Overview and Neurobiology of Attention-Deficit/Hyperactivity Disorder

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Although attention-deficit/hyperactivity disorder (ADHD) impairs millions of people worldwide, both the prevalence and existence of the disorder are being reevaluated at the phenotypic level. To safeguard against overdiagnosis, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), demands that individuals with ADHD have pervasive impairment, that is, impairment in more than 1 setting. However, the appropriateness of the DSM-IV classification of ADHD is also undergoing reevaluation. Like the symptoms of a developmental disability, the symptoms of ADHD must be evaluated in the context of age-based norms; therefore, the current criteria for ADHD, which are not age referenced, may minimize the rate of persistence of ADHD into adulthood. In an effort to better understand the pathophysiology of ADHD, recent research has focused on identifying the etiology of ADHD. These studies have revealed that the disorder is highly heritable and may be associated with neurobiological deficits in the prefrontal cortex and related subcortical systems. Etiologic studies have also identified candidate genes and prenatal and perinatal risk factors for ADHD. As the causes and course of ADHD are better understood, a new generation of medications is being developed for the disorder. Although stimulants are often effective in reducing the symptoms of the disorder, as a class they have limitations such as a lack of 24-hour-a-day coverage, unwanted side effects, potential for abuse, and lessened effectiveness in the context of some comorbidities. Therefore, the treatment characteristics of newer, more selective treatments such as atomoxetine should continue to be explored in ADHD.

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fundamental characteristics of this disorder. On the basis of the DSM-III-R criteria, more than 50% of patients no longer meet the full diagnostic criteria by age 20. With the DSM-IV childhood criteria—that is, 6 of 9 of either hyperactive or inattentive symptoms—the rate of persistence is similar. Although the DSM-IV includes the diagnosis of attention-deficit/hyperactivity disorder in partial remission for patients who have symptoms that cause functional impairment but are too few to meet the full diagnostic criteria, the DSM-IV continues to treat ADHD as a traditional psychiatric disorder with a single set of symptoms that characterize the disorder across the life span. Moreover, because adults in the normal population have fewer ADHD symptoms with age, Murphy and Barkley have proposed that the DSM-IV criteria are too stringent for adults.

Barkley has argued that ADHD more closely resembles a developmental disability such as mental retardation or dyslexia than a traditional psychiatric disorder. Because individuals with developmental disabilities experience delays in the rate at which a trait develops, not absolute losses of function, developmental disabilities are diagnosed on the basis of age-referenced criteria. Therefore, ADHD, if viewed as a developmental disability, should be diagnosed relative to characteristics of the individual’s age group. Barkley et al. compared diagnoses of ADHD using DSM criteria with those using developmental disorder criteria. He demonstrated that, depending on which model was applied, there was a difference in the persistence of ADHD into adulthood. When strict DSM-IV criteria were used, 58% of children with ADHD had the disorder by age 21. When developmentally referenced criteria and reports by others about the individual were used, the rate of persistence to adulthood was 66%.

How the rate of persistence of ADHD is judged also depends on the definition of remission. The mood disorder literature has a long tradition of examining subthreshold conditions and their relationship to function-
often are easily annoyed and exhibit hostile, defiant, spiteful, and negativistic behaviors. Like individuals with ADHD, those with major depressive disorder may show signs of inattention and become easily upset. However, they must have also experienced at least 2 weeks of depressed mood or loss of interest or pleasure in most activities, and they complain of easy fatigue and loss of energy, not hyperactivity. Mild or fluctuant cases of bipolar disorder, such as autism and Asperger’s disorder may exhibit hyperactivity or fidgeting and impaired social, academic, and occupational functioning. However, individuals with pervasive developmental disorders also exhibit a severe disinterest or inability to participate in social interaction or limited and stereotyped behavior, interests, and activities. Although, like ADHD, learning disorders may impair academic or occupational functioning, these disorders, which are frequently comorbid with ADHD, are characterized by a specific learning impairment as evidenced by a significant discrepancy between individuals’ performance on a standardized test in reading, mathematics, or written expression and their education and intelligence.

