Familial occurrence of bipolar disorder – case reports

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Abstract

Introduction. Bipolar Affective Disorder (BD) is a chronic mental illness afflicting approximately 1.5% of the population. A genetic contribution to the aetiology of this disorder is well-documented and estimated to be between 70and80%. In the case of familial occurrence of BD, an earlier onset is observed with a more severe course of the disease and poorer short- and long-term diagnosis.

Aim and method. This paper presents a case report of a 17-year old patient of the Adolescent Unit at the Department of Psychiatry Medical University in Lublin, from a family where BD has been transmitted for over three generations. In order to make the presentation clear, the case report is organized under the three following sections: 1. Socio-demographic characteristics of the patient; his psychomotor development in childhood before the disorder developed; family history of mental disorders, 2. The course of BD in the first-degree relatives (father) and second-degree relatives (grandmother) 3. The course of BD in the patient.

Conclusions: 1. Clear familial transmission of BD is associated with an earlier onset and more severe course of the disease as well as a poorer response to drug treatments. 2. Specialist care should be provided as early as during the prenatal period to monitor fetal development until birth in order to minimalize environmental factors contributing to the etiopathogenesis of BD and also to introduce early therapeutic interventions in the case of early symptoms.

Keywords: bipolar affective disorder, hereditary transmission, case report

Introduction

Bipolar Affective Disorder (BD) is a chronic mental illness afflicting approximately 1.5% of population [1]. A genetic contribution to the aetiology of this disorder is well-documented and estimated to be between 70 and 80% [2]. An estimated 7%of first-degree relatives of BD patients are likely to develop the disorder, which means the relative risk is 5-10% [1]. It has been found that the more family members suffering from BD and the earlier the onset of the disorder, the higher the morbid risk [3]. In the case of familial occurrence of BD, an earlier onset is observed with a more severe course of the disease and poorer short-term and long-term diagnosis [4]. In the last decade, the existence of three bipolar sub-groups based on the age of onset has been underlined, i.e. early (peaking at 17 years), intermediate (27 years) and late (46 years) homogeneous sub-groups of patients with BD [4]. The estimated proportions of the bipolar population belonging to the three sub-groups were 28, 50 and 22%, respectively. These AAO sub-groups may have a particular clinical profile, e.g. the early subgroup is characterized by a positive family history of affective disorders and comorbid symptoms, marked by suicidal behavior, psychotic symptoms and anxiety disorders, whereas the sex ratio and percentage of BD-I/BD-II does not differ between three sub-groups [5].

Aim and method

This paper presents a case report of a 17-year old patient of the Adolescent Unit at the Psychiatric Clinic from the family where BD has been transmitted for more than three generations.

Case Report

In order to make the presentation clear, the case report is organized under the three following sections:

1. Socio-demographic characteristics of the patient; his psychomotor development in childhood before the disorder developed; family history of mental disorders.
2. The course of BD in the first-degree relatives (father) and second-degree relatives (grandmother).
3. The course of BD in the patient.

The 17-year-old patient, 17, living with both parents and a 4 years younger brother, helping with running a family farm; has been treated for mental disorders since the age of 12 to date; psychiatrically hospitalized four times.

Birth and early childhood development

Born of the first and planned pregnancy; natural delivery at term; birth weight: 3330 g, APGAR Score: 9. The postnatal period developed without complications.

The patient developed normally during his early childhood. He started walking and talking on time. He entered nursery school at the age of 4 and was a lively, self-confident child, with no adaptive difficulties but showing discipline problems. In primary school, he was a mediocre pupil in grades 1-3. More severe learning problems began in grade 4, particularly with Polish grammar and mathematics. For this reason, the boy was examined in psychological and pedagogical counseling centre in 2004. His intellectual development was assessed as average but unbalanced and it was recommended that educational requirements should be adapted to match his individual abilities. He completed grade 4 with the a grade average of 3.8. Upon completion of junior high school, the patient attempted to continue his education in an automotive vocational school but finally left without passing to the second year. He has suffered neither from chronic somatic conditions nor serious head injuries. The family history of psychiatric illness was noted (Table 1).

FIRST GENERATION –the patients' grandmother

The first person in the family who has definitely been suffering from bipolar disorder is the grandmother of our patient. She was born in January in 1944. She has never had educational problems, has graduated from university, became a lawyer and has been professionally active. She has not suffered from any physical disease. She has given birth to four children and after her last pregnancy (1976) the periods of lowered mood occurred. In the beginning, her mental status was not disturbed enough to seek a physician's attention. After two years, periods of lowered mood became more severe and longer. They lasted for some weeks and were severe to such an extent as to seek out a general practitioner's and psychiatrists' help. The patient was treated with tricyclic antidepressants: amitryptilin and imipramin.

