REVIEW

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Cardiovascular anomalies and evolutionary risk factors in schizophrenia – multifactorial approach

LIANA DEHELEAN[1)], ILEANA MARINESCU[2)], PUIU OLIVIAN STOVICEK[3)], MINODORA ANDOR[4)]

[1)]*Department of Psychiatry–Neurosciences, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*
[2)]*Discipline of Psychiatry, 5th Department, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*
[3)]*Department of Pharmacology, Faculty of Nursing, Târgu Jiu Subsidiary, "Titu Maiorescu" University, Bucharest, Romania*
[4)]*Discipline of Medical Semiology II, 5th Department – Internal Medicine I, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

Abstract

Schizophrenia is a functional psychosis with a multifactorial etiopathogeny involving genetic, endocrine and immunological risk factors. The main pathogenic hypothesis involves dopamine dysregulation, with hyperfunction in the limbic system and hypofunction in the prefrontal cortex. Normal dopamine activity is critical for cognitive and emotional processing, but also for autonomic and immune regulation. Co-morbidity between schizophrenia and cardiovascular anomalies is complex. Genetic factors influence the development of brain, cardiac and vascular structures, as well as the activity of enzymes involved in dopamine synaptic turnover. Autoimmunity triggered by infections or related to systemic diseases affects both brain and heart in a direct manner through autoantibodies and/or indirectly through microvascular injury. In most cases, the co-morbidity between schizophrenia and cardiac diseases is secondary to metabolic dysfunctions induced by psychotropic medication or psychosis itself. Because of their diverse pharmacodynamic profiles, antipsychotics differ in their propensity to facilitate the development of the metabolic syndrome. The distress associated with acute psychotic symptoms or a sedentary lifestyle due to negative symptoms may have a negative impact on the energetic metabolism or cardiac function. *Conclusions*: An interdisciplinary approach is required between neurosciences and cardiology not only at the research level, but also in the clinical practice. Cardiac co-morbidity in subjects with schizophrenia may critically affect the survival rates of these patients. Moreover, the nature of the cardiac co-morbidity may guide the clinician in better understanding and differentiating functional psychoses from organic ones. The multifactorial approach can identify cardiovascular risk factors based on clinical, biological and neuroimaging markers.

Keywords: schizophrenia, cardiovascular anomalies, antipsychotic treatment, cognitive impairment.

Introduction

Schizophrenia is a functional psychosis resulting from neurodevelopmental impairments and leading, in the absence of treatment, to chronic and stable cognitive deficits which impair the individual's functionality in various domains of life. The main pathogenic hypothesis is based on imbalances involving several neurotransmitters, among which dopamine acting on its D2 receptors was considered to play a central role. Dopamine hyperfunction in the limbic system is responsible for psychotic symptoms, such as hallucinations and delusions, while its hypofunction in the prefrontal cortex is connected with negative symptoms and cognitive deficits. Normal dopamine function is important for cognitive and emotional processing, as well as for autonomic and immune regulation. The co-morbidity between schizophrenia and cardiac diseases is complex and challenging when searching for etiopathogenic links (same genetic diathesis, same environmental risk factors, or coincidental co-occurrence). Its clinical significance is nevertheless of highest importance for the long-term prognosis of the patients.

Congenital heart disease in patients with schizophrenia

The velocardiofacial syndrome (VCFS) is the most common genetic syndrome associated with schizophrenia [1] and is caused by 22q11.2 microdeletions (the 22q deletion syndrome or 22qDS). It has a variable phenotype consisting of a combination of defects or deficits: palatal (overt and submucous cleft palate), skeletal (malar hypoplasia, retrognathia, prominent nose, slender tapered fingers), cardiovascular (ventricle septal defect, tetralogy of Fallot, aortic arch anomalies), endocrine (thymic and parathyroid hypoplasia with immunodeficiency and hypokalemia, respectively) and cognitive (intellectual deficiency, psychosis). A diagnosis based only on clinical features may be inaccurate because of the phenotypic overlap that characterizes various genetic syndromes. Moreover, some of the clinical features are not seen at birth, but become evident later in life.