**ETIOLOGY OF ADHD**

The impairment of adaptive functioning in mental retardation is more severe than the social, academic, and occupational impairment associated with ADHD and occurs with an impairment of general intellectual functioning (i.e., an intelligence quotient [IQ] £ 75). Like individuals with ADHD, those with pervasive developmental disorders such as autism and Asperger’s disorder may exhibit hyperactivity or fidgeting and impaired social, academic, and occupational functioning. However, individuals with pervasive developmental disorders also exhibit a severe disinterest or inability to participate in social interaction or limited and stereotyped behavior, interests, and activities. Although, like ADHD, learning disorders may impair academic or occupational functioning, these disorders, which are frequently comorbid with ADHD, are characterized by a specific learning impairment as evidenced by a significant discrepancy between individuals’ performance on a standardized test in reading, mathematics, or written expression and their education and intelligence.
they used a mathematical model to separate each factor. For example, individuals with ADHD often use alcohol and/or cigarettes; therefore, one could suppose that having a parent with ADHD may contribute to the identification of exposure to alcohol and cigarettes in utero as risk factors for developing ADHD. However, with their analysis, Mick et al. found that, independent of whether a parent has ADHD, exposure to cigarettes or alcohol in utero is a specific teratogen for ADHD that, like low weight at birth, increases the risk of developing ADHD 2- to 3-fold. Parental ADHD, the genetic factor, increased the risk of developing this condition 8-fold. Brain injuries that occur in utero also contributed to the risk of developing ADHD. Socioeconomic status, the mother’s age at the time of the child’s birth, and parental IQ contributed little to either the risk of developing or protection from the disorder.

Heritability

Studies of dizygotic and monozygotic twins who have grown up in the same environment have been examined to determine the heritability of ADHD (Table 3). A heritability of 0 means that there is no genetic input, and a heritability of 1 means that the characteristic or disorder is completely determined by genetics. Because the identical twins have the same genes and the fraternal twins share only one half of their genes, these studies help to determine the genetic versus the environmental contribution. The mean heritability of ADHD from these studies is approximately 0.75, which means that about 75% of the etiology contributes to this disorder. Therefore, ADHD is more attributable to genetic factors than to depression (0.39 heritability), 45 generalized anxiety disorder (0.32 heritability), 46 breast cancer (0.27 heritability), 47 and asthma (0.39 heritability). 48

One reason for the variation in the heritability of ADHD in these studies is that they used different numbers of items to calculate heritability, from 2 or 3 items from the Rutter A scale to all 14–18 items in the ADHD criteria of various DSM editions. Generally, the studies that used more items showed a higher heritability than did the studies that used only 2 or 3 items. If corrected for unreliability on the basis of the type of scale and number of items used in each of these studies, the heritability of ADHD might be even higher than 0.75.

Candidate Genes

Once the extent of the genetic contribution to ADHD had been revealed, researchers began trying to identify the candidate genes. The association between ADHD and several genes, including those regulating dopamine, norepinephrine, serotonin, γ-aminobutyric acid (GABA), and androgens, has been studied. 49 While some studies 50 have not found an association between any of these genes and ADHD, 51 most did.

The gene association that has been most widely confirmed is the 7-repeat allele of the D4 dopamine receptor gene (DRD4*7). 52, 53 DRD4*7 is a defective gene found in about 30% of the general population and about 50% to 60% of the population with ADHD. 54 Multiple replication of a specific amino acid sequence in DRD4*7 has been related to a deficiency in translating the dopaminergic signal to the second messenger system. Specifically, there is an incomplete coupling of the receptor to the guanine nucleotide complex in the third cytoplasmic loop of the protein. 54 Other research 55 on the D4 receptor has shown that, in addition to dopamine, both epinephrine and norepinephrine are agonists at DRD4*7. Therefore, medications that affect either of these catecholamines could also affect this dopaminergic system.

