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Etiopathogenesis of bipolar affective disorder – the state of the art for 2021

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Summary

The contemporary clinical idea of bipolar affective disorder (BD) has been shaped as an aftermath of Emil Kraepelin's thought named "manisch-depressives Irresein," put forward in 1899, with essential modifications during the last half-century. A current paradigm for the etiopathogenesis of BD postulates the emergence of the illness as a result of an interaction between genetic and epigenetic factors with environmental influences. The most important for the molecular genetics of BD were the analyses of so-called candidate genes and genome-wide association studies (GWAS). The genetic BD profile includes many genes predisposing to other psychiatric disorders. Epigenetic disturbances constitute a mediating mechanism for the influence of environmental factors in the early period of life. Some neurobiological concepts of BD have a pharmacological origin, resulting from the mechanisms of the drugs used in the illness. They include catecholamine, cation transport, and purinergic theories. Such concepts as the neuroplasticity disturbances, "inflammatory" theory, and stress axis dysfunction resulted as an extrapolation of the initial pathogenetic hypotheses of depression. New pathogenetic theories of BD include the disturbances of biological rhythms and mitochondrial and oxidative stress dysfunctions. In BD there are abnormalities of the functions of the brain structures, in particular, the so-called anterior limbic system. Pathogenetic environmental influences include factors operating in pregnancy, early childhood trauma, stressful events in later life as well as seasonal and climatic factors. Both the pathogenesis and the course of BD are presently perceived in a developmental context, reflected by the staging concepts of the illness.

Key words: bipolar affective disorder, etiopathogenesis

The clinical concept of bipolar affective disorder and its etiopathogenetic paradigm

The contemporary clinical idea of bipolar affective disorder (BD) has been shaped as an aftermath of Emil Kraepelin's (1856-1926) thought named *manisch-depressives Irresein*, put forward in 1899 [1], with essential modifications during the last half-century [2].

In 1966, a separate heritability of BD and unipolar affective disorder was demonstrated by Swiss psychiatrist, Jules Angst [3] and Swedish psychiatrist of Italian origin, Carlo Perris (1928-2000) [4]. In 1974, American psychiatrists David Dunner and Ronald Fieve (1921-2018) [5] put forward a suggestion for a criterion of diagnosis of rapid cycling BD as the occurrence of at least four manic and/or depressive episodes during a year. In 1976, David Dunner et al. [6] proposed a distinction of BD into bipolar I, in which besides depressive episodes, manic episodes requiring hospitalization occur, and bipolar II, where besides depressive episodes, hypomanic states, not requiring hospitalization, appear. In 1984, Norman Rosenthal et al. [7] described a seasonal affective disorder in which during the fall-winter period depression occurs, while in the spring-summer months a normal or distinctly elevated mood appears, which indicates seasonal BD.

In the 1990s, Jules Angst proposed new diagnostic categories such as brief recurrent depression [8] and brief hypomania [9]. In the recent two decades he has created the Hypomania Checklist (HCL-32) scale for the assessment of the symptoms of hypomania [10], declared himself as an advocate of the diagnostic concept of unipolar mania [11], and in a recent study provided clinical evidence for differentiation between unipolar mania and bipolar I disorder [12]. A significant contribution to the issue of BD was also made by Hagop Akiskal, an American psychiatrist of Armenian origin. His most important achievements include the concept of the bipolar spectrum [13] and creating a temperament scale, TEMPS-A (Temperament Evaluation of Memphis, Pisa, and San Diego – Autoquestionnaire) [14].

The term "bipolar spectrum" has currently two connotations. On the one hand, it means a disorder placed in the diagnostic space between bipolar II and recurrent depression. On the other, it can denote the whole spectrum of bipolar disturbances [15]. In the area of *manisch-depressives Irresein*, Kraepelin included recurrent depression, and recently, some researchers postulate to bracket into bipolar spectrum the depressions frequently recurring, including brief recurrent depression. Such a "neo-Kraepelinian" approach was, among others, reflected in the title of the second edition of a "bible" of BD, authored by Frederick Goodwin (1936-2020) and Kay Jamison: *Manic-depressive illness: Bipolar disorders and recurrent depression* [16].