Shprintzen *et al.* were the first to report the presence of psychiatric disorders in VCFS [2]. Bassett *et al.* suggests that 22qDS represents a genetic subtype of schizophrenia with a later onset [3]. Clinical co-occurrence, neuro-developmental issues (genes involved in development and neural crest migration) and the dopamine hypothesis [catechol-O-methyltransferase (COMT)] link VCFS with schizophrenia [4]. Psychosis is 25 times more frequent in VCFS than in the general population [5]. Conversely, about 2% of the patients with schizophrenia have 22q11.2 deletions [6]. A deleted gene within the 22q11 region is coding for the COMT enzyme, which inactivates dopamine in the synaptic cleft. Both the low-activity allele (COMT

158 met) and the high-activity allele (COMT 158 val) are present in patients with 22qDS and psychosis [7].

Congenital heart disease is present in 70% of subjects with VCFS and some of the cardiac malformations, such as right sided aortic arch are clinically silent [5].

Acquired heart diseases and schizophrenia spectrum psychoses: the role of infection, inflammation, and autoimmunity

One hypothesis envisaging to explain the complex pathogeny and phenomenology of schizophrenia (genetic and environmental factors affecting neurodevelopment, the fluctuating course, the diversity of symptoms and the presence of the minor physical anomalies) focuses on the microvascular impairment [8]. According to this theory, inflammation of the microvessels affects the blood–brain barrier (BBB) and the cerebral flood flow disturbing the communication between neurons and astrocytes. In this respect, in schizophrenia, gene expression anomalies involving remodeling proteins and angiogenesis affect the microvascular system with negative consequences on the BBB permeability, blood flow and brain metabolism [9]. Treatment with potent D2 blocking antipsychotics may also alter the microvascular unit in the frontal cortex in patients with schizophrenia [10].

A 30-year population-based register study revealed that autoimmune diseases and infections requiring hospitalization are risk factors for schizophrenia [11]. Autoantibodies generated by autoimmune diseases, cancer or by post-infectious autoimmunity, reach the brain in the presence of a permeable BBB inducing neuropsychiatric symptoms. The mechanism by which systemic autoimmune diseases and paraneoplastic syndromes affect the brain may involve antibodies, such as *N*-methyl-D-aspartate receptors (NMDAR) autoantibodies, glutamic acid decarboxylase (GAD) autoantibodies, and anti-neuronal autoantibodies. Systemic lupus erythematosus (SLE) is a prototype for the autoimmune diseases affecting multiple organs and systems including heart and brain. Literature data suggests that psychotic symptoms may predate sometimes by many ears other symptoms of SLE and respond to steroid therapy [12, 13]. The majority of patients presenting SLE-related psychosis have also cutaneous involvement [13]. SLE-associated pancarditis involves pericardium, myocardium, endocardium and coronary arteries [14].

A two-hit hypothesis suggests that infection during gestation or early life activates microglia, inducing neurodevelopmental impairments. This will make the individual vulnerable for developing psychosis later in life in the presence of endocrine imbalances or infections that will further activate microglia [15]. Group A *Streptococcus* infection induces, probably through post-streptococcal autoimmunity, injuries of the heart, joints, skin and brain. The most vulnerable brain region appear to be the basal ganglia, resulting neuropsychiatric symptoms such as Sydenham's chorea, parkinsonism, tics and obsessive compulsive symptoms. The molecular mimicry between group A *Streptococcus* antigens and those expressed by neurons in the basal ganglia results in production of antibodies that cross-react with the basal ganglia antigens. Sydenham's chorea appears to be a multi-organ condition (associated in some cases with cardiac injury) while pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are brain-specific conditions [16]. Clinical studies and case reports evidenced the co-morbidity between schizophrenia with rheumatic fever [17] and PANDAS [18]. The morphopathogenic and physiopathogenic link between Sydenham's chorea, PANDAS and schizophrenia may be the involvement of the basal ganglia and dopamine transmission. According with Cunningham, antineuronal antibodies may induce an excessive release of dopamine from neuronal cells [19]. Non-streptococcal throat infections were equally found to be associated with an increased risk for obsessive-compulsive disorder and any mental disorder, though less important than streptococcal infections [20].

