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The Implications of Adverse Pharmacologic Reactions and Complex Pathogenic Mechanisms in Schizophrenia

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Abstract: *Schizophrenia is a major health problem in which diversification and increase in the quality of antipsychotic molecules did not yield the anticipated results. that the etiopathogenesis of schizophrenia accounts for a combination of genetic factors forming the genetic spectrum of vulnerability for schizophrenia. The neurodevelopmental anomalies correlated with the gestational period and obstetric traumatisms raises major pharmacological management issues. The two levels of vulnerability (genetic and neurodevelopmental) are the basis of the pathogeny of side effects induced by antipsychotic medication. The most severe side effects are related to extrapyramidal symptoms, hyperhomocysteinemia, hypofrontality, impairment of the neurovascular unit and neuronal metabolic processes. Understanding these particular mechanisms will allow the clinician to identify the pathogenic model of schizophrenia, customized for each specific case. The adverse drug reaction decreases the compliance and adherence to the treatment, determining repeated discontinuations with psychotic relapses, and may trigger psychopathogenic bursts deteriorating the structural and cerebral functional balance. The type of psychotropic medication must be taken into account, as well as the concomitant medication administered for comorbidities associated with schizophrenia. The cerebral vascular modifications are correlated with the metabolic syndrome induced by antipsychotic medication. This complex syndrome, associated also with modifications in the homocysteine metabolism, determines weight gain, obesity, high blood pressure, ischemic cardiopathy, hyperglycemia and dyslipidemia. Identification of possible biological or neuroimaging markers helps and their early correction may prevent the onset of neurodegenerative evolution and irreversible cerebral atrophies, as well as decrease the risk of side effect that may endanger the life of the schizophrenic patient. The complexity of the pathogenic mechanisms requires a prophylactic behavior, not based on therapeutic switch, but on the proactive, customized pharmacologic intervention, addressing the pathogenic chains.*

Keywords: *dopamine, extrapyramidal symptoms, homocysteine, prolactin, hypofrontality.*

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1. Introduction

Schizophrenia represents the most frightful psychotic disorder with an incidence rated at 0.34-0.85% in the general population (Simeone et al., 2015). The rates of incomplete remission on long term continue to be represented by approximately 40-60% of cases (Lambert et al., 2010), in contrast with the development and translational integration of etiopathogenic model based on fundamental research. At the same time, the diversification and increase in the quality of antipsychotic molecules did not yield the anticipated results. This context can be explained by the fact that the etiopathogenesis of schizophrenia accounts for a combination of genetic factors forming the genetic spectrum of vulnerability for schizophrenia. The neurodevelopmental anomalies correlated with the gestational period and obstetric traumatisms are engrafted on this fundament of vulnerabilities.

These two levels of vulnerability (genetic and neurodevelopmental) are the basis of the pathogeny of side effects induced by antipsychotic medication. Deciphering these particular mechanisms will allow the clinician to identify the pathogenic model of schizophrenia, customized for each specific case.

Acknowledging these mechanisms allows for a pharmacologic therapeutic approach based on informed anticipative expectation allowing the clinician to anticipate the risks of administering an antipsychotic depending on potential adverse reactions. The adverse reactions decrease the compliance and adherence to the treatment, determining repeated discontinuations with psychotic relapses, and may trigger psychopathogenic bursts deteriorating the structural and cerebral functional balance (Higashi et al., 2013). These cerebral neurobiological modifications may turn a functional disorder with important reversibility potential into an irreversible progressive lesional disorder. This explains the deteriorative chronic evolution in the patients with numerous episodes and treatment discontinuations. The multiple relapses with acute psychotic episodes worsen over time the negative symptomatology, cognitive deterioration and social dysfunctionality and lead to self-aggressive and hetero-aggressive behaviors. This evolutive clinical presentations (negative and dyscognitive-behavioral symptomatology) represents the basis of stigma for patients with schizophrenia.

2. White matter pathology

The increase in stigma and social isolation amplifies the social stress, initiating secondary biological mechanisms dominated by episodic hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis, with increased cortisol release that disrupts the immune process (Chan et al., 2010). Thus, the ratio between the immune reaction, inflammatory process and endothelial dysfunction is imbalanced, with the triggering of apoptotic mechanisms by glutamate activation at the expense of the gamma-aminobutyric acid (GABA) neuroprotection. The glutamate excitotoxicity causes apoptosis focal points as well as axonal dysfunctions materialized by demyelinating axonopathies disturbing the cortical-subcortical circuits. This pathogenic path can be distinguished by neuroimaging examination, performed with Magnetic resonance imaging (MRI), through identifying white matter hyperintensities (WMHs), which can be interpreted as belonging to neurodegenerative pathology from multiple sclerosis or auto-immune infectious pathology from multiple sclerosis (Figure 1).

