



## Anxiety disorders in childhood and adolescence: clinical and neurobiological aspects

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### Abstract

**Objective:** This article reviews the clinical and epidemiological aspects of anxiety disorders in youngsters, as well as current medical and psychological treatment strategies. The role of the neurobiological models possibly involved in the etiology of these disorders is also discussed.

**Sources of data:** MEDLINE search of papers published in English from 1981 to 2003. The following key words were used: anxiety disorders, neurobiology, childhood, adolescence.

**Summary of the findings:** Childhood-onset anxiety disorders are among the most frequent psychiatric conditions in children and adolescents. Epidemiological data estimate a prevalence of 10% in this population. The neurobiological models involved in the etiology of anxiety disorders in youngsters are closely related to neuroimaging studies with individuals presenting these pathologies. The role of the amygdala in the pathophysiology of these disorders is underscored. To be effective, treatment must combine several interventions, such as cognitive-behavioral, family, and, frequently, drug treatments.

**Conclusions:** Early identification and prompt treatment of anxiety disorders may prevent negative consequences, such as school absenteeism and frequent and unnecessary visits to pediatric services due to somatic complaints related to anxiety disorders. Moreover, it is possible that psychiatric problems could be avoided or attenuated in adulthood.

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### Introduction

After attention deficit hyperactivity disorder (ADHD) and conduct disorder, anxiety disorders are the most commonly observed psychiatric diseases in children and adolescents. Up to 10% of children and adolescents are affected by some kind of anxiety disorder (excluding obsessive-compulsive disorder – OCD – which affects up to 2% of children and adolescents – see chapter on OCD). More than 50% of anxious children will have a depressive episode as part of their anxiety disorder.

Except for posttraumatic stress disorder (PTSD), where an external traumatic factor is the primary cause, the major risk factor for childhood-onset anxiety disorder is

having a parent with anxiety disorder or depression. Therefore, as with most psychiatric diseases, anxiety disorders are associated with brain development, with significant genetic contribution.

In children, emotional development influences the causes and the way fears and worries (normal or pathological) become apparent. Differently from adults, children might not recognize their fears as exaggerated or irrational, especially the younger ones.<sup>1,2</sup>

Both anxiety and fear are regarded as pathological if they are excessive, disproportionate to the stimulus, or qualitatively different from that observed at this age, and if they interfere with the child's quality of life, emotional comfort or daily performance.<sup>3</sup> Such exaggerated reactions to the anxiogenic stimulus commonly occur in individuals with inherited neurobiological susceptibility.<sup>4</sup>

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Although there is one clinical picture for each anxiety syndrome, most children will have more than one anxiety disorder. It is estimated that approximately 50% of children with anxiety disorders also have a comorbid anxiety disorder.<sup>2</sup>

### **Epidemiology**

Approximately 10% of all children and adolescents are estimated to meet the diagnostic criteria for at least one anxiety disorder.<sup>5</sup> In children and adolescents, the most frequent conditions are separation anxiety disorder (SAD) with a prevalence around 4%,<sup>6</sup> generalized anxiety disorder (GAD) (GAD; 2.7% to 4.6%) and specific phobias (2.4% to 3.3%).<sup>7,8</sup> The prevalence of social phobia is around 1%<sup>7</sup> and that of panic disorder (PD) 0.6%.<sup>9</sup>

Gender distribution is equivalent, except for specific phobia, PTSD and PD, in which there is a female preponderance.<sup>1,2,8,9</sup> SAD and specific phobias are more often diagnosed in children, whereas PD and social phobias are more common in adolescents.

