

## Original Article

## White Matter Abnormalities and Virchow Robin Spaces in Patients with Psychotic Disorders

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### Abstract

In this study, we aimed to present white matter abnormalities and Virchow Robin spaces in patients with psychotic disorders and to discuss possible underlying mechanisms. The patient sample comprised 24 patients with psychotic disorders who had white matter abnormalities on MRI. Magnetic resonance imaging (MRI) appeared periventricular white matter changes in twelve patients (%50,0), frontal lesions in six patients (%25,0), parietal lesions in six patients (%25,0), temporal lesions in one patients (%4,2), infratentorial lesions in two patients (%8,3), and Virchow Robin spaces in eight patients (%33,3). This study suggested that there is a relationship between white matter abnormalities and psychotic disorders.

### Introduction

White matter (WM) consists of glial cells (astroglia and oligodendrocyte) and myelinated axons that nerve signals from one region of the central nervous system (CNS) to another and between the cerebral cortex and lower brain centers (1). White matter abnormalities (WMA), also known as subcortical hyperintense lesions on magnetic resonance imaging (MRI), may be seen in a variety of pathologic demyelinating and dysmyelinating processes that can include genetic, vascular, toxic, metabolic, infectious, inflammatory, traumatic, hydrocephalic, and neoplastic diseases (1-3). Demyelination describes destruction or loss of the myelin sheaths of a nerve fiber. Dysmyelinating disorders in which myelin fails to form properly are generally caused by enzymatic deficiencies frequently encountered children and young adults (1,3). In the general population, the risk factors most strongly associated with WMA are advanced age, diabetes mellitus, high blood pressure, and heart disease (4). Although chronic cerebral hypoperfusion due to ischemia can cause WMA that result from oligodendrocytes loss and myelin disruption, the pathogenesis of WMA is not completely understood (5). Therefore, the appearance of white matter disease on imaging studies is often nonspecific and the lesions may

occur multifocal, focal, or confluent (1). Cerebral WMA comprised of periventricular and deep subcortical alterations have been reported in psychiatric populations including patients with affective disorders, obsessive compulsive disorders, and psychotic disorders (6). In some studies, WMA has been associated with cognitive impairment, poor outcome and treatment resistance (4,6). These white matter changes may reflect tract abnormalities contributing to the clinical presentation and pathophysiology of mental disorders (4). In this study, we aimed to present white matter abnormalities in patients with psychotic disorders.

White matter structural changes can affect perception, thinking and behaviour (7). Structural brain abnormalities in patients with schizophrenia include volume alterations in the frontal lobe, cingulate cortex, temporal lobe and subcortical brain regions such as striatum, thalamus, corpus callosum, hippocampus, amygdala (6-8). Disturbances in connectivity between these cortical and subcortical regions manifest various signs and symptoms of the disease including hallucina-

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tions, delusions, behavioral and cognitive disorganization (8,9). White matter microstructural abnormalities have been described in some patients with schizophrenia and atypical psychosis and they have also been implicated in the pathophysiology of schizophrenia (7,10-12). The authors suggest that abnormalities along WM tracts providing structural and functional connectivity may be related to the origin of deficits in these patients (7-9).

Ultrastructural changes consistent with both necrotic and apoptotic processes of myelinated fibers and oligodendrocytes have been described in postmortem studies of schizophrenic patients (9). Animal models of perinatal hypoxic-ischemic brain white matter damage that are typified by reduced (hypomyelination) or abnormal (dysmyelination) formation of myelin have demonstrated the relationships between psychotic symptoms and white matter defects. Impaired motor coordination, prepulse inhibition and acoustic startle reflex observing schizophrenics have been detected (7). These findings provide evidence that WM impairment is related to specific network changes which can help better understand directly underlying cause of the psychotic disorders.

The Virchow-Robin spaces (VRS) or perivascular spaces are fluid-filled canals and pia-lined extensions surrounding the subcortical small cerebral blood vessels that penetrate the brain parenchyma from the subarachnoid space (13,14). VRS are normally very small, microscopic, but when dilated, they can be well visualized with MRI (13,15). Dilated VRS have been clinically associated with aging, hypertension, dementia, white matter lesions, cerebral small vessel disease, and other vascular risk factors (13,16). A number of theories have been proposed to explain the dilatation of VRS. These include

mechanical trauma resulting from cerebrospinal fluid (CSF) pressure or vascular ectasia, coiling of the aging artery particularly in hypertension due to pulsation, increased abnormal vascular permeability leading to fluid exudation, and the atrophy of brain tissue, perivascular myelin loss, ischemic perivascular tissue injury causing a secondary ex vacuo effect (13,14).

