systematic studies.

Contents

1. Introduction

Schizophrenia is a complex neuropsychiatric disorder characterized by delusions, hallucinations, formal thought disorder, personality disturbance, and cognitive dysfunction (APA, 1994). It affects 1% of the world population (Bresnahan et al., 2000). It also has a tremendous socioeconomic impact (Kaplan and Sadock,

* Corresponding author at: Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India.
Tel.: +91 080 26995256; fax: +91 80 26564830.
E-mail address: shvdgrt@gmail.com (V. Shivakumar).

http://dx.doi.org/10.1016/j.ajp.2014.02.007
1876-2018/

2006). The World Health Organization ranks it among the top ten disabling disorders (WHO, 2001). The etiopathogenetic basis of schizophrenia is yet to be ascertained (Keshavan et al., 2011).

Among the different causes, genetic basis has gained considerable evidence from family and monozygotic twin studies (Brown, 2011). However, genetic theories alone cannot explain schizophrenia completely, since the concordance rate in monozygotic twins is only 50%. Moreover, specific gene isolation has not been possible yet (McGuffin et al., 1995). Consequently it is tempting to postulate that environmental factors play a role in the pathogenesis (Brown, 2011). Environmental factors such as infections during pregnancy (Brown et al., 2004), and birth related complications (Mittal et al., 2008), Rh-factor incompatibility (Cannon et al., 2002), immunological factors, winter births and vitamin-D deficiency (McGrath, 1999) have been implicated. However, the contribution of these factors toward pathogenesis of schizophrenia is yet to be definitively established; nonetheless, it is important to note that most of these factors are linked with immune aberrations and an immune mediated pathogenesis is among the leading hypotheses for schizophrenia (Canetta and Brown, 2012; Horvath and Mirnics, 2014; Smith et al., 2007).

Prenatal immune abnormalities can result in persistent pro-inflammatory state that can adversely impact further neurodevelopment (Canetta and Brown, 2012). Indeed, it has been strongly hypothesized that schizophrenia could be due to a neurodevelopmental abnormality of brain (Fatemi and Folsom, 2009). The evidence for this is provided by the imaging studies which have largely demonstrated enlarged ventricles, smaller medial temporal lobes, and smaller cortical volume in first episode cases as well as in high-risk individuals. The fact that these brain changes are present even before the manifestation of illness, suggests a possible neurodevelopmental basis (Steen et al., 2006). Postmortem neuropathological studies have confirmed these imaging findings (Harrison, 2004). However, some researchers also hypothesize that schizophrenia could be due to progressive neurodevelopmental pathology (Woods, 1998).

2. Aging and schizophrenia

Kirkpatrick et al. (2008) in their review termed it as 'pathological aging' or 'accelerated aging process', because of increased incidence of premature onset of age-related physiological abnormalities and mortality. Papanastasiou et al. (2011), considered schizophrenia as 'segmental progeria' i.e., viewing schizophrenia as a whole body disorder rather than psychological disorder alone. The main driving factor in considering schizophrenia as an accelerated aging process is the early onset of aging changes in schizophrenia patients compared to their healthy counterparts. The factors in support of this hypothesis of accelerated aging in schizophrenia are the increased occurrence of structural and functional brain abnormalities as seen in elderly, increased incidence of aging-associated physiological abnormalities and disease (Fernandez-Egea et al., 2009b). Early cognitive decline and shorter natural life span than general population also support accelerated aging (Kirkpatrick et al., 2008). This is further supported by altered telomere dynamics seen in schizophrenia patients (Kao et al., 2008). Electrophysiological and visual motion discrimination abnormalities noted as in the elderly and absence of gliosis being attributed to apoptotic changes, provide a clue that neurodegenerative processes may be operative in this disorder. In this review an attempt has been made to collate all the evidences and relate them to the proposed hypothesis. Extending these postulates further, we also propose a role for vitamin-D, elevated oxidative stress & mitochondrial dysfunction and neuroimmunological changes as a common risk factor for both schizophrenia and aging thus adding the evidence base for "accelerated aging" in schizophrenia.

3. Age-related physiological abnormalities and metabolic syndromes in schizophrenia

Schizophrenia is associated with an increased incidence of age-related metabolic abnormalities like impaired glucose tolerance, insulin resistance and type II diabetes mellitus (Ryan and Thakore, 2002). It may be argued that these metabolic abnormalities could be secondary to antipsychotic usage; but these abnormalities were reported even prior to the advent of neuroleptics. However, studies have reported increased insulin resistance and glucose intolerance in antipsychotic-naïve schizophrenia patients compared to their healthy counterparts (Fernandez-Egea et al., 2009a; Ryan et al., 2003; Venkatasubramanian et al., 2007). Patients of schizophrenia have increased pulse pressure (Kirkpatrick et al., 2008); a risk factor for cardiovascular diseases, which commonly appears as age advances due to arterial stiffness. Indeed, pulse pressure changes are associated with insulin resistance and glucose intolerance (Sengstock et al., 2005). The prevalence of metabolic syndrome, though appears to be very common in schizophrenia, might be possibly due to the adverse impact of antipsychotic treatment (Mitchell et al., 2013). However, recent meta-analysis of prevalence of metabolic syndrome in schizophrenia reports a rate of 20.2% in un-medicated patients (Mitchell et al., 2013).

Schizophrenia is also associated with an increased mortality rate compared to normal population with cardiovascular disease accounting for many of the excessive deaths (Lwin et al., 2011). Though other factors like suicide, poor health care and medication side effects are considered the main cause of mortality, the metabolic abnormalities and resulting cardiovascular diseases cannot be neglected (Henderson et al., 2005; Venkatasubramanian et al., 2007).

Apart from this, efforts have been made to study other hormones which might act as aging indicators, in schizophrenia. One such hormone is androgen, which progressively declines with age (Kaufman and Vermeulen, 2005). Interestingly, a study conducted in male antipsychotic-naïve schizophrenia patients found that testosterone levels were significantly reduced (Fernandez-Egea et al., 2011). This adds to the line of evidences supporting the accelerated aging hypothesis.

4. Evidences from neuroimaging studies

Neuroimaging studies have reported significant decrease in the brain volume with advancing age (Fjell et al., 2009). Common findings include ventricular dilatation, volume loss in prefrontal and temporal cortices as well as reduction in hippocampal volume (Lemaitre et al., 2005). Interestingly, imaging studies in schizophrenia have also reported similar changes in these regions (Steen et al., 2006). Moreover, hippocampus, one of the prime structures implicated in schizophrenia (Whitworth et al., 2005), shows atrophy at a faster rate than any other structure in normal aging process (Lemaitre et al., 2005). Even within hippocampus, the CA1 and CA3 subfields are affected in healthy aging, age-related diseases like Alzheimer's as well as in schizophrenia (Small et al., 2011).

One might wonder how, the mere presence of these structural brain changes qualify for being an evidence for neurodegenerative process. Primarily these changes seem to progress over time even after the onset of illness, which support neurodegeneration theory in schizophrenia. This is vindicated in recent voxel-based morphometric studies (Mane et al., 2009). Earlier longitudinal studies did not indicate any progressive deterioration of the brain early in schizophrenia. However, a recent meta-analysis has demonstrated that patients with schizophrenia, compared with healthy controls, show a significantly higher progressive reduction in cortical gray matter volume over time with a moderate effect size of 0.5 (Olabi et al., 2011).

Please cite this article in press as: Shivakumar, V., et al., Do schizophrenia patients age early? Asian J. Psychiatry (2014), http://dx.doi.org/10.1016/j.ajp.2014.02.007