



LETTER TO THE EDITOR

Pathophysiological correlates of schizophrenia and incidental cerebral periventricular leukomalacia through a patient

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Dear Editor,

Schizophrenia is a complex behavioral and cognitive syndrome thought to be caused by impaired brain development caused by genetic or environmental factors or both. (1). While examining both structural and functional brain abnormalities to demonstrate the etiology of this multifactorial disorder, some consistent findings have been reported to some extent, such as diffuse gray and white matter deficits and enlarged lateral ventricles (2–4). Periventricular leukomalacia (PVL) is a neurostructural change caused by periventricular white matter ischemia and since it mostly occurs in infants exposed to perinatal complications, studies are linking this early-acquired lesion with some neuropsychiatric diseases, including psychotic disorders (5). Although PVL is suggested to be one of the structural brain abnormalities potentially associated with schizophrenia through ventricular expansion, it remains unclear how PVL causes brain circuit disruptions that lead to schizophrenia (6). Below, we reported a 23-year-old male patient diagnosed with schizophrenia with an incidental lesion compatible with PVL on cranial magnetic resonance imaging, and we aimed to highlight the potential role of

PVL in etiopathogenesis schizophrenia. A 23-year-old male patient diagnosed with schizophrenia two years ago, was admitted to the psychiatry outpatient clinic auditory hallucinations, persecutory delusions, and associated social withdrawal symptoms. He demonstrated agitated behavior related to auditory hallucinations that ordered him to harm and kill himself, hence, he was taken to the inpatient unit. His initial complaints were social withdrawal and elementary auditory hallucinations which emerged three years ago. Following an insidious prodromal phase, he had presented with disorganized and inappropriate behaviors including walking outside naked, and command auditory hallucinations within a year, and 4 mg/d risperidone p.o. was started on his first and only psychiatric admission with a diagnosis of schizophrenia 18 months ago. At the present admission, the Positive and Negative Syndrome Scale (PANSS) total score was 112. His caregivers claimed that he was noncompliant with antipsychotic treatment for at least a year, hence, they were unable to observe any improvement with regular treatment. The patient had no previous history of neurological diagnosis, no previous alcohol or substance abuse, and substance use was excluded through urine sampling. His mental state

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examination findings were as follows: he was cooperative and oriented, lacked verbal communication, and avoided eye contact, perseveration, commanding auditory hallucinations and persecutory delusions were noted. He had no insight. There was no pathological abnormality in physical and neurological examinations. Detailed blood screening, including hemogram and liver/renal functions, was within the normal range. A cranial magnetic resonance imaging (MRI) was performed as a routine admission protocol for inpatients. Multiple hyperintense lesions consistent with PVL located in the periventricular area of both lateral ventricles were reported, while mild bilateral cortical atrophy was observed (Fig. 1). According to the patient's early medical history, there were no perinatal complications described by his parents. The patient was started on risperidone 2 mg/d p.o. and gradually increased to 8 mg/d over three weeks. Auditory hallucinations started to improve on the tenth day of the treatment, while persecutory delusions started to resolve in the second week. Psychomotor agitation improved. The PANSS total score dropped to 74 on the 20th day of the treatment. He was discharged with r 8 mg oral risperidone daily and monthly admission to the outpatient clinic was recommended. Although the exact etiology of schizophrenia is still unclear, it has been suggested that the disorder is associated with a multifactorial etiology including abnormal brain structures, genetics, viral infections, and immune diseases (1). Early structural brain changes have been linked to the occurrence of schizophrenia due to

