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Risk Factors of Anxiety Disorders in Children

Malgorzata Dabkowska and Agnieszka Dabkowska-Mika

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Abstract

Anxiety disorders are common; lifetime prevalence for the group of disorders is estimated to be as high as 25%. The main question is What is the relative contribution of genetics and environment to etiology of anxiety disorders? The anxiety disorders are not, from a genetic perspective, etiologically homogeneous. Structural equation modeling provides estimates of variance in liability to a disorder that is attributable to additive genetic, common familial environmental, and individual-specific environmental factors. Familial aggregation that largely results from genetic risk factors has been documented for all of the major anxiety disorders. Genes predispose to two broad groups of disorders dichotomized as panic-generalized-agoraphobic anxiety versus specific phobias. The candidate genes are the ones encoding the central and peripheral nervous system receptors and transporters. Trauma in childhood disposes to further anxiety disorders through the hyperactivity of the HPA axis and the hypersecretion of CRF. Traumatic experience in developmental age leads to neurobiochemical changes in brain, typical for panic disorder or PTSD. Behavioral inhibition in early childhood is a predictor of further anxiety disorders. Some types of parental behaviors and family environment can lead to them, as well as improper interactions between parents and child.

Keywords: Anxiety disorders, children, risk factors, environmental, genes

1. Introduction

Anxiety disorders are among the most common psychological disorders in younger patients, affecting 6% to 20% of developed countries children and adolescents [1]. In the etiology of

anxiety disorders there is a complex interplay of biological and genetic vulnerabilities, temperamental qualities, negative environmental influences and negative attachment experiences, parental psychopathology, and disadvantageous sociocultural factors [2].

Biological risk factors include genetics and child temperament. Anxiety disorders are highly comorbid with each other and with mood disorders. There is a growing number of studies searching for candidate genes of anxiety disorders through human genome scan. Studies of environmental risk factors in the development of childhood anxiety disorders have focused on parent–child interactions and parental anxiety.

2. Environmental risk factors

2.1. Gender

Girls are more vulnerable than boys for anxiety. Female sex consistently emerges as a risk factor for the development of anxiety disorders. Females are about twice as likely as males to develop each of the anxiety disorders [3]. The female preponderance emerges early in life, and retrospective data indicate that at age 6, females are already twice as likely to have experienced an anxiety disorder as are males [4].

2.2. Age

There is a typical age of onset for different kinds of anxiety disorders—separation anxiety disorder and some specific phobias usually start before age of 12 years [5]; social phobia in late childhood, adolescence, and very rarely after 25 years [5,6]. Agoraphobia, panic disorder, and general anxiety disorder usually emerge later in adolescence or early adulthood, with some cases starting even before 12 [5, 7].

2.3. Temperament

The importance of emotional deregulation is emphasized in anxiety disorders. Negative emotional responses are more frequent and intensive in anxious children, as well as difficulties in reappraisal according to negative emotional situations. These children trust more on emotion regulation strategies. All of that can lead to functional impairment, intensive negative emotions, and disturbing in emotion regulation self-efficacy [8]. The vigilance–avoidance attention pattern is found in anxious adults and children, who initially gaze more at threatening pictures than nonanxious adults and children (vigilance) but subsequently gaze less at them than nonanxious adults and children (avoidance) [9]. Children and adolescents with anxiety disorders could have different temperaments and character profiles in accordance with diagnostic groups, which imply the specific pathophysiological mechanism of each anxiety disorder [10]. Behavioral inhibition in early childhood is a predictor of further anxiety disorders. Some types of parental behaviors and family environment can lead to them, as well as improper interactions between parents and child. Both parental acceptance and parental overcontrol are related to anxiety. It is confirmed that the overcontrolling behavior of parents

