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BLOOD INJURY PHOBIA: AN OVERVIEW OF GENDER SPECIFIC BRAIN DIFFERENCES

KAN- YARALANMA FOBİSİ: CİNSİYETE ÖZGÜ BEYİN FARKLILIKLARINA GENEL BAKIŞ

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Abstract

Blood injury injection phobia (BII) involves an intense fear of situations, in which an individual is directly or indirectly exposed to blood, injections or viewing injuries, along with a tendency to avoid these situations. BII phobia is highly prevalent in females as compared to males. It is virtually the only specific phobia and the only anxiety disorder, in which fainting occurs. Although fainting is much distressed to the BII phobic individuals, but it may have developed in the humans at the time when they needed it much as a survival mechanism. In this article we discuss how in the humans there may have developed the trait of BII phobia in the ancestors, including the variation in the symptoms among sexes. There are not studies which specifically examine the syncope related brain differences among genders. But there are other well defined studies which highlight marked differences among male and female brains. Considering this we also review some recent breakthrough discoveries showing differences in the brain of males and females at gene expression level which leads to the variation in brain and behaviour related problems among genders. There is an exigent need to understand the brain behavioral problems through multiple perspectives.

Keywords: Blood Phobia, Fainting, Gender Specificity, Brain, Behaviour

Özet

Kan-enjeksiyon- yaralanma fobisi (BII) bir bireyin direkt ya da dolaylı olarak kana, enjeksiyonlara ya da yara görmeye maruz kaldığı ve bu durumlardan kaçınma eğiliminin olduğu aşırı korku durumudur. BII fobisi erkeklere göre kadınlarda daha yaygındır. Bu fobi bayılmanın olduğu hemen hemen tek spesifik fobi ve tek kaygı bozukluğudur. Bayılma, BII fobili bireylere daha fazla endişe verse de aslında bayılma bu bireyler bir çeşit hayatta kalma mekanizmasına ihtiyaç duydukları zamanlarda da oluşabilir. Cinsiyetler arasındaki semptom farklılıklarını içeren bu makalede soylardaki BII fobisinin insanlarda nasıl oluşmuş olabileceğini tartışacağız. Cinsiyetler arasındaki beyin farklılıklarına bağlı olan bayılmayı özel olarak inceleyen çalışmalar yoktur. Fakat kadın ve erkek beyinlerindeki farklılıkları inceleyen iyi yapılmış çalışmalar mevcuttur. Bunu düşünerek cinsiyetler arasındaki problemlere bağlı olan beyin ve davranış farklılıklarına sebep olan gen ifade seviyesinde kadın ve erkek beyinlerindeki farklılıkları gösteren bazı yeni buluşları da yeniden inceleyeceğiz. Beynin davranışsal problemlerini anlamak için çok yönlü bir perspektif zorunlu bir ihtiyaçtır.

Anahtar Kelimeler: Kan fobisi, Baygınlık, Cinsiyete Özgünlük, Beyin, Davranış

1. Introduction

Blood injury injection (BII) phobia involves an intense fear of situations, in which an individual is directly or indirectly exposed to blood, injections or viewing injuries, along with a tendency to avoid these situations. Blood injury phobia is classified as a subtype of specific phobia in the diagnostic and statistical manual of mental disorders (DSM, APA, 2013).

BII phobia is virtually the only specific phobia, and the only anxiety disorder, in which fainting occurs. It has been estimated that as many as 70% of the individuals with blood injury injection phobia have fainted at least once upon exposure to blood injection injury stimuli (Ost, 1992; Olatunji et al., 1992). It is important to note

that there are individuals who met diagnostic criteria for blood injection injury phobia but donot have a history of fainting. In one of the most comprehensive studies of blood injury injection phobia, 30% of blood phobics and 44% of injection phobics who met diagnostic criteria for blood, injection injury phobia reported never having fainted in the phobic situation (Ost, 1992).

Primarily BII phobia involves three types of reactions the common two are emotional response fear and the behavioral response avoidance. These two are generally shared with other phobias. The third response is fainting also known as vasovagal syncope or faintness. This vasovagal syncope is not associated with any of the anxiety disorders or any other phobia but is specific to

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BII phobia (Kaloupek et al., 1985; Grubb and Olshansky, 1998; Daroff and Carlson, 2001; DSM, APA, 2013). It was Marks and colleagues at the first time that draws attention to the specificity of fainting when they found that fainting was reported by only 0.02% of their sample of "mixed phobias" and by 100% of their sample of BII phobia patients (Marks, 1988). These findings lead to further studies for confirming the association of fainting and BII phobia.

