

Bipolar disorder(BPD):epidemiological characteristics, current situation and treatment

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Abstract. Bipolar disorder (BPD) is a common mental disease. Patients have both depressive symptoms and manic symptoms, which affect the quality of life of patients. At the same time, it can be complicated with somatic symptoms. Patients often feel incompetent, or even commit suicide. BPD has a high misdiagnosis rate, accompanied by high morbidity and mortality, so people should pay more attention to BPD. Many factors may lead to BPD, such as the high recurrence rate of patients in families with high emotional expression; the recovery period of patients with negative life events was prolonged; patients with bad social adaptation and environmental stress have an increased probability of serious emotional symptoms or affective disorders; Patients with irregular life are prone to attack when facing negative life events, but most of them are from heredity or environment. According to the pathogenesis or characteristics of BPD, many epidemiological studies have been carried out clinically, such as family research, adoption research, twins research, etc. the treatment of bipolar disorder, in the maintenance treatment of drugs, There are sufficient evidences that lithium salt are effective for both acute manic episodes and depressive episodes, does not cause manic depressive transition, and long-term use can prevent recurrence, also reduce the suicide rate of patients.

Keywords: Bipolar Disorder, Epidemiology, Current Situation, Treatment.

1. Introduction

Bipolar disorder (BPD) is a common and severe mental disease which has a pathological feature of periods in one's mood, energy and functional ability including extremely highs (mania) and extremely lows (depression). According to Miller et al, lifetime prevalence of BPD has been reported that in the general population, it is about 2-3% [1]. This mental disorder significantly affects the quality of life of child or adult patients which results their self-injury behavior and a death rate of suicide approximately to 19% [2]. Even in the well-treated individuals, there is a high relapse rate indicating that BPD is a refractory disease. Due to the diagnosis of bipolar disorder takes a long time, it is easy to be misdiagnosed as "monophasic" depression, schizophrenia and so on. In medical practice, patients and their families cannot pay enough attention to it, and the interval between the first onset of the disease and receiving treatment is long, which delays the opportunity of treatment. In addition, patients of BPD also suffer from high health care cost and reduced working capacity that in turn lead to their poverty. A study in 2020 estimates that in US, national economic cost of BPD has been reached to 219.1 billion dollar and 88,443 dollars per person, showing a great burden in national fiscal expenditure [3]. BPD is caused by genetic factors, life events, family upbringing and personality factors before illness. Other molecular genetic study such as genome-wide association study (GWAS) also indicate multiple functional genes participating in the pathogeny of BPD [4].

This article briefly reviews current evidence and studies for genetic and environmental influences on BPD, describe possible genome-wide loci may play a role in BPD, and prospect the possible future directions of early prevention and treatment due to specific risk factors.

2. The clinical criteria of BPD

BPD has its own specific characteristics. At present, this kind of disease still has a high risk of misdiagnosis, which provides a diagnostic basis for further standardizing the clinical diagnosis of bipolar disorder and the clinical diagnosis of this kind of disease.

Modern diagnostic criteria in DSM-5 classified BPD into three subtypes: bipolar I disorder (BP-I), bipolar II disorder (BP-II) and cyclothymic disorder. BP-I is the most known subtype which can be diagnosed by experiencing at least one manic episode and at least one depression episode and their symptoms are generally intense. BP-II involves a milder manic symptom named hypomania. To confirm to diagnostic criteria, individuals have to experience at least one episode of hypomania and at least one episode of depression. For cyclothymic disorder, Individuals show fluctuation of hypomanic symptoms and mild depressive symptoms. The duration of each episode is usually short, it occurs many times in at least two years, however. Previous research using adoption, family and twin studies have confirmed that BPD has a high heritability and concordance rate [5].

A person who can be diagnosed as BPD must have experienced episodes of mania and hypomania. The definition of mania contains at least one week and almost every day presenting. Hypomania lasts at least 4 days and occupy almost all day. While the patients talk with a doctor, following symptoms may be questioned: losing need for sleep, tending to do activities that may lead to painful results for themselves, cannot concentrate their attention, becoming talkative, accelerated thinking, inflated self-esteem, increase in goal-directed activity. If three or more symptoms are presented, they may be considered mania. Five or more of following symptoms are needed to diagnose depression: having a low mood almost every day in a period, losing interest for almost all activities, abnormal weight gain or loss, tend to engage in non-targeted activities, lack of energy in daily life, feeling that life is meaningless, cannot make decision or losing ability to concentration, repeated thoughts of suicide or have put into effect.

