

# Choroid plexus calcification: clinical, neuroimaging and histopathological correlations in schizophrenia

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## Abstract

Schizophrenia is recognized as a psychiatric disorder that causes the most pronounced disturbances of cognition and social integration. In the etiopathogenesis of the disease, genetic, neurobiological and vascular factors are involved. Functional integrity of the brain can be correlated with the integrity of the blood-brain barrier (BBB), and the dysfunction of this barrier is an indicator that suggests neurodevelopmental abnormalities, injuries of various etiologies and dysfunctions within the small vessels of the brain that disrupt the calcium homeostasis. Neuroimaging shows that in patients with poor evolution, cognitive dysfunction and therapeutic resistance, the presence of choroid plexus calcification associated with hippocampal, frontal, temporoparietal and cerebellar atrophies. Antipsychotics with high capacity to block D2 dopamine receptors (haloperidol model) can aggravate apoptotic mechanisms of the brain areas involved in cognition and disrupts the functional integrity of the BBB due to decreased of choroid plexus blood flow because of the narrowing of cerebral small vessels. Choroid plexus calcification may be a predictive indicator of poor evolution or of a neurodegenerative type.

**Keywords:** blood-brain barrier dysfunction, small vessel disease, cognitive dysfunction.

## Introduction

Choroid plexus are specific histological structures that are part of the blood-brain barrier (BBB), providing neuroprotection of the brain, cerebrospinal fluid (CSF) secretion and represents a mandatory entry gate for that activity of psychotropic drugs. Psychopharmacological studies have aimed to correlate the effectiveness of psychotropic substances to penetrate the BBB, the peak achieved in the CSF and their efficacy or adverse effects. BBB's epithelial cells secrete a number of protein substances and represent the filter for some molecules that can be genuine markers for neurodegenerative diseases, and that make up the models for the neurodegenerative concept of schizophrenia: Parkinson's disease [1] and Alzheimer's dementia [2].

Schizophrenia is a multisystemic disease of the brain, in which the level of the genetic vulnerability and neurodevelopmental elements are involved, that determines a disruption of intersynaptic communication for neurotransmitters: dopamine, serotonin, norepinephrine, acetylcholine, glutamate, GABA. The resemblance between schizophrenia and Alzheimer's disease and the neurodegenerative model are supported by the existence in the central axis of this major psychiatric disorder of the cognitive impairment, schizophrenia being initially defined as dementia praecox.

An important role in deciphering the etiopathogenic mechanisms of schizophrenia is represented by the neurodevelopmental theory of schizophrenia [3, 4], which in the view of current biological psychiatry researches supports the existence of neurodevelopmental model that can be correlated with the evidence from brain

pathology (ventriculomegaly, decrease of gray and white matters), and causes represented by obstetrical complications (hypoxia and brain traumas at birth), prenatal viral or bacterial infections [5].

## Patients and Methods

The study followed a group of 12 patients, males and females, diagnosed with paranoid schizophrenia according to DSM IV TR, hospitalized in the 1<sup>st</sup> Clinic of Psychiatry of Craiova, Romania, between January 1<sup>st</sup>, 2011–December 31<sup>st</sup>, 2012, aged between 22 and 45 years, with poor evolution showed by the persistence of negative symptoms and important cognitive dysfunction, incomplete remissions and multiple hospitalizations, disruption of interpersonal relations with impaired social functioning. All patients in the study group presented positive anamnesis data for obstetrical trauma and birth hypoxia or the presence of febrile seizure type events. The psychopharmacological criterion for enrollment was the presence of neuroleptic therapy for at least 18 months.

