โรคจิตเภท: ความผิดปกติจากการพัฒนาระบบประสาทในวัยเด็ก

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บทคัดย่อ

โรคจิตเภท เป็นกลุ่มอาการของโรคที่มีความผิดปกติของความคิด โดยในช่วงทศวรรษที่ผ่านมาได้มีการศึกษาถึงสาเหตุของการเกิดโรคจิตเภทอย่างจริงจัง ซึ่งมีรายงานว่าปัจจัยหลายอย่าง เช่น พันธุกรรม ภูมิคุ้มกัน สิ่งแวดล้อม รวมถึงแรงผลักดันด้านจิตใจ ล้วนมีส่วนทำให้เกิดโรคจิตเภทได้ทั้งสิ้น อย่างไรก็ตาม ถึงแม้ว่าการศึกษาระยะยาว (Longitudinal studies) และการศึกษาด้านพยาธิวิทยาระบบประสาท (Neuropathological studies) หลายการศึกษาสนับสนุนแนวคิดที่ว่าโรคจิตเภทเป็นโรคที่เกิดจากความเสื่อมของระบบประสาท (Neurodegenerative disorder) แต่หลักฐานในยุคใหม่จากเทคโนโลยีที่มีความทันสมัย เช่น การศึกษาการทำงานของสมอง (Neuroimaging) และการศึกษาด้านพันธุศาสตร์ (Genetic studies) บ่งชี้ว่าโรคจิตเภทเป็นโรคที่เกิดจากความผิดปกติจากการพัฒนาของระบบประสาท (Neurodevelopmental disorder) จึงทำให้เกิดการเปลี่ยนแปลงแนวคิดเกี่ยวกับทฤษฎีการเกิดโรคจิตเภทจากความเสื่อมของระบบประสาท เป็นความผิดปกติจากการพัฒนาระบบประสาทเพิ่มมากขึ้น ซึ่งบทความวิชาการฉบับนี้ได้อ้างอิงหลักฐานจากการศึกษาและงานวิจัยต่างๆ ที่สนับสนุนทฤษฎีการเกิดโรคจิตเภทอันเนื่องมาจากความผิดปกติของการพัฒนาระบบประสาท

คำสำคัญ: โรคจิตเภท ความผิดปกติของการพัฒนาระบบประสาท สาเหตุการเกิดโรคจิตเภท

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Schizophrenia: A persuasive review on its causes in early brain development

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Abstract

The etiology of schizophrenia has been intensively studied over the last decades. A number of issues including genetics, autoimmune, environmental and psychodynamic factors have been reported to contribute towards the causation of this disorder. Although various longitudinal and neuropathological studies support that schizophrenia is a neurodegenerative disorder, more recent and advanced evidence such as neuroimaging and genetic studies have strengthened the neurodevelopmental hypothesis. The theoretical perspectives of schizophrenia, therefore, have shifted from a neurodegenerative to more likely neurodevelopmental disorder. The following review attempts to provide evidence and various research findings to support the neurodevelopmental hypothesis in explicating the causation of schizophrenia.

Keywords: schizophrenia, neurodevelopmental hypothesis, etiology

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Background

Schizophrenia is a debilitating neuropsychiatric disorder of which lifetime risk is approximately 1% in the general population.[1] Three major symptoms officially used to characterize schizophrenia are positive symptoms including hallucinations and delusions, negative symptoms including decreased motivation and emotional expression, and cognitive deficits including disturbance in executive functions, attention and working memory. The schizophrenic symptoms typically first appear between ages 18-25. Generally, changes in behavior and social functioning of a patient can be observed together with these characteristic symptoms.[2] However, the causes of schizophrenia remain poorly clarified.

A number of hypotheses, ranging from psychosocial ideas to environmental and neurobiological premises, have been used to explain the pathogenesis of schizophrenia. The neurodevelopmental hypothesis is a commonly accepted hypothesis applied to explicate the causes of illness. It is proposed that schizophrenia originates from genetics and/or environmental factors occurring during prenatal, perinatal, or early childhood stage. These causes result in altered early brain functions and structure, subsequently leading to schizophrenia in adolescence and adulthood.[3] Several lines of evidence corroborating the neurodevelopmental hypothesis derive from diverse research findings and highlight that early brain development is a noteworthy hypothesis to explain the etiology of schizophrenia.

Underlining the inter-relationship between genetic, brain, and environmental exposures across the developmental lifespan of schizophrenia patients, could enormously help researchers and psychiatrists design preventive innovation, as well as provide proper treatment or rehabilitation for those patients to ameliorate disease progression.

