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Drug-Induced Hyperprolactinemia and Hyponatremia - Biological Markers of Unfavorable Evolution in Schizophrenia

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Abstract: *Adverse reactions to psychotropic medication can be considered as risk indicators for an unfavorable evolution of patients with schizophrenia, based on particular pathogenic mechanisms that can be used in the personalized therapeutic approach. The combination of antidepressants with antipsychotic drugs in schizophrenia has a risk of synergistic action of excessive blockade of dopamine receptors, which causes hyperprolactinemia. Primary hyponatremia occurs during pregnancy and can be an important marker for signaling neurodevelopmental abnormalities, while secondary hyponatremia has a major clinical dimension and is induced by psychotropic drugs. The pathogenic mechanisms presented can be objectified by neuroimaging examinations that bring benefits in the diagnostic accuracy and re-evaluation of the therapeutic approach, especially in correlation with the severity of biological markers such as prolactin and sodium. The persistence of high prolactin and low sodium levels is an alarm signal that announces a negative evolution of the patient or a major risk of severe cardiac, metabolic, vascular or renal comorbidities. Recognition of pathogenic mechanisms of neurodevelopment, including ventriculomegaly, hyponatremia, focal cortical dysplasia, hippocampal or temporal lobe lesions, in association with a positive history of neonatal or febrile seizures, requires prophylaxis due to high risk of onset of schizophrenia in childhood. Fetal cortical dysplasia is associated with the risk of neonatal seizures. This vulnerability favors the appearance of febrile convulsions or enuresis with changes in brain structure. Enuresis may be an important marker of neurodevelopmental potential for schizophrenia. Neonatal seizures are correlated with hyponatremia and severe hypertension, which appeared in the third trimester of pregnancy, can trigger eclampsia. Neuroimaging monitoring in patients with neurodevelopmental abnormalities, hyperprolactinemia and primary or secondary hyponatremia, acquires a major importance, being able to delimit the boundary between a functional lesion, potentially reversible, with an irreversible lesion.*

Keywords: *schizophrenia, hyperprolactinemia, hyponatremia, dopamine, demyelination.*

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1. Introduction

Psychopharmacological advances that have aimed to achieve a positive report between the therapeutic benefits and risks of side effects, did not bring the expected results. Schizophrenia is a formidable condition in terms of the most frequently incomplete therapeutic response, but also the risk of various side effects, which can sometimes be severe. Our clinical experience highlights the possibility of addressing the adverse reactions and events of psychotropic medication administered in schizophrenia, as risk indicators for an unfavorable evolution. In some situations, the onset of a side effects may lead the clinical psychopharmacologist to identify particular pathogenic mechanisms that can be used in the personalized therapeutic approach (Radulescu et al., 2020).

Based on these premises, we tried to present the link between hyperprolactinemia, an adverse drug reaction that occurred frequently in daily practice but often minimized, hyponatremia and neurobiological vulnerabilities. This connection can be considered as a risk factor for a negative evolution of schizophrenia, in the short term, but with severe potential, in the long term and with the risk of multiple comorbidities.

2. The consequences of drug-induced hyperprolactinemia

The increase in blood levels of prolactin can be determined directly by the excessive blockade of dopamine D2 receptors in the tuberoinfundibular pathway, as well as indirectly by the increase in serotonin levels which causes a secondary hypodopaminergy. Hyperprolactinemia is amplified by the frequent use of the association between antipsychotics and antidepressants (Torre & Falorni, 2007). It has been shown that depression can occur in about 25% of patients with schizophrenia. Frequently, this depressive symptomatology may constitute a clinical picture of the onset of schizophrenia, leading to delayed diagnosis (Mao & Zhang, 2015). The pharmacological approach with antidepressants in these patients may increase dopamine deficiency, which is why the therapeutic response is incomplete. In this case, the therapeutic adequacy is not observed and the antipsychotic treatment is unreasonably delayed.