### Patients and Methods

The sample comprised 24 patients with psychotic disorders (six women, eighteen men, mean age=37,2 years, SD=17,6, range=14-71). The patients have following diagnosis: 7 schizophrenia (4 of them were the first episode), 4 atypical psychosis, 4 organic psychotic disorders (2 toxic brucellosis, 1 wilson disease?, 1 traumatic brain injury caused by traffic accident), 4 psychotic depression, 2 brief psychotic disorders, 1 schizophreniform disorder, 1 schizoaffective disorder, and 1 substance (cannabis)-induced psychosis. Table 1 presents the diagnosis of psychotic patients, patient no, and patient age. All patients who were admitted to the University School of Medicine Department of Psychiatry underwent a detailed clinical evaluation including neurological examination in order to exclude other medical conditions. Magnetic resonance imaging (MRI) were used to rule out intracranial pathology or to detect lesions. The diagnosis made by means of Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-IV). The severity of illnesses measured with The Brief Psychiatric Rating Scale (BPRS), The Scale for The Assessment of Negative Symptoms (SANS), The Scale for The Assessment of Positive Symptoms (SAPS). The mean age, the mean BPRS, SANS and SAPS scores, duration of the current period, and total duration of illness (months) of the patients are presented in Table 2. The patients treated

**Table 1. The diagnosis of psychotic patients, patient(s) no, and patient(s) age.**

	n (24)	Percent (%)	Patient no	Patient age (years)
Schizophrenia	7	29,2	1-7*	20,23,25,27,42,51,58
Atypical psychosis	4	16,7	8-11	28,30,34,64
Organic psychosis	4	16,7	12-15	14,15,17,50
Psychotic depression	4	16,7	16-19	48,61,63,71
Brief psychotic disorder	2	8,3	20,21	36,48
Schizophreniform disorder	1	4,2	22	39
Schizoaffective disorder	1	4,2	23	20
Substance induced psychosis	1	4,2	24	20

\*1-4: First episode

**Table 2. Age, BPRS, SANS, SAPS, duration of the current period and total duration of illness of patients.**

	Mean	SD
Age	37,2	17,6
BPRS	35,1	7,5
SANS	51,5	11,1
SAPS	33,6	15,8
Duration of the current period (months)	5,9	7,5
Total Duration of illness (months)	98,2	109,3

BPRS: Brief Psychiatric Rating Scale;  
SANS: Scale for Assessment of Negative Symptoms;  
SAPS: Scale for Assessment of Positive Symptoms

**Table 3. Localization of white matter abnormalities and Virchow Robin space.**

	n=24 (%)	Patients no
Periventricular lesions	12 (%50,0)	8-15,19,20,21,23
Frontal lesions	6 (%25,0)	4,5,11,13,22,23
Parietal lesions	6 (%25,0)	8,11,12,13,21,22
Temporal lesion	1 (%4,2)	2
Infratentorial lesions	2 (%8,3)	7,21
Virchow Robin space	8 (%33,3)	1,2,3,6,7,11,18,24

with monotherapy or combination antipsychotic medications including haloperidone, olanzapine, quetiapine, amisulpiride, oral and enjectable form of risperidone and paliperidone.

### Statistical analysis

Descriptive statistics for continuous variables (characteristics) were presented as mean, standard deviation, minimum and maximum values. The SPSS (ver. 13) statistical program was used for all statistical computations.