Early life environmental exposure: a provocative risk of schizophrenia

There are a number of significant studies supporting the association between early life exposure and risk of schizophrenia. Some epidemiological studies suggested that the risk factors can be derived from location and season of birth. For example, the children being born in urban areas or in spring/winter seasons seem to have higher risk for schizophrenia.[4-5] However, the neural related mechanisms in developing later schizophrenia are still unknown. Moreover, other studies demonstrated that the prenatal exposure to infections such as rubella, influenza and toxoplasma are correlated with increased risk for schizophrenia.[6]

Clinically relevant evidence also showed a connection between obstetric complications (OCs) and later psychotic symptoms of schizophrenia.[7-8] This meta-analysis study revealed that certain OCs including pregnancy complications (e.g. bleeding, rhesus incompatibility, and pre-eclampsia), delivery complications (e.g. emergency cesarean section, asphyxia, and uterine atony) and aberrant fetal growth (e.g. congenital anomalies, small head circumference and low birth weight) significantly increased risk for schizophrenia.[9] The effect sizes of this phenomenon were quite small due to the limitation of statistical power and information about prenatal stage, but impact of the relationship between OCs and the later developing schizophrenia was remarkable.

In addition, people with schizophrenia may have dermatoglyphic features and minor physical anomalies such as altered hairline, low-set ears and high-arched palate that underlie impaired brain development at the shared ectodermal origins.[10] This abnormal physical evidence emphasizes the prenatal disruption in schizophrenic patients. Therefore, additional postulation which could be made according to the early

neurodevelopmental hypothesis is that the patients with the history of disturbed intrauterine environment during prenatal period or suffering from OCs tend to have higher risk of developing schizophrenia.

Longitudinal studies of premorbid neurodevelopmental abnormalities

Many longitudinal studies have illustrated that schizophrenia patients possess minor neurodevelopmental deficits in several domains including cognitive, social and motor deficits in pre-schizophrenic children.[11]

The recent study of a Copenhagen birth cohort showed that adults having history of delayed development in the first year tend to develop schizophrenia.[12] Furthermore, the retrospective studies also demonstrated delayed development in language, motor milestone and poor coordination in pre-schizophrenic children.[13] The National Survey of Health illustrated that social isolation, social anxiety and unfavorable peer relationships are correlated with increased risk of schizophrenia.[14] Likewise, the Dunedin birth cohort study demonstrated that children with early and constantly reduced intelligence quotient (IQ) are prone to develop schizophrenia.[15-16] These consistent premorbid deficits underline the abnormal early neurodevelopment as plausible cause of later diagnosed schizophrenia.

The relevance of neuroimaging and post-mortem evidence for neurodevelopment

The recent advances of neuroimaging expand more understanding in the neurodevelopmental processes of schizophrenia. A meta-analysis study employing MRI scan exhibited that schizophrenia patients featured diminution of temporal lobe and hippocampal volume as well as ventricular enlargement.[17] In schizophrenia patients, the ventricular enlargement is typically found at the onset of disease.[18-19] These brain aberrations are likely neurodevelopmental processes rather than neurodegenerative mechanisms since they seem to be non-progressive and are found in both newly diagnosed and chronic schizophrenic patients.[3] The disease progression is of interest since the non-progressive lesions in schizophrenia refer to the lack of extended brain damage, thus classifying as the non-degenerative process.

More supportive information about developmental mechanism as the cause of schizophrenia derives from a series of longitudinal MRI studies, especially the alterations of cortical grey matter volume. For example, Rapoport et al.[20] have examined cortical change in healthy adolescents compared with childhood-onset schizophrenia (COS) patients. The follow up data were collected from all subjects after 3 years of the first MRI scan. The results showed that there was significant decrease in cortical gray matter volume in the frontal and parietal regions in both COS patients and healthy controls.

In fact, the normal grey matter pattern of a healthy individual shows an increased volume in late childhood and decreased volume in adolescence.[21] The pattern of this change covers a widespread region proceeding from the parietal to frontal areas during adolescent years and become steady in early adulthood.[22] However, this trajectory of neurodevelopment was also found in the COS and adulthood onset schizophrenia (AOS) with significantly greater decrease in grey matter volume as seen in figure 1[11, 23] suggesting that the pattern of abnormal grey matter loss in COS would eventually resemble that of AOS. Hence, these findings support the continuation between the COS and AOS, as well as emphasize the basis of neurodevelopmental models that the grey matter loss in early brain plays an important part in developing schizophrenia.