From our point of view, although it is considered useful association of antidepressants in the treatment of schizophrenia, there is a risk of synergistic action of inhibiting the dopamine system and excessive blockade of dopamine receptors, which causes a high increase in prolactin levels. Low doses of antipsychotics or selective serotonin reuptake inhibitor (SSRI)

antidepressants that cause hyperprolactinemia or galactorrhea are a pharmacological indicator that suggests a neurodevelopmental anomaly. In this context, the presence of ventriculomegaly at neuroimaging examination, suggests lesions in the subventricular zone, which diminishes the process of neurogenesis (Todd et al., 2018).

The appearance of dysfunctions or microlesions in the hippocampus and hypothalamus, anticipates the risk of frontal atrophy. Frontal lobe lesions may be exacerbated by the imbalance of the gamma-aminobutyric acid (GABA)/glutamate balance and the cytotoxic effect of glutamate, decreased dopamine levels with the onset of hypofrontality syndrome or dopamine D2 receptor blockade. Through these brain mechanisms, prolactin levels rise excessively and correlate with a high risk of severe hyponatremia and thrombotic events (van Zaane et al., 2011) (Figure 1).

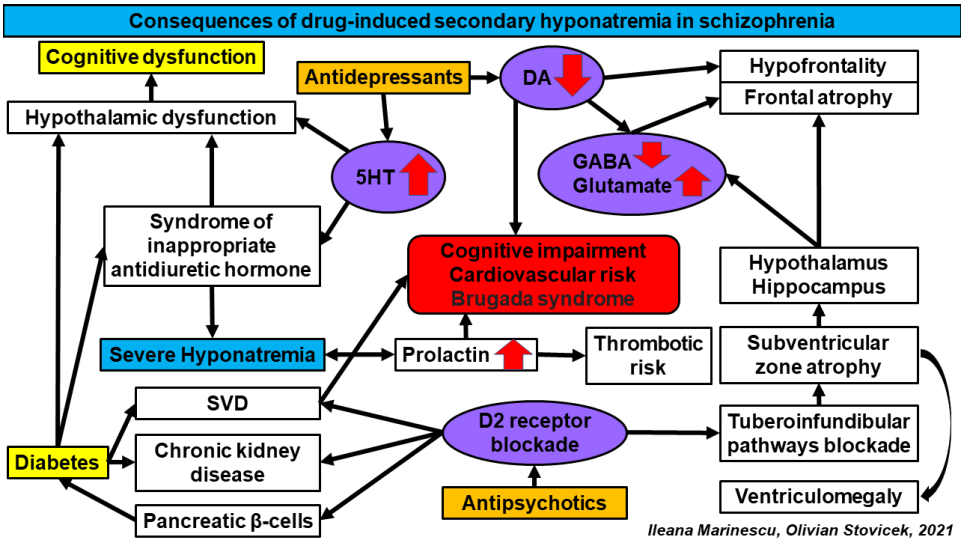


Figure 1. Consequences of drug-induced secondary hyponatremia in schizophrenia

Source: van Zaane et al., 2011

Long-term hyperprolactinemia can cause severe changes in heart rhythm as in congenital long QT syndrome (Schwartz et al., 2009), which, although it has a low incidence, becomes a major contraindication to the administration of psychotropic drugs that prolong the QT interval. Specific to the increase in serum prolactin, may be the prolongation of the QT interval characteristic of Brugada syndrome, which is clinically underestimated. This syndrome is associated with severe ventricular

repolarization disorders or the risk of sudden death (Antzelevitch et al., 2003). Brugada syndrome has also been identified in teenage girl with anorexia. If anorexic onset may be correlated with body dysmorphic disorder, it should be considered that chronic anorexia may become circumstance with a major cardiac risk. Consequently, any onset with anorexia manifestations of a psychotic disorder requires a cardiological evaluation and electrocardiographic examination, prior to any psychotropic pharmacological intervention (Docx et al., 2014). Treatment with antipsychotics even at low doses or with antidepressants has a major risk of severe cardiac events, by prolonging the QT interval, with the development of Brugada syndrome or sudden death (Sicouri & Antzelevitch, 2018).