3. Genetic factors and related studies of BPD

3.1. Family study

Family study is a useful research method of traditional genetic epidemiology, which attempt to figure out if an illness generally happened in a family. This method is aiming at finding the existence of family aggregation of a specific trait or disease. To do this, researchers generally compare the prevalence rate of specific trait or disease among first-degree relatives of case group to the prevalence rate among first-degree relatives of control group. If the result indicates a relatively higher prevalence rate in case group, there may be a familial factor for this trait or disease. However, a higher prevalence rate doesn't necessarily indicate that it is caused by genetic factor. Family study doesn't directly exclude share environmental factor so both genetic and environmental factor may have interaction to it. To conduct a family study, investigating targets' family history or directly interviewing can be important methods.

Earlier articles of family study did not include a clear distinction between BPD and unipolar disorder. In addition, lack of control group and small number of samples can also be limitations. One article in 1974 firstly give a classification of BPD and unipolar disorder. They compared a total number of 606 and 544 in different classes of first-degree relatives at risk for BPD and unipolar respectively. The results of their family study among various class of relatives at risk indicated that there was an increasing morbidity risk in the family. The morbid risk for BPD was estimated about 15.5% and 19.8 for unipolar. They also found a sex distribution when compared different sex of the proband. For male probands, there was a significant number of mothers and daughters affected by diseases compared with fathers and sons. Female relatives had a remarkable number with affective disease than male probands. In 1975, researchers firstly use controlled studies to report 3.8% risk of BPD among 54 BPD probands of first-degree relatives, while in control groups the rate is estimated about 0.2%. The risk had significantly increased by 19 folds in BPD relatives. Another large family study conducted in 2015 in Sweden containing about over 2 million samples showed that in the first-degree relatives of BPD probands the risk of BPD was about 7.9-fold higher than controls, the second-degree relatives is 3.3-fold and the third-degree relatives is 1.6-fold. The result provides additional evidence that BPD strongly transmitted among generations in a family[6].

3.2. Adoption study

Adoption study is an effective method to investigate the genetic and environmental influence on a trait or disease. It creates an environment that separates biological and adoptive parents with adoptees, so that the research can indicate the share and non-share environmental factors and genetic factors making up the shortcomings of family study. Adoptees compares with biological and adoptive parents showing genetic influence and compares with non-biological siblings raising in same family showing shared environmental influence. If genes play an important role in a specific trait or disorder, biological parents should behave more similarly with adoptees than adoptive parents do. However, these studies are logistically difficult to process and may face a variety of difficulties, the availability of applying adoption study in BPD research has been limited.

Although there are several limitations in adoption study, some of the research indicated that biological parents have much higher prevalence rate than adoptive parents in BPD. First study using modern diagnosis criteria of the phenotype was conducted in 1977 by Rainer et al. They researched 29 bipolar adoptee and their adoptive and biological parents. Three control groups were set: 22 unaffected adoptees, 31 BPD patients' parents who did not adopt and parents of 20 patients of polio to control the environment which is raising disabled child. The risk of mood disorder is significantly higher in biological parents than adoptive parents with a rate of 31% and 12% respectively. Biological and adoptive parents of normal adoptees and polio child have relatively lower risk. These results indicate that genetic factors play an important role in affective illness.

Another article published in 1986 showed similar results. They investigate 71 adoptees as well as their biological and adoptive parents including 27 unipolar and 10 bipolar type. Control group was setting by 71 adoptees with similar sex, age, economic status, and time when they were adopted. An obviously higher illness rate was found in biological parents of unipolar and bipolar disorder affected adoptees than in control group. Although the statistic results are limited by relatively small number of samples, it provides evidence that the genetic transmission is existed in the risk of mood disorder, including unipolar and bipolar disorder^[6].

With the offset of the deficiency in small sample size, researchers in 2014 providing a national size of population statistic result for BPD and other mood disorder. To reduce the error in result, they exclude samples who have biological relationships with adoptees and adoptive siblings. As a result, adoptees whose biological parents are diagnosed as BPD or biological parents who has BPD affected offspring had higher risk of suffering from BPD with a relative risk of 5.0 and 4.5 respectively. Risk was also increasing in adoptive parents and their adoptees, but it is not significant, indicating that there may existing environmental influence in triggering BPD. Additionally, familial aggregation has been found between BPD and several mood disorder such as schizophrenia (SZ) and ADHD. If adoptees who have BPD has siblings, even they are reared in different families their siblings also have increased risk for major depression, ASD, and personality disorder^[7].