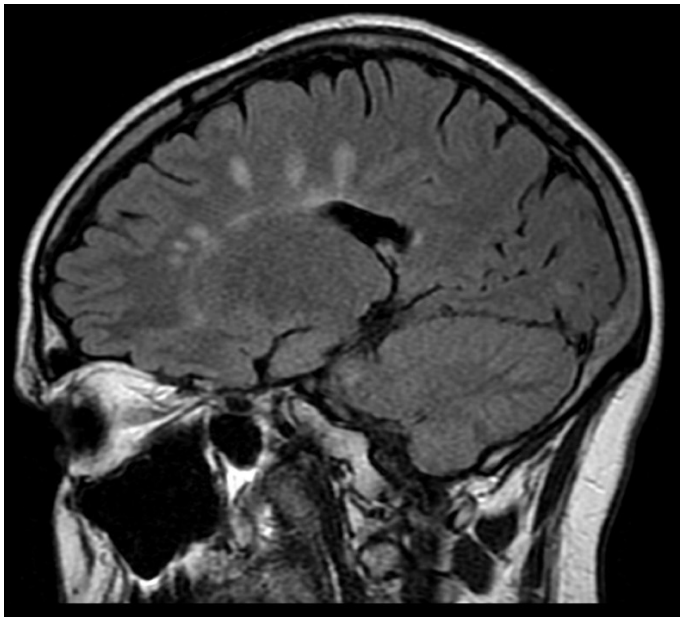


Figure 1. MRI-scan, sagittal fluid-attenuated inversion recovery (FLAIR) show: multiple white matter hyperintensities (demyelinating lesions), some of them are perpendicular to the corpus callosum. Typical appearance for multiple sclerosis
Source: Authors' personal archives

WMHs can be correlated also with neurodevelopmental anomalies, especially hypoxic ischemic encephalopathy (HIE). In such cases, the white matter deterioration is located periventricular, (periventricular leukomalacia), and anticipates the risk of developing ventriculomegaly (VM), which is a neuroimaging indicator suggestive for schizophrenia with unfavorable evolution and therapeutic resistance.

Secondary to HIE, punctual hyperintensities may appear in different white matter areas, whose presence is associated with the risk of stroke and leukoaraiosis development similar to cerebral small vessel disease like disorders (CSVD-ld) (Marinescu et al, 2021). In schizophrenic patients, the predominant WMHs in the left cerebral hemisphere indicate the risk of developing a post-neuroleptic depressive episode or suicide risk under reactive psychic stress (Iosifescu, et al., 2006). In the patients with chronic evolution and advanced age, the dynamic monitoring of the number and ratio between white and grey matter allows the anticipation of deteriorative-cognitive evolution, in direct ratio with the increased total number of hyperintensities (Höistad et al., 2009).

From our point of view, we consider that the increase of WMHs number raises the cerebral vascular risk in schizophrenia, while the higher number of hyperintensities in the grey matter suggests a pseudo-dementia evolution (the old term of „vesanic dementia") (Kapczinski & Streb, 2014).

The cerebral vascular modifications are correlated with the metabolic syndrome induced by antipsychotic medication. This complex syndrome determines weight gain, obesity, high blood pressure, ischemic cardiopathy, hyperglycemia and dyslipidemia. The metabolic syndrome is the consequence of genetic vulnerability, which is why the atypical antipsychotic inducing such syndrome must be avoided, depending on the number of genetic risk factors identified at family level (positive family history). A specific condition fostering the metabolic syndrome is indicated by the presence in the patient's medical history, even in childhood, of a somatic pathogenic underlayer that requires long term glucocorticoid therapy or Cushing disease spectrum. This syndrome is associated also with modifications in the homocysteine metabolism. Hyperhomocysteinemia determines toxic cardiomyopathy, provokes cortical atrophies through neurotoxic effect and can be an adverse reaction to clozapine administration (Alberich et al, 2019).

The interhemispheric dysconnectivity is favored by the dysfunctions or partial or total agenesis of corpus callosum, frequently determined by fetal alcoholism. WMHs associated with partial or total agenesis of the corpus callosum represent an important marker of the unfavorable evolution of

schizophrenia, with important behavioral and cognitive deficit, and therapeutic resistance (Figure 2).

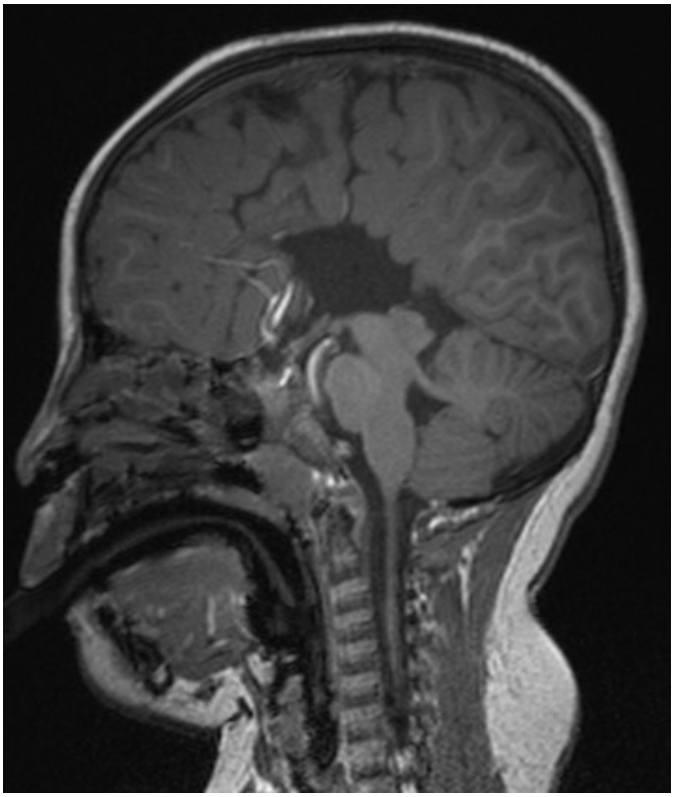


Figure 2. MRI scan, sagittal T1 sequence show the corpus callosum with completely absent-agenesis of the corpus callosum
Source: Authors' personal archives

The debut of schizophrenia can be precipitated by the use of psychotropic medication disturbing the neurobiochemical homeostasis or triggering some autoimmune mechanisms leading to cerebral vasculitis processes. Although rare and sometimes ignored, these modifications can be highlighted in neuroimaging examinations. The sensory deficits, especially in the onset period, can by compensated by the glutamate activation inducing auditive or visual hallucination episodes (Jardri et al., 2016). A mistaken diagnostic evaluation, such as acute psychotic syndrome and pharmacologic approach with dopamine blocking antipsychotics leads to depletion of

glutamate levels, with the emergence of auditive and visual deficits, suggesting SUSAC syndrome (Figure 3).