If left untreated, anxiety disorders in childhood and adolescence (ADCA) have a chronic, albeit oscillating and episodic, course.<sup>10</sup>

### **Course of ADCA**

The various anxiety disorders in childhood and adolescence often develop during specific developmental stages. SAD is more common than GAD in younger children (6-8 years), whereas in adolescents, GAD is more frequent than SAD,<sup>11</sup> being possibly correlated with levels of social maturity.<sup>12</sup> ADCA may continue into adulthood. Childhood-onset SAD may precede PD and agoraphobia in adults.<sup>13</sup> Adolescents with specific phobias are at a greater risk for specific phobias in adulthood, and adolescents with social phobias have a higher risk for social phobias in adulthood. Likewise, adolescents with GAD, PD or major depression are at a greater risk for developing these disorders, or their combination, in adulthood.<sup>14</sup>

### **Clinical course and treatment**

Evidence that some forms of childhood anxiety may be related to anxiety disorders in adulthood contributed to the development of specific diagnostic, treatment and prevention strategies for children and adolescents.<sup>15</sup> Although the diagnostic methods for anxiety disorders in children are similar to those used in adults, the assessment and treatment of pathological anxiety in children have peculiar characteristics.

Most children with anxiety disorders are referred for mental health services due to behavioral problems related to their relationships and school environment. Given the major symptoms, clinicians have to understand these behaviors in a context of restrictions on normal

development, which underlie these behaviors. Thus, it is possible to establish a hierarchy of differential diagnosis that will guide treatment. In general, the treatment consists of a multimodal approach, which includes guidance to parents and child, psychotherapy, use of psychotropic drugs, and family interventions.<sup>16</sup>

Review studies suggest that cognitive-behavioral therapy (CBT) is a provably efficient psychological treatment for ADCA.<sup>17-21</sup> Although no comparative studies exist on the efficacy of different cognitive-behavioral techniques for the treatment of anxiety disorders in this specific age group, treatments that combine CBT with target symptoms (e.g.: relaxation in predominantly tense children and exposure in children with phobias) are more efficient than those that randomly use a collection of techniques.<sup>22,23</sup> CBT emphasizes the correction of distorted thoughts, social skills training, in addition to gradual exposure and prevention of responses based on a hierarchy of symptoms (beginning with less intense symptoms, and gradually exposing the patient to more severe symptoms). The treatment consists of three stages: psychoeducational (which includes the maximum information on the disease and its neurobiological and psychological aspects), cognitive restructuring and interventions based on exposure and prevention of response to phobic stimuli. Instead of regarding the child or his family as the source of the problem, this therapeutic approach considers the anxiety disorder to be the problem, thus giving the child strength to endure the hardship imposed on his life. Moreover, family interventions often play a key role in the treatment.

Differently from what occurs in the treatment of adults, psychoactive drugs such as antidepressants and anxiolytics are not regarded as first-line treatment for children and adolescents with anxiety disorders. For many children and adolescents, especially when symptoms are very intense and/or the patient refuses to be exposed, CBT is not efficient. In these cases, pharmacotherapy as monotherapy or combined with CBT may be the treatment of choice. Despite clinical evidence, there are no controlled studies comparing the efficacy of CBT, pharmacotherapy and their combination.<sup>24</sup>

Clinical courses and the respective treatments recommended for ADCA are described next:

#### ***Separation anxiety disorder (SAD)***

SAD is characterized by excess anxiety about separation from parents or substitutes, inappropriate to the level of development, persisting for at least four weeks. Symptoms cause intense distress and significantly interfere in different aspects of children's and adolescents' lives.<sup>6</sup>

Children or adolescents, when left alone, fear that something bad might happen to their parents or to themselves, such as diseases, accidents, kidnapping, robbery, which could separate them from their parents for good. Consequently, they get excessively attached to their caregivers, not allowing them to be away. At home,

they have problems sleeping, and need constant company. They often have nightmares about their fears of separation. Refusal to go to school is also common among these patients.<sup>10,24</sup> The child wants to go to school, shows good adaptation, but shows great distress when he/she needs to stay away from home. The symptoms described above are usually accompanied by somatic anxiety symptoms, such as abdominal pain, headache, nausea, and vomiting. Older children may have cardiovascular symptoms such as palpitations, dizziness and fainting sensation. These symptoms hinder the child's autonomy, may restrict his/her academic, social and family activities, producing significant personal or family stress. They feel humiliated and fearful, which results in low self-esteem.