The loss of grey matter volume in cortical region was thought to result in the reduction of neural numbers, size, or density. However, the replicated studies have

shown inconsistent findings.[24] Some post-mortem studies showed an increase in neural cell density in temporal lobe[25] and hippocampus.[26] These findings have led to the "reduced neuropil hypothesis" which proposed that the decrease in cortical volume of schizophrenic patients is a result of decreased dendritic trees, cortical afferents and interneural neuropil, while the number of neurons remains the same as the normal cortex.[27] Others altered neural cytoarchitecture in schizophrenia patients include smaller neuron, shorter dendrites and increased neuronal density in the subcortical white matter.[28] The findings of these mis-sized, misplaced, and disorganized neurons can potentially explain neurodevelopmental process because abnormal neuronal migration usually occurs in second trimester of gestation.[29]

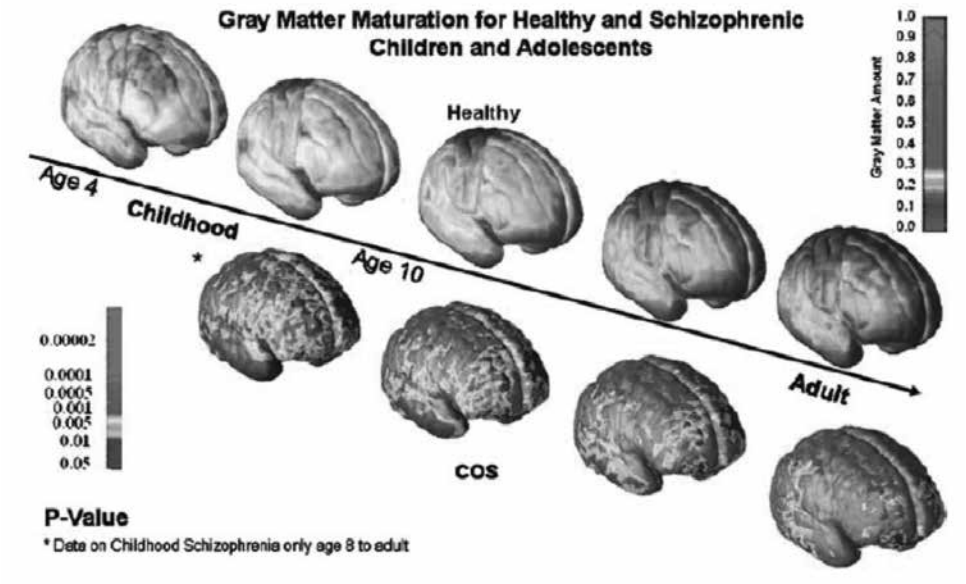

Figure 1: Pattern of change in grey matter volume for healthy and schizophrenic children and adolescence (Adapted from Rapoport et al[11]).

Additional intriguing evidence to reinforce the neurodevelopmental hypothesis is an absence of gliosis in post-mortem schizophrenic brains.[30] Reactive astrocytosis also known as gliosis is a cellular response to injury of astrocytes[3] and has been widely used as general characteristic pattern of neurodegenerative disorders. The loss of gliosis in schizophrenia patients, therefore, indicates the non-involvement of neurodegenerative process. Besides, the normal brain asymmetries which are essentially formed during second trimester of pregnancy were found to be disrupted in schizophrenia patients. This evidence designates an occurrence of early neurodevelopmental impairment.[31]

Implication of genetic components in neurodevelopmental processes of schizophrenia

Genetic variation has been found to be implicated in the emergence of schizophrenia which

constitutes approximately 80% heritability.[32] Genome-wide association studies (GWASs) provide crucial evidence involving common gene variants such as ZNF804A, TCF4 and MIR137 with relatively small impact on schizophrenia risk. On the other hand, rare gene mutations such as DISC1 and NRXN1 are irregularly found but have stronger influence on the risk for schizophrenia.[33-34] These susceptibility genes play crucial roles in early brain development in which altered genetic processes can increase risk of schizophrenia.[35] For instance, mutation of MIR137 seems to impact neurodevelopmental process by regulating neural development.[36] Furthermore, altered protein structured or expression of 'Disrupted in schizophrenia 1' (DISC1) can affect neural migration and neurite outgrowth during pre/perinatal stage, thus predisposing an individual to schizophrenia.[37]

The copy number variations (CNVs) are also markedly associated with schizophrenia, particularly 22q11.2 deletion. This genetic condition is commonly found in Velo-cardio-facial syndrome (VCFS) and can significantly increase prevalence of schizophrenia.[38] Moreover, grey matter loss related 22q11.2 was found to be the possible cause of cognitive deficits.[39] Heightened risk of schizophrenia caused by the 22q11 deletion is probably due to the disruption of multiple genes at the locus, including several with apparent neurodevelopmental roles.[40] Raznahan et al.[41] have further investigated the relationship between genetic susceptibility and early brain developmental processes regarding cortical maturation using neuroimaging techniques. The results illustrated that increase in valine (Val) dosing of Val158 Met polymorphism of catechol-O-methyltransferase (COMT) leaded to intensified loss of cortical grey matter volume in prefrontal cortex of COS probands. Comparing to the patient group, this relationship in healthy controls was significantly different. By their adulthood, the COS patients with Val homozygotes tend to have relentless impairment of cortical thickness compared to the controls as seen in figure 2. Hence, such important evidence indicates that specific genetic risk factors are associated with the abnormalities of brain developmental processes in patients with schizophrenia, especially in COS.