can be a predictor of anxiety in a child and is connected with constant fear in adolescence. What is more, an absence of maternal overcontrol can diminish the significance of high behavioral inhibition on further social anxiety symptoms. It has occurred that there is a significant connection between parents' avoiding behavior and symptoms of anxiety in child. Some studies indicate that among environmental risk factors, an inhibited temperament has the greatest impact and can moderate others' factors influence. Some results suggest that the association between behavioral inhibition and anxiety disorder is accounted for by children who have stable behavioral inhibition. Children who remained inhibited at 4, 5 1/2, and 7 1/2 years had higher rates of anxiety disorders than children who were not consistently inhibited. With few exceptions, behavioral inhibition was shown to be a risk factor for the development of anxiety disorders [11–13]. There are also indications for specificity in this association within anxiety disorders (strong associations particularly to social phobia). Toddlers and preschoolers with behavioral inhibition and a family history of anxiety disorder and stable inhibition have an increased risk of anxiety disorders, particularly social phobia, and may benefit from preventative parenting interventions. Avoidant personality disorder is reported to be espe-cially prevalent in people with anxiety disorders. Approximately 10–50% of people who have panic disorder with agoraphobia have avoidant personality disorder, as well as about 20–40% of people who have social phobia; 45% among people with generalized anxiety disorder have avoidant personality disorder [14].

2.4. Parental factors

Infants who were anxiously attached in infancy develop more anxiety disorders during childhood and adolescence than infants who were securely attached [15]. Parents affected by anxiety disorders usually cannot learn how to manage anxiety in their children because they do not have this ability themselves. These children develop anxiety disorders more often, sometimes as early as in toddlerhood [16]. Anxiety disorders are common among offspring of anxious and depressed parents. Offspring of anxious parents were significantly more likely to have only anxiety disorders. Offspring of depressed or mixed anxious/depressed parents had a broader range of disorders and more comorbid disorders [17]. A large body of work has demonstrated that parent anxiety disorders increase the risk for similar problems in children. Parent anxiety symptoms moderated the relationship between parent- and child-externalizing symptoms, such that the strength of this relationship was reduced in the presence of high levels of parent anxiety symptoms [18]. Parental psychopathology and rearing were associated with offspring social phobia, independently as well as in their interaction. The examination the role of parental psychopathology and family environment for the risk of social phobia in a large sample of adolescents showed that parental social phobia was associated with offspring's risk to develop social phobia. Other parental anxiety disorders, depression, and alcohol use disorders were also associated with offspring social phobia. Parental rearing styles of over-protection, rejection, and lack of emotional warmth were associated with offspring social phobia. Observations suggested a continued graded relationship between familial risk factors and offspring SAD [19,20]. The risk factor of anxiety disorders during childhood is parenting behavior as a possible factor in the transmission of anxiety from parent to child. The emotions in families with an anxious parent differed significantly from families without an anxious parent [21].

Environmental mechanisms (e.g., maternal anxious attachment perceptions, maladaptive parenting practices, parental modeling of anxiety, and avoidance) may account for the observed association between parent and child anxiety [22]. The potential role of learning from parents in the development of child anxiety has three specific mechanisms: parental modeling, information transfer, and parental reinforcement of anxious/avoidant behavior. A variety of parenting practices (i.e., parental overcontrol, parental overprotection, parental emotional warmth/positivity, parental rejection/criticism, and parenting styles) could be factors that may pose risk for the development of child anxiety [23]. Both parental use of aversive control and nonresponsiveness were directly related to overall levels of child anxiety disorder-related behavior [24]. Parenting stress, parental psychopathology, and family functioning are associated with child anxiety [25,26]. Anxious attachment may lead to separation anxiety. Children with temperamental vulnerability may develop anxiety disorders, when their mastery and autonomy are restricted by overcontrolling, overprotective, and overly critical parenting styles. Parental rejection and control may lead to later anxiety and depression [27]. Anxiety disorders in children may be caused by insecure (especially anxious/resistant) attachment relationships with caregivers [27, 15]. Different attachment patterns (secure, ambivalent, avoidant, and disorganized) may relate to different types of anxiety symptoms and that behavioral inhibition may moderate these relations.

2.5. Culture factors

The culture-specific expression of anxiety is a risk factor for anxiety disorders, for example, Asian cultures typically show the lowest rates, whereas Russian and US samples show the highest rates of social anxiety disorder. The prevalence and expression of social anxiety depends on the particular culture. Social anxiety is assumed to be related to cultural norms across countries. In some works, researchers compared individualistic and collectivistic countries and found higher social anxiety and more positive attitudes toward socially avoidant behaviors in collectivistic rather than in individualistic countries [28–30].