There is no possibility to have access to the patient's documentation of the first 14 years of treatment. According to the patient's account, she was psychiatrically hospitalized once in that period of time due to severe sadness with fear, anhedonia, sleep disturbances with early waking-up, and lack of appetite.

Her further treatment is known: during the first examination (May 1991), the doctor noted: gradual worsening of her mental state over 6 months, lowered mood, lack of appetite, shortened sleep duration with waking-up 3-4 hours earlier then usually, loss of vital energy, anhedonia, motor retardation, disturbed cognitive functions, including remembering and recalling, obsessive thoughts, particularly increased in early morning hours. He also noted some earlier periods of time when the patient had been in elevated mood with increased motor activity, decreased need for sleep, restlessness, but without need for hospitalization.

The doctor continued treatment with imiprimin that had been started previously, but elevated the dose to 100mg per day. After 3 weeks, when the patient's mental status was normalized, the dose of imiprimin was gradually decreased and carbamazepine was introduced as a mood stabilizer. After next 4 weeks of carbamazepine she was switched to lithium with a dose of 875mg/day and the imipramin was discontinued.

During the next 13 years, there were no mood disturbances. Concentration of lithium in blood serum was checked regularly and fluctuated within 0.69-0.85mEq/l. At that time, the dosage of lithium was changed from 750mg to 1000mg per day. After 4 years of treatment with lithium, a slight increase in thyroid glandule volume was observed but was not accompanied by changed levels of thyroid hormones.

A further worsening of her mental state was noted in 2004. The recorded symptoms were: lowered mood, fear, shortened sleep duration with early-morning awakenings, intrusive thoughts. Treatment with citalopram was started and after next 4 weeks the dose was increased to 40mg per day. After next 8 weeks improvement to euthymia was achieved and citalopram was gradually discontinued.

Table 1. Psychiatric family history

Degree of relationship	Psychiatric family history	
	on the mother's side	on the father's side
1st degree	–	• Father – BipolarII
2nd degree	• Grandmother – psychiatrically hospitalized due to anxiety and sleep disorder (dgn?)	• Grandmother – Bipolar II • Father's brother –treated as an outpatient for a brief period due to mood swings
3rd degree	–	• Grandmother's twin brother – committed suicide at the age of 53, after struggling with recurrent depressive disorder • Grandmother's sister – treated due to BD
Distant cousins	–	• Son of father's sister – committed suicide at the age of 19

At the same time, walproate as the second mood stabilizer was administered. Since then the patient has remained euthymic and has continued to receive lithium and walproate.

SECOND GENERATION –the patient's father

One of four children of the patient presented above (i.e. of our patient's grandmother), born when she was 24 years old, male, started suffering from bipolar disorder at age 12. There was the possibility to access the patient's medical records covering the last 20 years of treatment. Initial symptoms were sensitivity and lowered mood. Due to sensitivity and anxiety he was hospitalized and his disturbance was diagnosed as developmental disturbances. At the same time, his mother observed one/two-week periods of elevated mood and motor activity and usually 1-week long periods of lowered mood and motor activity.

During the first 9 years of disease symptoms were rather not severe and 6-month periods of euthymia were noted several times. During the first examination, the doctor noted a slight tendency towards tension and dysphoria. Such a state lasted for 3 weeks, was marked by lowered mood and motor activity, anhedonia, a lack of appetite, shortened night sleep, which was preceded by 4 months of typical hypomania. After the first examination, the psychiatrist prescribed lithium and lewomepromazine. After 3 weeks the mood was proper and stable. Lewomepromazine was replaced with perazine to be used ad hoc if difficulty in falling asleep occurred. In order to adjust therapeutically lithium blood concentration, the patient was administered 750 mg to 1000 mg per day. After 15 months of taking lithium, one week with a tendency for dysphoria occurred. Since the patient's mother informed his physician of this fact 3 months later, no drug changes were made.

One year later, when the patient was 21, the psychiatrist made a note of drinking alcohol by the patient. Two years later, after his son had been born, the patient stopped taking his medication and at the same time used alcohol which led to initial symptoms of hypomania with predominant dysphoria. The return to therapy with lithium normalized his mood after 3 weeks. Through the next 5 years the patient was treated by a general practitioner and continued taking lithium but did not check his lithium blood concentration. In subsequent years, he visited a psychiatrist once a year reporting stable mood with no disturbances. He did not check his lithium blood concentration as he had been asked to.