Acquired heart diseases and psychosis: the role of the metabolic syndrome

The main cause of premature deaths among subjects with schizophrenia is coronary heart disease (CHD) [21], the metabolic syndrome and excessive smoking being considered independent risk factors. The *2006 International Diabetes Federation Criteria* for the metabolic syndrome are represented by: obesity, dyslipidemia [hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C)], hyperglycemia, and hypertension [22]. The metabolic syndrome appears at a younger age in patients with chronic schizophrenia, compared with general population [23]. It is more frequent in patients taking antipsychotics and is associated with increased 10 years risk of CHD [24]. Antipsychotics differ in their propensity to induce the development of the metabolic syndrome, according to their pharmacodynamic profile. Antagonistic effects on histaminic H1 receptor, serotonin 5HT2c receptor and muscarinic M3 receptor increase the risk of metabolic dysfunctions. Because patients' adherence to antipsychotic treatment is low in psychotic disorders, several studies enrolling subjects treated with long-acting injectable (LAI) antipsychotics showed that these patients have a high prevalence of the metabolic syndrome and a high cardiovascular risk [25]. On the other hand, schizophrenia spectrum patients presenting deficit symptoms have a higher CHD risk than those without deficit symptoms [26]. This is consistent with retrospective data collected on patients with psychosis before the use of antipsychotics, suggesting that the disease itself contributes to metabolic dysfunctions [27].

Morphopathological and physiopathological changes in patients with schizophrenia receiving antipsychotics

Killian *et al.* established a causal association between Clozapine and myocarditis [28], while further research by Coulter *et al.* found this association significantly more frequent than with other antipsychotics [29]. The incidence varies from 0.015% to 1.3% [30]. Careful monitoring consisting in electrocardiography, echocardiography, troponin I or T levels, and C-reactive protein (CRP) level should be conducted in the first four or six weeks [31, 32].

High body temperature (>37ºC) and high CRP level are early indicators of myocarditis [33], while the clinical examination may also reveal persistent sinus tachycardia, hypotension, chest pain, and heart failure.

Studies conducted by Kelly *et al.* found no autopsy differences between Clozapine and Risperidone in respect with the occurrence of cardiac abnormalities in deceased patients [34] or with cardiovascular disease mortality [35].

From animal studies, it is known that some antipsychotics induce myocardial lesions, such as ventricular hypertrophy (Olanzapine), necrosis (Amisulpride or Haloperidol) or endocardial fibrosis (Levomepromazine). Other antipsychotic have lesser effects (Risperidone), while combinations (Levomepromazine with Haloperidol or with Risperidone) have marked effects [36].

A cardiac magnetic resonance imaging (MRI) study revealed that by contrast with healthy subjects, patients with schizophrenia treated with antipsychotics (Clozapine and other antipsychotics) presented structural and functional changes: longer native myocardial T1 time (longitudinal relaxation time constant of the myocardium), lower left ventricle mass, lower left/right ventricular end-diastolic and stroke volumes with no significant differences in left/right end-systolic volumes and ejection fractions between groups. Under the reserve that the T1 relaxation time is not a specific marker of fibrosis, the authors infer that these findings may suggest an early diffuse myocardial fibrosis and/or sub-clinical myocardial inflammation independent of cardiovascular risk factors [37].

The mechanism by which antipsychotics may influence cardiac function is through D2 dopaminergic receptor antagonism. Activation of D2 receptors has an antiapoptotic effect [38]. By contrast, Raclopride is a D2 receptor antagonist which upregulates autophagy in cardiac myocytes *via* Rab9, which is a member of rat sarcoma (RAS) guanosine triphosphatase (GTPase) superfamily that regulates the membrane trafficking and fusion [39].

Echocardiographic changes in patients taking oral antipsychotics for at least one year show subclinical left ventricular impairment, which is more pronounced in patients taking Clozapine. The degree of the left ventricular dysfunction is independently associated with markers of inflammation, such as elevated neutrophil count and low HDL-C secondary to Clozapine treatment [40].

In a study on patients with schizophrenia and schizoaffective disorder treated with LAI antipsychotics, Risperidone was more frequent associated with regional contractility abnormalities and diastolic dysfunction than Olanzapine. The period spent on LAI treatment was longer in patients treated with Risperidone and in those presenting regional contractility abnormalities [41]. On the other hand, the delay in initiating the LAI treatment of patients with schizophrenia spectrum disorders represents a risk factor for cardiovascular impairments, such as the relaxation dysfunction of the left ventricle [42].