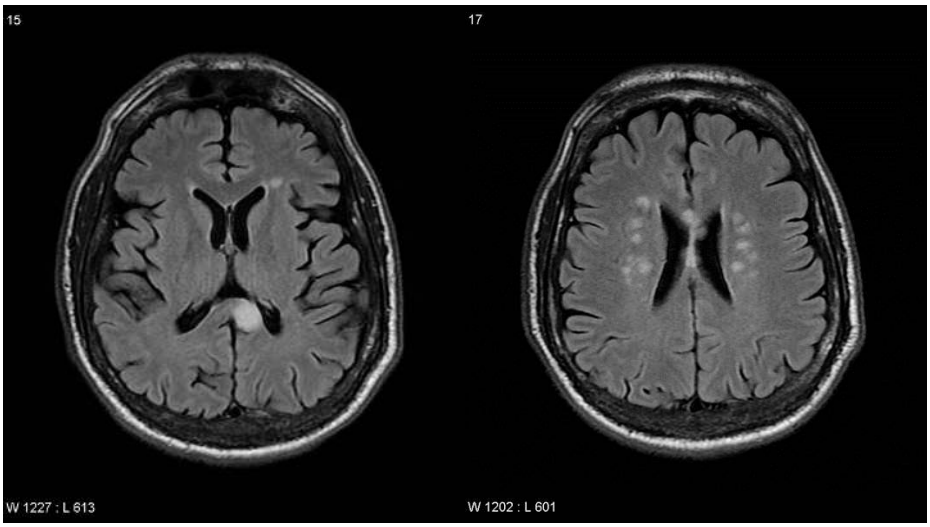


Figure 3. MRI-scan, axial FLAIR show: multiple flair hyperintense lesions in the corpus callosum, the largest in the splenium on the left. Numerous bilateral white matter lesions with central distribution, suggestive for Susac syndrome (different sections)
Source: Authors' personal archives

3. Neurodevelopmental anomalies

VM is associated with neurodevelopmental anomalies and has double significance from the biologic psychiatric perspective. In the first case, VM is consequent to the destruction of the periventricular areas (leukomalacia) consecutive to HIE, and suggests an alteration of the axonal tracts with primary horizontal dysconnectivity between the frontal pole and occipital pole of the brain. The glutamate hyperactivity generates also focal lesions in the cortical zones predominantly in the frontal, limbic and parietotemporal areas, leading to focus triggering convulsive manifestations (focal epilepsy) (Lewerenz & Maher, 2015). In the frontal lobe, enuresis manifestations may appear, together with electroencephalogram (EEG) modifications, fitting within epileptic crises of the frontal pole. These crises represent risk factors for subsequent development of schizophrenia (Hyde et al., 2008).

In the second case, VM is the consequence of the destruction of subventricular granular area, the main region quartering stem cells which, in the neurogenesis processes, may have a restoring role in the hippocampal level by developing the pyramidal neurons dentate gyrus and in Ammon's horn (CA1 and CA2) (Coletti et al., 2018). Primary VM, with onset as consequence from the disturbance of the cerebrospinal fluid (CSF) pressure is frequently associated with fetal growth restriction (FGR) anomalies, premature birth and low or very low birth weight. Consequences of VM through FGR seem to be less severe due to relative conservation of the subventricular granular area, a premature birth favors functional potentiation of stem cells (Miller, Huppi & Mallard, 2016). The restorative resilience capacity of the hippocampus is depending on the correct care of the premature baby. This is an important aspect because FGR associates also the hippocampal atrophy with irreversible alteration of cognitive functions (Figure 4).

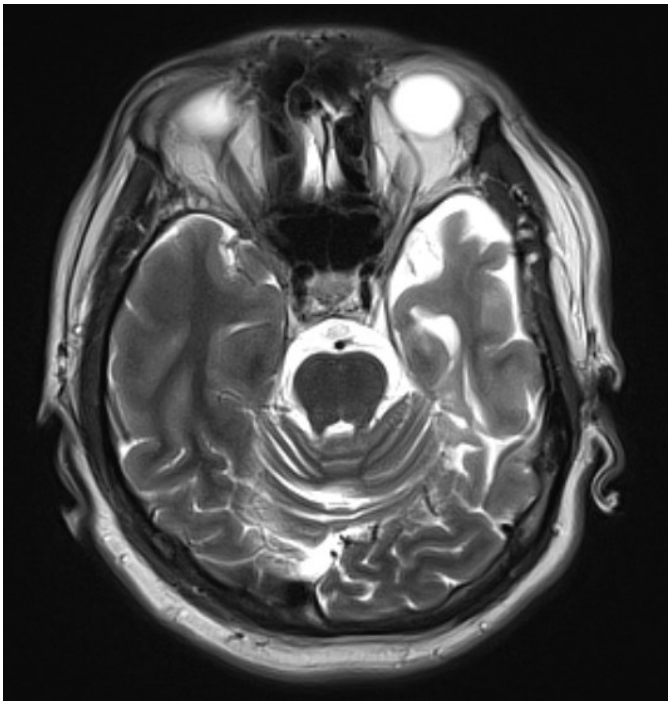


Figure 4. MRI scan, axial T2 sequence show left temporal lobe atrophy, with marked volume loss of the left hippocampus (structural cause for epilepsy)
Source: Authors' personal archives

