Genetic explanation of Borderline personality disorder

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SUMMARY: In this article attention is drawn to the causes of BPD (Borderline personality disorder). It is becoming a frequent disease, indeed, almost 2% of the general population suffers from it. Often called „Emotional instability", the key trait of BPD is instability in areas such as relationships, behavior, mood and self image. People with BPD were once maligned by the clinicians as difficult or attention seeking, but recent research in brain anatomy, neurobiology and genetics has offered a more comprehensive look on the causes of this disorder. Sveral theories about the etiology of BPD have emerged over time: Genetic theory, Neurotransmitter and hormone theory, Neuroanatomical theory and Environmental theory. It appears that genes are in many ways linked to every specific theory and thus may help in building a more consistant picture of BPD genesis. It is also likely that genetic predisposition is the most important factor in developing BPD. However it is not an independent factor, as it requires environmental influence to develop BPD.

KEYWORDS: BDNF, BPD, Child abuse, Genes, Neuroanatomy, Serotonine,

The term „borderline" might mislead one to think Borderline personality disorder (BPD) borders with normal personality, however, that is not the case; it originates from the time experts thought of BPD as a borderline verion of other known disorders. Today, many advocate for a more accurate term, such as "emotional regulation disorder" or "emotional dysregulation disorder." Indeed, in ICD-10 (International Statistical Classification of Diseases and Related Health Problems) it is recognised as Emotionally unstable personality disorder.[1] DSM 5 follows similar pattern. According to the DSM 5 (Diagnostic and Statistical Manual of Mental Disorders) there are three clusters of personality disorders, where Borderline personality disorder (BPD) is listed among Cluster B disorders, of which each is characterised by specific patterns of dramatic, emotional or erratic behavior. BPD is a cluster-B personality disorder, the essential feature of which is a pattern of marked impulsivity and instability of affects, interpersonal relationships, and self-image.[2] The pattern is present by early adulthood and occurs across a variety of situations and contexts. The key feature of BPD is instability in areas such as relationships, behaviour, mood and self-image. It is estimated that 1.6% Americans suffer from BPD whilst women are three times more at risk of developing BPD than men. The disorder is only made worse by the fact that 85% of people with BPD also meet the diagnostic criteria for another mental illness among which are major depression, anxiety disorders, post traumatic stress disorder or eating disorders. Also, an increasing number of incarcerated population is now being diagnosed with BPD.[1]

Causes of BPD

The exact cause of BPD remains unknown, however, four major theories have emerged over time. Those are: Genetic theory, Neurotransmitter and hormone theory, Neuroanatomical theory and Environmental theory. Each of them advocates for a different factor as a decisive one for the development of BPD. Genetic theory claims there are specific genes responsible for certain traits of BPD such as impulsive aggression or inhibitory control. Neurotransmitter and hormone theory sugguests that changes in hormonal and neurotransmitter physiology may be linked with BPD. Neuroanatomical theory argues that the certain abnormalities in brain sructures are responsible for emotional response regulation such as hippocampus, prefrontal cortex and amygdala; that may underlie the development of BPD. Last but not least, the environmental theory sees the main cause of BPD in troublesome childhood. This may include child abuse (sexual, physical and emotional) and unresolved fear, anger and distress from childhood.[3] Detecting the right cause of BPD is made more difficult by the fact that many of the above mentioned factors are involved in pathogenesis of other mental illnesses, many of which co occurred with BPD. For instance, abnormalities in amygdala structure and function can be found both in depression and BPD. However, many recent studies have come to associate genes and their abnormalities with all all of the other theories.

Genes and neurotransmitters

Over the last decade or so an extensive research in the genetic anomalies underlying the BPD has been undertaken. So far, the findings suggest there is a link between genetic abnormalities and some BPD traits. A multinational, large-scale twin study implicated genetic factors play a role in individual differences in BPD features in Western society. Genetic influences explain 42% of the variation in borderline personality disorder features in both men and women and that this heritability estimate is similar across The Netherlands, Belgium and Australia. Unique environmental influences explain the remaining 58% of the variance. [4] A further study into the genetic covariance structure among the four main features of BPD (affective dysregulation, cognitive disturbance, disturbed relatedness and behavioral dysregulation) suggested that a single genetic factor underlies most