In March 2009, after one year of alcohol abuse with no parallel mood disturbances, a lowered mood and hypoactivity, anhedonia, occurred. An antidepressant was introduced that brought improvement and the depressive symptoms passed. The antidepressant was gradually withdrawn and valproate was introduced. A therapeutical level of valproate in blood serum was attained at the dose 1500 mg/day. Since then the patient has been in stable euthymia but the psychiatrist noted periodically a lack of compliance with regard to non-taking of prescribed drugs and the use of alcohol.

THIRD GENERATION – MD

Born in 1993, the patient is a son of the patient described above.

The first instance concerning psychic disturbances was recorded in the medical record when the patient was 8 years old. Family members observed over excitability and an aggressive attitude towards other children.

First symptoms were observed when the patient entered grade 5 of primary school: he was reluctant to go to school, was not interested in any classes, could not concentrate on his homework, and performed badly at school, stopped talking about school at home, spoke quietly, did not smile and became depressed. In October of 2004, reduced activity, obsessive thoughts concerning health, a loss of appetite, and lowered mood were observed. Two months later, depressive symptoms switched to a mixed state with aggressive behavior, labile mood with a predominant depressive, increased tendency to cry, excessively talkative. From the beginning of December 2004, the boy was re-examined by a psychologist and his intellectual development was described as slightly below average (89 in Full Scale) with the dominance of verbal conceptual ability (100) over executive functions (79).

The patient's **firsth thospitalization** in December 2004 lasting 8 weeks was caused by deterioration of his mental status with the symptoms described above. Multiform psychotic disturbances of the developmental period, disharmonic development of intellectual functions and chronic obsessive-compulsive reactions were diagnosed. Computer tomography and hormone levels showed no abnormalities. He was treated with perazine and risperidon. At the time of discharge, the continuation of risperidone1.5 mg was recommended as well as family therapy and an individual learning course.

In June 2005, the family reported 3-4day periods of depressive mood (with crying and thoughts of being seriously ill) and subsequent 3-4 week periods of increased activity, elevated mood, sexual arousal towards his mother, slightly reduced need to sleep. Therapy with lithium (750mg) and valproate (600mg) brought no significant improvement in the patient's mental state. Chlorpromazine, gradually elevated to 200mg per day, reduced the symptoms listed above. The next autumn, the patient displayed obsessive thoughts concerning his health

(physical state) and hypoactivity. Valproate was elevated to 1g per day and treatment with lithium was continued. Since the patient was 13, the psychiatrist noted several times there were improper educational methods which enhanced or maintained the patient's disturbed behavior (e.g. no reactions to sexual aggression towards his mother). During the following months the patient presented a relative stable and good mental condition. However, lowered mood with obsessive thoughts, dysphoria and hypoactivity recurred in March 2007. This time, sexual obsessive thoughts and compulsive behavior, as arranging books in line, also appeared.

Fluoxetine increased dysphoria and aggressiveness towards the family members, including sexual assaults towards mother. The patient was referred to hospital but his mother refused hospitalization. He missed psychiatric appointments for 5 months, then re-attended, presenting stable mood for next 18 months.

His **second hospitalization**, with the diagnosis: 'pediatric affective disorder with psychotic episodes', was caused by 'social maladjustment, aggressive behavior towards his mother and brother. Other examples of his misbehavior included exposing oneself, using his bedroom instead of the toilet, keeping dirty dishes and rubbish under furniture, making offensive sexual remarks on his mother, increased appetite, compulsions: closing the door, checking, arranging items in a specific order and naming them aloud, rituals related to getting dressed. Rejected by his peer group due to his vulgarity, he generally exhibited inappropriate behavior at home. At the hospital discharge, risperidone, 2 mg/d, was recommended, as well as participation in a therapeutic behavioral intervention and the continuation of family therapy.

In April 2009 he was hospitalized at the Toxicology Centre due to deterioration of mental state and alcohol abuse, with the diagnosis of 'Acute ethyl alcohol intoxication (3.32g/l), observation for lithium intoxication in a chronically treated patient for Bipolar Affective Disorder'.