In the current medical practice, this type of neurodevelopmental disorder associated congenital cardiac anomalies. The seriousness of these anomalies will determine the severity of cerebral hypoperfusion, which triggers apoptotic mechanisms. Neuronal death determines the destruction of subventricular granular area and VM accentuation. Cardiac vulnerability of premature baby, but also of infant with HIE, will be an important somatic stigma, even in the conditions of missing severe congenital cardiac anomaly. In both pathogenic circumstances, a dysautonomia of the newborn is triggered. The intensification of the sympathomimetic activities will lead to severe hypotension, and the hyperactivity of the parasympathetic system will generate anomalies in the cardiac rhythm, the most frequent being the prolonging or shortening of the QT interval, as in Brugada syndrome (Brugada, P. & Brugada, J., 1992). Identifying these cardiac disorders, previous to the first psychotic episode, will reduce the risks of arrhythmic cardiac adverse reactions induced by psychotropic (Wenzel-Seifert, Wittmann & Haen, 2011) and non-psychotropic medications, by modification of QT interval. The most used classes of non-psychotropic drugs that can alter the QT interval are antiarrhythmics, antibiotics, antihistamines (Nachimuthu, Assar & Schussler, 2012). Ventricular fibrillation and torsade syndrome, genetically or drug induced may sudden cardiac death.

Recognition of causal factors for FGR, especially use or abuse of drugs in pregnancy, TORCH infection with Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes simplex, maternal hypertension, fetal diseases, may be the basis for a primary prevention project of the risks of cerebral neurodevelopmental abnormalities and congenital heart disease (Fleiss et al., 2019).

In the case of infectious pathogenic conditions in the current Coronavirus disease (COVID-19) pandemic, severe issues are raised due to maternal stress determining glucocorticoid release. This context may lead to onset of gestational diabetes and hippocampal atrophy of the newborn due to the neurotoxic action of cortisol in the fetal brain. Recent studies showed the neurotoxic effect of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as well as the multisystemic inflammatory processes, secondary to the cytokine storm. These mechanisms can endanger the life of the mother and the fetus.

4. Extrapyramidal symptoms

The most frequent neurobiological correlation in the models of side effects induced by psychotropic medication administered in schizophrenia is represented by extrapyramidal symptoms (EPS). EPS can be primary, within neurodevelopment anomalies, and are based on various pathogenic mechanisms: neurotoxic, neuroinflammatory, decrease of cerebral blood flow (CBF), hypoxia, severe anemia, exposure to radiation or electromagnetic waves, bacterial or viral infections. A particular aspect is represented by the infection with group A β-hemolytic streptococcus (Streptococcus pyogenes) provoking Sydenham chorea by alteration of the basal ganglia area or Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) syndrome by alteration of the frontal area (Orefici et al., 2016, Untu et al, 2015).

In rare cases, as in Fahr`s disease, this type of pathology is favored by the calcification of basal ganglia, highlighted on computed tomography (CT) scan, and is associated with clinical symptomatology of schizophrenia like psychosis (Mufaddel & Al-Hassani, 2014) (Figure 5).

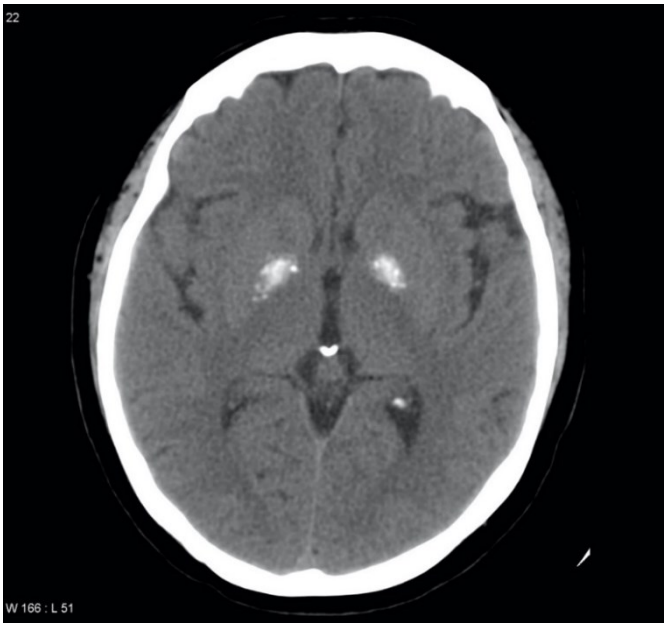


Figure 5. CT scan show incidental dystrophic basal ganglia calcification
Source: Authors' personal archives

EPS onset prior to a treatment with psychotropic medication can be correlated with some genetic anomalies, thus explaining the clinical variability of motor manifestations: PARK1 and PARK2 genes are associated with parkinsonism, with DYT1, DYT3, DYT12, DYT16 genes with dystonic syndrome (Shetty, Bhatia & Lang, 2019). Akathisia is less found in the neurodevelopment anomalies, being correlated with the administration during pregnancy of antipsychotics or SSRI antidepressants. EPS induced pharmacologically by psychotropic or non-psychotropic medication were correlated mainly with motor disorders. Main side effects are: drug-induced parkinsonism, acute dystonia, tardive dyskinetic syndrome, acute or tardive akathisia, restless legs syndrome (Blair & Dauner, 1992). This motor clinical presentation associates also non-motor symptomatology, represented especially by cognitive dysfunction, depression and dysautonomia, similar with the non-motor manifestation in Parkinson's disease (PD). Especially in cases of genetic vulnerability, dysautonomia may be exacerbated by mild TBI and cause disruption of dopaminergic transmission (Stovicek et al., 2020). The association of hyperhomocysteinemia, mild TBI and fetal alcoholism, determines a high risk for a neurodegenerative evolution as in Alzheimer's disease (AD) or PD (Campdelacreu, 2014).