of the genetic variance in BPD symptoms.[5] The two studeies basically show that genes are responsible for the main symptoms of BPD, and that it is probably a specific yet unknown set of genes. Bearing this in mind, another study was conducted on 711 pairs of siblings and 561 additional parents. The study identified the genetic material on chromosomes 1, 4, 9 and 18 to be linked with BPD. Among those, chromosome 9, more precisely the region 9p24, had the highest linkage peak. What is interesting is that genes responsible for other mental disorders are located on the same chromosomes near the assumed genes that influence BPD, namely, areas on chromosomes 1 and 4 were linked to schizophrenia, and areas on chromosome 18 with bipolar disorder. Schizophrenia and bipolar disorder also have areas associated with them on chromosome 9, very close to 9p24.[6] This finding may account for the overlap of the BPD symptomes and those of bipolar disorder. However, the specific genes responsible for the BPD symptomes haven't been identified, but the search has non the less been narrowed to distinct chromosome areas. On the other hand there are some specific genes which may offer a different insight in the etiology of BPD. A study about genes for BDNF (Brain derived neurotrophic factor), a nerve growth factor important for survival of existing neurons, and growth and differentiation of new neurons and synapses has shed some light on the development of BPD. An increased methylation of BDNFgene promoters has been noticed among patients suffering from BPD. The methylation is associated with down-regulation of BDNFgene. A further positive correlation between child maltreatment and higher DNA methylation of BDNF was discovered. In addition to that, patients who underwent an intensive dialectical behavioural therapy (therapy concentrated on helping patients identify their strengths and build upon them, identifying impairing thoughts, beliefs and assumptions and learning new ways of thinking and acting that will help the patients to live a more functional life.[7]) and had a positive response to it, showed a decrease in methylation. Accordingly, they showed positive changes in depression scores, hopelessness scores and impulsivity.[8] This research is important because it showed that changes in epigenetic status of certain genes may underlie changes in cognitive functions related to BPD, that these changes can be brought about by the experience of child maltreatment, and that they can be corrected through psychotherapeutic approach. Genes linked to serotonin (5-hydroxytryptamine (5-HT)), a neurotransmitter involved in the regulation of mood, appetite, and sleep, have also been the subject of some studies that associated them with BPD susceptibility. Among several genetic mutations that were brought into connection with BPD, the most significantly associated were those discovered in 5-HT2C and TPH2.[9] (5HT2C is a serotonin receptor that regulates mood, anxiety, feeding, and reproductive behaviour through the release of dopamine, and TPH2 is an enzyme in the serotonergic neurons of the brain that regulates the synthesis and levels of serotonin). A study from 2014 showed how vital the interaction between the two enzymes could be. The study first determined the importance of TPH2 abnormalities for deficits in cognitive flexibility, a symptom observed in number of different mental illnesses. The expression of loss-of-function mutant TPH2 in mice was associated with impairments in reversal learning and cognitive flexibility, accompanied by perseverative behaviours similar to those observed in human clinical studies . When the mice were treated with 5HT2C agonist the production of serotonin was restored, thus reducing cognitive deficit. This suggests a potential avenue to explore for the personalized treatment of cognitive symptoms in humans with reduced 5-HT synthesis and TPH2 abnormalities.[10] Thus far, genes prooved to be related to variety of symptoms diplayed in BPD and also for specific anomalies in function of some neurotransmitters.

Genes, neuroanatomy and environment

Genes are also closely intertwined with neuroanatomical and environmental aspects of BPD. Since the beginning of BPD exploration numerous studies have implied there are neuroanatomical discrepancies between the brains of healthy individuals and those suffering from BPD, particularly in the regions involved in emotional regulation. One of the more recent studies supports these claims and reports that processing of negative emotions in BPD might be subserved by an abnormal reciprocal relationship between limbic structures representing the degree of subjectively experienced negative emotion and anterior brain regions that support the regulation of emotion.[11] An earlier study associated a functional polymorphism (a genetic anomaly) of the 5-HTR1A gene (gene for the serotonine receptor vital for neuromodulating) with structural changes of the amygdala in patients with BPD. They confirmed that BPD patients showed a smaller amygdala (a structure crucial for experiencing emotions) volume in the presence of this anomaly. Second, evidence was provided that effects of MDE (Major depressive episode, which often coocurres with BPD) on amygdala volume in BPD might be modified by this 5-HTR1A polymorphism. In conclusion, their results support the assumption that both MDE and 5-HTR1A polymorphism are moderating factors that might affect amygdala volume in BPD and may therefore contribute to discrepant findings regarding structur-