3.3. Twin study

To figure out the influence of environment, twin study compares twin pairs with different genetic similarity rearing in a shared environment. Twins have two types, monozygotic (MZ) and dizygotic (DZ) twins. MZ twins are grown from one fertilized egg with almost same genes. DZ twins as a comparison group to MZ twins are derive from two independent fertilized eggs. So, they have 50 percent genetic similarity to compare with MZ twins with 100%. If a trait or disorder is hypothesized that genetic influence is important, MZ twins should have more similar phenotype than DZ twins. MZ and DZ twins can be identified by DNA marker with great precision.

Twin study has been used to determine the concordance rate and heritability of BPD for several decades. Heritability is interpreted as how strong the genetic influence is in a specific trait or disorder within a population, not refer to an individual. Early twin study of BPD had similar limitation with small sample number or not used clear diagnostic criteria of phenotype. Unipolar type did not separate from bipolar disorder so the error may be increased in results. In 2003 an article analyzed the heritability of BPD by twin study including 67 twin pairs^[8]. 30 MZ and 37 DZ twins who were

diagnosed as BPD through DSM-IV criteria in lifetime were contained and MZ or DZ type was verified by interviews and blood type. Another group including 68 MZ and 109 DZ pairs was analyzed for comparison. Information of zygosity or status was setting blindly for both groups. It is reported that the concordance rate was greater in MZ pairs than DZ pairs which was defined as broadly or narrowly. Both concordance rate was best described by genetic and shared-environmental factors model with the heritability of 0.89 for broad and 0.85 for narrow diagnosis. Similar conclusions were published in 2014 by researching nationwide twin population with bipolar I disorder[9]. This research applied more accurately method by analyzing DNA markers to distinguish MZ and DZ twins. A significantly higher concordance rates were showed in MZ twins with a rate of 0.43 in comparison of DZ twins with a rate of 0.06. Genetic and shared- environmental factors model showed best fitting with a heritability of 0.93. Another large twin study of BPD in Swedish nationwide population was reported with a heritability of 60.4% for BPD with an optimized statistical method. Although the results showed larger number of females were affected by BPD, there is no significant evidence in statistic for sex distribution in BPD heritability.

3.4. Molecular genetic study

Apart from classical behavioral genetics study methods in above, modern research methods are attempting to explain the mechanism of BPD from the molecular level. Genome-wide association studies (GWAS) is a modern research method to find specific risk genes. It has the advantages of large sample number, multiple centers, and high reliability in analysis of disease. Most importantly, GWAS doesn't rely on correct hypotheses to detect target genes. This benefit is obvious in investigate multiple genes caused diseases which most genetic diseases are and avoid inaccurate evidence in candidate gene research. This method parses the mechanism of risk loci participating in specific disease in molecular level and do not limit in the analysis of family history. GWAS has been applied in detecting risk genes of BPD since 2006.

Prata et al. established a review about GWAS findings in BPD and SZ from the first GWAS research in 2006 to 2013[10]. A specific gene encoding diacylglycerol kinase (DGKH) has been preliminarily confirmed that has connection with BPD and has been confirmed with significant p value for Single-Nucleotide Polymorphism (SNP) test on chromosome 13q14.11. DGKH can phosphorylate the activator of protein kinase C (PKC) to regulate PKC mediated pathway or directly interact with signal proteins. Drugs such as lithium and valproate to stabilize BPD are sensitive to DGKH and have ability to induce its expression. CACNA1C encoding L-type voltage dependent calcium channel subunit protein can cause cardiovascular diseases. Previous study has found significant correlation between CACNA1C mutations and several mood disorder such as BPD and SZ with a p value at 7×10^{-8} . CACNA1C converts electrical activities into intracellular signals, including changes in the concentration of Ca^{2+} on the cell membrane. Animal model study knocked out CACNA1C in forebrain of mice and find that some of the brain regions are changed. In addition, mice showed anxiety symptoms in experiment. ANK3 gene encoding neuronal adapter protein Ankyrin-G is widely expressed in brain and participate in the regulation of nervous system development. Previous animal model study also provide evidence in mouse brain function of lithium sensitivity. Recent research in 2021 showed additional evidence of ANK3 genetic function in BPD. The risk-T allele of SNP rs10994336 within ANK3 gene was found to play a role in BPD by GWAS. The methylation level of CpG site was affected by ANK3 gene at position rs10994336 in BPD group and health-controlled group to mediate the executive function of rs10994336. This study is the first record to demonstrate the relationship between a specific genetic variant of the ANK3 gene and function affected by methylation in BPD[11].