### Results

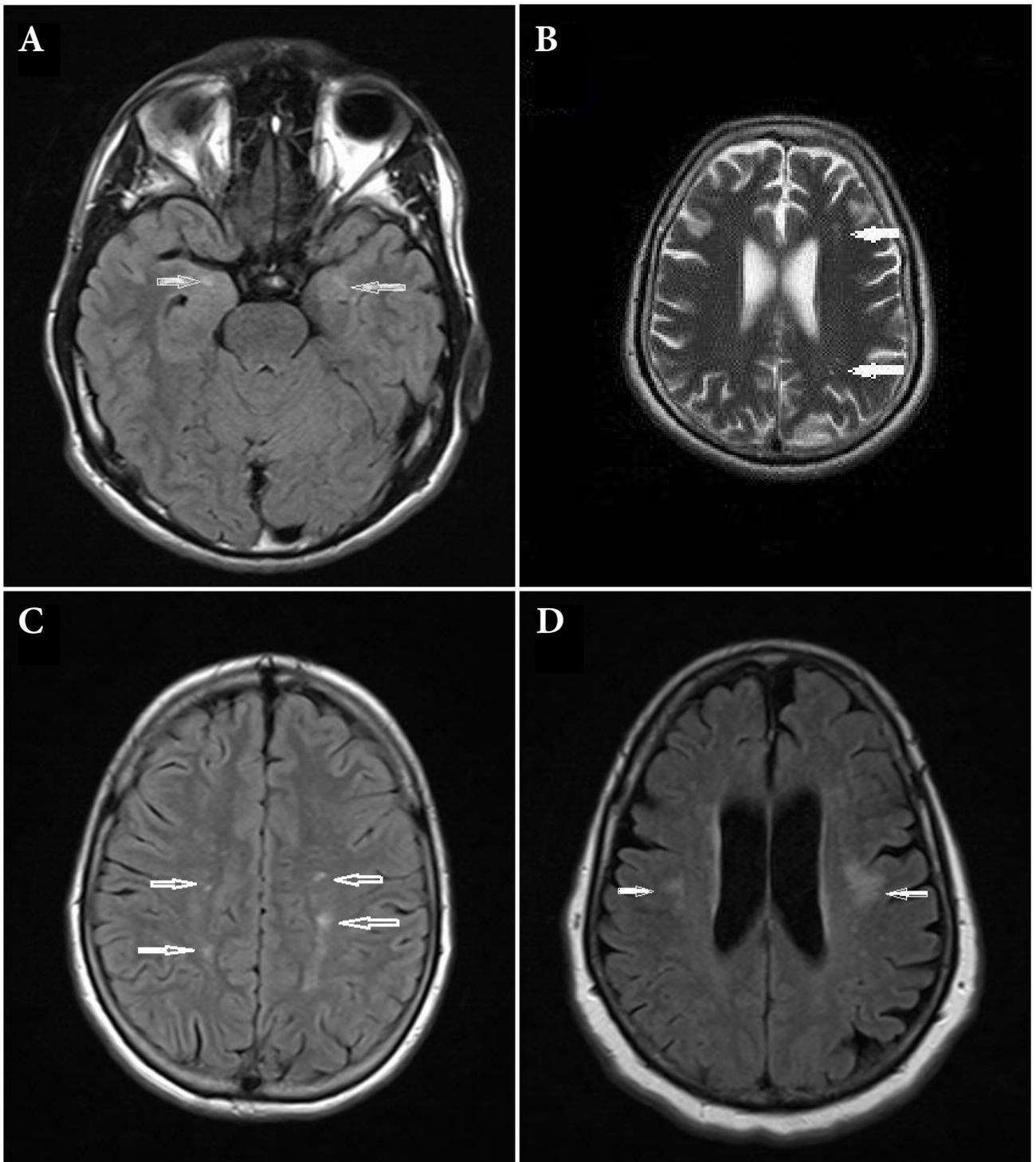
Localization of white matter abnormalities and Virchow Robin spaces are shown in Table 3. Magnetic resonance imaging (MRI) appeared periventricular white matter changes in twelve patients (%50,0), frontal lesions in six patients (%25,0), parietal lesions in six patients (%25,0), temporal lesions in one patients (%4,2), infratentorial lesions in two patients (%8,3), and Virchow Robin spaces in eight patients (%33,3) (see Figure 1 for some examples). Also, six patients (%25,0) had atrophic changes (patients no: 6,11,14,18,19,21) and five (%20,8) had choroid or arachnoid cysts (patients no: 1,3,6,7,18).

### Discussion

This study suggested that there is relationship between white matter abnormalities and psychotic disorders. White matter microstructural abnormalities are likely to develop schizophrenia and other psychotic disorders. Disrupted white matter connectivity may represent the disease or common latent vulnerability feature for disease. Moreover, WMA can be associated with poor clinical outcomes including long duration of illness, severity and treatment resistance. To our knowledge, so far, there are no studies assessing white matter microstructural abnormalities and Virchow Robin spaces in patients with psychosis.

Although neuroimaging studies have been determined the presence of white matter changes in patients with psychosis, yet the underlying mechanisms are not completely understood (17,18). White matter areas of the nervous system are composed primarily of myelinated axons produced by oligodendrocytes (8,9). Altered glial structure and function and reduced oligodendrocyte-specific gene expression affecting myelination have been proposed as a potential mechanisms (19). A reduced number of oligodendroglial cells, abnormalities in the expression of myelination-related genes, and changes in the white matter tract integrity have been shown in first episode psychosis, before antipsychotic treatment, and even in individuals at high risk of developing a psychotic disorders (10,20,21). Similarly, neuropathological studies were reported a significant reduction of oligodendrocytes density in schizophrenia patients. This has been suggested that impaired integrity of white matter tracts may be a key feature predisposing of psychotic disorders (20).