permanently impaired neural circuits (2). PVL, which is primarily caused by perinatal damage of the developing brain, is associated with perinatal adversities including very preterm birth, and the risk of psychiatric disorders increases in individuals with perinatal complications (5). Ventricular enlargement led by PVL is associated with white matter damage, abnormal neurodevelopment, and disrupted neural networks that maintain appropriate cognitive, emotional, and behavioral functions (7,8). Furthermore, it has been suggested that the increased release of pro-inflammatory cytokines related to perinatal immune activation caused by infections, hypoxia, or premature birth may lead to PVL, white matter damage, and ventricular dilation, all of which are included in the etiopathogenesis of schizophrenia (9–12). In particular, perinatal hypoxia has been suggested to cause selective long-term disturbances of the dopaminergic systems in experimental models (13). On the other hand, PVL interferes with the regular stratification of the cortex and causes a failure in normal brain development early in life. PVL and other white matter lesions are mainly repaired by Cajal-Retzius cells, however, the survival of these morphologically and molecularly distinct types of neurons on the surface of the developing cerebral cortex has been found to reduce in schizophrenia patients, particularly in young adulthood (11), indicating the presence of an insufficient neuronal regeneration process in schizophrenia. Strikingly, perinatal hypoxia and neuroinflammation, which are well-known causes of PVL, are also associated with schizophrenia independent of white matter

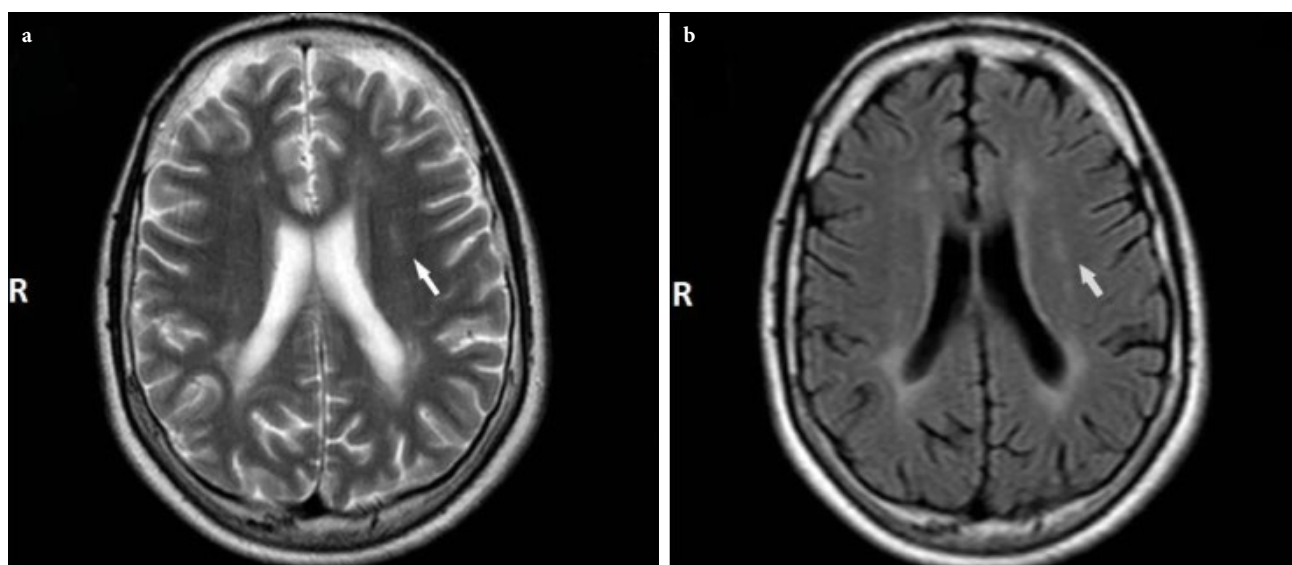


Figure 1. Hyperintense lesions consistent with periventricular leukomalacia surrounding both lateral ventricles in axial MRI scans (a) T2-weighted, (b) FLAIR sequence.

abnormalities and ventricular enlargement (11,14,15). All of the abovementioned findings suggest that the causality between PVL and schizophrenia cannot be solely attributed to a neurostructural abnormality-schizophrenia nexus, and that the shared multifactorial etiology including neuroinflammation that leads to both pathologies, should be comprehensively examined to provide a deeper appreciation of the underpinnings of the involvement of impaired neurodevelopmental processes in the schizophrenia etiopathogenesis.

Informed Consent: All procedures followed were under the ethical standards stated in the Helsinki Declaration of 1975 (in its most recently amended version). Informed consent was obtained from the patient after explaining to him why we request his permission to use his clinical information in a scientific work.

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