Instead of GWAS detecting risk genes in chromatin, researchers have paid attention into mitochondrial DNA (mtDNA). Mitochondria are double structured organelles located in cytoplasm with their unique DNA sequence. Mitochondria generally function as power generation of the cell by produce adenosine triphosphate (ATP). ATP generation process is dependent on oxidative phosphorylation through respiratory chain which is describe as a continuous system arranging

electron and hydrogen transport reactions in order. More functions as programmed cell death and reactive oxygen species (ROS) production are involved in mitochondria. It is obviously the activity of mitochondria is strongly related to nervous system. Mitochondrial dysfunction happens in cellular level may trigger mood or neurological diseases. For example, the 3644C mutation which may decrease the membrane potential of mitochondria and respiratory chain activity have correlation with BPD morbidity risk by replacing a base repair that cause an amino acid substituted error in complex I [12].

4. Treatment of the BPD

BPD is a complex and severe illness with several possibility causes which lead to prudent treatment selection. The aims of treatment are relieving symptoms, prevention of recurrence and return of normal functional state. It is recommended in DSM-V to treat depression and mania by stage. Initial stage includes Lurasidone, Lamotrigine, Quetiapine or Lithium monotherapy for depression, and Aripiprazole, Asenapine, Divalproex, etc. monotherapy for mania. If initial treatment is ineffective, using of two drugs including in initial stage is considerable but it should be avoided to use two antipsychotic medications. Level 3 stage is available to apply electroconvulsive therapy substituted for above. Level 4 stage should be considered when all previous stages are invalid, including transcranial magnetic stimulation, SSRIs, Pramipexole, or three drugs combination.

Among all these treatments, Lithium has a long history and still widely use until today. The history of using Lithium as drugs can be traced to 19 centuries. In 1961, Lithium was first to be permitted in BPD treatment in France. However, the mechanism of Lithium treatment is remained unclear. Possible function may be revealed by medical imaging technology through specific protein probes. Recent research designed a DNA enzyme that can interact with RNA probe to release strong fluorescent signal while enzyme molecules are highly sensitive to Lithium ion. After injecting this biosensor and Lithium to cultured neurons of BPD patients and healthy individuals, Lithium are found to be concentrated in mature neurons of BPD group than healthy cells. This result may help figure out the function of Lithium in BPD treatment in future.

Additional treat methods are developing based on the pathogenesis of BPD. As mentioned before, mitochondrial dysfunction becomes a new target of therapy to research new drugs. N-Acetylcysteine, a precursor of glutathione, has the benefit of prevention of inflammatory effects and regulation of programmed cellular death. NCA adjuvant therapy has been reported to be beneficial for BPD. After 24 weeks adjuvant therapy, BPD patients significantly relieved symptoms than placebo group. Creatine is the substrate of ATP and has been proposed to treat BPD by oral intake. Increased creatine concentration may prohibit the transparent change of mitochondrial membrane to protect nervous cells. Adding creatine to treat BPD showed greater advantageous in control symptoms than placebo. However, most of the design are lack of sample size. The mitochondrial dysfunction may not exist in all BPD patients, so that the therapeutic efficacy may be lower in some individuals[12].

5. Conclusion

This paper gives a modern definition of BPD referred to DSM-V criteria and browse several research projects of traditional genetic epidemiology applied in BPD investigation to summarized a typical family aggregation phenomenon. High heritability of 0.60 to 0.93 is presented in genetic influence. To find out the risk factors in molecular level, GWAS has offered a wide detection with DGKH, CACNA1C, ANK3, etc. located as suspected risk genes. Nuclear DNA and mtDNA have cooperated function in regulation of cellular biological process. Thus, mtDNA gained sights for specific effect in BPD and been preliminary determined several mutations may participate in morbidity.

The treatment of BPD is different from that of monophasic depression/mania, and long-term prevention and treatment should be considered. In the future, more efficient treatment can be invented

according to different pathogenic mechanism. Specific environmental risk factors should also be paid attention so that BPD may be prevented earlier.

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