Individual lifestyle and environment can also pose an effect on epigenetic changes which contribute to early neurodevelopment. These findings have encouraged the expansion of epigenetic investigations in relation to schizophrenia. Methylomic studies of human fetal cortex highlighted that schizophrenia related differentially methylated positions (DMPs) are potentially enriched for loci in which DNA methylation is actively adjusted during the developmental stage of fetal brain development.[42] Therefore, this evidence underscores that the disturbance of epigenetic processes during early brain development may exert a key role in increasing risk of schizophrenia.

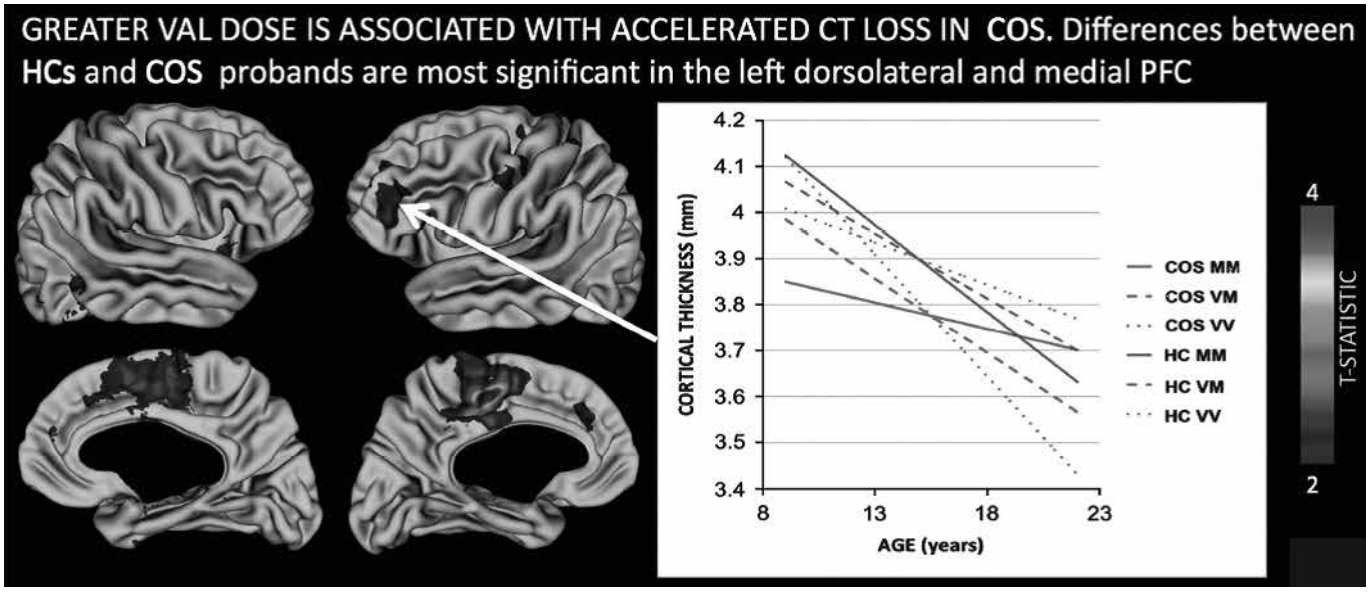

Figure 2: Val dosing associated with cortical thickness loss in childhood onset schizophrenia (COS) and healthy controls (HCs); MM: Methionine/Methionine, VM: Valine/Methionine, VV: Valine/Valine (Adapted from Raznahan et al).[41]

In addition, the evidence of human-induced pluripotent stem cells (hiPSCs) is thought to be ideal for the investigation of neurodevelopmental disorders. The hiPSCs studies can examine neuronal brain development, thus clarifying the cellular and molecular abnormalities of schizophrenia. These studies also provide the information of developmental disturbance in neuronal connectivity. The fibroblasts of schizophrenia patients which were reprogrammed into hiPSCs and followed by differentiation into neuron showed reduced connectivity of neuron together with diminished neurite number, and decreased gene expression of glutamate and PSD95-proteins.[43] Hence, it could be concluded from these findings that variability of neuronal hiPSC and changes in gene expression correlate with schizophrenia.

Conclusively, a number of assorted studies have elucidated an increased incident of gestational and perinatal insults in schizophrenia patients. The rise in prevalence of cognitive social and motor deficits as well as genetic alteration prior to the illness onset is particularly beneficial in understanding the altered brain development. The insights of epidemiology, post-mortem evidence and advances in neuroimaging together with genetics approaches have been addressed to affirm that disruption of early brain development is the potential origin of schizophrenia. The neurodevelopmental hypothesis, therefore, remains influential and is fundamental to etiology of schizophrenia.

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