BII phobia is different from other phobias because of its specific character of vasovagal fainting. Almost 75% of the individuals who has BII phobia fainted at least once in such situations (Thyer et al., 1985). There are other studies which however show less number of fainting individuals among BII phobics (Wani et al., 2014). In BII phobia the deceleration of blood pressure results in the onset of fainting. Studies have summed up a varied response of BII phobia patients towards visiting health care clinics. Patients with BII phobia generally avoid health care clinics, medical or hospital appointments and other important life saving surgeries (Marks, 1988). However in the Baltimore Epidemiological Catchment Area (ECA) study, Bienvenu and Eaton found that generally BII Phobics avoid needle sticks; they do not appear to avoid appointment to medical doctors, outpatient health centres, or hospitals (Bienvenu and Eaton, 1998) There are other studies which show BII phobia found in comorbidity with others like doctor phobia, hospital phobia, acquired immunodeficiency syndrome phobia, cancer phobia, dentist phobia, and social phobia (Kendler et al., 2011). Others studied BII phobia in comorbidity with depression, diabetes and other medical disorders (Kendler et al., 2011; Page and Martin, 1998). There are patients who otherwise qualify for the BII phobics according to the Diagnostic and Stastical Manual for Mental Disorders (DSM) but are not fainted at the sight of blood or other related ques which arouse an anxiety in the patient. Patients suffer from BII phobia avoid medical or hospital appointments (Marks, 1988). This makes the problem of phobia more serious as the sufferers avoid most of the medical procedures for other medical problems. Other phobias are more similar to other anxiety disorders than to BII phobia as per their symptoms are concerned. There are many individuals who generally faint at the time when they receive injections. This habitual fainting precedes the appearance of BII phobia in many subjects (Page and Martin, 1998). There is a clear difference in the fainting spells between males and females showed by various studies. Some authors argue that such individual differences of fainting at the sight of blood had been developed via conditioned learning (Page, 1998). The more recent studies have shown genetic differences in the brains of male and female. These studies show variations in the number of genes expressed in brain cells of males and females which perhaps may be one of the factors why there are differences in BII phobia related fainting among male and female.

2. Blood Phobia and Associated Fainting

Although syncope doesn't harm the patient at its first place, but often there are chances that a patient can

get a serious injury based on a place of fall. It is often a frustrating symptom to faint at the situations like vaccination, an injection or the sight of a syringe or blood. Such patients can easily be found at the primary health care centres. There are chances that in case of modern wars there may be ample number of soldiers who fear the blood, and they don't let themselves to involve in direct confrontation. For health professionals, it is often complicated and puzzling to see the patient faint at the sight of blood, injury or injection etc. Many of such patients faint while just at the sitting position (Grubb and Karas, 1998). The cases of vasovagal fainting with their description and sequence of autonomic nervous system are largely present in cardiological literature (Grubb and Karas, 1998). In no other anxiety disorders including phobias other than BII phobia, this condition seems to match. It is unique to BII phobia that patients often faint following the initial increase in blood pressure. This situation has often puzzled to cardiologists. This extreme heart rate variability actually has increased the chances of survival for the fainters of BII phobia.

Multiple patients of BII phobia are often heterogeneous in their symptomatology which also prevents to categorize the sufferers based on their symptoms. This heterogeneity then lead a problem in combating the symptoms because often there may be multiple set of pathways by which these symptoms occur in different sufferers. There is a possibility that in different individuals there is a different course of symptom development. The heterogeneity is not linked only to BII phobia but is almost associated with all neuropsychiatric disorders. A considerable number of BII phobia patients have a familial history of the same phobia. The fainting associated with BII phobia is found to have higher heritability estimates than fear and phobia (Kleinknecht, 1987). The familial history for BII phobia is well recognised and almost two thirds to three fourths of patients with BII phobia have at least one first-degree relative affected with BII phobia. Some workers have attributed faintness as familial and solely as learned within a shared household environment (Marks, 1988). That is to be stated the other way that fainting with BII phobia is just with learning and is less likely or no role played by other factors. There are noted twin studies which show a significant genetic contribution to the etiology of BII phobia and particularly fainting (Kleinknecht, 1987). However a very recent research suggests that memories can be passed down to later generations through genetic switches that allow offspring to inherit the experience of their ancestors. According to that it is possible for some information to be inherited biologically through chemical changes that occur in DNA (Dias and Ressler, 2014).