Inclusion criteria were based on the following objective data provided by the assessment tools:

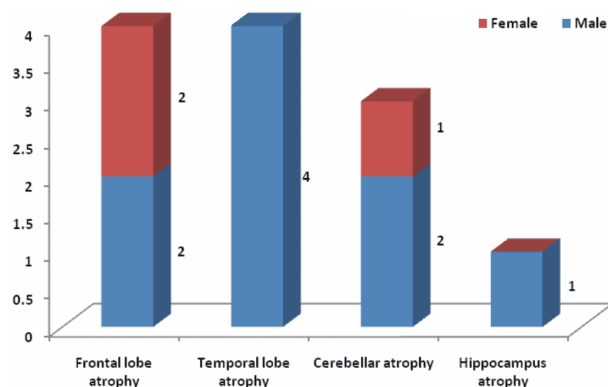
- Presence of extrapyramidal phenomena consecutive to therapy with antipsychotics showed by Barnes and AIMS scales;
- Persistent negative symptoms showed by PANSS negative subscale scores >30 (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking);

- Clinical Global Impression (CGI > 3);
- Cognitive impairment (MMSE < 21).

CT and MRI examinations were performed to all patients in order to emphasize structural brain abnormalities associated with poor quality of evolution.

## Results

Neuroimaging assessment identified in all patients calcification of choroid plexus associated with the following patterns of cerebral structural changes: frontal lobe atrophy (four patients, two males and two females), temporal lobe atrophy, unilateral or bilateral (four males), cerebellar atrophy (three patients, two males and one female) and right hippocampus atrophy (one male patient) (Figure 1).



**Figure 1** – Distribution of the study group by gender and brain structural abnormalities.

The patterns of brain structural abnormalities revealed by neuroimaging were as follows:

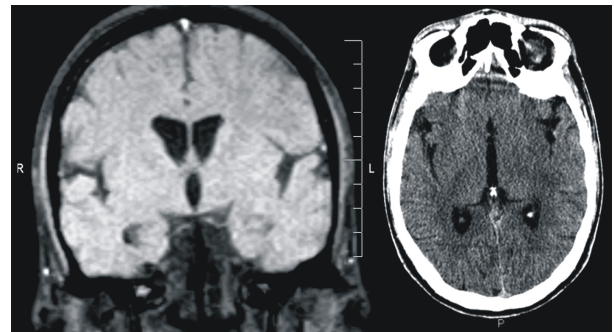
1<sup>o</sup>. Hippocampus atrophy, bilateral, predominantly right, present in a patient with positive history for febrile seizures associated with cognitive impairment, persistence

of negative symptoms and incomplete therapeutic response (Figure 2).

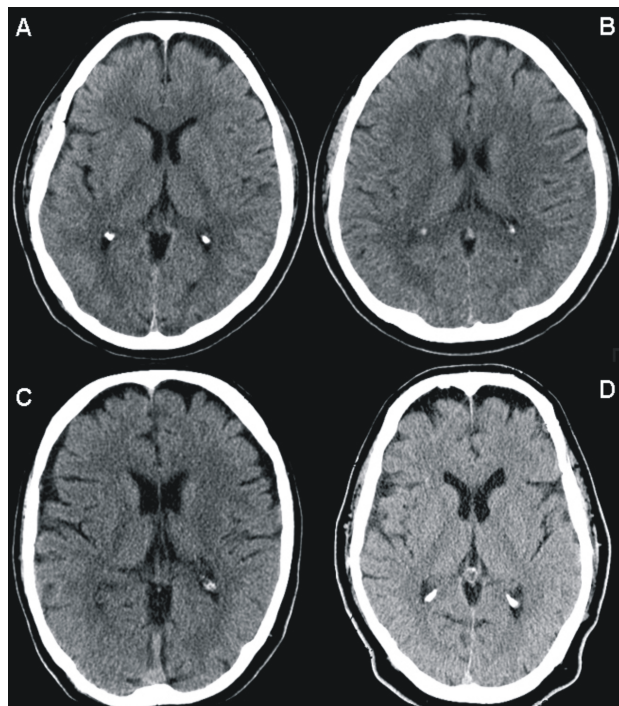
2<sup>o</sup>. Frontal cortex atrophy (Figure 3) identified in four patients, two females (A, B) and two males (C, D) with predominance of negative symptoms and cognitive impairment. The degree of frontal atrophy varied from one case to another, being more intense in men.

3<sup>o</sup>. Temporoparietal atrophies (Figure 4) identified in four males patients who presented a history of multiple delusional and hallucinatory episodes, and subsequently, the evolution being dominated by social and cognitive impairment. In one patient (C) is noted the presence of bilateral atrophic areas in the occipital cortex.