In the International Classification of Diseases (ICD) and the American Diagnostic and Statistical Manual (DSM), bipolar disorder in their versions ICD-10 [17] and DSM-IV [18] is a part of the group of affective (mood) disorders. However, in the recent edition of DSM-5 [19] BD appeared as a separate diagnostic category. The subclassification into bipolar I and II has been reflected in DSM, beginning from the DSM-III, and in the ICD, will take place in just ICD-11. Unipolar mania is likely to wait for being considered in future classifications.

In the 21st century, evidence has been produced for the significant frequency of various forms of bipolar illness. Current epidemiological data indicate that the lifetime risk for bipolar disorder, type I, is 1%, whereas for bipolar II and bipolar spectrum combined is about 3.5% [20].

A current paradigm for the etiopathogenesis of BD postulates the emergence of the illness as a result of an interaction between genetic and epigenetic factors with environmental influences. A strong heritability of BD, amounting to 60-80%, has been demonstrated by the research performed for 100 years [21, 22]. The pathogenetic studies on BD were done mostly on patients with bipolar I illness and to a lesser extent on bipolar II. Patients with bipolar spectrum were taken into account mainly in epidemiologic research and the studies on therapeutic interventions.

Genetic and epigenetic factors

The progress in molecular-genetic studies has aroused hope for the identification of the individual genes predisposing to BD. The first publication of results from a study using this method appeared in 1987 showing that in the Amish people living in Pennsylvania, a predisposition to BD is connected with DNA markers located on the short arm of chromosome 11 [23]. Further analyses have not confirmed this finding in other populations; however, a presence in this locus of several "candidate" genes for BD was demonstrated, such as the *BDNF* (brain-derived neurotrophic factor) gene or the tyrosine hydroxylase gene. The strategy of candidate genes was widely prevalent in molecular-genetic studies of BD until the first decade of the 21st century. In this approach, polymorphism frequency is tested of a particular gene, which, based on the results of neurobiological and pharmacological studies, can play a role in the pathogenesis of illness. The studies using this method showed a possible association of at least several dozen genes with a predisposition to BD. Such a polygenic nature of inheritance is common for many psychiatric and medical diseases. Among the studies performed in a center in Poznan, an association with BD was found of the polymorphism of the tyrosine kinase *FYN* gene, connected with an interaction between BDNF and the glutamatergic N-methyl-D-aspartate (NMDA) receptor [24], the polymorphism of the beta-synthase cystathionine gene, connected with homocysteine synthesis [25], and the polymorphism of the matrix metalloproteinase-9 (*MMP-9)* gene [26].

For more than a decade, the most important method of genetic research has been the genome-wide association study (GWAS). Encompassing a large number of patients, the method allows for the identification of millions of polymorphisms of the whole human genome and detection of normally "unpredictable" genes connected with a given illness. The recent GWAS study performed in 2019 included 20 thousand BD patients and 31 thousand healthy subjects. The association with BD was demonstrated for 30 genes, including a confirmation for 10 genes identified in the previous studies [27]. Among the replicated genes, there is the *CACNA1C* (Calcium Voltage-Gated Channel Subunit Alpha1 C) gene, connected with calcium ion transport across the cell membrane; the *ANK3* (Ankyrin-3) gene, connected with synaptic plasticity proteins; the *TRANK1* (Tetratricopeptide Repeat And Ankyrin Repeat Containing 1) gene, coding a protein in the nervous system; the *NCAN* (Neurocan) gene, coding a protein of the extracellular

matrix; the *ODZ4* (Teneurin-4) gene, coding a protein connected with the development of synaptic connections; and the *FADS2* (Fatty acid desaturase 2) gene, connected with fatty acid metabolism. The *CACNA1C* gene is probably the only gene having therapeutic implications in BD such as using calcium channel inhibitors in ultra-rapid cycling BD [28]. Among the newly identified genes, the *SHANK2* (SH3 and multiple ankyrin repeat domains protein 2) gene, the *ZNF592 (*zinc finger 592) gene, and the *GRIN2A* (Glutamate Ionotropic Receptor NMDA Type Subunit 2A) gene, coding the proteins connected with nervous system development should be mentioned.