Autonomic and electrocardiographic changes in patients with schizophrenia

Cardiac function is under the control of the autonomic nervous system (ANS), with its sympathetic and parasympathetic components. Heart rate variability (HRV) or R–R interval variability reflects ANS capacity to ensure adjustment to the variable outer and inner environments. A low HRV reveals an impaired autonomic activity. By comparison with healthy subjects, the cardiac vagal function of patients with schizophrenia is decreased, a finding that is further accentuated in patients receiving atypical antipsychotics [43]. In this respect, Mujica-Parodi *et al.* proposed that the low HRV mainly of the low-frequency range may be the effect of the limbic system dysregulation associated with schizophrenia or with psychosis in general [43]. A study comparing healthy subjects and patients with schizophrenia treated with psychotropic medication, found a significant decrease in both low- and high-frequency components of the HRV. In patients with schizophrenia, the low HRV was dose-dependent and associated with higher antipsychotic doses, but not with the daily dose of anticholinergic antiparkinsonian or anxiolytic drugs. It was not influenced by the severity or the duration of illness [44]. When comparing the HRV of patients with schizophrenia before and after eight weeks of treatment with Olanzapine or Paliperidone-extended release, a significant change was found for both antipsychotics [45]. LAI antipsychotics appear to have fewer adverse effects on ANS activity (particularly the low-frequency component) than oral antipsychotics, possibly because of their different pharmacokinetic profile [46].

Another issue regarding the use of antipsychotic and other psychotropic drugs in patients with schizophrenia is the risk of sudden death, mainly due to arrhythmias. In this regard, the prolongation of the corrected QT (QTc) interval is a risk factor for arrhythmias, such as torsade de pointes. Female gender, older age (>65 years), genetics, and pre-existing cardiovascular diseases are risk factors [47, 48]. Both conventional [49] and atypical antipsychotics [50] may prolong the QTc interval, especially Pimozide, Thioridazine, Sertindole and Ziprasidone. Among atypical antipsychotics, the highest risk for QTc prolongation has Ziprasidone and the lowest Aripiprazole [51]. The mechanism through which antipsychotics induce arrhythmia is probably the blockade of cardiac potassium channels, also known as human ether-à-go-go-related gene (hERG) channels. In addition, antipsychotics induce tachycardia *via* their anticholinergic and alpha-adrenergic blockade. A recent cross-sectional study revealed that primary care patients with schizophrenia compared with controls without psychiatric disorders presented on electrocardiogram recordings higher prevalence of elevated heart rate and QTc prolongation [52]. However, arrhythmia is rare and is triggered by a combination of risk factors, such as bradycardia, hypokalemia, hypomagnesemia or antipsychotic polypharmacy [53, 54]. Overall, a review of literature data found that clinically meaningful QT prolongation induced by psychotropic agents (antipsychotics, antidepressants, Lithium salts) is rare [51].

Clinical approach and future perspectives

The theoretical arguments presented highlight the cardiovascular risks in schizophrenia and outline a multisystemic theoretical model. The proposed model may bring clinical and therapeutic benefits in schizophrenia.

The vulnerability in the small arterial vessels represents one of the major factors involved in the vascular risks at cardiac or cerebral level, in patients with schizophrenia.

The microarterial pathology can be associated with several particular genetic vulnerabilities, among the most important being: neuromuscular disorders [55], with or without deficiency in the dystrophin-associated glycoprotein complex (DGC) [56], cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) spectrum [57] or anomalies in types I and III [58] and type IV [59] collagen.

The spectrum of neuromuscular disorders is a rare cause, but with severe consequences. Signs of dilated cardiomyopathy (DCM) and heart failure phenomena may occur in childhood or adolescence. The association with DGC-type genetic vulnerability most often causes schizophreniform-type psychotic disorders.

The CADASIL spectrum is a subcortical microangiopathy associated with ischemic stroke of subcortical infarction, has a dominant hereditary imprint through the mutation of the *NOTCH3* gene and causes a leukoencephalopathy with progressive cognitive impairment. CADASIL may be associated with myocardial lesions of acute coronary syndrome (ACS) type and with a significant risk for myocardial infarction [60].

The clinical significance of the involvement of mechanisms triggered by genetic collagen abnormalities is suggested by myocardial collagen volume fraction (CVF) values, which represent the ratio of type I to type III collagen. Increasing this ratio by a large volume of type I collagen fibrils indicates myocardial ischemic disorders, associated with hypertensive heart disease. Decreased CVF by increasing type III collagen is correlated with DCM associated with the risk of heart failure, following ACS [61]. The excess of collagen fibrils shown on histopathological images, are present from the early stages of DCM (Figure 1), and anticipates cardiac fibrosis [58].

Translational research on animal models shows that arteriolar narrowing is associated with type I collagen [62], while type III collagen is associated with the pathogenesis of cerebral aneurysms of small vessels and with arterial fragility [63]. Increased levels of cluster of differentiation 68 (CD68) (inflammatory CD68-positive cells), total collagen, or especially type III collagen, suggest a high risk of cerebral aneurysm rupture [64]. Type IV collagen is involved in the alteration of the vascular basal membrane [65], as well as in Alzheimer's disease, and may indicate a neurodegenerative evolution of schizophrenia. The presence of aneurysm can be suspected in patients with schizophrenia and a positive history of migraine episodes, especially migraine with aura.