2.6. Toxic environment

Patients with environmental illness experience a large number of psychiatric symptoms. Anxiety disorders were significantly more frequent in patients with environmental illness [31]. Organic brain damage with cognitive and behavioral impairment can be caused by acute and toxic exposure. Even low-to-moderate exposure, when it is chronic, may lead to anxiety and mood disturbances. Lead exposure particularly can result in anxiety and depression [32, 33].

2.7. A unique environmental factor and common shared environmental factor

It is said that two groups of disorders (specific phobias versus generalized/panic anxiety and agoraphobia, with social phobia between them) are associated with two genetic factors. Common and (in a greater degree) unique environmental factors shared across the disorders can explain remaining associations between the disorders. In the results of analyses from more than 5000 members of male–male and female–female twin pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders, it occurred that shared environmental

influences do not play a major role, as a single common factor was calculated below 12% of the total variance for any disorder. Researchers describe unique environmental factors as single common factor plus effects, which are characteristic for a disease [34]. During a lifetime, life experiences (unique for the patient or shared with other family members) may further influence the risk for anxiety disorders. It would have different significance, depending on the disorder. Something called a "set of unique environmental factors" can lead to one or another anxiety disorder [34].

2.8. Life experience/childhood adversities

The experience of a traumatic event may influence the development of anxiety disorders. Trauma in childhood disposes to further anxiety disorders through the hyperactivity of the HPA axis and the hypersecretion of CRF. Traumatic experience in developmental age leads to neurobiochemical changes in brain, typical for panic disorder or PTSD. Because of early trauma, there is change of genes and increase in anxiety sensitivity.

Experience of childhood trauma (e.g., sexual abuse) increases the risk of psychiatric or substance use disorder in maturity. Exposure of children to early adverse experiences is a risk factor for developing anxiety disorders. Early life stress, causing the chronic sensitization of those central nervous system circuits, which regulate stress and emotion, may be a biological explanation of increased vulnerability to stress and further development of anxiety. Childhood maltreatment has been linked to a variety of changes in brain structure and function and stress-responsive neurobiological systems. Deprivation of developmentally appropriate experience may reduce neuronal activity, resulting in a generalized decrease in neurotrophin production, synaptic connectivity, and neuronal survival, resulting in profound abnormalities in brain organization and structure [35]. Thus, childhood abuse and exposure to domestic violence can lead to numerous differences in the structure and physiology of the brain that expectedly would affect multiple human functions and behaviors [36, 37]. Neurobiological evidence supports the hypothesis of dysfunction in hippocampus, amygdala, medial prefrontal cortex, and other limbic structures believed to mediate anxiety and mood dysregulation following early abuse [37]. There are similarities in neurobiological results between some studies on early life stress in children and in animals. For example, children who suffer from generalized anxiety disorders and anticipated a laboratory stress task had increased levels of ACTH and normal levels of cortisol [38]. Altered behavioral and hormonal responses to central noradre-nergic stimulation have been observed in children with several anxiety disorders. Neurobiological alterations are also present in children with PTSD related to early trauma. It may be that early life stress affects neurobiological function in children with other anxiety disorders as well, similar to findings in early-onset depression [39]. The adverse childhood experiences including abuse, witnessing domestic violence, and serious household dysfunction had a strong, graded relationship to the prevalence and risk of affective disturbances. For children with more than four experiences, the risk of panic reactions and anxiety was increased 2.5- and 2.4 -fold, respectively [40]. There is an etiological relation between stressful life events (unique to the individual or common to other members of the family) and anxiety disorders. Its effects on disorders are probably nonspecific, as many kinds of childhood adversity (loss events—

e.g., parental divorce; parental psychopathologies—e.g., maternal depression; interpersonal traumas—e.g., rape and natural disaster) are associated with adult psychiatric outcomes with little specificity, including anxiety disorders [41, 42]. These adversities were consistently associated with onset, but not persistence, of anxiety disorders [41].