Contemporary molecular-genetic studies point to the common genes for BD and other psychiatric disturbances. In 2009, Swedish researchers analyzing more than 2 million families showed a genetic overlap between BD and schizophrenia: the first-degree relatives of patients with these two illnesses were at increased risk for both disorders [29]. In a GWAS study performed in 2013, the common genes were demonstrated for schizophrenia, BD, recurrent depression, autism spectrum disorder, and attention-deficit hyperactivity disorder (ADHD) [30]. A group of genes characteristic for BD was also identified, creating the polygenic risk score for bipolar disorder [31]. In 2014, a population study was performed where a separate inheritance for mania and depression was found [32]. This corresponds with the recent GWAS analysis of bipolar spectrum, including 185 thousand patients and 439 thousand healthy persons, showing a genetic relationship between bipolar II and recurrent depression [33].

The results of the GWAS studies can explain differential diagnostic difficulties of BD pointing to the common genes with ADHD [34], as well as the borderline personality disorder [35]. They can also interpret the overrepresentation of BD among creative persons indicating the common genes for BD, intelligence, and creativity [36, 37].

In BD, there have also been epigenetic changes, such as abnormal DNA methylation and histone modification which can modulate gene expression without influencing the genome structure. These changes can constitute a mediating mechanism for environmental factors in the early period of life and may play a role in leading to the first episode of the illness [38]. The *BDNF* gene is especially susceptible to epigenetic influences [39].

Pathogenetic concepts of bipolar disorder of pharmacological origin

Some pathogenetic concepts of BD are of pharmacological origin, connected with the mechanisms of the drugs used in the illness. In 1965, the catecholamine theory of BD was formulated. Its authors were American psychiatrists Joseph Schildkraut [40] as well as William Bunney and John Davis [41]. Invoking the pharmacological data, including, among others, the mechanism of action of imipramine, monoamine oxidase inhibitors, and reserpine, they proposed norepinephrine deficit in depression and its excess in mania. Ten years after, Bunney pointed to a more significant role of another catecholamine, namely dopamine, allowing to explain the action of antimanic

drugs [42]. The recent version of the dopamine theory of BD was presented in 2017 by Ashok et al. [43]. They suggest dopamine hyperactivity in mania, especially that of dopaminergic receptors D2 and D3 as well as enhanced activity of the dopaminergic reward system, allowing the interpretation of the antimanic effect of the antidopaminergic drugs. Conversely, in depression, increased activity of the dopamine active transporter (DAT) in the striatum was found, which may underlie decreased dopaminergic activity in depression.

In the 1970s, connected with demonstrating psychotropic properties of lithium, the element belonging, similar to sodium and potassium, to the first group of the Mendeleev's periodic table, a possibility of the abnormalities of cation transport across the cell membrane (including lithium transport) and the activity of adenosine triphosphatase (ATPase) was indicated. The research in this area was also carried out by the author of this paper, using the model of the erythrocyte cell membrane. In BD, lithium transport out of the cell by the lithium-sodium countertransport system is diminished, which is reflected by the higher erythrocyte lithium index both in an acute episode and in remission [44, 45]. Also, impaired activity of sodium-potassium ATPase both during an episode of mania as well as depression was showed [46].

Contemporary molecular-genetic research has shown a connection between abnormalities of various ATPase variants and a predisposition to BD. Darier's disease is a dermatologic condition, characterized by disturbances of keratinization of skin, nails, and mucous membranes. It is caused by a mutation in the *ATP2A2* gene connected with the activity of calcium ATPase isoform and inherited in an autosomal dominant manner. Several cases showing family co-morbidity of Darier's disease and bipolar disorder have been reported. Swedish researchers based on a population study found that patients with Darier's disease have a 4.3-fold higher risk of bipolar disorder compared with the general population [47]. Wilson's disease is caused by mutations in the *ATP7B* gene coding the ATPase connected with copper transport across the cell membrane. Italian researchers showed that patients with Wilson's disease have a nearly 13-fold increased risk for BD compared with the general population [48].

