Familial occurrence of bipolar disorder – review

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Abstract

Since the very origin of Emil Kraepelin's concept of recurrent psychoses the knowledge concerning affective disorders has developed significantly. Nowadays bipolar disorder is a separate disease and it is still not sure if we deal with a single illness or with many ones resembling each other. Basing on clinical course, four types of bipolar disorders are presently distinguished. They differ significantly and have tendency to familial occurrence. This familial occurrence may be sometimes a key to better and quicker diagnosing of disturbances occurring in children and adolescents. Atypical symptoms of bipolar disorder in the young are rather a rule than an exception. Symptoms leading to diagnosing of ADHD or conduct disorder may be early forms of affective disturbances. Even if not, their over incidental co-occurrence should lead psychiatrists to monitor any signs of affective disorder. The additional fact is that diagnosis of bipolar disorder is usually given between 16-25thyear of life. Therefore it is very important to know, as precisely as possible, the family history of any psychiatric disturbances. Data show that cases of bipolar disorder but also other mood disturbances and drug or alcohol abuse, conduct disorder, attention deficiency hyperkinetic disorder, personality disturbances, anxiety disturbances including panic ones, should be perceived as bipolar spectrum disorder. In this review of literature we analyze subtypes of bipolar disorder, comorbidity, clinical connections and familial correlations.

Keywords: bipolar affective disorder, family occurrence, comorbidity

Introduction

Bipolar disorder (BD) has become of greater interest in recent years. At the very origin Emil Kraepelin distinguished recurrent psychoses but did not divide them and did not separate bipolar disturbances. Such division was performed by Angst and Perris. It was a step forward and led to widened psychiatrists' perception of affective disorders. Distinguishing recurrent depressive episodes from bipolar affective disturbances led not only to theoretical knowledge but also to therapeutic implications. Further investigations led to next conclusions concerning occurrence of types of bipolar disorder (BD) and bipolar spectrum disorders, comorbidity, cognitive disturbances and also familial occurrence of the mentioned disease.

BD, not only in drug resistant cases or lack of compliance, significantly influences the quality of life and employment. The illustration of the scale of the problem is the fact that direct and indirect costs generated by this disease in the USA have been estimated at $45 billion [1]. Depressive states usually predominate in the course of BD. They are up to 3 times longer in comparison to depressive periods in BP-I and even up to 39 times in BP-II [1]. It is obvious that lowered mood influences the quality of life but elated mood also leads to many consequences. Disturbed insight and criticism influence patients' social relations, including employment. Within family relations it may lead to divorces. Some patients fall into money problems or even may squander a fortune.

It is still not exactly known what underlies the disease. Several dysregulations are suspected to have influence on developing BD. Studies point at the role of disturbed serotonin, noradrenergic, dopaminergic regulation, GABA system, glutamate system [2]. There are numerous proteins which are suspected of playing role in development BD. One of them is beta catenin [3]. Because of polygenic origin and possibly/probably heterogeneity of BD we have to wait for more univocal conclusions concerning the influence of genes.

Epidemiology

Community studies ascertained the prevalence of bipolar disorder from 0.5-1.5%[4].Results of some studies show that lifetime prevalence of BD concerns up to 4% of general population and bipolar spectrum diagnoses even up to 8.3%[5, 6].The prevalence of BD may differ in numerous studies due to used criteria. If subsyndromal symptoms were taken into account, the proportion of early-onset cases would likely be higher [7].

Many studies have showed that the origin of the disease usually takes place between 16 - 25thyear of life. The study among211 families with 1856 subjects showed a normal distribution of age at onset with means 16.6 (79.7%), 26(7.2%) and 34.7 (13.1%)[8].

In the past the prevalence of BD was not so high because of under diagnoses. There has been more than 40-fold increase in rates of diagnoses within 10 years and presently BD seems to be even over diagnosed [9]. Additional fact is that all diagnosed cases don't include all real ones, which remain not found. Conversely, not all diagnosed BD really exist.