Pharmacologically induced EPS, indifferent from the predominant clinical manifestation, is frequently caused by a genetic spectrum. Pathogenic underlayer is based on the reduction of dopaminergic transmission with dysconnectivity from the emerging basal area of the dopamine neurotransmission (ventral tegmental area, substantia nigra) and basal ganglia (globus pallidus, striatum, putamen). Excessive blocking through antipsychotics of D2 receptors from the basal ganglia determine mesencephalic hypodopaminergia in the level of nucleus accumbens. The uncoupling of the nucleus accumbens from the dopamine transmission determines its dysconnectivity with the frontal cortex, limbic system, amygdala, hippocampus and thalamus. If, in the short term, D2 receptor blockade triggers ESP, in the long-term dopamine supersensitivity psychosis may occur (Marinescu et al., 2019, Chirita et al, 2012).

For the clinician psychiatrist, the onset of any EPS motor clinical symptom will raise the issue of neurodegenerative evolution of schizophrenia, drugs side effects mechanisms enhancing the genetic neurodegenerative factors. The uncoupling of the nucleus accumbens and the complexity of the non-motor manifestations of this mechanism explains the association of motor effects adverse to EPS with cognitive dysfunction predominantly in the frontal cortex and with alteration of integrating

emotional cognition in an ethical decision system based on the possibility to control the impulsive-aggressive behavior. Conservation of the dopaminergic structure in the amygdala is responsible for the conservation of the impulsive-aggressive behavior.

5. Hypofrontality syndrome

Dopamine decreases in the frontal cortex, consecutive to EPS motor symptoms, determines Hypofrontality syndrome (HS), characterized by the predominance of negative symptomatology, of psychomotor inhibition with apathy and adynamia, pronounced cognitive deficit. At cognitive level the working memory, attention, cognitive flexibility is mainly affected. HS is associated with the increase of GABAergic interneurons activity and glutamate decrease (Marek et al., 2010).

From the clinical point of view, HS may debut in the prodromal period of schizophrenia and has a long evolution, reason why the real onset of schizophrenia is actually taking place years before the apparent debut with the first psychotic episode with positive symptomatology. Thus, the long period without treatment triggers compensatory mechanisms that reverse the GABA/glutamate ratio in the frontal lobe. The glutamate increase plays a major role in activating dopaminergic transmission (positive symptoms), noradrenergic (psychomotor restlessness), acetylcholinergic (confusional episodes) and serotoninergic (hallucinations with therapeutic resistance to dopaminergic blocking action antipsychotics).

From the biological point of view, HS can be primary, with a potentially reversible functional character, generated by alteration in the glutamate secretion controlling genes. Potential markers could be the decrease in glutamine synthetase, increase in vesicular glutamate transporters, reduction of N1 and N2 subunits of NMDA receptors (Krzystanek & Pałasz, 2019, Ciubara et al, 2015). Increase of GABA activity is dependent on the increase in glutamic acid decarboxylase (GAD). In this type of hypofrontality, the dysfunction of mirror neuron system (MNS) is involved, by the disturbance in the communication between the right frontal cortex and the left temporal limbic one, consecutive to the corpus callosum dysfunction.

6. Cerebellar dysfunction

The immediate consequence of the frontal temporal limbic interhemispheric dysconnectivity is the cerebellar dysconnectivity with the onset of motor symptoms like ataxia and dysmetria. Cerebellar cognitive

affective syndrome may further appear (Schmahmann & Sherman, 1998). The cerebellar motor symptoms are associated with cognitive anomalies and are caused by the dysfunctionality of the circuit between the anterior vermis and fastigial nucleus, but also the cortico-cerebellar-thalamic-cortical circuit (CCTCC) (Sears, Andreasen & O'Leary, 2000).