Retrospective studies suggest that the presence of separation anxiety in children is a risk factor for the development of several anxiety disorders, including panic disorders and mood disorders in adulthood.<sup>25</sup>

#### *Treatment*

Cognitive-behavioral therapy used in children who refuse to go to school for the fear of being away from their parents recommends that these children should return to school (target exposure). However, this exposure must be gradual, allowing for the children to adapt to anxiety and respecting their limitations, suffering and involvement. School, parents and therapist must share the same objectives, conduct and management. Family interventions aim at raising the family's awareness of the disorder and helping them increase their child's autonomy and competence and reassure their achievements.<sup>16</sup>

Pharmacological interventions are necessary when symptoms are severe and incapacitating, although controlled studies on their use are scarce. The use of tricyclic antidepressants (e.g.: imipramine) has yielded contradictory results. Benzodiazepines are used to treat anticipatory anxiety and to relieve the symptoms during the latent period of antidepressants, despite the fact that there are no controlled studies about their efficacy. Selective serotonin reuptake inhibitors (SSRI) may be effective in alleviating anxiety symptoms, being regarded as first-line treatment due to their side effects, increased safety, ease of administration, and when there is comorbidity with mood disorder. Recently, fluvoxamine and fluoxetine proved to be efficient for short-term treatment of SAD.<sup>16,26,27</sup>

#### **Panic disorder (PD)**

Characterized by panic attacks (exacerbated fear of death associated with numerous autonomic symptoms such as tachycardia, sweating, dizziness, shortness of breath, chest pain, abdominal pain, tremors), followed by persistent preoccupation with having new attacks.<sup>28</sup>

Rarely observed in young children, its frequency increases a lot by the end of adolescence. 30 to 50% of patients have agoraphobia (anxiety about being in places

or situations from which escape might be difficult in the event of having an unexpected or situationally predisposed panic attack or panic-like symptoms. E.g.: closed places such as movie theaters, and crowded places such as start and finish time of classes at schools).<sup>29</sup>

#### *Treatment*

Drug therapy and psychological treatment of PD in children and adolescents are based on information obtained from adult patients or case reports. So far, no controlled studies on the treatment of PD in youths have been conducted. CBT is the treatment of choice for PD with or without agoraphobia. Includes exposure to phobic situations, cognitive restructuring and relaxation training. Several open-label studies and case reports corroborate the use of SSRI or benzodiazepines as drug therapy for PD in children and adolescents.<sup>30</sup>

#### **Generalized anxiety disorder (GAD)**

Children with GAD have irrational, exaggerated fears and worries about several situations. They are always tense and give the impression that any situation could trigger anxiety. They worry a lot about what other people think of their performance in different areas and they desperately need to be reassured or calmed down. They hardly relax, often have somatic complaints without any apparent cause, signs of autonomic hyperactivity (e.g.: pallor, sweating, tachypnea, tachycardia, muscle tension and hyperarousal).<sup>2,16</sup>

GAD usually has an insidious onset; parents do not know exactly when it started, they just say it got worse and worse until it became intolerable, and that is when they often seek medical help.<sup>2,16</sup>

#### *Treatment*

The cognitive-behavioral approach basically consists of a change in the way individuals perceive the environment, specifically on what is causing anxiety (cognitive therapy) and changes in the anxiety behavior (behavioral therapy). Parents actively participate in the therapy with their children, differently from the therapy involving adult patients. Parents and children agree that exaggerated questions will not be answered, reassuring children of the importance of this attitude in order to alleviate their suffering. Thus, the more attention this altered behavior (comforting or aggressive answers aimed at controlling the child's anxiety) receives, the more likely this behavior will be endorsed and intensified; on the other hand, keeping calm and diverting attention away from this behavior will make anxiety subside.<sup>2,24</sup>