High levels of serum prolactin are also associated with the risk of breast cancer in women (Wang et al., 2016), prostate cancer in men (Crépin et al., 2007), gastrointestinal or endometrial cancer (Lopez-Vicchi & Becu-Villalobos, 2017). Cases of breast cancer have also been reported in men with hyperprolactinemia (Haga et al., 1993). Prostate cancer can have an acinar, neuroendocrine or mixed proliferation, depending on the activity of interleukin-8 (IL-8) and the expression of IL-8 receptors, which can modulate the tumor by autocrine or paracrine pathway (Stănculeanu et al., 2017). Treatment with antipsychotics that cause hyperprolactinemia has an oncological risk due to its action on the prolactin-Janus kinase 2 (JAK2) and signal transducer and activator of transcription 5 (STAT5) signaling pathway, which stimulates cell differentiation and inhibits cell apoptosis (Johnston et al., 2018). In terms of clinical manifestations, the long-term effects of hyperprolactinemia may be galactorrhea and amenorrhea in women or erectile dysfunction with azoospermia in men (Hao et al., 2020).

3. Secondary hyponatremia, induced by psychotropic drugs

Pharmacological treatment with antipsychotics, mood stabilizers and especially with SSRI antidepressants, may have as an adverse reaction hyponatremia, characterized by decreased in serum sodium levels below 135 millimoles per liter (mmol/L) (Cortés & Muñoz, 2018). Symptoms may include apathy, adynamia, fatigue, and are sometimes misinterpreted as belonging to depression. Postpsychotic depression (after an acute episode of schizophrenia) is a hypodopaminergic-type depression that will not respond to antidepressant treatment, but will increase the risk of hyperprolactinemia (Untu et al., 2015).

In patients treated with psychotropic drugs, hyponatremia may be aggravated by the presence of risk factors such as age, early onset of

psychiatric disorder, mild traumatic brain injury (mTBI), oncological risk, the presence of other metabolic or cardiovascular somatic comorbidities (Ather Siddiqui et al., 2018). Given that a relatively small decrease of 10 mmol/L in serum sodium levels in severe hyponatremia (below 125 mmol/L) causes a major risk of coma and death, sodium evaluation becomes an important biological marker indicating re-evaluation of diagnosis and discontinuation of psychotropic treatment. An important problem in clinical practice is the difficulty of the differential clinical diagnosis between hyponatremia and neuroleptic malignant syndrome (NMS), especially if these pathologies are associated with convulsive symptoms (Looi et al., 1995). NMS can also be induced by psychiatric drugs, especially those with antidopaminergic action on dopamine D2 receptors (Ananth et al., 2004).

Rapid therapeutic intervention to correct sodium levels may lead to the onset of myelinolysis syndrome or osmotic demyelination syndrome (Mascarenhas & Jude, 2014), which frequently occurs at the pontine level (Martin, 2004) or extrapontine (Zunga et al., 2015). Extrapontine myelinolysis may be favored by severe renal failure (Tarhan et al., 2004). Patients with cognitive impairment and neurological disorders, especially motor deficit such as parkinsonism, should be evaluated neuroimaging by magnetic resonance imaging (MRI) for early identification of demyelinating changes and should be monitored dynamically for serum sodium levels (Chirita et al., 2012; Mascarenhas & Jude, 2014).