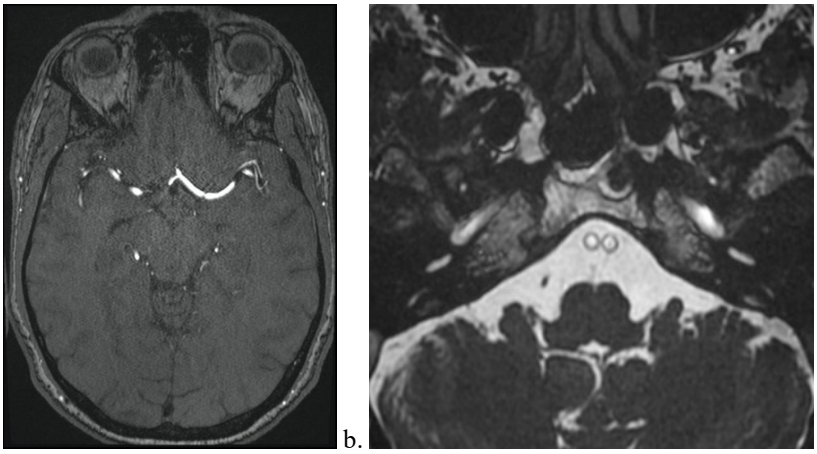
The presence of cerebellar anomalies is suggested by the presence of saccadic eye movement, which associated with ataxia, dysmetria and dysdiadochokinesia or other neurological soft signs, indicates a disturbance of the integrative neuromotor functions (Bodranghien et al., 2016). As early as the end of the XXth century, the saccadic eye movement identified through the pendulum test (Robinson, 1964) was considered the main risk factor for developing schizophrenia (Caldani et al., 2017). Biologically, it signals a dysconnectivity between the cerebellar structures responsible for movement coordination and prefrontal cortex. The other symptoms (ataxia, dysmetria and dysdiadocochinezia) are caused by intrauterine traumatic lesions or vascular dysfunctions in the posterior circulation of the fetus cerebral arteries, which can be favored in our opinion by pelvic presentation. Such a context requires special monitoring, especially if associated with umbilical cord loops (nuchal cords) and imminence of HIE onset. A primary prophylactic attitude is recommended, by cesarean delivery, ensuring specific neuroprotection and pharmacologic therapies to improve blood oxygenation. Saccadic eye movement can be a phenotype marker for high risk of psychosis (Obyedkov et al., 2019).

The variability and intensity of symptoms is dependent on the cerebellar vascular factor and suggest a CBF dysfunction in the posterior vascular territory and a possible alteration of the circulation speed in circle of Willis, unable to ensure the compensation by increase in the blood flow. From the diagnosis point of view, the transcranial echography and echography evaluation of fetal CBF may show a global decrease of the blood circulation speed in circle of Willis (Owega et al., 1998). The decrease in the cerebellar flow in the anterior pole (Figure 6a) is associated with HS while a a decrease in the posterior pole (Figure 6b, 6c) is correlated with anomalies in the CCTCC circuit. The circle of Willis anomalies can be fostered by genetic anomalies in type III and IV collagens controlling the correct bifurcation of small cerebral vessels, but also by elastin anomalies determining vascular rigidity or hyper elasticity with risk of cerebral aneurysms (Canham et al. 2006).

During evolution of schizophrenia, the cerebellar dysfunction is associated with cognitive deficit and cerebellum atrophy (Figure 7) as a sign

of exhaustion of the resilience mechanisms in the cerebellar mechanisms and their connections with the frontal, temporal and parietal cortex.

a. b.



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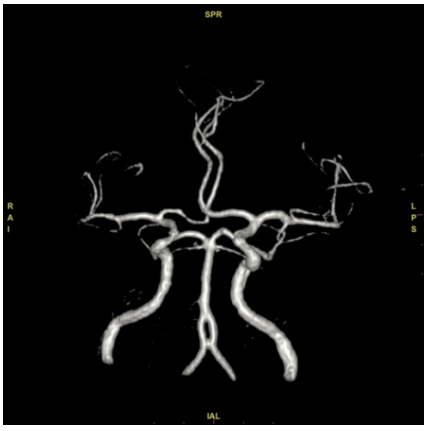

Figure 6. Vascular anomalies of circle of Willis. a. MRI scan, axial Magnetic resonance angiography (MRA) magnetic resonance angiography 3D Time-of-Flight (3D-TOF) show aplastic A1 segment of right anterior cerebral artery (ACA). b. MRI scan, axial T2 (part 1) and c. magnetic resonance angiography coronary maximum intensity projection (MRA COR MIP) reconstruction show basilar artery fenestration
Source: Authors' personal archives

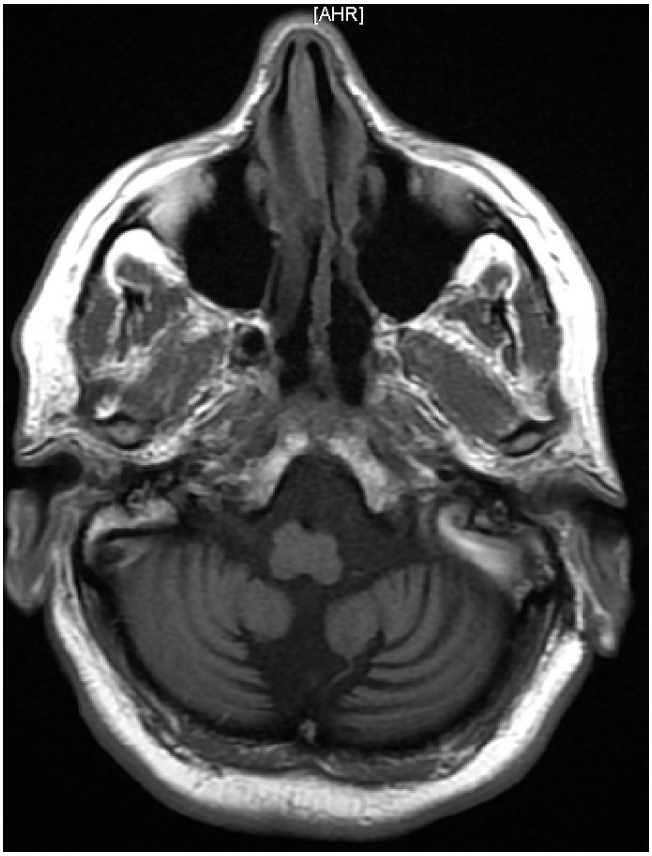

Figure 7. MRI scan, axial T1 sequence show diffuse cerebellar atrophy
Source: Authors' personal archives

The dysconnectivity between cerebellum and thalamus determine a severe form of cognitive deterioration, because the thalamus plays a major role in the conservation of attention and memory. The integration of sensitive and sensory processes in the learning and linguistic awareness is deeply altered, going up to personal identity amnesia, with patient incapacity of reconstructing his past, aspect specific to thalamic dementia (Saalmann & Kastner 2015) (Figure 8).