2.9. Parental loss

Childhood parental loss or separation has been linked to various forms of adult psychopathologic characteristic [43, 44]. The study evaluating the relationship between parental loss prior to age 17 years and adult psychopathology in 1018 pairs of female twins from a population-based registry has shown the impact of parent death or separation for the risk of anxiety disorders. Researchers found association between parental separation (but not parental death) and increased risk for generalized anxiety disorders. Parental death and separation from mother (but not father) were related to panic disorder. A higher probability of developing phobia due to parental death (but no parental separation) was described. A model that includes parental loss as a form of specified family environment shows if it is truly an environmental risk factor for adult psychopathologic conditions [44]. Not only loss of parent has a relationship with affective disorders but also lack of adequate parental care takes important role in the increased risk of psychiatric disorders in adulthood. Studies on caregiving arrangements indicate that lack of care (characterized as neglecting rather than adverse behavior of parent) is associated with higher risk of depression. It is loss of mother rather than father that has impact more frequent [45].

2.10. Sexual abuse

Childhood sexual abuse is a strong risk factor of anxiety disorders. A study about the consequences of childhood sexual abuse in a birth cohort of more than 1,000 New Zealand children studied at the age of 18 years showed that children reporting sexual abuse had higher rates of anxiety disorder than those not reporting. The findings suggest that sexual abuse, particularly severe childhood sexual abuse, was associated with increased risk of psychiatric disorder in young adults even when due allowance was made for prospectively measured confounding factors [46]. Childhood sexual abuse has been found to elevate the risk for adult GAD and panic disorder, as well as other psychiatric and substance use disorders [46, 47]. Studies of the impact of traumatic events on health have shown that the history of childhood sexual or physical abuse was significantly more frequent in patients with panic disorder than those with social phobia. Rates of abuse of patients with generalized anxiety disorder were between results of these other groups, without significant differences [42]. Women with childhood sexual abuse have a substantially increased risk for developing a wide range of psychopathology. Most of this association is due to more severe forms of sexual abuse. The significant ORs for GAD and panic disorder were all approximately 1.9 [47]. In a group of 1411 women who report childhood sexual abuse (three levels: nongenital, genital, and intercourse), association with psychiatric disorders was assessed. Self-reported childhood sexual abuse was positively associated with all disorders, the most with genital and especially intercourse sexual abuse.

2.11. Peer violence

Bullying behavior is a frequent risk factor of anxiety disorder among adolescents. Twenty-percent of victims scored within the clinical range on a standard depression and anxiety measure [48].

Peer victimization was positively related to child-reported anxiety, social physique anxiety, and loneliness [49]. Bullying experiences are connected not only to concurrent psychiatric symptoms but also to future psychiatric symptoms, especially anxiety disorders [50, 51].

Bullying should be seen as an indicator of risk of various mental disorders in adolescence. Finnish adolescents taking part in the School Health Promotion Study were surveyed about bullying and victimization in relation to several psychiatric disorders. Anxiety was most frequent among bully victims and equally common among bullies and victims [52]. The relationship among bullying, victimization, and anxiety may be connected with sex. Sex differences were noted on measures of peer victimization and anxiety with boys reporting more victimization but less anxiety than girls [53].

2.12. Economical factors

Most children with anxiety disorders are from middle- to upper-middle class families; however, 50–75% of those with separation anxiety disorder come from low socioeconomic status homes [54–56]. Rates of anxiety disorders are greater for those with socioeconomic status disadvantage [57]. Socioeconomic status is one of many possible antecedents in the development of social anxiety disorder [58].

3. Genetic factors

Genetic factors play a significant role in etiology of anxiety disorders; for example, inherited risk factor for social phobia is estimated as 47% [59].

Increased risk for anxiety disorder in children occurs if at least one parent has anxiety disorder [60], or if both parents are affected [61, 62]. Common genetic risk factors for major depression and anxiety disorder have been described as "bidirectional"; both parental major depression increased the risk of anxiety disorder in child [63, 64], and parental anxiety disorder increased risk of depression in child [62, 65].