Diagnosis of BD is not stable. Longitudinal studies show changes in diagnoses: 11-year follow-up study of 559 patients with depression showed that 3.9% subsequently "switched" to mania (bipolar I) and 8.6% switched to hypomania (bipolar II) [10]. It seems to be impossible to give the final diagnose in any case of mood disorder, especially in children[11]. We found that children with prepubertal major depression switched to BP I in 33% until average age 20.7 years.

Under diagnoses may concern subjects with atypical or treatment resistant depression, ADHD, OCD, anxiety disturbances. High rates of BD-II have been reported in patients suffering from obsessive-compulsive disorder, panic disorder, social anxiety disorder or dysmorphic disorder [12].

Spectrum of disturbance and comorbidity

Two main types of BD have been stated. The first one (BP-I) concerns typical course of disorder with mania and depression. To diagnose BP-I the presence of lowered mood is not needed. The second type (BP-II) concerns the course with hypomania and depression. The third subtype of BD (BP-III) was proposed for cases characterized by depressive episodes with antidepressant-induced hypomanic episodes. The fourth type (BP-IV) was proposed to describe patients with premorbid hyperthymic temperament punctuated by episodes of depression. Cyclothymic disorder, included in DSM-IV, is a diagnosis used for subjects with chronic, frequent shifts from mild hypomania to mild depression without at least two month period of normal mood. It may be difficult to distinguish it from temperament, especially from cyclothymic one. DSM-IV gives possibility to diagnose NOS (not otherwise specified) BD, which may be characterized by insufficient duration of symptoms or their severity or number. These types of BD usually are not taken into account in studies on prevalence of BD.

Independently from severity and the course of episodes which are the main factors for distinguishing types of BD, also symptomatological types are distinguished. They are: classical, psychosis spectrum and characterological ones and they differ not only with respect

to clinical presentation but also of course to the illness, family history, treatment response [13].

Also responding to different mood stabilizers seems to be the factor indicating heterogeneity of the disease. Lithium responders are characterized by family history of BD and its episodic course. Lamotrigine responders are characterized by family occurrence of anxiety disorders and major depression but not BD. They also frequently have diagnoses of anxiety-panic disorder spectrum [13].

Comorbidity in BD

There are several studies reporting comorbidity with BD. They may occur before or after stating BD diagnosis. A study conducted by Lin [8] showed that comorbid disorders usually develop after the onset of BD. In this study in case of over two-thirds of subjects alcohol or drug abuse followed BD diagnosis [8].Conversely, ADHD is a diagnosis given prior to BD

ADHD. The occurrence of ADHD in case of patients suffering from BD and its familial co-occurrence are statistically significant. There are some possible explanations for such situation. It is so because: comorbidity is an artifact of overlapping phenomena, comorbidity is due to a common diathesis that leaves patients vulnerable to separate illness, comorbidity is a chance phenomenon, symptoms of ADHD are just kind of prepubertal expression of BD that would develop into typical bipolar disorder in the future [14]. Study performed by Tillman and Geller [15] showed that 28.4% of patients with diagnosed ADHD switched to BP I during 8 year follow up. Wozniak et al showed that 94% of 262 children met criteria for both BD and ADHD [16]. The same study showed that all diagnoses of ADHD preceded later diagnosis bipolar disorder.

Atypical course and symptoms observed in children and adolescents make differentiating diagnostic process difficult. To distinguish BD from ADHD better, special diagnostic tools have been constructed [17] but they are not able to point the strict line between those two disturbances. We have to wait for more studies that would be able to explain the essence of this significant comorbidity.

Alcohol and drug use

Frye et al[18] showed that 49% of men and 29% of women with BD met criteria for lifetime alcoholism. Although in case of men the percentage value is higher, the score doesn't show reality of increased risk in comparison to general population. The risk of alcoholism was greater for women with bipolar disorder (odds ratio=7.35) than for men with bipolar disorder (odds ratio=2.77), compared with the general population. It shows that women with BD are at higher risk of suffering from alcoholism than men. Additionally, women suffering from BD tended significantly to use polysubstance. In the same study patients with BD I had the highest rate of alcoholism. Especially patients with depressive onset of disease are more likely to abuse alcohol [19]. It is probably caused by euphoric and anxiety relieving effect of alcohol.