The third and fourth hospitalization. In October 2010 the patient was hospitalized with the diagnosis 'Paranoid Syndrome' due to aggression towards the family members (he claimed his parents were poisoning him and wanted him to die); he refused to take medicines (he insisted that drugs had damaged his kidneys and they stopped working); he experienced suicidal ideation and attempted suicide (by hanging) four days prior to the hospitalization; he expressed delusional beliefs about being poisoned, delusions with a hypochondriac and persecutory content, delusions of reference: He claimed that his body was infested with worms, gave a delusional interpretation on bodily sensations, and claimed that he needed to remove toxins from his body. The patient experienced lowering of mood and psychomotor drive, periodic agitation, displayed verbal aggression, and his obsessive thoughts and compulsions became more severe. He had missed classes for six months.

Subsequently, the patient was transferred to the local clinic where he stayed for 16 weeks with a diagnosis of 'Bipolar affective disorder, a depressive phase with psychotic symptoms'. Lowering of mood and drive was observed, together with anxiety and a feeling of being in danger. He reported somatic complaints, experienced nihilistic delusions ('my kidneys have been damaged, they aren't working, I'm likely to be dialyzed, I'm not giving consent'; 'I've got holes in my brain made by medicines'; 'Worms are eating my body'), delusions of control ('My dead brother has taken power over me, he's calling me, he's controlling me'), delusions of guilt, and auditory command hallucinations encouraging the patient to commit suicide.

The results of psychological testing were as follows:

- 'The Wechsler Adult Intelligence Scale, WAIS-R (PL) Intelligence Quotient in Verbal Scale 76 (borderline intellectual functioning), in Performance Scale – 69 (mild mental retardation), in Full Scale 73 (borderline intellectual functioning).
- Three tests for visual-spatial memory and cognitive organization of visual-spatial material: Benton Visual Retention Test, Test Bender-Gestalt, Test Graham-Kendall): lack of significant impairment.
- Trail Making Test: A – a slowdown in psychomotor speed, B –cognitive plasticity and working memory deficits.
- WCST – executive functions and working memory deficits.

Olanzapine monotherapy was introduced (up to 20mg), replaced by risperidone and then by quetiapine (900mg/d) together with valproate (900mg/d) that finally brought about improvement.

Because of multiple intelligence testing, WISC/WAIS results should be interpreted with caution, however it should be noted that despite four time examination, tests results have not improved. It may additionally indicate a disruption of the learning process.

The fifth hospitalization. According to the anamnesis, the patient experienced the deterioration on his mental state, dysphoria. He behaved vulgarly towards his mother, stayed idle during the day, did not leave home, periodically showed increased drive, akathisia, aimlessly drove a tractor, demanded money, sweets, beer and cigarettes from his mother and responded aggressively to the refusal. During this stay at hospital, the patient initially displayed an elevated mood, and a lack of insight, was anxious, entered his inmates' personal space and showed sexually disinhibited behavior towards them, unwilling to

Table 2. The patient's WAIS scores (2004-2011)

Year	IQ - Verbal Scale	IQ - Non Verbal Scale	IQ - Full Scale
2004	**100** (IQ average)	**79** (Borderline Intellectual Functioning)	**89** (IQ low average)
2007	**85** (IQ low average)	**72** (Borderline Intellectual Functioning)	**76** (Borderline Intellectual Functioning)
2010	**82** (IQ low average)	**77** Borderline Intellectual Functioning)	**79** Borderline Intellectual Functioning)
2011	**76** (Borderline Intellectual Functioning)	**69** (mild mental retardation)	**73** (Borderline Intellectual Functioning)

Table 3. The course of BD in the successive generations

	1st generation (Grandmother)	**2nd generation (Father)**	**3rd generation (Patient)**
The onset of the disease	32	12	12
The course of the disease	Mild, with clinical presentation of BD-II, without psychiatric hospitalizations; 1 hospitalization – a depressive episode	Moderate, clinical presentation of BD-II, 1 psychiatric hospitalization	Very severe, clinical presentation of BD-I, 5 psychiatric hospitalizations, major depression with Cotard syndrome, mania with high agitation and disinhibition of instinctual drives
I episode	Postpartum depression	Depression	Depression
Response to treatment	Response to lithium – positive. Treated with lithium since she was about 47. Initially, a short period of treatment with carbamazepine. Depression relapse after 13-year treatment with lithium and euthymia; since then valproate has been added.	Response to lithium – positive. He has been taking lithium since he was 20, since he was 41 valproate has been added.	Valproate, lithium, carbamazepine, typical and atypical antipsychotics – a partial response.
Education	University	Vocational agricultural	Junior high school
Social functioning	Good; efficient in her family and occupational roles	Work in a family farm	Poor; he wasn't able to complete an occupational therapy program.
Comorbidity with other psychiatric disorders	–	Periodic alcohol abuse	Disharmonic intellectual development; conduct disorder in childhood; periodic alcohol abuse.
Suicide attempts	–	–	1

attend therapy, became active in the afternoon and evening. He went into other patients' bedrooms, searched their cupboards, and stole their food. A change in pharmacotherapy along with a consistent use of behavioral approach brought about the resolution of symptoms, partial judgment, and improved social functioning. Following passes checking his state and behavior at home, the patient was discharged.