3. Blood-Induced Fainting- An adapted defense behavior

Regarding advances in brain sciences, there are some fundamental questions which are still unanswered like why females are more prevalent in fainting than males. In relation to the faintness of the blood phobics at the sight of blood or other related ques, there are several hypotheses regarding the significant relation of blood phobia and fainting. These are based on blood-loss

minimization and on disgust sensitivity. These existing evolutionary biological hypotheses regarding fainting are pan-mammalian. Such hypotheses have argued that the inclination to fainting at the sight of blood is not a new one, but has evolved prior to emergence of genus Homo (Bracha, 2004). However there are several situations where these hypothesis seems incomplete and doesn't seem to fit in many cases, for example why only some people develop fainting trait while others don't.

In order to reach up to the stage of faintness, there is initially decrease in the blood pressure. As with decrease in blood pressure and slowing down of heart, the brain doesn't get a sufficient supply of blood. Due to this decrease there are chances of cardiovascular shock. So it can be assumed that it may be an adapted mechanism from early ancestry to faint and prevent a cardiovascular shock (Graham, 1961; Engel, 1978). The fainting at the sight of blood can put an individual in a horizontal position due to fall. As horizontal position doesn't need blood with increased pressure, a low pressure blood can reach up to brain. This way it helps preventing blood loss and the symptoms like stroke. However this hypothesis doesn't explain many things like why fainting that is triggered by injection or trivial skin injury occurs which does not involve the loss of blood as argued by page (Page, 1994). Some have argued that fainting is not experienced until there is a 30% reduction in blood volume (Berntson et al., 1994).

There are recent findings which show the inheritance of memories in case of phobias and fear. The recent research shows that the memories in the brain can inherit from generation to generation (Dias and Ressler, 2014). The phobias along with the capacity of fainting can be memories in the brain. The memories may perhaps signal the physiological changes like fainting in case of BII phobia. Based on this it can be hypothesised that there are ample chances that memories may also exist for fainting or there may be several attributes related to fainting in the brain which may inherit from parent to younger generation, there by helps the trait to survive from generation to generation.

BII phobia is also found to be highly associated with the emotion of disgust. There is a similar physiological mechanism for factors which are involved for controlling both the traits of fainting and disgust (Marks, 1988; Page, 1994). There are hypothesis from early theorists that in some individuals the sight at their own blood induces a disgust reaction (Marks, 1988). There are no studies however whether the strength of disgust from one's own blood is same to the disgust at the sight of other fellow's blood. Some researchers suggest that the fainting reaction observed in BII phobia occurs only in response to disgust (Rachman, 1990). Others think that it occurs in response to a combination of fear and disgust (Olatunji, 2006; Kleinknecht, 1997). We presume that in addition to these there may also be the role of synapse disruption. The fainting could possibly be also due to the disruption of synapse in the brain which could lead the individual unconscious. As the blood related fainting can be from the time of pan mammalian, it is assumed that the humans from their ancestry have built up such memories

which gets imprinted in the brain and may act as phobic memories from generation to generation.

4. Evolutionary perspective in understanding of Traits

One author has proposed a human specific adaptationist proposal for faintness (Bracha, 2004). Many workers consider sex as having a greater influence which shows a variation in traits among males and females. Darwin has also dedicated considerable portion of his work by dividing traits in relation to sex (Darwin, 1874). Due to the differences in the expression of number of genes in the brain of male and female, fainting also seems a trait which gets fixed with sex related differences or it may also be the product of emotional distress. In order to avoid the emotional distress in presence of certain situations like that of blood, injury or injection. It is assumed that BII phobic patients faint to avoid further increase in disgust. Many theorists have related the blood related faintness as the product of early human warfare in the Neolithic period (Bracha, 2004).