In the 19th century, the application of lithium for the treatment of periodic depression by a Danish researcher, Carl Lange, was done in the context of his "uric acid diathesis" theory of depression [49], whereas the introduction of lithium to contemporary psychiatry by an Australian psychiatrist, John Cade, had been preceded by his experiments pointing to a pathogenic role of uric acid in mania [50]. Uric acid is a final metabolite of purine bases, and in recent decades it has been demonstrated that the purinergic system can play a role in the regulation of mental processes, including mood and activity. This resulted in the development of the purinergic hypothesis of psychiatric disturbances, mostly that of BD [51]. An epidemiological premise of the pathogenic role of uric acid in BD is the increased frequency of gout in patients with this illness [52]. In BD, the uric acid concentration is increased [53], and allopurinol,

the drug reducing uric acid level, can augment the therapeutic action of mood stabilizing drugs in mania [54]. In this illness, a decreased concentration of adenosine [55], as well as changes in the purinergic receptor P2X7, connected with the processes of apoptosis and secretion of pro-inflammatory cytokines were found [56].

The most important cellular mechanisms of lithium in BD include the inhibition of the enzyme glycogen synthase kinase-3beta (GSK-3β), and the effect on intracellular signaling, especially on the phosphatidylinositol (PI) system [57]. However, the studies on possible disturbances of these processes in BD have neither brought about definite results nor new therapeutic proposals. An exception can be tamoxifen, the drug, similar to lithium and another mood stabilizer, valproate, inhibiting the activity of protein kinase C, the enzyme of intracellular signaling (promising results of tamoxifen in the treatment of mania have been described [58]).

Pathogenetic concepts of bipolar disorder as an extrapolation of the pathogenesis of depression

The disturbances of many neurobiological processes in mood disorders had been initially found in depression, and next, it turned out that they could be extrapolated to BD. One such pathogenetic concept is an impairment of neuronal neuroplasticity and neurotrophic processes. The American neuroscientist, Ronald Duman (1954-2020) showed in the mid 1990s that antidepressant drugs increase the expression of the *BDNF* gene in the hippocampus [59]. Two years later, researchers from Yale University, led by Duman, published the article "A molecular and cellular theory of depression." They hypothesized that in depressive patients there is an impairment of neurotrophic processes and neurogenesis due to stress and that antidepressants can normalize this [60]. In subsequent years, the impairment of these processes in BD has been demonstrated. Also, investigating the influence of drugs used in BD, a neuroprotective effect of lithium was found [61].

The studies on BD have been to a great extent connected with the most important neurotrophin, namely BDNF. The Val allele of the Val/Met polymorphism of the *BDNF* gene is associated with a predisposition to BD. Serum BDNF concentration is lower during both manic and depressive episodes and increases after the treatment [62]. Low serum BDNF is regarded as an indicator of the late-stage BD [63]. In our own studies, we demonstrated that Val/Met polymorphism of the *BDNF* gene is associated with the quality of performance on cognitive tests, connected with the activity of the prefrontal cortex; persons with the Val/Val genotype achieve significantly better results [64]. Such a phenomenon is characteristic of only BD and is not present in schizophrenia or healthy subjects [65]. Our results can indicate an evolutionary trade-off, where a predisposition to the illness can be connected with better cognitive functions in afflicted subjects.

The next pathogenetic concept is the "inflammatory" hypothesis postulating a pathological activation of the immune system. The case for this hypothesis in depres-

sion may be a frequent occurrence of the so-called acute phase response as well as increased secretion of pro-inflammatory cytokines [66]. Further research indicated that a pathological "pro-inflammatory" activation occurs also in BD and the illness itself can be regarded as "low-grade inflammation." In recent years, attention has also been paid to immune activation within the central nervous system called "neuroinflammation," where the most important role is played by microglial cells. In these mechanisms, stress, genetic and epigenetic factors, as well as gut microbiota, may also be relevant [67]. Similarly, as in depression, attempts of the therapeutic use of drugs modifying the activity of the immune system have been made in BD, usually as an add-on to the administered drugs [68].