GAD has gained little attention from researchers in pediatric psychopharmacology. Open-label studies have shown significant improvement of symptoms with the use of either fluoxetine or buspirone.<sup>3</sup> Three controlled studies with sertraline, fluvoxamine and fluoxetine have demonstrated the short-term efficacy of these SSRI.<sup>26,27</sup>

**Specific phobias**

A specific phobia is an excessive and persistent fear of a certain object or situation other than fear of public exposure or of panic attacks. Typical reactions in children with this type of phobia include clinging to a parent or to someone who makes them feel safe, crying, despair, immobility, psychomotor agitation, or even a panic attack.<sup>2,24</sup>

The most common specific phobias observed in children include fear of animals, fear of injections, fear of the dark, fear of heights, and fear of loud sounds.<sup>2,14</sup>

Specific phobias differ from normal fears in that they are an exaggerated and persistent reaction that gets out of control and leads to escape reactions, preventing the child from functioning.

*Treatment*

Cognitive-behavioral therapy has been the treatment of choice for specific phobias. Although widely employed, the efficiency of CBT has been underinvestigated, since we lack controlled studies with a reasonable number of patients, with standardized diagnosis and systematic follow-up.<sup>31,32</sup> In short, the techniques used consist of the exposure of the child to the phobic stimulus so as to eliminate the exaggerated fear. Desensitization is the most commonly used technique (which employs a hierarchical list of dreaded situations or objects). Exposure-based treatments often are associated with other cognitive-behavioral approaches ("modeling" – practical demonstration by the therapist and imitation by the patient during the sessions; management of contingencies–identification and modification of situations related to phobic stimulus other than the stimulus itself; self-control and relaxation techniques).

Pharmacological treatment of specific phobias is seldom used in clinical practice, and there is a paucity of studies on the use of medications to treat these disorders.<sup>30-33</sup>

**Social phobia**

As occurs with adults, social phobia in children and adolescents is characterized by intense and persistent fear of being scrutinized by others and of being embarrassed or humiliated by their own actions. Young individuals may express their anxiety by crying, "fits of anger", or withdrawal from social situations in which unfamiliar people are present.

Socially-anxious children say that they feel uncomfortable in the following situations: talking in class, eating in the cafeteria with the other kids, going to parties, writing in front of others, using public restrooms, talking to people in authority such as teachers and coaches, in addition to talks/games with other children. In this case, physical symptoms such as palpitations, tremors, shortness of breath, hot and cold sensations, sweating, and nausea are observed.<sup>34</sup>

*Treatment*

Several cognitive-behavioral methods have been used to treat the fear of social situations or of social withdrawal in children. Cognitive treatment of social phobia primarily focuses on correcting faulty conceptions that seem to contribute to social avoidance. Negative internal dialogs are common in children with social anxiety (e.g.: "everyone will look at me"; "what if I do something wrong?").<sup>32</sup> Behavioral therapy is based on gradual exposure to the phobic stimulus (e.g.: "a child who is unable to eat in the cafeteria for feeling bad and fearing that he/she could throw up in front of other children is encouraged to stay in the cafeteria for longer periods every day, initially without eating, and gradually buying some snack and eating it close to his/her colleagues").