Model of Executive Dysfunctions

The change in the nosology from hyperactivity early in the 20th century to ADHD by the early 1980s paralleled the shift in thinking from the belief that this disorder was caused by primarily bad behavior to the hypothesis that the disorder represents a cognitive brain problem that results in associated maladaptive behavior. Now we have a more sophisticated model of the brain dysfunctions that lead to problems with attention, impulsivity, and hyperactivity.

Barkley 56 proposed a model of executive dysfunctions located in the prefrontal cortex that explains the cognitive and behavioral deficits associated with ADHD. Barkley’s model comprises 5 major executive functions that enable individuals to recognize and control their actions to achieve a goal: response inhibition, nonverbal working memory, verbal working memory, self-regulation of emotion and motivation, and reconstitution. Response inhibition delays and interrupts responses and controls interference to allow individuals to control verbal and motor impulses. Nonverbal working memory enables a person to have a sense of the past and future and a cognitive
awareness of self. Verbal working memory gives people the ability to internalize receptive and expressive language for self-questioning, self-description, and establishing rules for behavior. Together, the nonverbal and verbal working memories provide the ability for reading comprehension and moral conduct. Through internalizing visual and verbal stimuli, the 2 working memories also lead to the development of the self-regulation of emotion and motivation, which provides individuals the ability to control their emotions and the motivation and persistence necessary to meet their goals. The last major executive function, reconstitution, is a form of play that allows people to analyze the experiences in their working memories to synthesize new responses, which they accept or reject based on the likelihood that the response can help them to achieve their goal. Barkley has proposed that, of these 5 executive functions, response inhibition is most obviously deficient in individuals with ADHD and that this deficit may lead to the impairments observed in the psychological and social abilities associated with the other 4 executive functions.

Brain Imaging

Neurologic differences have been documented in the brains of individuals with and without ADHD through structural and functional magnetic resonance imaging (fMRI). The circuits that control attention are smaller and less active in individuals with ADHD than in controls. The circuits that control attention are smaller and less active in individuals with ADHD than in controls. Medication and neurotransmitter studies but also studies of the cognitive division of the anterior cingulate cortex in the brains of individuals with ADHD and controls without ADHD. In their study, unmedicated adults with ADHD and adults without ADHD were given the Counting Stroop test, a variation of the Color Stroop, which measures response inhibition. During the Counting Stroop task, a set of 1 to 4 identical words appear on a screen, and subjects are told to identify the number of words on the screen by pressing 1 of 4 buttons, which, from left to right, represent the numbers 1–4. The neutral trials consist of sets of identical common animal names, while the interference trials include sets of identical number words that do not correspond with the number of words appearing on the screen. For example, the word 2 will appear in sets of only 1, 3, or 4. While subjects performed the Counting Stroop, fMRI measured the blood flow in their brains, specifically in the cingulate cortex, to determine which areas were being used during the task.

Metabolism increased in the area of the brain that was used while the task was being performed and diminished when the task was stopped. During a 4-minute span, subjects completed 30-second blocks of alternating neutral and interference trials, each of which contained 20 sets of words. This replication showed that the activity performed during the Counting Stroop is a distinct function that is controlled by a distinct part of the brain. According to the analysis of subjects’ reaction times, adults with ADHD took longer to perform the task than the controls. The results of the fMRI showed that the 2 groups also activated different parts of the brain to complete the task. While adult controls activated the cognitive division of the anterior cingulate cortex during the task, adults with ADHD activated a fronto-striato-insular-thalamic network. The use of ancillary areas of the brain by individuals with ADHD demonstrates that, while the brain may compensate for its deficits, these compensations are not perfect and correlate with inefficient processing.