At that point, a battery of neuropsychological tests and clinical trials was administered to him. As a result, the following deficits were revealed:

- Cognitive impairment in: logical reasoning, abstract thinking, drawing conclusions, making predictions;
- Disturbances in cognitive productivity and plasticity;
- Immature strategies of visual-spatial information processing ;
- Inability to organize learning material purposefully;
- Abnormalities in social reasoning and regulation of his own social behavior;
- Disrupted emotion recognition;
- Disturbances in social cognition.

The aforementioned results may be supposedly indicative of:

- general immaturity of the nervous system,
- dysfunctions of frontal lobes, right hemisphere, cortical-subcortical connections of limbic system and frontal cortex.

Table 3 contains the most important data showing the course of BD in the successive generations.

Discussion

The analyzed case of a positive family history of BD in three successive generations accompanied by familial aggregation of 7 cases of BD in the closest family is consistent with other reports in the literature.

The risk of BD development increases along with the number of affected family members, the degree of relationship and the onset of the disease. The review of over 100 studies concerning more than 30 risk factors [6] showed that family history of bipolar disorder is the only established risk factor for BD. Basing on such founding, Youngstrom and Duax [7] provided a normogram to assess the probability of falling into BD in case of family history of the disease.

Family studies demonstrated that age of onset predicts the extent of familial aggregation of BD [8,9,10] and early-onset patients had a greater morbid risk than late-onset patients [11]. Relatives of early-onset patients are 1.1-3.9 times more likely to develop affective disorder than are the relatives of late-onset patients. This was consistent with recent meta-analysis study showing that early onset in the bipolar parent was associated with an increase in the offspring [12].

Severity of symptoms in children relates to age of onset of BD in parents and to number of affected parents [13]. The late onset of the disease of the patient's grandmother may be linked to a relatively mild course of the patient's father. The early onset in the patient's father and the patient himself contributed to a very severe course of the patient's disease, involving Cotard syndrome, mania episodes with disinhibiton of instinctual drives and short-term remissions.

Bipolar disorder with an early onset seriously disrupts the development and emotional growth of the children and teenagers concerned [4]. It is associated with high rates of suicide attempts and completions, academic failure, substance abuse, disturbed interpersonal relationships, and multiple hospitalizations [14,15].

Also Perlis et al. [16] found that compared with patients with onset of mood symptoms after age 18 years, those with onset before age 13 experienced earlier recurrence of mood episodes after initial remission, fewer days euthymic, and greater impairment in function and quality of life over two-year follow-up.

The early onset of the disease in our patient has been associated with clearly poor social functioning, dropping out of school, alcohol abuse, a lack of social relationships and a number of hospitalizations, in contrast to competent occupational, social and family functioning of his grandmother and relatively worse functioning of his father.

Several studies have reported that early-onset BD patients have prototypic clinical characteristics, such as more frequent psychotic symptoms during affective episodes [11,17,18,19], more manic episodes [20], more mixed states [21] and high rates of comorbid conditions such as alcohol abuse and drug addiction [22].

Early onset is associated with greater severity and poorer long-term outcome, as shown by the chronic nature of this disorder, its resistance to mood-stabilizers [17,18,23,24,25,26].

Unlike the papers showing a similar familial response to lithium treatment [27], in the present case the effectiveness of lithium therapy was not linked to a positive response in the patient.

Duffy et al. [28] indicate that 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 also have broad range of psychopathology, more comorbid diagnoses and chronic course. However, whereas these results are consistent with those pertaining to the course of the disease of the patient's father, they are not in line with the observations concerning the case of the patient. Results by Tighe and Mahon [29] suggest that the patient's early onset may be associated with his poor response to normothymic drugs.

Conclusions

1. Clear familial transmission of BD is associated with an earlier onset and more severe course of the disease as well as poorer drug response.
2. The specialist care should be provided as early as in the prenatal period to monitor fetal development un-

til birth in order to minimalize environmental factors contributing to the etiopathogenesis of BD and introduce early therapeutic interventions in the case of first symptoms.

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