

# Accelerated aging in schizophrenia: Shortened telomeres, mitochondrial dysfunction, inflammation, and oxidative stress

**Several lines of evidence are coalescing into a critical scientific insight: Persons with schizophrenia show evidence of accelerated aging.<sup>1</sup>**

This implies early senescence, segmental aging, and, in young adult patients, premature onset of multi-system medical illnesses associated with aging, including cardiovascular disease, cancer, brain atrophy, and cognitive decline. This might be the real reason why persons with schizophrenia die 25 to 30 years too early, not only because of an unhealthy lifestyle and iatrogenic cardio-metabolic adverse effects.

One of the most consistent observations pointing to accelerated aging in schizophrenia is shortened telomeres.<sup>2,3</sup> Telomeres are the terminal part of chromosomes (similar to the plastic aglets of shoelaces), which are known to shorten with each cell division because of “end replication losses.” Telomeres are measured in lymphocytes, which researchers regard as “windows to the brain” because they reflect brain aging.<sup>4</sup> One study of lymphocytes in patients with schizo-

phrenia found that they appear to be approximately 25 years older than the lymphocytes of healthy individuals!<sup>4</sup>

## **Possible causes of accelerated aging**

**Inflammation.** The leading hypothesis for accelerated aging in schizophrenia is based on the inflammatory theory of aging. Schizophrenia has been strongly linked to immune dysregulation and neuroinflammation.<sup>5</sup> Other components of the accelerated aging hypothesis include oxidative and nitrosative stress, which is associated with high levels of free radicals, and, importantly, mitochondrial dysfunction that fails to generate antioxidants (glutathione peroxidase, superoxide dismutase, and catalase) that can neutralize free radicals and reverse oxidative stress, as numerous studies have shown.

Clinically, and at a relatively young age, persons with schizophrenia show many physical features consistent with aging,<sup>6</sup> including the following system changes:

- **CNS:** dilated ventricles, reduced brain volume and gray matter volume; hypofrontality, neurocognitive deficits



**Henry A. Nasrallah, MD**  
Editor-in-Chief

**At a relatively young age, persons with schizophrenia manifest biological and clinical features consistent with premature aging**

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such as executive functioning, working memory, and attention; neurophysiologic (low amplitudes on evoked potentials)

- **Musculoskeletal system:** abnormalities in muscle fibers; altered nerve conduction velocity; reduced bone density

- **Skin:** aging skin

- **Eyes:** increased rate of cataracts (not caused by medications); degradation in motion discrimination

- **Endocrine system:** abnormal gonadal hormones; low estrogen; low androgen; thyroid dysfunction, elevated cortisol

- **Metabolism:** increased rates of obesity; glucose dysregulation even before antipsychotic treatment; increased insulin resistance; abnormal glucose tolerance; reduced insulin-like growth factor-1 levels

- **Immune system:** increased pro-inflammatory cytokines (interleukin [IL]-1B, IL-6, IL-3, IL-4, IL-10, IL-13, tumor necrosis factor- $\alpha$ ) and decrease in anti-inflammatory cytokines (IL-2, interferon [INF]- $\alpha$ , INF- $\gamma$ ) and vitamin D

- **Cardiovascular:** systolic hypertension, increased pulse pressure

- **Oxidative stress and mitochondrial dysfunction:** increase in reactive oxygen species in brain tissue and increased DNA and RNA oxidation markers

- **Telomere dynamics:** significantly higher rates of telomere loss.

#### The mitochondrial theory of aging.<sup>7</sup>

The origin of this theory dates back to the landmark work of Denham Harman more than 2 decades ago in which he proposed a connection between free radicals and aging, which is associated with cell mutations and cancer.<sup>8</sup> He suggested that because mitochondrial DNA is not protected by histones as DNA in the nucleus is, it might be the main target for free radicals, making the mitochondria

more susceptible to oxidative damage. Therefore, it is possible that the high oxidative stress of schizophrenia could contribute to mitochondrial dysfunction, which leads to further telomere erosion.<sup>9</sup> Perhaps reducing oxidative stress in schizophrenia with a powerful antioxidant, such as the supplement *N*-acetylcysteine,<sup>10</sup> could help repair the dysfunctional mitochondria found in patients with schizophrenia and might mitigate accelerated aging.

I would like to propose a bolder, even radical, “out-of-the-box” therapeutic strategy for accelerated aging: mitochondrial transplantation. In fact, “mitochondrial donation” and transplant has been performed on fetuses with genetically defective mitochondria, which has prevented rapid death after birth.<sup>11</sup>

**Similarities with progeria.** The accumulating evidence for accelerated aging in schizophrenia has promoted some researchers to consider it a form of progeria<sup>12</sup> because of the accelerated aging features that patients with schizophrenia manifest. Patients with schizophrenia share some risk factors with patients with progeria, including high paternal age, prenatal stress, prenatal famine, low birth weight, and premature cognitive decline. Both progeria and schizophrenia are associated with increased apoptosis and cell senescence, which could reduce the risk of cancer but result in premature aging along with age-related medical disorders that lead to mortality in the elderly.

This is why collaborative care between psychiatrists and primary care providers is so vital for patients with schizophrenia from the onset of the illness during the teens and young adulthood, not after years of treatment and unhealthy lifestyle habits (smoking, sedentary living, high-fat and

high-calorie diet), which add insult to injury, culminating in loss of 25 to 30 years of potential life. Preventative medical care starting when schizophrenia is first diagnosed is vital, in addition to comprehensive psychiatric care, because premature mortality is the worst outcome in medicine.



**Henry A. Nasrallah, MD**  
Editor-in-Chief

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Preventative medical care starting when schizophrenia is first diagnosed is vital because premature mortality is the worst outcome in medicine

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