4. Syndrome of inappropriate antidiuretic hormone secretion and diabetes

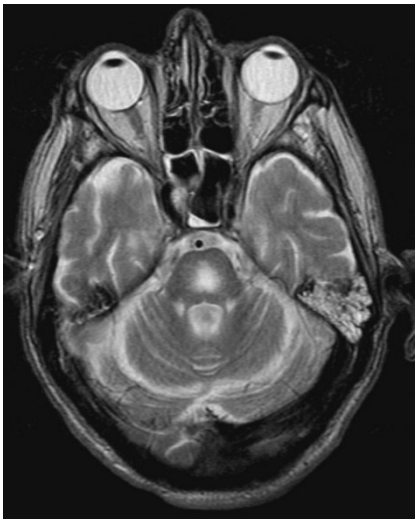
Antipsychotic-induced dopamine D2 receptor blockade may affect pancreatic β-cells function, promoting the onset of diabetes. Diabetes affects renal function that may worsen in the context of small vessel disease (SVD)-type pathology, which at the renal level becomes an etiopathogenic factor of chronic renal failure. Diabetes and cardiometabolic syndrome can be considered as side effects of some antipsychotic drugs (Holt, 2019). Diabetes treatment in patients with schizophrenia is difficult due to low adherence and compliance to treatment. For this reason, the course of metabolic disease can be severe causing syndrome of inappropriate antidiuretic hormone secretion (SIADH), which amplifies the risk of severe hyponatremia (Harrois & Anstey, 2019). On the other hand, impaired functionality of cerebral small vessels and chronic cerebral ischemia syndrome cause hypothalamic dysfunction and cognitive deficit (Sacuiu et al., 2012). Thalamic dysfunction and SIADH may be exacerbated by

increased serotonin levels induced by proserotonergic antidepressant drugs (Pillai et al., 2011).

5. Neuroimaging evaluation

The pathogenic mechanisms presented can be objectified by neuroimaging examinations, which can bring benefits in the diagnostic accuracy and re-evaluation of the therapeutic approach, especially in correlation with the severity of biological markers (Ciubara et al., 2015). It is important to monitor biological markers over time, especially prolactin and sodium, their severe change being an indication for neuroimaging examination. MRI assessment can identify pontine demyelinating changes (Figure 2). Extrapontine demyelination can be located in the corpus callosum (Figure 3) or in the cerebellum (Figure 4). Ventriculomegaly can be highlighted following atrophy of the subventricular zone and periventricular leukomalacia (Figure 5). SVD changes in the brain can be easily identified by white matter hyperintensities at the periventricular level (Figure 6).

In case of persistent hyperprolactinemia, the diagnosis of prolactinoma should be eliminated. Under conditions of psychotropic treatments that induce massive prolactin release, an enlargement of the pituitary gland due to hyperfunction was found (Figure 7). The use of these neuroimaging markers in times of uncertainty diagnose or lack of therapeutic response may be of major importance to the patient. The occurrence of pontine myelinolysis can help the differential diagnosis with NMS and requires the rebalancing of hyponatremia, accompanied or not by extrapontine demyelination syndrome.



Source: Authors' own conception

Figure 2. MRI image with oval lesion on pons that has hyperintense signal on fluid-attenuated inversion recovery (FLAIR) sequence, symmetrical, with no mass effect (central pontine myelinolysis).

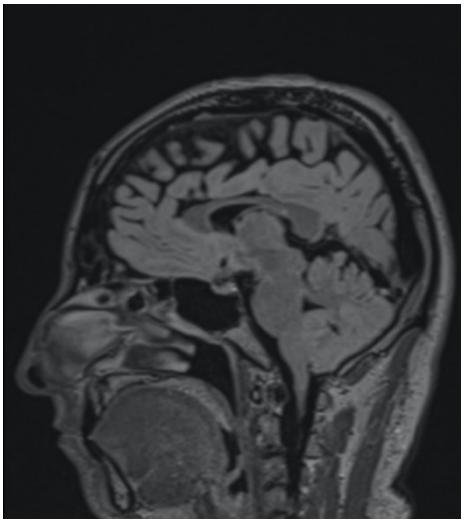
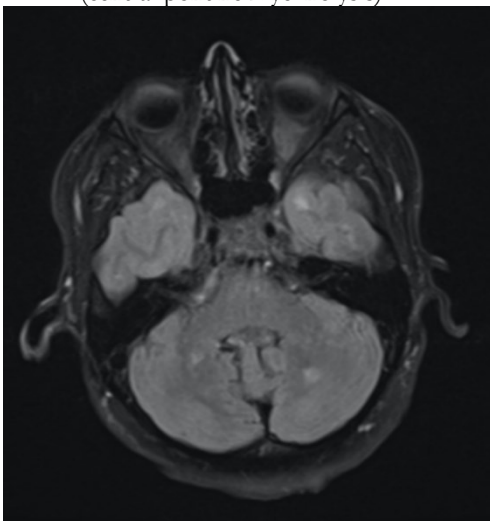