Panic disorder

The occurrence of panic disorder is connected with affective disorder especially in female relatives [20]. In the study performed by MacKinnon et al[20] more than 90% of probands and first-degree relatives with panic disorder also had an affective disorder diagnosis. Familial occurrence of panic attacks seems to be connected with rapid mood switching even independently from suffering from panic disorder by the affected ones[21]. Other studies show that having panic attacks tends to occur in patients with depressive origin of BD[19].

Borderline personality disorder is also considered as mood spectrum disturbance but this idea remains very controversial [22]. Despite some overlaps it seems that there are too many significant differences between those psychic states to treat both of them as the unity [23].

Familial occurrence

Approximate lifetime risk of bipolar disorder in relatives of a bipolar proband are: monozygotic co-twin 40-70%; first-degree relative 5-10%; unrelated person 0.5-1.5% [24]. National register based study among2.7 million persons born in Denmark showed interesting data. Cumulative incidence of being admitted with BD by age 52 years of children whose parents were treated because of BD, was 24.95%. In cases where only one parent had diagnosis of BD this risk ratio was 4.4%, while such risk in general population was 0.48%. If unipolar depressive disorders were taken into account this ratio would be 75.0% and would enhance the fact of familial occurrence of mood disorders.

Also the familial occurrence of schizophrenia was significantly important. If one parent was hospitalized because of bipolar disorder and the other was admitted with diagnosis of schizophrenia, the incidence of BD in their offspring was 11.7%. Subsequently, if both parents had been treated because of schizophrenia the incidence for bipolar disorder in their offspring was 10.8%. For children of both parents with diagnosed BD the risk for any psychiatric diagnosis was 44.2% compared to 11.9% for general population [25].Meta-analysis of 17 studies found that the rate of any psychiatric disorder was 2.7-fold higher and the rate of mood disorders was 4-fold higher in the children of parents with bipolar mood disorder [26]. Analysis of studies suggest that children (up to 21 years old) of BD parents are at increased risk for developing mood and other disorders (anxiety, disruptive) compared to general population [27]. Another important data, which confirm clinical observations, is that the risk for diagnosing BD doesn't disappear by the age of 52 years as it happens in case of schizophrenia [25].

Some studies, but not all, reported occurrence of several disturbances present in children of BD patients. Rates of mood disorders and of other psychopathology were significantly higher in offspring of BD parents in comparison to healthy ones [27].Such children have diagnoses of mood disorders as BD, dysthymia, major depression and cyclothymia but also the ones exceeding strict affective domain [7]. They are internalizing disorders, such as anxiety disorders, and externalizing disorders, such as oppositional defiant disorder (ODD), conduct disorder (CD), and attention deficit-hyperactivity disorder (ADHD), as well as drug dependency [28].

There are studies showing differences in heritability of disease with two-fold rate of maternal transmission. On the one hand it may reflect differences in maternal and paternal disease, on the other it may due to non-genetic factors [29].

Type of disease, age and polarity of onset, severity and comorbidity seem to be familial.

Siblings of patients with early onset (average age=16.6 years, SD=5.1) compared to ones with late onset (average age=26.0; SD=1.4 or older) are more likely to have early origin of BD and also have higher risk of psychiatric disturbances as alcoholism, drug abuse and suicidality [8]. Independently from age of onset suicidal behavior seems to be familial and pathways associated with familial transmission of mood disorder and suicide attempt are similar but not identical [30].

The presence of delusions or hallucinations is higher in patients with familial occurrence of such symptoms in affected members of family compared to those without familial occurrence of psychotic symptoms. Psychotic symptoms are connected with more severe mental state and are more likely to occur in patients with BP-I and are connected with higher number of hospitalizations within affected family members [31]. Severity of symptoms present in children relates to age of onset of BD in parents and to number of affected parents [28].

There are reports pointing that polarity at onset of disease is familial trait and has additive predictive value. Relatives are about twice as likely to have the same polarity at onset. The polarity at onset seems to be greater in monozygotic twins compared to dizygotic ones [19]. Patients with mania at onset were 3 years older if compared to those with depressive origin. Mania at onset also tends to decrease the number of depressive episodes in the course of disease. However depression at onset seems not to influence lifetime number of mania episodes [19]. Intrafamilial resemblance of age at onset was also shown in other studies [32] as also as puerperal psychosis [33] and suicidal ideation [34].Study performed on 160 sibling pairs [35] showed within-pair correlation in: age of onset, proportion of manic to depressive episodes, dimensional measure of psychosis.