3.1. Twin studies

Torgersen [66] found that anxiety disorders (in total) are two times more frequent in MZ than in DZ co-twins; GAD is two times more frequent in MZ than in DZ co-twins. In a group with panic disorders and agoraphobia with panic attacks, anxiety disorders with panic attacks were even more than five times as frequent in MZ as in DZ.

There was research on 1030 pairs of twins about interrelationship between genetic and environmental risk factors for pairs of anxiety disorders and other mental diseases. The

researchers found that anxiety disorders are genetically heterogeneous. However, there is one common genetic risk factor (with great impact) for phobia, panic disorder, and bulimia nervosa and another factor for major depression and generalized anxiety disorder [67].

A cohort study on 1412 pairs of MZ and DZ twins, ages 8–16 years [68], suggested that genetic influences on anxiety in childhood differ according to sex (greater extent in girls than in boys). Additive genetic effects play a moderate role in the etiology of manifest anxiety among females, but a more modest role for males. Moderate additive genetic effects were reported in another study on adult patients with generalized anxiety [69].

A significant familial aggregation according to panic disorder, GAD, and phobias was shown in meta-analysis based on family and twin studies [70].

Quite often, there is a comorbidity of anxiety disorder and another anxiety disorder or mood disorder [71]. It is consistent with the results indicating the same genetic factors for GAD and major depression [72, 73].

It is shown that polymorphism in the serotonin transporter gene regulatory region is associated with anxiety-related traits (3–4% of total variation and 7–9% of inherited variance in patients and their sibships) [74].

Through human scan genome, chromosomes 1, 7, 9, and 11 were linked to panic attacks and chromosome 3 to agoraphobia [75–77]. Analysis of links exhibits loci for panic attacks on chromosome 9q [77].

There is a growing number of studies about the significant role of FK506-binding protein 51 (FKBP5), a co-chaperone of steroid hormone receptors. It regulates stress-induced GR-mediated effects. Polymorphism in this gene is related with GR sensitivity and can regulate stress hormone system. Specific alleles of FKBP5 are associated with major depression, bipolar disorder, and posttraumatic stress disorder, as well as with faster response to antidepressant treatment [78]. It can lead to increased risk of stress-related psychiatric disorders when its genetic variation interacts with early life stress (ELS) to epigenetically program GR-induced transcription of FKBP5 [79].

Demethylation of allele-specific FKBP5 DNA interacts between childhood trauma and gene transcription, leading to dysfunction of the stress hormone system, immune cells, and those brain areas, which are associated with stress regulation [80].

4. Summary

An anxiety disorder during adolescence confers a strong risk for recurrent anxiety disorders during early adulthood [81]. In the future, adolescents with anxiety disorders are at an increased risk of subsequent anxiety, depression, illicit drug dependence, and educational underachievement as young adults.

Clinical features of anxiety (e.g., higher severity, duration, and avoidance) as well as comorbid other mental disorders are particularly useful for predicting an unfavorable course of anxiety

disorders [82]. Early psychoeducation program for parents could decrease risk for anxiety disorder. As environmental risk factors are already well known, the next step is to distinguish what predictors have the greatest impact and how to moderate them. Vantage sensitivity hypothesis said that some genetic variants moderate outcome of positive intervention [83]. Through studies on trajectories of behaviorally inhibited children, it occurred that some inhibited infants and toddlers develop into normal children [84].

Knowledge of risk factors enables preventive actions with respect to the developing anxiety disorders in children. It seems important to undertake actions to increase the resilience capacity of individuals to cope with traumatic events. Donovan and Spence [85] present the results of research regarding the prevention of anxiety disorders. The main protective factors are social support in the presence of traumatic experiences and coping skills in the resilience to anxiety. Methods of prevention of childhood anxiety disorders could be divided to child, parent, and environment strategies.

Author details

Malgorzata Dabkowska[1*] and Agnieszka Dabkowska-Mika[2*]

*Address all correspondence to: gosiadab@interia.pl doagnieszki@interia.pl

1 Collegium Medicum, Nicolaus Copernicus University, Torun, Bydgoszcz, Poland

2 Psychiatry Clinic, Clinical Hospital of K. Jonscher, Poznan, Poland

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