Figure 3. MRI image with demyelinating lesion of the corpus callosum, with FLAIR hyperintense signal.



Source: Authors' own conception

Figure 4. Axial FLAIR MRI image with a consistent with bilateral cerebellar white matter lesions (infratentorial demyelinating lesion).

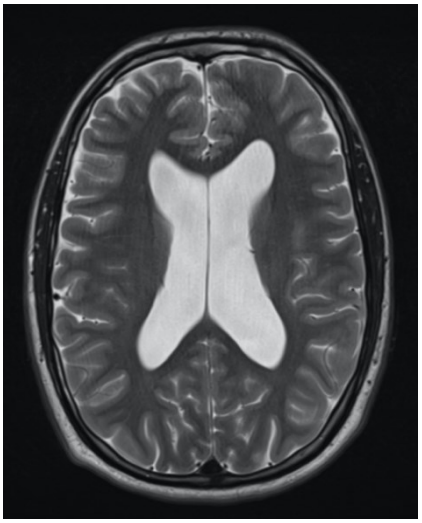
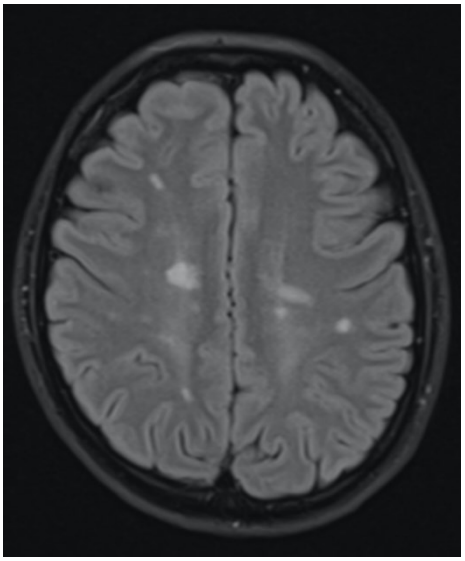
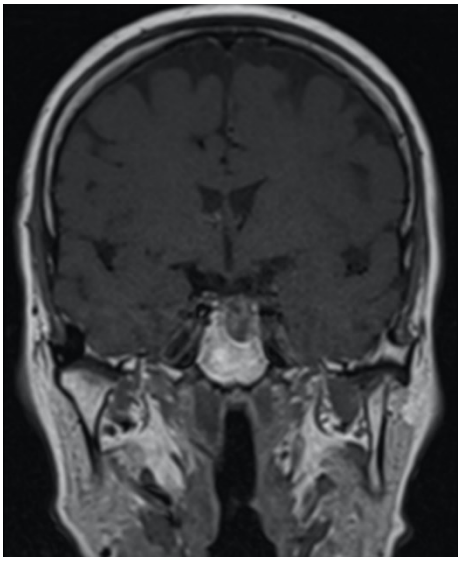


Figure 5. Axial T2 MRI image demonstrate marked dilatation of the ventricular system (ventriculomegaly); there is no transependymal edema (chronic dilatation).





Source: Authors' own conception

Figure 6. MRI image with multiple periventricular white matter lesions (demyelinating lesions).

Figure 7. MRI image of the pituitary-dynamic contrast enhanced sequence demonstrates a mass, in the left pituitary gland, with remodeling of the sellar floor.