The study performed by Schulze et al [36] among1246 individuals showed that quality of social

relations which is traditionally not associated with mood disorders, is highly familial in families of probands with BD. The same study showed strong evidence for familial co-occurrence of substance abuse, alcoholism, psychosis and suicide attempt. Authors pointed also several factors as potentially significant: subtype of BD, suicidal ideation, poor judgment, number of hypomanic symptoms, panic disorder, age at onset, racing thoughts, employment, dysthymia, agitation/retardation, grandiosity, direct switch to opposite polarity.

Rapid cycling also seems to be familial and it is combined with higher comorbidity rates (anxiety and substance abuse disorders and more hospitalizations)[37].

The review of over 100 studies concerning more than 30 risk factors [38] showed that family history of bipolar disorder is the only established risk factor for BD. Basing on such founding Youngstrom and Duax [39] provided a normogram to assess the probability of falling into BD in case of family history of the disease.

There are also observations concerning different familial patterns of disease if lithium responsiveness is taken into account. Children of lithium responders, if compared to lithium non responders, manifest disturbances within affective domain, episodic course and few comorbid disturbances. Children of lithium non-responders have broad range of psychopatology, more comorbid diagnoses and chronic course [7].

Factors as BD type, comorbidity, age at onset, severity, suicidality indicate that probably we face heterogenetic disease. It may be supported by numerous genetic studies, which showed several genes to be suspected in origin of BD. They are located on every chromosome and are responsible for several different types of gene products. They are receptors (serotonin receptor type 4 and 2A, dopamine receptors type 3 and 4, 5, glutamate receptor 2B, somatostatin receptor 5, GABA receptor α3, NMDA subunit 1 receptor, adrenergic receptors), enzymes (DOPA decarboxylase, tyrosine hydroxylase, tyrosinase enzyme, GTP hydroxylase enzyme, myo-inositol mono phosphatase, G protein subunit and phospholipase C gamma 1 enzyme, catechol-o-methyltransferase, G-protein receptor kinase), transporters (dopamine transporter, vesicular monoamine transporter 1, serotonin transporter) and other [40]. A long list of "suspected" proteins shows that we may face polygenic disease, the course of which depends on many inherited single genes.

Prepubertal and adolescent BD

Perlis and colleagues [41] found that compared with patients with onset of mood symptoms over 18 years old (n=1187), those with onset below 13 years old (n=1068) experienced earlier recurrence of mood episodes after initial remission, fewer euthymic days, and greater impairment in function and quality of life over two-year follow-up. Scores cited above also show significant differences as to the type of BD, severity, comorbidity, alcohol abuse, course of the illness, rapid cycling that are present in early onset BD. Such differences are significant if we compared children and adolescents with older ones. The study conducted on patients with BD with late onset showed that those with disturbance origin below40 years of age did not differ from the ones with the origin above this age except for reduced overall psychopathology in those with late-onset. Such, congruent with other authors' data led to conclusion that distinguishing older adults with BD by early or late age at onset has limited clinical usefulness [42].

The symptoms of bipolar disorder in children often differ from those in adult ones. In case of depression children usually present different symptoms depending on their age and the way of expression. They may present anxiety, cognitive impairment, somatic complaints, phobias, withdrawal, loss of energy, fear of death, enuresis, may snivel or be irritable or aggressive, may experience sleep disturbance, psychomotor retardation, loss of appetite. Single symptoms may predominate and cover other ones. Non specific symptoms may be predominant, giving the picture of atypical depression. Symptoms vary with age and usually younger children tend to present somatic symptoms of depression [43]. Anhedonia seems to be one of the most important features of child depression. Other authors point missing school or irritability as quite typical features of childhood depression. All mentioned symptoms don't point the origin of lowered mood. They are also the ways of children's expression and may be due to states different from depression. Some studies were designed to find out typical child depression symptoms. Feighner [44] included low self-esteem and dysphoric mood together with at least two of eight additional depressive symptoms which are present for at least one month (aggressive behavior or agitation), sleep disorder, change in school performance, poor social interaction, changes in attitude towards school, somatic symptoms, loss of energy and appetite, and weight loss). The symptoms maybe represented as a change in children's general behavior. Pearce [45] together with depressive mood points to morbid or suicidal thoughts, sleep disorders, eating disorder, obsessions, hipochondriasis, irritability, refusal to go to school, impaired perception (including delusions), low self esteem and excessive guilt. The study conducted by Lima [43] among 2689 children aged between 12-15 years showed the prevalence of symptoms present in depression. They were: sadness, suicidal ideation, threats or attempts, refusal to go to school or phobias, irritability, isolated phobias, rumination, obsessions and rituals, eating disorders, sleep disorders.