At the Department of Adult Psychiatry in Poznan, in collaboration with the Szczecin center, we compared the very-small-embryonic-like stem cells (VSELs) and neural and glial markers in peripheral blood of patients with BD and control subjects. It was found that in patients there were features of excessive regenerative and inflammatory processes, reflected by increased concentration of the VSELs and the mRNA expression of neural and glial markers. Increased VSELs level correlated with the duration of illness, indicating that it can serve as a marker of its progression [69].

The association between depression and disturbances of the "stress" (limbic-hypothalamic-pituitary-adrenal – LHPA) axis has been postulated for many decades. From the area of the stress axis descends the first diagnostic experiment for depression, the dexamethasone suppression test [70]. The LHPA axis modifies brain activity as a consequence of stress events both occurring in early childhood as well as preceding further episodes. In BD, similarly as in depression, various disturbances have been found such as hypercortisolemia, excessive secretion of the corticotropin-releasing factor (CRH), and abnormalities in glucocorticoid receptors. The polymorphisms of the stress axis genes are not directly connected with a predisposition to BD; however, the changes of activity of this axis make an example of generating a pathogenetic mechanism resulting from the interaction of a genetic predisposition with stress factors [71]. In Poznan, unique research was performed employing the CRH-dexamethasone test, showing that a dysregulation of the LHPA axis in depression in the course of BD is greater than in unipolar depression [72].

New pathogenetic concepts of bipolar disorder

Seasonal BD may reflect a disturbance of the circannual biological rhythm in this illness. In BD, there are also many abnormalities in the circadian biological rhythms that gave rise to the pathogenetic concept of this illness as a biological rhythm disorder. Examples of circadian disruption can be disturbances of the sleep/wake processes, daily mood fluctuations as well as abnormalities in the diurnal rhythm of cortisol and melatonin secretion [73]. Characteristic for BD subjects is the so-called "evening" chronotype [74]. Genetic studies point to a contribution of the "clock" genes connected

with biological rhythms for a predisposition to BD and determination of its course [75]. The concept of BD as a biological rhythm disorder gave rise to such therapeutic methods as chronotherapy of treatment-resistant BD [76] and interpersonal and social rhythm therapy [77].

In the Department of Adult Psychiatry in Poznan, in collaboration with the Krakow center, chronobiological studies of BD were performed using the BRIAN (Biological Rhythms Interview of Assessment in Neuropsychiatry) scale. It was found that in bipolar patients, the biological rhythms measured by this scale are disturbed and correlated with affective temperaments and schizotypy dimensions [78]. It was also observed that lithium administration can transform the chronotype into a "morning" one [79].

Some new studies point to BD as an illness of mitochondrial dysfunction. Mitochondria are intracellular organelles that contain their own DNA (mtDNA). They constitute a source of energy in the form of adenosine triphosphate (ATP), produced in the process of oxidative phosphorylation via the electron transport chain. Mitochondria play an important role in many cellular functions such as reactive oxygen species production, apoptosis, synaptic plasticity, and calcium ion homeostasis. The hypothesis of mitochondrial dysfunction in BD can integrate various pathogenetic concepts such as the inflammatory theory, cation transport disturbances, impaired synaptic plasticity, and oxidative stress abnormality [80]. Recently, it was found that in patients with primary mitochondrial diseases caused by mutations in nuclear DNA-encoded and mitochondrial DNA-encoded genes, there is a multifold increased risk of bipolar I illness [81].

Brain neuroimaging changes in bipolar disorder

In 2012, American researchers led by Stephen Strakowski developed a consensus model of the functional neuroanatomy of BD, covering the brain structures connected with emotional processes. According to them, in the premorbid period, a decreased connectivity among ventral prefrontal networks and limbic brain regions, with the amygdala as their main structure, develops. The abnormalities of this network, further called the anterior limbic network, including also, among others, the cingulate and nucleus accumbens, underlie the onset of mania, and next, generate a bipolar course of the illness [82]. By the way, the "roots" of Stephen Strakowski date back to the vicinity of Poznan, and his Polish ancestors had the name "Strzałkowski."