Several critical studies and investigations have documented that there had been extensive Homo sapien warfare's in the middle paleolithic period in which Homo sapiens was predominantly pre-verbal [(Morgan, 1990; Ortnet and Putschar, 1985; Leblanc and Register, 2003; Lacey and Danziger, 1999; Salazar, 2000). To be pre-verbal at that period it can be assumed that they may prefer to give indications and convey messages or communicate mostly by actions and other types of demonstrations. This may had been the time when the humans were probably not good in understanding of languages between peoples and intra groups. In this age of warfare's sharp objects easily penetrating the skin was the frequent cause of death among paleolithic humans. As this may have been the age when getting slight injury, or infection was difficult thing to overcome. This has often proving fatal because of inadequacy of the facilities for treating infection in that age (Larsen, 1999; Klein and Edgar, 2002). In situations where inadequacy of treating wounds and infections are prevailed, receiving a non-lethal wound was almost as dangerous as receiving a fatal combat wound. With this perspective it is assumed that fainting in response to the sight of blood may have evolved as an alternate distress reaction, or adaptation that aided the survival of non-combatants in combating situations. The opponent can simply ignore the fainting person because it cannot be an immediate threat to them. It is also assumed that fainting had got evolutionary significance in order to avoid the distress caused by witnessing the wars or blood, injury etc. The question of fainting as more prevalent in females and children appears to be of higher consideration in the literature. However there is a void in the literature regarding whether there is any difference in the brain of male and female which specifically lead to fainting variability among the genders. These things should need to be analysed by multiple ways in order to get the actual picture of the possible selection of fainting trait.

Almost in every war fought in earlier times, there had been the general rule of not killing the women and children.

As they were not directly involved in the conflict, so they had not been a part of any distress which may bring any sort of fatality to the opponents. As women and children are weaker groups of the society both physically and emotionally the trait of fainting at the sight of blood during earlier wars bears additional significance. The inheritance of such polymorphism may possess a survival advantage for generations from the time where it originally develops due to Neolithic combats. As is evident from the history of mankind that all types of inter-group and intra-group violence mainly occurs among men, while as women and children are considered as the passive members and not as the direct targets. Studies have been taken place for analysing the mitochondrial DNA for female lineage and male Y- chromosome for male lineage (Underhill et al., 2001). Such analysis has shown that invaders during the violent confrontations usually kill the post pubertal males and take the females and children as captives (Seielstad et al., 1998). Thus it seems that the post pubertal males which are engaged in combats during paleolithic conflicts are poorly adapted for fainting, which makes them to be cautious of the enemy. This way it acts as a good characteristic which helps the post pubertal males to be active in the battle fields and fought their best.

Besides this there is increasing evidence through some recent researches which shows that some X-linked genes are expressed differently, depending on whether they are in male or female brains. In mice, six X-linked homologues of Y-linked genes (Usp9x, Ube1x, Smcx, Eif2s3x, Utx and Dbx) were expressed in the brain of mice at significantly higher levels in adulthood in females than in males, irrespective of their X-inactivation status (Xu et al., 2002). The X- and Y-homologues of three genes in particular, Usp9x/y, Ube1x/y and Eif2s3x/y, appeared to have acquired different functions and expression patterns in males and females. The research shows that there are considerable differences in the brain of males and females either in structure, organization or expression of genes. This variability might lead to the variation in the vulnerability of different brain disease. The prevalence of Blood phobia in females is almost double the prevalence in males, indicating that this may also be in relation with the variability in gene expression between males and females.

5. Gender Specific differences and brain behavioural outcomes

There is a bias in the expression of genes in the brain between males and females which lead to differences in the behaviour and in the incidence of various diseases. With regard to specific gender bias in neuropsychiatric disorders let us take an example of PCDH11Y gene which is an attractive proposition because of numerous factors. It appears to be expressed in a highly regulated and spatiotemporally dynamic manner in males and is involved in synapse formation and neuronal path finding in the brain and in other processes which doesn't go in right course in many male-biased mental conditions (Grant, 2003). There are several mentally ill conditions which are more prevalent in males while others are more prevalent in females. This may perhaps be due to the differences

in the expression of genes in brain among the two sexes. Several genes are weakly expressed, some may be over expressed and still others may not express at all. This conundrum of gene expression differently in different sexes is still not understood well. The low expression or no expression of PCDH11Y in the cerebellum and perhaps its expression somewhere else in the brain, could potentially explain why males are especially vulnerable to disorders like ADHD and autism (Kopsida et al., 2009). There is also large number of variations among the individuals in their prevalence, onset and other factors related to various diseases among males and females based on the environmental risk factors experienced in life. It may be the expression pattern of the gene which may be modulated epigenetically via environmental influences.