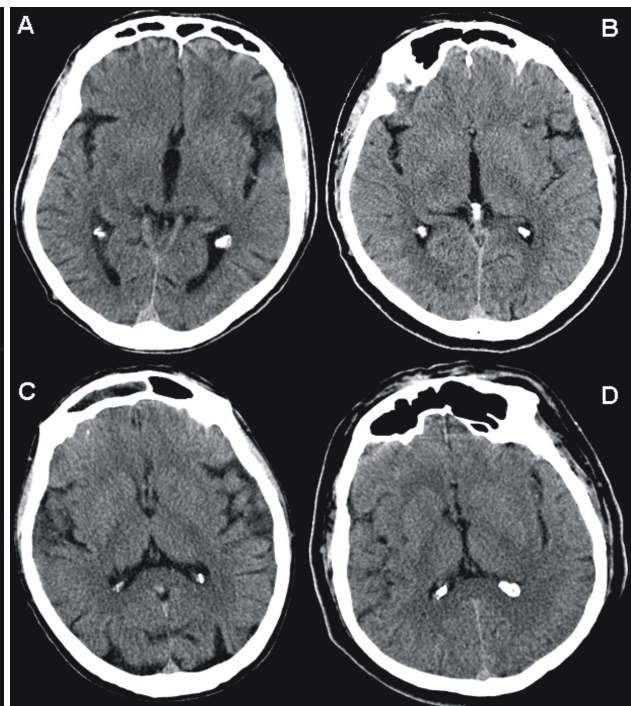
4<sup>o</sup>. Cerebellar atrophies (Figure 5) associated with ventriculomegaly and minimal atrophic changes in the frontal lobe were identified in three patients, two males (A, B) and one female (C) with significant cognitive impairment and therapeutic resistance. Cerebellar atrophy confirms fronto-cerebellar cognitive dysmetria hypothesis presents in cases with poor evolution and sustained by research of Andreasen NC *et al.* [6].



**Figure 2** – Hippocampal atrophy and pineal gland and choroid plexus calcifications in a patient with schizophrenia, poor evolution and cognitive impairment, with history of febrile seizures.

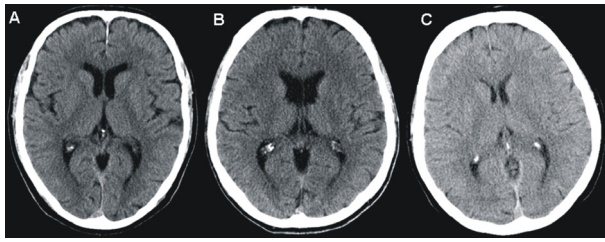


**Figure 3** – (A–D) Frontal cortex atrophy and choroid plexus calcifications.



**Figure 4** – (A–D) Temporoparietal atrophy choroid plexus calcifications.



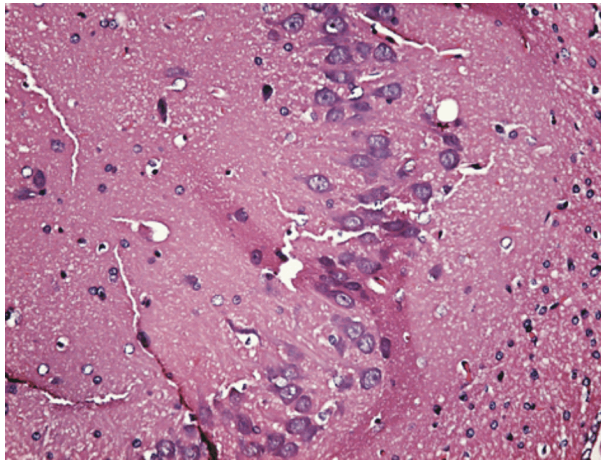


**Figure 5 – (A–C) Cerebellar atrophy and calcification of choroid plexus in three patients with schizophrenia and poor evolution.**

## Discussion

Cognitive circuits involved in the pathophysiology of schizophrenia are complex, partially understood, being recognized the involvement of the prefrontal cortex, the parietal-temporal area, entorhinal cortex and hippocampal area. Hippocampus has a major role supported by bilateral atrophic changes in schizophrenia with cognitive impairment and poor evolution [7].