Serum markers for collagen (propeptide of type I and type III procollagen) and CVF assessment may be important in assessing clinical progress and in predicting cardiovascular pathology in patients with schizophrenia treated with antipsychotics [66]. Also, the importance of serum markers for collagen was highlighted, in prediction of acute coronary risk from non-atherosclerotic DCM [67]. Cardiometabolic syndrome and dyslipidemia favor the development of DCM in patients with genetic risk, diabetes, obesity or other metabolic disorders induced by antipsychotic medication (Figure 2).

On this genetic vulnerability background, a major role in triggering pathological changes in the cerebral and coronary arteries in schizophrenia is played by the imbalance of the hypothalamic–pituitary–adrenal (HPA) axis and hypothalamic–locus coeruleus–prefrontal cortex (hypothalamic–LC–PFC) axis [68]. These changes are fostered by short-term stress as well as long-term stress (Figures 3 and 4). The involvement of stress can be present even from the prodromal period of schizophrenia and its early detection is possible by the psychometric evaluation [69]. Personalized approach to stress factors can be an important target of prophylactic strategies to limit cardiovascular risks in schizophrenia.

In the model proposed by our team, epigenetic stressors have a bimodal effect, depending on their duration of action. Short-term stress initially causes hyperactivation of the HPA axis, with massive release of endogenous cortisol. The increase of cortisol produces at the level of the dorsal raphe nucleus, an important increase in the number of serotonin transporters. This mechanism decreases the level of serotonin release at presynaptic level. The presynaptic hyposerotoninergic status causes a predominantly depressive-anxious symptomatology and a high vulnerability for small cerebral and coronary vessels.

For compensatory purposes, also by cortisone activation, at the level of the *locus coeruleus* increases the release of noradrenaline, favoring arterial spasm, which is one of the mechanisms of production of ACS, and migraine accompanied by aura at the cerebral level [70]. Administration of serotonin activators in migraine (triptans class) favors rebalancing cerebral arterial circulation by mediating vascular contraction, with improved cerebral perfusion in the affected territory. Pharmacological agonist effect mediated by serotoninergic receptors of type 5-HT1B and 5-HT1D, confirms the imbalance of the serotonin/noradrenaline ratio in the pathophysiology of migraines [71].

The dual activation mechanisms lead mostly at hypoperfusion, both at cerebral and cardiac level. At cerebral level, the hypoperfusion initiated by the arterial spasm is compensated by an adaptive hyperperfusion mechanism. The repetitive hypo-/hyperperfusion alternance compromises the arteriovenous shunts and the small vessels endothelial integrity. Thus, it encourages the onset of small vessel disease (SVD) pathology at brain level and of the subcortical vascular lesions, which affects the white brain matter. At the cardiac level, the contractile capacity of the myocardium is affected by the progressive development of DCM and coronary atherosclerosis (Figures 5 and 6), with increased risk of ACS or stroke. White matter lesions can be detected in neuroimaging assessments since the first psychotic episode of schizophrenia [72]. White matter hyperintensities and constant progression of cognitive deficits may be neuroimaging and clinical markers for predicting cardiovascular risk in schizophrenia [73].

Cortisol hyperactivity stimulates excessive dopamine release in the mesolimbic area [74]. This mechanism may be involved in therapeutic resistance to antipsychotic therapy and in the onset of dopamine supersensitivity psychosis under the conditions of the therapeutic switches or of the drug associations in the treatment of schizophrenia [75]. Cardiovascular or cerebrovascular pathologies involved in schizophrenia require permanent monitoring and personalization of treatment according to the degree of

genetic vulnerability and psychostress. It is necessary to reassess the cases with therapeutic resistance at the initial antipsychotic medication.