The differences in the brain of male and female becomes more compounded, because of the functional differences which might be related to differences in brain structure. For example men have more neurons in the neocortex where women have more synapses revealed from a study of postmortem histologic examination (Myers, 1999; Rabinowicz et al., 1999). There are several studies which have found out that several synaptic genes are expressed differently between the two sexes (Amateau, 2004; Xu et al., 2005b). In one study 4508 genes were detected to be transcribed actively in the brain by a comprehensive microarray analysis, among which 355 genes are expressed more highly in females and 257 genes more highly in males (Yang et al., 2006). Sex specific differences in the brain have further elaborated by many workers and the variation in brain structure and gene expression have been proven to be due to testosterone and its metabolites which act in the developing brain and help in permanently wire the brain in a sex specific fashion (McCarthy and Konkle, 2005; Becker et al., 2005; Morris et al., 2004).

The X chromosome is much bigger than Y chromosome; the X chromosome consists of almost 3000 genes while as Y chromosome consists of only 300-400 genes. Many X chromosome genes are suggested to involve in the normal development of brain and behaviour. Furthermore an evidence indicates that X linked genes are expressed at a higher level in brain than in other tissues (Nguyen and Disteche, 2006). The expression of X-linked genes is thought to be balanced between males and females due to inactivation of one X-chromosome in females which silence gene transcription in that X-chromosome (Lyon, 1961). X-linked genes are therefore not traditionally considered to play any role in differentiation. However some chromatin enzymes, such as histone demethylases JARID1C and UTX, are coded by X-linked genes which are not X-inactivated in females. The higher expression of JARID1C and UTX in females could therefore contribute to sex differences in brain development and behavior (Xu and Andreassi, 2011). Such type of changes may perhaps also contribute to the variations in the fainting experiences between males and females.

Epigenetics a new field of research is also considered to play a major role in the variation in behaviors among different individuals. The changes in the expression of genes without any change in the primary sequence of

DNA are called epigenetics (Pennisi, 2001). Epigenetic modifications generally caused by DNA methylation and chromatin modification (Mehler, 2008). DNA methylation at H3, Lysine 9 and Lysine 27, etc. and Deacetylation of H3 and H4 and DNA methylation at CpG islands immediately called into action on the inactive X to help in long-term transcription suppression (Chow et al., 2005; Heard and Disteché, 2006). Such transcription suppression may have ample chances of consisting of non-formation of class of proteins factors or neurotic factors in the brain which also lead to variations of certain number of psychoneurotic disorders which may also include fainting in case of BII phobia.

The genes USP9X and UBE1X encode ubiquitin enzymes. The human USP9X has found to escape X-inactivation which leads to its overexpression in female brain. This leads to high prevalence of certain mental illness in females and also plays a role in sexual dimorphism in synaptic structure. From such variation in gene expression in brain, it is assumed that based on the differential expression of certain genes in the brain of male and female, there arises variation in the onset of symptoms and prevalence of mental illnesses, in which females are usually higher in number. However a study on mice has detected no sex differences in USP9X expression in neonatal brain or in adult peripheral tissues (Xu et al, 2005a).

Specific enzymes like DNA methyltransferases, histone methyltransferase, acetylase, and deacetylase involves in the regulation of DNA methylation and histone modification (Peterson and Laniel, 2004). There is a difference in the concentration of these enzymes in tissue type and they also show differences with development and aging. Tissue specific and temporal changes in the X-inactivation status of some genes can be explained on the basis of differences in the concentration of these enzymes. Inactivated X-linked genes are potentially reactivated due to decrease in the level of DNA methyltransferase in the brain (Xu and Disteché, 2006).

6. Conclusion

BII phobia is a unique phobia in which fainting occurs. Females and children are more prevalent both for BII phobia as a whole and fainting as a particular symptom. However the trait of fainting in both sexes may have selected at the period when it has got a survival value. The early combats might have created long term memories from the experiences which survived till modern times, may be in the form of DNA epimarks through epigenetic mechanisms. Although survived through difficult times in the past, such experiences may have persuaded variation in the expression of a number of genes in the brains of both male and female. Such variations in brain gene expression may result differences in prevalence, onset of disease, and variation in diseases related symptoms to a considerable degree.

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