Based on these assumptions and considering the presence of hippocampal atrophy highlighted in the patient with a history of febrile convulsions, we support the importance of neuroprotective different qualities of neuroleptic medication. Neuroprotective qualities were shown by studies made on animal model (rats) and highlighted the lack of protection of first generation neuroleptics (haloperidol) (Figure 6) [8].



**Figure 6 – Rat hippocampus after intramuscular administration of haloperidol decanoate (0.5 mg/kg/week) during 14 days and sacrificed on the 15<sup>th</sup> day. It highlights destruction of neurons, neuronal loss, pyknocytosis, granule cell dispersion, important vacuolization, discrete blood infiltrates. Hematoxylin–Eosin stain, ×200.**

Specialized literature data [9] emphasize the presence of hippocampal sclerosis, predominantly in temporal lobe epilepsy (50–75%), frequently associated with psychotic symptoms such as schizophrenia like psychosis. ECT is still used to treat schizophrenia and may increase the hippocampal lesions and exacerbate cognitive impairment. Frequent febrile seizures may be a marker for neurodevelopmental abnormalities correlated with hippocampal sclerosis [10].

The presence of choroid plexus calcifications in all 12 studied patients raises questions about BBB

dysfunction and permeability in schizophrenia, because of neurodevelopmental abnormalities, obstetrical trauma or brain trauma in small childhood with medium intensity, causing axonal dysfunction [11]. BBB dysfunction is correlated with  $\text{Ca}^{2+}$ -dependent phospholipase A2 activity dysfunction, considered to be an important marker for blood-CSF barrier permeability, along with S100beta [12].

Calcium homeostasis has a crucial implication in many neuropsychiatric disorders, especially in chronic psychiatric disorders, influencing neuronal development, apoptosis and autophagy, release control of neurotransmitters by secondary and tertiary messengers (adenylyl cyclase and NAADP receptors), cell membrane control and smooth muscle of small cerebral vessels [13]. Storage of  $\text{Ca}^{2+}$  in specific brain areas is attributed to vascular disruption [14]. Involvement of vascular factor in schizophrenia is supported by evidence of D2 receptor blockade by neuroleptic medications, causing significantly decreased choroid plexus blood flow that can boost hyperpermeability for calcium [15].

Recent data links the risk for schizophrenia with maternal iron deficiency justified by the quality of hemoglobin [16]. This observation calls into question the importance of the vascular factor in schizophrenia and impaired functional integrity of astrocytes neuronal and epithelial structures within BBB, the dysfunction of this structure being considered an important marker of neurodevelopmental disturbance, showed by the frequency of soft neurological signs [17] or epileptic manifestations [18]. The dysfunction of BBB has been linked to a peripheral marker, S100beta [19]. Massive elevations of them S100beta may be a valid indicator for brain damage, poor evolution, cognitive impairment and therapeutically resistance in schizophrenia.

BBB ensures the calcium ( $\text{Ca}^{2+}$ ) movement.  $\text{Ca}^{2+}$  controls the mechanisms for releasing neurotransmitters (electrical synapse) and the function of the NMDA receptors [20]. NMDA receptors decreased activity is involved in the etiopathogenesis of schizophrenia (psychosis model produced by NMDA antagonists, that can cause serious side effects: acute neurodegenerative changes in corticolimbic regions of the adult rat brain and psychotic reactions in adult humans) [21] causing an excessive entry of  $\text{Ca}^{2+}$  in neural structures, resulting in excitotoxicity and destruction of neurons, the deficiency of extracellular  $\text{Ca}^{2+}$  not being able to ensure NMDA receptor stimulation. The presence of the choroid plexus calcifications may be an important marker of this type of mechanisms associated with brain damage, poor evolution, and cognitive impairment in schizophrenia and therapeutically resistance in schizophrenia.