Elevated mood, dependently from its severity, may differ. Several symptoms may occur such as irritability, restless,

faster speech, concentration disturbances with its exceeded switching, decreased need for sleep. Disturbed self esteem and criticism together with increased motor activity may be perceived as conduct disorder or ADHD.

Basing on greater severity, longer episode duration, preponderance of mania, comorbid ADHD, higher rates of rapid and ultradian rapid cycling, there were attempts to find out whether prepubertal and early adolescent bipolar I disorder is a different disease from the one diagnosed in adults [46].

There are no evident data which could support such division. It seems that it is the same polygenic disease with more severe course.

The presence of mood disorder significantly influences young people's life including social interactions and education. It may lead to improper development of personality. Especially BP-II is of higher risk, because symptoms may be not enough severe to be perceived as illness. In such situation patients' behavior is treated as their will what is followed by lack of acceptance or even aggression. Research findings show that patients with comorbid personality disorders are younger at onset and exhibit more suicidal behaviors compared to patients without personality disorders [47]. The risk for completed suicide is very high reaching from 8-19% in population of patients suffering from BD [48]. Childhood onset of BD is very strong risk factor for suicide attempts [21]. Such situation may be due to not only severity of symptoms but also to difficulties in development of personality and the model of family. Young people are strictly dependent on their parents in terms of emotional and material aspects and functioning of family has direct impact on youths. In the study performed by Geller et al [49] low mother's warmth predicted more relapses to mania and more weeks of illness. Olsen et al [50] pointed two areas of family functioning – cohesion and adaptability. Cohesion refers to emotional closeness and warmth between family members. Adaptability refers to flexibility and ability to change in case of stressors. Families of attempting suicide youths are characterized mainly by lower levels of cohesion. Data show that not the structure of family but the interaction within it influences developing suicide behaviors and attempts [50]. Stress in family life is a significant factor for increased suicidality. It may be caused by unfavorable life circumstances, illness of member of family or unemployment.

Study performed by MacKinnon et al [37] showed that early age at onset (especially less than 15 years of age) was connected with more frequent occurrence of rapid cycling. The same study showed correlation between rapid switching and familial rapid switching as well as antidepressant triggered mania [37]. Younger age influenced higher number of manic and mixed episodes in follow up study performed by Geller et al [49].

Making diagnosis may be a real challenge especially in younger patients. To manage it better, numerous scales are used in BD assessment: broadband checklists, mania and depression rating tests, scales assessing global functioning and quality of life.

In assessment of child psychic state, separate scales or their versions should be used (e.g. KSADS, PGBI, MDQ, CMRS). They base on psychiatric examination of patient but also on parents interview. Findings show that validity of parents' report is of greatest value (especially in comparison with affected youths and their teachers) [51] even when the parent has a diagnosed mood disorder [52]. It points to an old truth that completing detailed data from close relatives, especially mother, is very important and often crucial.

To sum up this review we daresay that there are two possibilities that we have to consider. The first is that BD is one disease of different severity and courses. The second, in our opinion even more probable, is that we deal with several disturbances of different origins and courses.

It is very important to take into account family history of any psychiatric disturbances which may lead to proper diagnosis in case of presence of atypical symptoms or other disturbances. Proper and quick diagnose may prevent suicidal attempts and development of personality disturbances, improve quality of life and provide proper and effective treatment.

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