NEED FOR NEW TREATMENTS

While stimulants, the traditional medications for ADHD, are remarkably effective in the treatment of this disorder, their use has some limitations. For example, ADHD lasts 24 hours per day, but we lack 24-hour-per-day treatments. Immediate-release formulations of stimu-

Table 3. Average Genetic Contribution of Attention-Deficit/Hyperactivity Disorder From Studies of Twins Between the Ages of 4 and 16 Years

<table>
<thead>
<tr>
<th>Study</th>
<th>Twin Pairs (N)</th>
<th>Diagnosis</th>
<th>Measure</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eaves et al, 1997</td>
<td>1355</td>
<td>Hyperactivity</td>
<td>Mothers’ completion of Rutter A scale</td>
<td>0.60–0.80</td>
</tr>
<tr>
<td>Edelbrock et al, 1995</td>
<td>181</td>
<td>Attention problems</td>
<td>Parents’ completion of CBCL</td>
<td>0.66</td>
</tr>
<tr>
<td>Gillis et al, 1992</td>
<td>74</td>
<td>DSM-III-R ADHD</td>
<td>Structured interviews with parents using DICA-R</td>
<td>0.91</td>
</tr>
<tr>
<td>Gjone et al, 1996</td>
<td>915</td>
<td>Attention problems</td>
<td>Mothers’ completion of CBCL</td>
<td>0.73–0.79</td>
</tr>
<tr>
<td>Hudziak et al, 2000</td>
<td>492</td>
<td>Attention problems</td>
<td>Parents’ completion of CBCL</td>
<td>0.60–0.68</td>
</tr>
<tr>
<td>Levy et al, 1997</td>
<td>1634</td>
<td>DSM-III-R ADHD</td>
<td>DSM-III-R–based maternal rating scale</td>
<td>0.75–0.91</td>
</tr>
<tr>
<td>Sherman et al, 1997</td>
<td>288</td>
<td>DSM-III ADD-H and R</td>
<td>Teacher rating form of MTFS and structured maternal interviews using DICA-R</td>
<td>0.73–0.89</td>
</tr>
<tr>
<td>Thapar et al, 1995</td>
<td>281</td>
<td>Hyperactivity</td>
<td>Mothers’ completion of Rutter A scale</td>
<td>0.88</td>
</tr>
</tbody>
</table>

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lants must be taken in repeated doses throughout the day. The extended-release formulations of the stimulants are effective for 8 to 12 hours. While these longer acting formulations have been a major advance in our pharmacotherapeutic armamentarium, additional strategies must be employed to cover longer periods. In addition, stimulants have the potential for abuse and may not be optimal in several comorbid conditions such as tic disorders.

Because of stimulants’ limitations, a number of alternative medications have been explored in ADHD. Tricyclic antidepressants (TCAs), which affect norepinephrine, may be efficacious in ADHD, but their action is not selective. The effects of TCAs on other neurotransmitter systems can cause side effects such as dry mouth, constipation, sedation, weight gain, changes in blood pressure, and delays in cardiac conduction and repolarization. Selective serotonin reuptake inhibitors (SSRIs) have also been explored as a possible treatment for ADHD, but they have shown no evidence of efficacy. Although antihypertensive medications may help with symptoms of ADHD, these drugs are complicated to use in children because they may be sedating and may cause hypertension if they are abruptly discontinued. Recently, researchers have explored the efficacy of the investigative nonstimulant atomoxetine in the treatment of ADHD. Atomoxetine, which was initially examined under the name tofotexetine as an antidepressant, may be efficacious in ADHD and appears to be a potent and specific norepinephrine reuptake inhibitor.

CONCLUSION

Developmentally sensitive, age-appropriate criteria would help clinicians to more accurately diagnose ADHD in both children and adults. As studies provide more insight into the genetic, environmental, and neurobiological causes of this disorder, the effects of medications on ADHD may be better understood. Expanded medication options will help physicians to choose the most effective and safest treatment for their patients with ADHD, thereby increasing effective therapy and reducing the wide range of ADHD-associated impairments.

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, atomoxetine is not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.

REFERENCES

44. Thapar A, Hervas A, McGuffin P. Childhood hyperactivity scores are highlyheritable and show sibling competition effects: twin study evidence. Behav Genet 1995;25:537–544
47. Hemminki K, Mutanen P. Genetic epidemiology of multistage carcinogenesis. Mutat Res 2001;473:11–21
68. Hemminki K, Mutanen P. Genetic epidemiology of multistage carcinogenesis. Mutat Res 2001;473:11–21