Recently, research was performed aimed to map the brain substrate associated with a manic state which may occur both in the course of BD as well as following focal brain damage. While the lesion locations associated with mania were markedly heterogenous, they showed a unique pattern of functional connectivity to the right orbitofrontal cortex, right inferior temporal gyrus, and right frontal pole [83].

Environmental factors in bipolar disorder

Environmental factors superimpose on a genetic predisposition to BD and epigenetic changes. A recent review of such factors, operating during the prenatal period as well as in the early period of life and later was performed by German researchers [84].

The study on infectious factors in pregnancy showed their slightly lesser association with the occurrence of BD than schizophrenia in adult life. However, research should be mentioned showing that maternal influenza exposure was related to a five-fold greater risk of adult BD with psychotic features [85]. Maternal smoking during pregnancy increases by two-fold the risk of BD of the offspring in adulthood [86].

Early life stress (so-called early childhood trauma) plays an important role in the appearance and course of many psychiatric illnesses, including BD. In the pioneering study of 1999, Israeli researchers found that parental loss, especially before 9 years of age, increases by 2.8-fold the risk of BD [87]. Further studies demonstrated that in persons experiencing various childhood trauma (e.g., emotional, physical, and sexual abuse or neglect) there is an increased risk of developing BD and its course is more severe [88]. In the research performed in Poznan, compared with the control group, bipolar patients showed a higher level of indices of physical abuse, emotional abuse, sexual abuse, emotional neglect, physical neglect and also experienced more frequently such negative childhood events as alcoholism, psychiatric illness and suicide in the family, parental abandonment, divorce, death of a parent, and prolonged separation from parents [89]. The study of an association between childhood trauma and BD showed that emotional abuse and neglect were the main causes connected with an unfavorable course of the illness [90]. Genetic and epigenetic mechanisms are the intervening factors between early childhood trauma and the appearance and course of the illness. Among "mediating" genes, probably the most important is the serotonin transporter gene, and among stress axis genes, the FK506 binding protein 5 *(FKBP5)* gene [91].

In adulthood, stressful life events can trigger both manic and depressive episodes. The results of a prospective study of 222 patients with BD can serve as an example: in more than 60% of these patients, at least one life event 6 months before a new episode was detected [92].

Seasonality can play a certain role in the manifestation of manic and depressive episodes. Manic episodes peak during late spring and summer and depressive episodes at the turn of autumn and winter. This corresponds in a way with the concept of seasonal affective disorder [93]. The studies performed in various locations across the globe also showed the relevance of climatic factors, pointing to a relationship between sunlight and the age of onset of the first BD episode [94].

Summary

In recent decades, considerable progress has been made both in clinical identification of BD as well as its pathogenesis, in the context of the interaction of genetic and epigenetic factors with environmental influences. A significant element of this progress is the development of molecular genetics, especially GWAS research. Using this powerful research tool allowed to identify the new genes, point to the placement of BD among other psychiatric disorders and find the association between BD and such phenomena as, e.g., creativity. A developmental model of the illness has been suggested and research has also been focused on its further course and the definition of its staging [95].

The search for new pathogenetic areas of BD has been underway, raising hope to find possible targets for new therapeutic interventions. However, it should be stated that so far, the development of psychopharmacology and psychotherapy of BD has been based mainly on clinical experiences, and pathogenetic concepts resulted to a great extent from the therapeutic accomplishments. Current praxis and theory of using medications, especially mood stabilizers of the 1st and 2nd generation [96], allows for an optimization of the therapeutic interventions in acute episodes, as well as appropriate prophylaxis. As a consequence of new pathogenetic explorations, the therapeutic methods targeting the immune system or biological rhythms can be mentioned. New therapeutic proposals can also result from taking into account the "developmental" model of BD, indicating that therapeutic interventions can be specific, depending on the staging of the illness [97].

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