al amygdala alterations in previous studies of this disorder.[12] Genes can be linked to yet another important factor for BPD, the environment. Indeed they form a kind of a bridge between the environment and hard, structural changes that occur in BPD. Child abuse is of particular importance since it has been associated with the onset of BPD for a long time and has often been opposed to genetics as a leading cause of BPD. New research shows that there is indeed connection between child abuse and reduced volume of right ventrolateral prefrontal cortex (part of the brain that controls emotions).[13] As mentioned in the paragraph above, child abuse can affect the mathylation and thus the expression of BDNF, an important factor of neuroplasticity.[8] Another research sougt to investigate the popular idea that BPD occurs in people who had been treumatised as children, but only if they are genetically predisposed for the disorder. The scientists focused their research on TPH1gene, a gene for one form of an enzyme crucial in serotonine synthesis, just as the afore mentioned TPH2. The study showed that abnormalities in TPH1gene moderate the association between a history of childhood abuse and the risk for developing BPD later in life, and that increasing severity of abuse may be associated with increasing BPD risk in those carrying the TPH1abnormalities. In addition, the interaction between abuse history and individual genotypes, not only increased risk for a BPD diagnosis, but also seemed to influence severity of psychopathology, as indicated by the number of DSM-IV diagnostic criteria met for BPD.14 A different study implied that the association between childhood abuse and BPD traits stems from common genetic influences, which is inconsistent with the widely held assumption that childhood abuse causes BPD, and suggests that BPD traits in adulthood are better accounted for by heritable vulnerabilities.[15] Thus, the genes seem to be decisive in the eventual development of BPD as a reaction to difficult childhood.

Conclusion

So far, genes proved to be of major importance in understanding many aspects of BPD. They help to explain symptoms, their variety and genesis. They also offer a link with other theories about BPD, suggesting an ovelap among of all of them. Genes seem to be the only thing that links everything else what is known about BPD. Perhaps the most important question they hepled to answer is wether environment or genes is deciseful for the onset of BPD. However, that only seems for the time being, before new evidence comes to light. It doesn't imply childhood abuse plays no role in BPD, but rather identifies it as a trigger that helps to set in motion the mechanisms already prepaired in people's minds. However, further research is required for better understanding of their role in BPD, as well as in other mental illnesses.

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Genska podloga graničnog poremećaja ličnosti

SAŽETAK: U ovom članku pokušava se objasniti genetska pozadina BPD-a (Borderline personality disorder), tj. graničnog poremećaja ličnosti. BPD je unazad nekoliko godina postao česta dijagnoza i procjenjuje se da otprilike 2% opće populacije boluje od ovog poremećaja. Poznat i kao emocionalna nestabilnost, njegova ključna osobina upravo je nestabilnost u području emocionalnih veza, ponašanja, raspoloženja i slike o samom sebi. Osobe s BPD-om su nekoć bile objeđivane od strane liječnika kao nemoguće, teške osobe koje zahtjevaju pažnju, ali istraživanja iz neuroanatomije, genetike i neurobiologije pružila su sadržajniji i porptuniji poged na uzroke ovog poremećaja. Nekoliko teorija o etiologiji BPD-a se razvilo tokom vremena: Genetska teorija, Neurotransmiterska i hormonska teorija, Neuroanatomska teorija i Okolišna teorija. Činise da su geni zajednički nazivnik svih navedenih teorija i stoga bi mogli pomoći u stvaranju kompletnije i konzistentnije slike postanka BPD-a. Također je izgledno da je upravo genetska predispozicija najvažniji faktor za razvoj BPD-a. Međutim, oni nisu neovisan čimbenik, već im je za razvoj pormećaja nužan poticaj iz okoliša.

KLJUČNE RIJEČI: BDNF, BPD, Geni, Neuroanatomija, Serotonin, Zlostavljanje djece