6. Primary hyponatremia in pregnancy

If the secondary hyponatremia induced by psychotropic drugs has a major clinical dimension, the primary hyponatremia that appeared since the gestational period can be an important marker for signaling neurodevelopmental abnormalities. Frequently, the pregnant woman may have different types of hypertensions: pre-existing pregnancy and under treatment, started during pregnancy (gestational hypertension) or in the third trimester of pregnancy when it can announce the risk of eclampsia.

Pregnant women with hypertension treated with diuretics or SSRI antidepressants for pre-pregnancy depression may have low serum sodium from the first weeks of pregnancy (Braunthal & Brateanu, 2019). At the same time, pregnancy predisposes to changes in plasma osmolarity that may occur in early pregnancy and announces vulnerability to the onset of SIADH (Sutton et al., 1993). The presence of kidney disease amplifies this risk and serum sodium values require strict monitoring, due to the constant decrease that can cause severe hyponatremia. Therapy with antihypertensive drugs can trigger gestational hypotension, and by crossing the placenta, at the level

of cerebral neurodevelopment of the fetus, manifestations of focal cortical dysplasia may occur (Kabat & Król, 2012).

At the same time, intrauterine growth restriction (IUGR) pathology is installed, which favors premature birth and obstetric complications with risk of maternal death. Fetal growth restrictions cause astrocyte dysfunction which, in a first stage, tries to compensate for the effects of hyponatremia in the fetal brain. When this compensating capacity is exceeded, the phenomenon of microglial activation is triggered. Activation of the M1 phenotype is associated with hyperpermeability lesions of the blood-brain barrier (BBB) that may trigger epileptic seizures in childhood (Orihuela et al., 2016). On the other hand, BBB dysfunction caused by hyperglutamatergia, simultaneously with depression and non-responsiveness to oncological treatment, may be an alarm signal for the occurrence of brain metastases in prostate cancer (Marinescu et al., 2019). Microglial activation increases neuronal destruction by proinflammatory and cytokine mechanisms, with the occurrence of cognitive deficit, especially in patients who had mTBI in childhood (Ciobotea et al., 2016; Stovicek et al., 2020). In this way we can explain the neurodegenerative symptoms of schizophrenia.

Imbalance of the M1/M2 phenotypic balance causes hippocampal and temporal lobe atrophies in the fetal brain (Figure 8). These lesions cause temporal lobe epilepsy or schizophrenia-like psychosis in childhood or adolescence (Finegersh et al., 2011). Fetal cortical dysplasia is associated with the risk of neonatal seizures. In young children this vulnerability favors the appearance of febrile convulsions or enuresis with changes in brain structure and electroencephalogram examination (Figure 9).

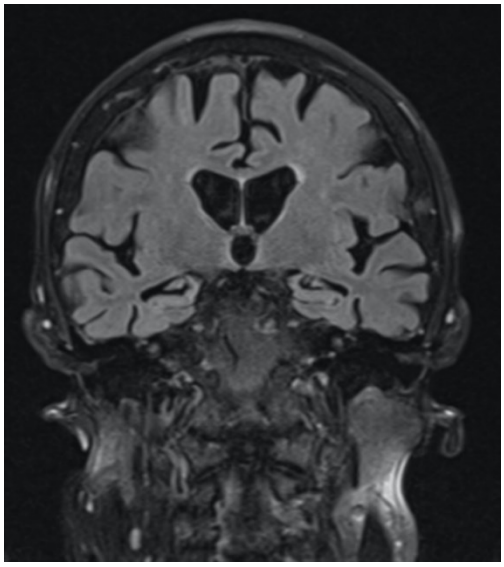


Figure 8. Coronal FLAIR sequence MRI image demonstrates moderate degree of volume loss of the left temporal lobe; the temporal horns are dilated, with volume loss of the hippocampus. *Source:* Authors' own conception