Several potential biological markers can be used to predict cardiac risk in schizophrenia. A first biological marker for predicting cardiac risk in patients with schizophrenia may be protein tyrosine phosphatase (PTP) especially by the striatal variant – striatal-enriched protein tyrosine phosphatase (STEP) [76]. PTP is a powerful regulator of NMDAR activity, and increasing the STEP variant of this modulating protein indicates a decrease in the number and activity of NMDAR and increased glutamate and dopamine levels, which is the central pathogenic mechanism of schizophrenia [77]. This genetic spectrum may be a variant of disrupted-in-schizophrenia-1 (DISC1) genetic dysfunction [78]. In ACS, myocardial necrosis processes are favored by T-cell activation and dysregulation of immune mechanisms modulated by PTP non-receptor type 22 (PTP–N22) [79]. The use of PTP/PTP-N22 inhibitors in the treatment of ACS suggests a common genetic component of them with schizophrenia. Monitoring of PTP/PTP-N22 levels during antipsychotic therapy can predict cardiac risk [80].

The second biological marker that can be used for early identification of cardiac risks in schizophrenia is atrial natriuretic peptide (ANP). Increased ANP activity causes a high decrease in sodium, with major neuropsychological changes and significant risk for ACS. The risk is amplified in the conditions of the progressive increase of cortisol in patients with schizophrenia, during antipsychotic therapy. The presence of this marker suggests primary and secondary preventive interventions, according to the ANP and serum sodium levels in patients with schizophrenia under antipsychotic treatment [81, 82].

Long-term stress in patients with schizophrenia is determined by the evolution with multiple episodes, with incomplete remissions and residual symptoms of negative, cognitive and social dysfunction type. Under the conditions of long-term stress, the episodes of hypoperfusion alternate with those of hyperperfusion, at the cerebral and coronary levels. This alternation causes an alteration of the neuromodulation mechanisms, between the cortical and subcortical areas, thus producing the disconnectivity of the prefrontal circuits with the subcortical level [83].

Excessive blockade of type D2 receptors by antipsychotic drugs favors hypoperfusion in the frontal cortex, especially the prefrontal and orbitofrontal area [10]. The hypoperfusion caused by the oxidative stress induced by the prolonged hypodopaminergy due to the action of the antipsychotics, potentiates excitotoxicity and apoptotic mechanisms by increasing glutamate (Figure 7).

Oxidative stress, apoptosis and SVD causes atrophy in hippocampus, cerebral amygdala and frontal cortex, explaining the persistence of a residual syndrome in the patient with schizophrenia. On the other hand, in depression induced by antipsychotic therapy by blocking D2 receptors, dopamine deficiency favors cerebral and coronary vasoconstriction, increasing the risk of apoptotic mechanisms but also of proinflammatory processes and endothelial dysfunction. The combination of the antipsychotic medication with antidepressant drugs in any depressive syndrome of hypodopaminergic type, can lead to the therapeutic resistance through neuronal injuries in the cognitive circuits [84].

The risk of therapeutic resistance in schizophrenia and the risk of depression in schizophrenia, increase with maintaining high levels of endogenous cortisol, which causes excessive release of corticotrophin-releasing factor (CRF). By triggering a type "activating cascade" mechanism, which amplifies the side effects of endogenous hypercortisolemia, occurs activation of pro-inflammatory mechanisms and endothelial dysfunction factors and decreased immune factors. High levels of cortisol induce structural alterations in hippocampus that will determine the inefficiency of cognitive circuits. Thus, in schizophrenia, negative symptoms, depressive symptoms with apathy and anhedonia and a major cognitive dysfunction will predominate.

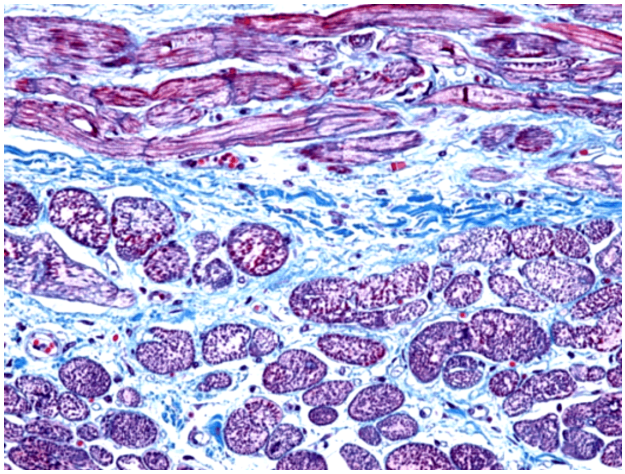

Figure 1 – ***Dilated cardiomyopathy imaging showing myocardial fibers in longitudinal and cross-section. One can observe rarefaction, reduction of number and thickening of remaining myofibrils, their non-homogenous placement in myocardiocytes and vacuolization of sarcoplasma. The interstitial conjunctive tissue has increased quantities of fiber collagen and reduced number of blood vessels. Goldner–Szekely (GS) trichrome staining, ×200.***