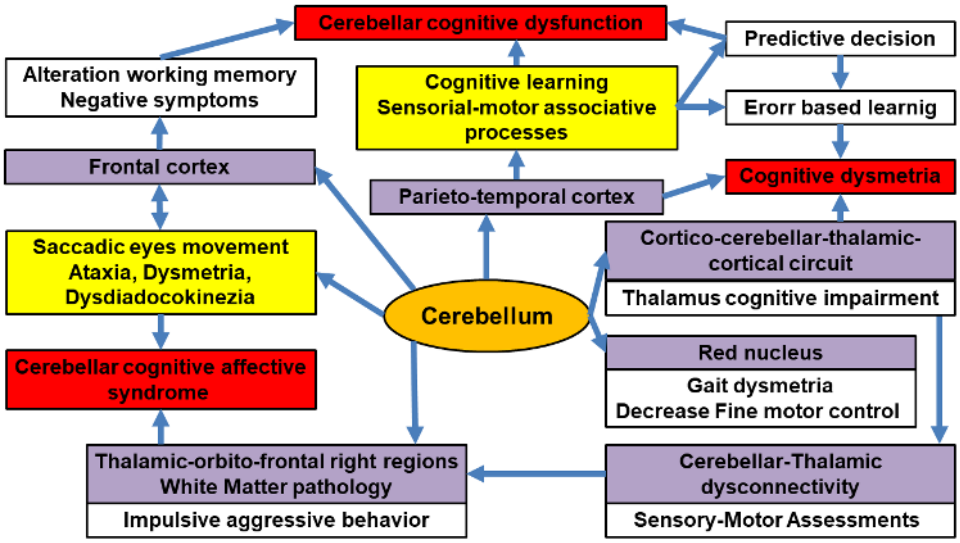

Figure 8. Cerebellar dysfunction in the pathogenesis of schizophrenia
Source: Authors' own conception

The anatomic underlayer of the speech disorder is the dysconnectivity of arcuate fasciculus and may appear as prodromal syndrome in schizophrenia, preceded by dyslexia. In this case, the affected circuits are the visual ones and the neuro-motor sensitive integration, the early recognition and correction of causes, allowing the prevention of progression in dysconnectivity elements (Revheim et al., 2014). The neuropsychologic evaluations can identify dysfunctional thalamus-related networks, which can be a marker for schizophrenia (Andreasen et al., 1997; Pinault, 2011).

HS can also be secondary, induced by neurodevelopment anomalies or by dopamine blocking effects from antipsychotics. It is considered a lesional syndrome with reduced reversibility potential. HIE is the main neurodevelopment anomaly determining the glutamate activity increase, favored also by the dysfunctionality in the parvalbumin GABAergic interneurons. The destruction of these neurons can have also an autoimmune mechanism by increased antibodies for parvalbumin GABAergic interneurons (Kaar et al., 2019, Sacuiu et al 2012). The GAD decrease is another important market of GABA activity decrease and signaling the risk for frontal cortical atrophy through neuronal apoptosis consecutive to glutamate excitotoxicity (Figure 9).

The symptomatology of movement disorders preceding schizophrenia is in approximately 50% of cases correlated with neurodevelopment anomalies and is generally dominated by EPS (Varambally, Venkatasubramanian & Gangadhar 2012). Starting from the assumption that any EPS motor disorder represents a genetic vulnerability of PD, we appreciate that this symptomatology must be interpreted as a risk factor for neurodegenerative evolution. PD and EPS determine a homocysteine increase, through the existence of a genetic vulnerability. The decrease in the methylenetetrahydrofolate reductase and cystathionine beta-synthase activities can be considered genetic markers for risk of developing schizophrenia. (Muntjewerff et al., 2006; Enokido et al., 2005).

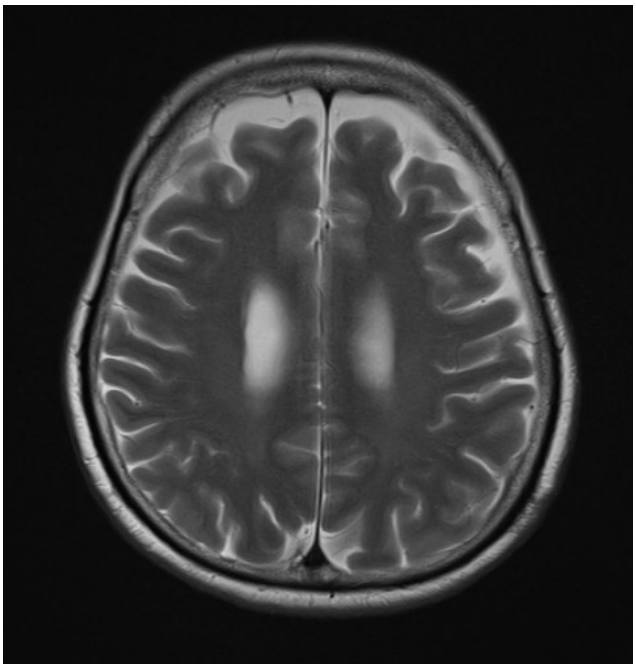

Figure 9. MRI scan, axial T2 sequence show bilateral frontal atrophy
Source: Authors' personal archives