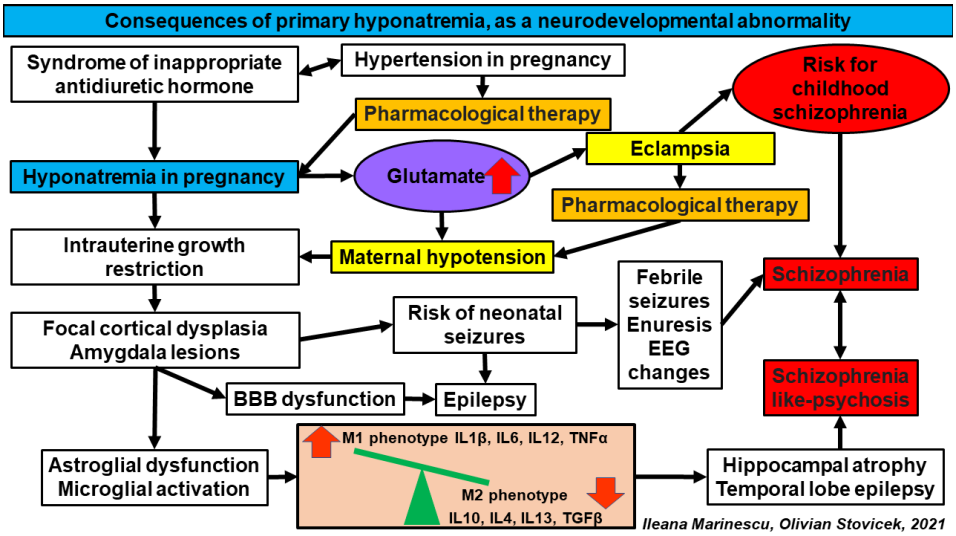


Figure 9. Consequences of primary hyponatremia, as a neurodevelopmental abnormality

Source: Finegersh et al., 2011

Enuresis may be an important marker of neurodevelopmental potential for schizophrenia, along with neuroimaging changes that highlight gray matter losses in the frontal lobe (Hyde et al., 2008). Neonatal seizures are also associated with hyponatremia (Pasi et al., 2019). Hypertension in the third trimester of pregnancy, with severe evolution can trigger eclampsia, which can be a risk marker for the further development of schizophrenia (Cannon et al., 2002), while pregnant patients with schizophrenia have a higher risk of pre-eclampsia and thrombotic events (Raimondi & Sheiner, 2015).

7. Conclusions

The pathogenic models presented have clinical applicability, patients with schizophrenia needing to identify biological indicators such as prolactin and sodium, before administering psychotropic drugs. Monitoring must be done continuously, the persistence of high prolactin values and low sodium levels being an alarm signal that announces a negative evolution of the patient or a major risk of severe cardiac, metabolic, vascular or renal comorbidities. Neuroimaging monitoring in patients with neurodevelopmental abnormalities, hyperprolactinemia and primary or secondary hyponatremia, acquires a major importance, being able to delimit the boundary between a functional lesion, potentially reversible, with a lesion, irreversible. Recognition of pathogenic neurodevelopmental mechanisms that include ventriculomegaly, hyponatremia, focal cortical dysplasia, hippocampal or temporal lobe lesions, in association with a positive history of neonatal or febrile seizures, requires prophylactic measures due to the high risk of onset of schizophrenia in childhood or adolescence. Prolactin monitoring should become a routine for the clinical psychiatrist, being a short-term or medium-term predictive indicator for the unfavorable evolution of schizophrenia, with the appearance of cognitive impairment and hypofrontality syndrome, accompanied by negative symptoms and depression. Cardiovascular risk is represented by severe heart rhythm abnormalities or thrombotic risk. The association of antidepressants with antipsychotics in the therapy of schizophrenia brings limited therapeutic benefits, but the medium-term and long-term risks are major and contribute to unfavorable evolution, somatic comorbidities and decreased quality of life of the patient.

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