SSRI are the drugs of choice to treat social phobia. Two controlled studies show the short-term efficiency of fluoxetine and fluvoxamine in treating young patients with social phobia.<sup>26,27</sup> Moreover, case reports demonstrate that alprazolam may be useful in minimizing social avoidance in children with social phobia.<sup>35</sup>

**Posttraumatic stress disorder (PTSD)**

Children and adolescents are particularly vulnerable to violence and sexual abuse. Traumatic experiences may have a strong and long-lasting effect on them. PTSD is regarded as a risk factor for the later development of psychiatric diseases.<sup>36,37</sup>

PTSD is the intense fear, feeling of powerlessness or horror due to the exposure to an extreme trauma, such as life threat or sexual assault. The probability of developing PTSD is reliant on the severity, length, and time of exposure of the individual to the traumatic event. Remarkable changes in behavior are observed, including excessive shyness or disinhibition, agitation, excessive emotional reactivity, hyperarousal, besides obsessive thoughts with the traumatic experience (while awake or in nightmares). Quite frequently, patients avoid stimuli associated with the traumatic event, associated with the compromise of their daily activities.<sup>36,37</sup> Patients avoid talking about the event, which seemingly worsens the symptoms, as often occurs in all anxiety disorders. Younger children have difficulty understanding the event clearly and talking about it.<sup>36</sup> In these children, issues related to the trauma often are expressed in repetitive games or plays.

*Treatment*

There are some studies (mostly case reports) showing that CBT and brief dynamic psychotherapy are efficient in treating PTSD in children and adolescents. In younger children, therapy should include objects such as toys or drawings in order to facilitate communication, in an attempt to avoid interpretations, without confirmation of what actually happened, and to provide subsidies that allow the therapist to understand the traumatic experience.<sup>30,36</sup>

CBT is centered on the target symptom(s) and aims at reversing the anxiety reaction through exposure to the phobic stimulus. The therapist should help the child or adolescent to come to grips with the dreaded object by talking about the traumatic event, telling the patient not to avoid the topic or thoughts related to it (exposure in imagination).<sup>36</sup>

Clinical experience with drug therapy in children and adolescents with PTSD corroborates the results obtained in studies with adults. Both tricyclic antidepressants (imipramine, amitriptyline) and SSRI seem to be efficacious in treating the central symptoms of PTSD in adults. These drugs also have been used in young patients. Concern with the mortality related to the use of tricyclics and the constant necessity for electrocardiogram monitoring can make physicians opt for SSRI instead of tricyclics.<sup>38</sup> In addition to antidepressants, only one study with propranolol showed favorable results in children with PTSD.<sup>39</sup>

### Neurobiology

Considerable improvement has been attained in understanding the neurobiology of anxiety. Scientific evidence has demonstrated that early and long-lasting temperament traits might be correlated with anxiety. Originally described by Kagan in 1987, "behavioral inhibition" (BI) refers to the temperamental tendency to be quiet and restrained in unfamiliar social situations. Behaviorally inhibited children seem to be at greater risk for developing an anxiety disorder, especially social phobia, in childhood or later on in adulthood.<sup>40</sup> However, this relationship is observed only in children who have a persistent pattern of inhibition for several years.

Special attention has been paid to possible genetic aspects associated with anxiety disorders. Family and twin studies show that genetic factors play a crucial role in the etiology of PD, in which increased serotonergic transmission may cause or be related to this disorder. It has been suggested that serotonin receptor genes, especially the HTR2A gene, play an important role in the pathogenesis of PD.<sup>41</sup> Another line of genetic research suggests an association between the enzyme activity of catechol-O-methyltransferase (COMT) and PD. There is an increase in COMT genotype in PD patients.<sup>42</sup>

In addition to genetic studies and investigations into temperament traits, specific brain regions have been analyzed in neuroimaging studies of patients with different anxiety disorders, especially PD, social phobia, specific phobias and PTSD.