7. Homocysteine

The impact on homocysteine metabolism from the prenatal period with the homocysteine increase in fetal brain favors fetal hypoxia by decreased quality of blood perfusion, as well as aberrant DNA methylation, considered epigenetic risk factor in schizophrenia (Nishioka et al., 2012). The disturbance of homocysteine homeostasis in fetal ontogenesis is

correlated with the one-carbon metabolism dysfunction, mitochondrial dysfunction and congenital cardiovascular or cerebrovascular pathology. The association between the genetic dysfunction involved in the alteration of homocysteine metabolism and genetic factors from PD spectrum may amplify the congenital and neurodevelopment anomalies, as well as neurodegenerative evolution. In PD, the hyperhomocysteinemia induced by dopaminergic antiparkinsonian medication (levodopa) suggests that the dopamine deficit is not the primary factor for development of neurodegenerative phenomena. At the same time, the hyperhomocysteinemia and its genetic determinism may activate the PARK1 gene and trigger the pathologic burst of alpha-synuclein (Coppedè, 2012). If for the elderly persons, the PD onset can be frequently associated with megaloblastic anemic syndrome with vitamin B12 and folic acid deficit, for the youngsters, the aberrant genetic spectrum for PD and hyperhomocysteinemia syndrome can be indicated by EPS (Burada et al., 2019). This leads to a real vicious circle, EPS being the consequence of neurodevelopment anomalies that can amplify hyperhomocysteinemia and may trigger gene activation mechanism that control PD neurodegenerative evolution.

The increase in the homocysteine level in schizophrenia is associated with a major potential of inducing cerebral atrophies through neurotoxic effect and enhancing oxidative stress, excitotoxicity and neuronal apoptosis (Sachdev, 2005). The decrease of the high homocysteine level becomes an important therapeutic target for conserving the structural and functional integrity of the brain. In schizophrenia, the hyperhomocysteinemia can be favored by administration of clozapine, levodopa type medication, hypolipidemic agents, mood stabilizing antiepileptics. (Siniscalchi et al., 2005; Wysokiński & Kłoszewska, 2013).

Homocysteine is involved in several other mechanisms correlated with side effects from antipsychotics administered in schizophrenia. The main side effects are: CBF decrease, predisposition for CSVD-ld, WMHs, endothelial dysfunction with predisposition for thromboembolism, demyelination processes and axonopathies, increased insulin resistance, diabetes, metabolic syndrome, heart attack, stroke (Hassan et al., 2004) (Figure 10).

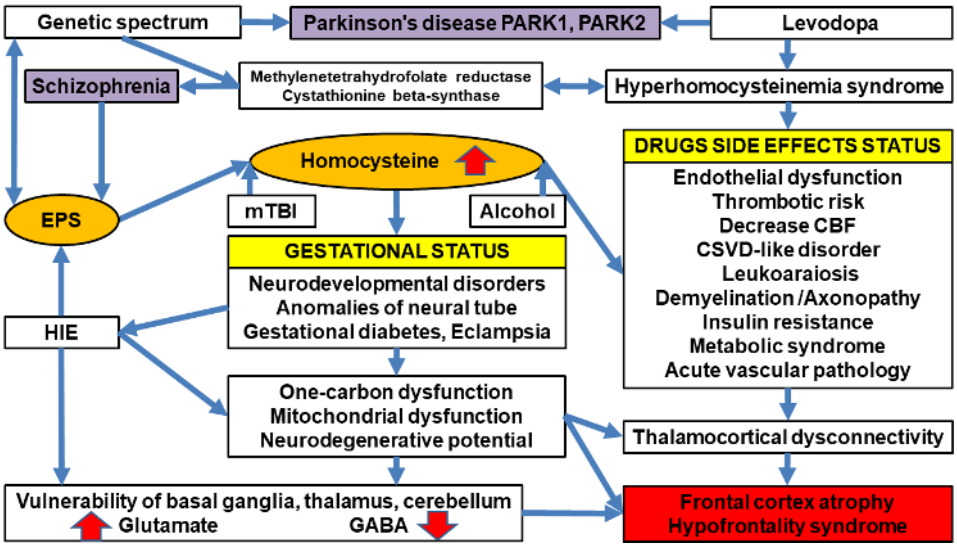

Figure 10. The complex role of homocysteine in the evolution and treatment of schizophrenia
Source: Authors' own conception

The CBF imbalance between the anterior and posterior poles, favored by the hypoperfusion of the posterior pole after acute psychotic episodes, where the hyperperfusion is located in the frontal pole, may be associated with anomalies of the circle of Willis or of artery of Percheron irrigating the thalamus (Anghelescu, 2018). In the case of hypoperfusion in arterial supply of choroid plexus, the excessive release of extracellular calcium determines calcification of choroid plexus and pineal gland. These modifications are regarded by us as predictive indicators for unfavorable evolution of schizophrenia.

10. Conclusions

The evaluation of antipsychotic induced side effects must benefit from a correct identification of the pathogenic conditions. The complexity of the pathogenic mechanisms requires a prophylactic behavior, not based on therapeutic switch, but on the proactive, customized pharmacologic intervention, addressing the pathogenic chains. Identification of hyperhomocysteinemia and its early correction may prevent the onset of neurodegenerative evolution and irreversible cerebral atrophies, as well as decrease the risk of side effect that may endanger the life of the

schizophrenic patient (cardiometabolic syndrome, diabetes, stroke, heart attack, sudden death).

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