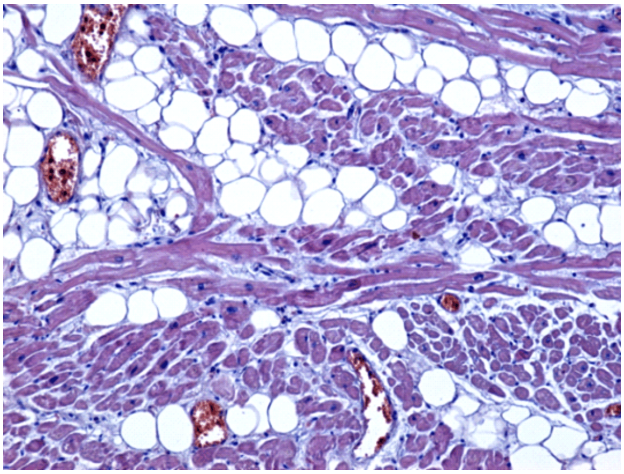

Figure 2 – ***Myocardial wall showing the increased quantity of conjunctive matrix and disarray of myocardial fibers by adipocytes appeared in the myocardial stroma in a person with dilated cardiomyopathy and grade II obesity. GS trichrome staining, x 100.***

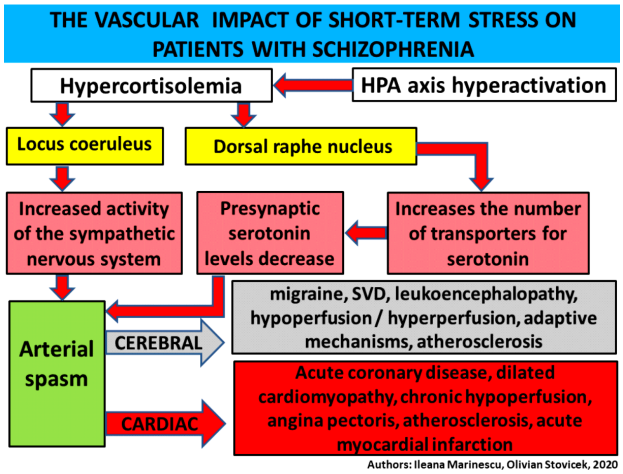

Figure 3 – *Multifactorial theoretical model of vascular impact of short-term stress in patients with schizophrenia. HPA: Hypothalamic–pituitary–adrenal; SVD: Small vessel disease.*

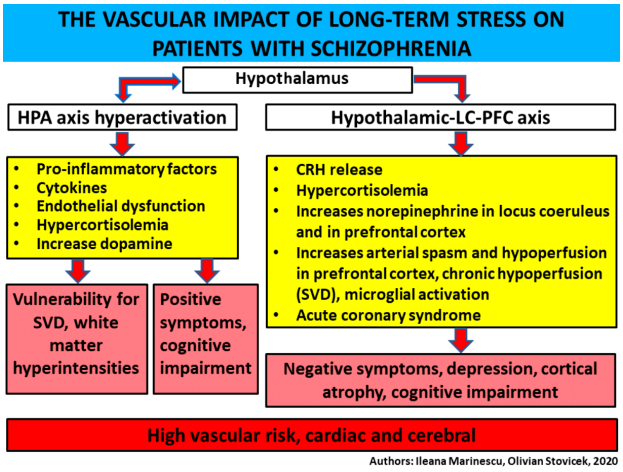

Figure 4 – *Multifactorial theoretical model of vascular impact of long-term stress in patients with schizophrenia. HPA: Hypothalamic–pituitary–adrenal; LC–PFC axis: Hypothalamic–locus coeruleus–prefrontal cortex; SVD: Small vessel disease; CRH: Corticotropin-releasing hormone.*