Other possibilities include inflammatory markers including proinflammatory cytokines and chemokines that are also implicated in the pathophysiology of psychosis. Elevation of these inflammation related molecules in the brain tissue indicating immunological dysfunction and abnormal inflammatory responses can contribute to brain cell injury (7). Hyperglutamatergic transmission has been suggested in the pathophysiology of schizophrenia. While the cause of such putative link between glutamatergic activation and psychosis is not clear, there is evidence to suggest the existence of induced central inflammatory process. This inflammatory response may lead to activation of glutamatergic neurons (9). It has been known that oligodendrocytes are highly vulnerable to glutamate induced excitotoxic



**Figure 1.** **A:** patient no: 2. Bilateral hippocampal lesions, **B:** patient no: 19. Periventricular confluent white matter changes, **C:** patient no: 24. Virchow robin spaces, **D:** patient no: 5. Subcortical white matter changes.

ity. Repeated episodes, long duration of such excitotoxicity and the toxic effects of other factors to neurones may contribute to further functional impairment of myelinated fiber tracts and may increase the probability of subsequent psychotic episodes (9).

Periventricular white matter abnormalities may be

correlated with astrogliosis characterized by disruption of the ependymal layer allowing the CSF to flow into the brain tissue (22,23). Otherwise, vascular changes are considered to be an important development of white matter abnormalities (22). Hypoxic-ischemic brain injury during delivery have been identified as a risk fac-

tor for schizophrenia (8). In vivo studies of neonatal rat brain have shown that oligodendrocytes are more sensitive to hypoxia than astrocytes and microglia (20). Many studies have reported that WMA are associated with subcortical microvasculopathy, or microvascular disease, or small vessel disease, affecting the small arteries, arterioles, venules, and capillaries of the brain (6,16,24). Age-related and hypertension-related small vessels diseases and cerebral amyloid angiopathy are the most common forms (24).

It has also been suggested that dilated VRS are MRI markers of inflammatory and immunological mediated cerebral small vessel disease (13,16,22). Animal studies, in both acute and chronic experimental autoimmune encephalomyelitis as a model for multiple sclerosis, have shown increased number of inflammatory cells in the VRS, even before any neurological signs or deficits appear (25). The presence of an excess of activated monocytes/macrophages located in the VRS play an important role in the pathophysiology of cerebral small vessel disease (25,26). The authors have also hypothesized that mechanisms for vascular damage may be associated with injured endothelium characterized by endothelial cell activation, dysfunction and inflammation (26). White matter and subcortical limbic structures more sensitive to inflammation and more vulnerable to ischemia than cortical grey matter and primary sensory cortices (22). Disruption of the myelinated nerve fibers containing dopaminergic neurotransmission can cause the loss of interactions between perception, attention, complex processing of information, and behavior in psychosis (9).

On MR imaging, ischemic lesions caused by small vessel disease are associated with white matter changes (13,24). Thickening of the vessel wall and reduction in lumen size can induce loss of autoregulation and chronic hypoperfusion leading to white matter lesions. This ischemic mechanism may also result in degeneration of myelinated nerve fibers due to oligodendrocyte death. Alternatively, it has been postulated that small vessel temporary occlusion may cause focal ischemia and tissue necrosis (24). Blood brain barrier damage through various mechanisms including inflammatory and infectious processes encompassing enlarged of Virchow Robin spaces is other possible mechanism (15,24).

Some studies have reported that white matter microstructure are associated with antipsychotic medications and chronicity in patients with schizophrenia

(27,28). On the contrary, in other studies, disruption of the white matter integrity, tract defects, and volumetric reductions have been identified in first episode psychosis, in schizophrenia especially during the prodromal, in the earliest stages of psychosis, in first degree relatives and individuals at ultra high risk for psychosis (7,9,10,18,20,21). In addition, some authors reported that white matter alterations may be reversible with pharmacotherapy (9). Our study confirmed that structural brain changes are present at illness onset in psychosis. These findings suggest that abnormality of the white matter that connects spatially distinct and functionally separate regions of the brain may help to determine basic characteristics of psychosis.

Previous neuroimaging studies of schizophrenia have demonstrated structural abnormalities in multiple brain regions including basal ganglia, thalamus, the corpus callosum tracts linking frontal and temporal regions (17,18). Also, significant white matter changes in the frontal and temporal regions have been observed in psychotic patients compared with matched healthy controls (29). The severity of these abnormalities was greater in temporal regions, and more so in the right hemisphere (21). The authors argued that these findings may be evidence of hypofrontality and fronto-temporal disconnectivity (21,29). In this study, magnetic resonance imaging (MRI) detected periventricular, frontal, parietal temporal and infratentorial white matter changes.

In conclusion, our findings suggested that deep white matter and periventricular changes and microvascular disease are common in patients with psychosis. The growing number of studies provide evidence for the abnormal brain structure including frontal, temporal, and midline limbic structures of psychotic patients. Microstructural brain abnormalities may provide potential neurobiological markers of psychotic disorders (30,31). These brain imaging abnormalities are more likely to be neurodegenerative than neurodevelopmental in origin (32). The main causes, clinical features and course, risk factors, of these abnormalities aren't completely understood, and warrant further study.

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