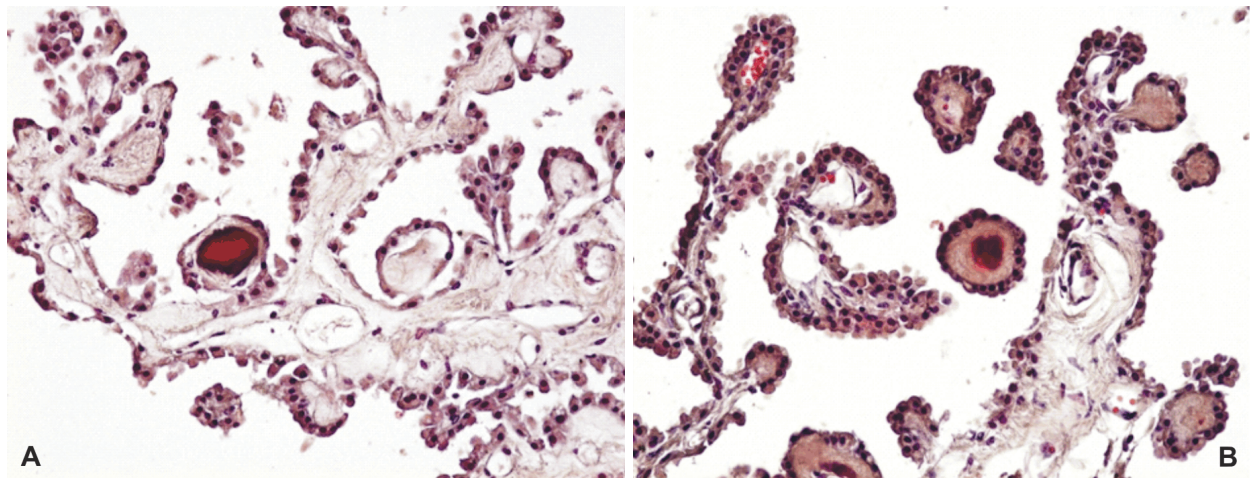
The cognitive structures involved in the mechanisms of schizophrenia are the prefrontal cortex, temporal lobe and hippocampus. Functional and structural alterations of these brain areas are associated with schizophrenia and worsening atrophy of these areas is an indicator of poor evolution [7, 22–25].

Antipsychotic drugs have different neuroprotective qualities for the hippocampus and frontal cortex demonstrated in animal model studies [8]. For these reasons, the therapeutically decision can be influenced in a favorable way by the correlation of clinical and

neuroimaging indicators suited for neurodevelopmental disorders within schizophrenia with histopathological data revealed by animal model studies.

Vulnerability of vascular factor in calcification of

the choroid plexus is supported by highlighting of such anomalies on *post-mortem* histopathological studies on samples obtained from patients with stroke (Figure 7).



**Figure 7 – (A and B) Calcium deposits in the choroid plexus. Post-mortem histopathology examination in patients with stroke (Prof. Laurențiu Mogoantă collection). Hematoxylin–Eosin stain,  $\times 200$ .**

Choroid plexus calcifications support the serotonin hypothesis of schizophrenia, the increase of serotonin level being a consequence of  $\text{Ca}^{2+}$  homeostasis disruption and involvement of bradykinin and endothelin-1 [26]. Serotonin elevates intracellular  $\text{Ca}^{2+}$  may be a consequence of excessive actions on 5HT<sub>2C</sub> receptors, proved by animal model studies [27].

## ✚ Conclusions

Choroid plexus calcification is commonly associated with frontal cortex, parietal-temporal and cerebellum atrophies, being in our opinion a neuroimaging indicator predicting cognitive impairment and poor quality evolution of schizophrenia. Poor quality response to atypical antipsychotic substances can be explained by the predominantly serotonergic mechanisms, choroid plexus calcifications becoming a possible indicator of this neuro-biochemical model of schizophrenia. This anomaly suggests the BBB hyperpermeability is consecutive to obstetrical trauma or minor brain trauma and cerebral vascular component involved in the pathogenesis of schizophrenia.

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