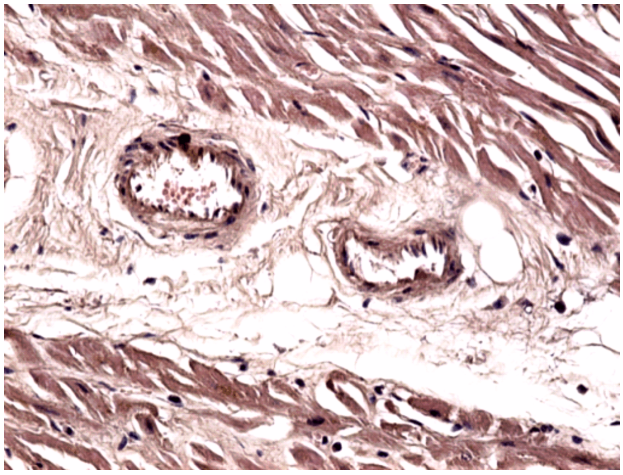

Figure 5 – *Myocardial arterioles with wall highly affected by arteriosclerosis, associated with almost complete disappearance of myocytes in the vascular wall. Hematoxylin–Eosin (HE) staining, ×200.*

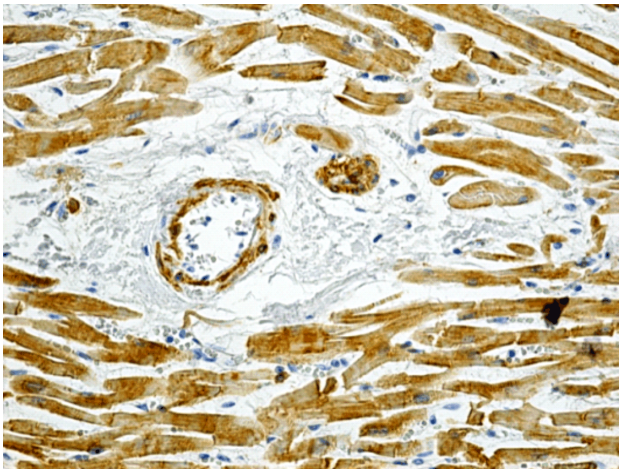

Figure 6 – *Myocardial vessels (arterioles) with unevenly thickened wall due to arteriosclerosis process consisting of replacement of myocytes from the middle tunic of the arteriole, with collagen fibers. Immunostaining with anti-alpha-smooth muscle actin (α-SMA) antibodies, ×200.*

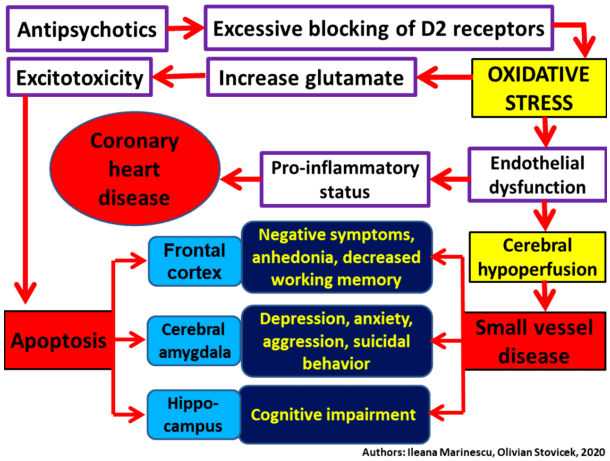

Figure 7 – *Coronary and cerebral hypoperfusion induced by excessive blockade of D2 receptors by antipsychotic drugs.*

Conclusions

The co-morbidity between schizophrenia and cardiovascular anomalies is multifactorial. In the majority of cases, it is secondary to the metabolic syndrome induced by psychotropic medication and/or the psychosis itself. The distress coupled with delusions and hallucinations or the sedentary lifestyle linked with the deficit syndrome increase the chances of developing the metabolic syndrome. Antipsychotics, which block histaminic H1, serotonin 5HT2c and muscarinic M3 receptors may further increase the patients' risk to develop metabolic syndrome. In very rare cases, both schizophrenia and cardiac anomalies are secondary to genetic factors, such as in the case of 22qDS. There are also circumstances when both schizophrenia and cardiac disorders share an autoimmune microvascular or antibody pathogeny. Because in clinical practice there are situations when psychotic symptoms predate somatic signs

in case of co-morbidity, a careful differential diagnosis is required to distinguish a functional psychosis from an organic induced one. Cardiac co-morbidity in subjects with schizophrenia may affect both the quality of life and the survival rates. An interdisciplinary approach between neurosciences and cardiology may be useful in clinical practice as well as in research. The multifactorial theoretical model presented offers the possibility of monitoring cardiovascular risks in patients with schizophrenia by identifying biological, neuroimaging and clinical markers that can improve the evolution of the disease and the functional and social recovery of patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author
Ileana Marinescu, Lecturer, MD, PhD, Discipline of Psychiatry, 5th Department, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40251–522 458, e-mail: marinescu_psy@yahoo.com

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