Results obtained from neuroimaging studies with PD patients show abnormal findings in the hippocampus of resting patients; when symptomatic, these patients show activation of the insular and striatal motor cortices, as well as decreased activity in cortical regions such as the prefrontal cortex. Likewise, studies involving neurotransmitter systems suggest diffuse alterations in the GABAergic/benzodiazepine system, which are more

pronounced in the prefrontal and insular regions. In support of the current theory of neurobiological models of PD, major changes in the monoaminergic neurotransmitter systems (originating from the brainstem) are likely to underlie metabolic, hemodynamic and biochemical disorders observed diffusely in the cortex. On top of that, medial temporal lobe disorders reinforce theories that involve dysfunctions of the hippocampus and amygdala in PD.<sup>43,44</sup>

Neuroimaging studies are restricted in social phobia and specific phobias, though. In social phobias, there is an exaggerated response of medial temporal structures during symptom provocation and in response to aversive and nonaversive symptoms triggered by images of human faces. This reinforces the hypothesis of a hypersensitive system in the assessment of threats regarding stimuli provoked by human faces, as a neural substrate for anxiety occurring in social situations in social phobias.<sup>45,46</sup> Results of neuroimaging studies with patients who suffer from specific phobias suggest activation of the sensory cortex when exposed to phobic stimulus (e.g.: individuals who have fear of snakes show activation of the visual cortex when they see images of snakes on video). Such results reinforce the hypothesis of a hypersensitive system for the assessment of (and/or in response to) specific threatening stimuli (in this system, the amygdala would play a central role). However, results of neuroimaging studies still have not provided clear anatomical information on the pathophysiology of specific phobias.<sup>43,47</sup>

Neuroimaging studies reinforce the neurobiological model of PTSD, which emphasizes the functional relationship between amygdala, prefrontal cortex and hippocampus. When exposed to memories of traumatic events, individuals with PTSD seem to activate anterior paralimbic regions. In comparison with the control group, however, PTSD patients show less activation of the anterior cingulate cortex, exaggerated increase in blood flow in the amygdala region, in addition to exaggerated decrease in blood flow in diffuse areas associated with higher cognitive functions.<sup>48,49,50</sup>

In short, the various anxiety disorders share similarities as to the brain circuits involved in the etiology of symptoms. Nevertheless, their heterogeneity also suggests some peculiarities regarding their psychopathologies. Neuroimaging studies seek to identify single and combined patterns of activated or dysregulated brain regions in certain anxiety disorders. For instance, obsessive-compulsive disorder may involve the orbitofrontal cortex, basal ganglia and thalamus;<sup>43</sup> PD includes the hippocampus, parahippocampus, and amygdala;<sup>3-5</sup> social phobia involves the corpus striatum and amygdala; finally, PTSD affects the amygdala, hippocampus and anterior cingulate cortex. Studies on the time dynamics of certain brain regions (e.g.: amygdala habituation) will also guide future research. A study suggests that the right amygdala is part of the dynamic, time-sensitive system for detection of emotional stimuli, whereas the left amygdala specializes

in assessing continuous stimuli and is sensitive to their emotional value. Thus, anxiety disorders seem to be associated with problems in the right amygdala, while mood disorders seem to be related to the left amygdala.<sup>43</sup>

Until the 1980s, it was believed that fears and preoccupations during childhood were transient and benign. It is known today that they can represent frequent pathological disorders, causing distress and interfering with several daily activities. The early detection of anxiety disorders may avoid negative effects such as excessive school absence and consequent dropout, overuse of pediatric services to treat somatic symptoms associated with anxiety, and possibly, the occurrence of psychiatric disorders in adulthood.

Despite their high prevalence, childhood-onset anxiety disorders are underinvestigated. If left untreated, they can deprive children from family, social and educational interactions. Efficient treatment consists of different interventions, such as cognitive-behavioral therapy, family intervention, and also drug therapy.

Neuroimaging studies have remarkably influenced the neurobiological models of anxiety disorders. While the amygdala plays a central role in pathophysiological theories of PTSD and social phobias, diffuse alterations characterize the pathophysiology of PD. Appropriate models have to be developed for specific phobias and GAD. Improved knowledge about the functions of amygdala in healthy individuals can help us understand the pathophysiological mechanisms involved in anxiety disorders, thus allowing us to provide proper treatment.

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