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J. GORDON MILLICHAP, MD. EDITOR
JOHN J. MILLICHAP, MD. ASSOCIATE EDITOR

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CAUSATIVE FACTORS FOR ADHD

PERINATAL RISK FACTORS

Investigators at Seoul National Hospital, and other centers in Seoul, Korea, studied the genetic, perinatal, and developmental risk factors in 147 children, ages 6 to 15 years, diagnosed with ADHD. Compared to a healthy control group of 502 children without ADHD, the ADHD-Combined subtype children showed more severe externalizing symptoms, more deficits in a continuous performance test, and were more likely to have comorbid disorders. Risk factors for both ADD-Inattentive and ADHD-Combined subtypes included maternal stress during pregnancy, postpartum depression, and changes in the primary caretaker during first 3 years. The ADD-I group was less likely to have received prenatal check-ups and more likely to have had postnatal medical illness than the ADHD-C group. The genotype frequencies of the dopamine transporter (DAT1) and serotonin transporter-linked polymorphisms were the same for the two subtypes. The inattentive subtype, ADD-I, differs from the combined subtype, ADHD-C, in having less severe symptoms, less comorbidity, and fewer environmental risk factors. (Park S, Cho SC, Kim JW, et al. Differential perinatal risk factors in children with attention-deficit/hyperactivity disorder by subtype. **Psychiatry Res** 2014 May 28).

COMMENTARY. In addition to the genetic factor, acquired environmental causes may contribute to the etiology of ADHD and these are classified according to the time of their occurrence: 1) *pregnancy- and birth-related (pre- and perinatal) risk factors*, and 2) *childhood (postnatal) illnesses.* Nutritional and dietary factors also play a role; of the numerous environmental causes listed, a deficiency of omega-3 fatty acid and treatment with supplemental fatty acid are receiving most attention [1][2].

Treatment is occasionally determined by etiological environmental factors (e.g. thyroid, dietary), but usually a correction of deficient catecholamine metabolism using methylphenidate or amphetamine medication is the primary aim of treatment. Variability of response to medication may be explained by the occurrence and variability of environmental etiological factors. Gene-environment interaction is increasingly recognized as an important mechanism in the etiology and development of ADHD [3]. In therapy of ADHD, a combination of stimulant medication and supplemental omega-3 fatty acid may provide a better response than stimulant alone [4].

In previous clinical and animal studies, patients with the highest levels of motor activity were more likely to respond to methylphenidate therapy [5][6]. In addition, the most active patients had the highest number of neurological soft-sign abnormalities, and in animals rendered hyperactive by prefrontal cerebral lesions, the more severe brain damage [5]. It is not surprising that the ADHD-C patient group in the Korean study [7] have more severe symptoms compared to the ADD-I subtype, greater comorbidity, and more evidence of environmental etiologic factors.

References.

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ROLE OF THYROID STIMULATING HORMONE RECEPTOR IN ADHD

Investigators from Meijo and Nagoya Universities, Nagoya, Japan, studied the role for thyroid stimulating hormone receptor (TSHR) in TSHR knockout mice with phenotypes of ADHD such as hyperactivity, impulsiveness, and impairment of short-term memory. Administration of methylphenidate reversed impulsiveness, aggression and object recognition memory impairment. Monoaminergic changes in the brain, including an increase in the ratio of homovanillic acid/dopamine, were accompanied by an increase in the expression of noradrenaline transporter in the frontal cortex. These changes were attributed to the loss of the TSH-TSHR pathway, suggesting a novel role for TSHR in behavioral and neurological phenotypes of ADHD. (Mouri A, et al. Thyrotropin receptor knockout changes monoaminergic neuronal system and produces methylphenidate-sensitive emotional and cognitive dysfunction. **Psychoneuroendocrinology** 2014 Jun 24;48C:147-161).

COMMENTARY. Dysregulation of TSH and its receptor TSHR is implicated in the pathophysiology of ADHD, and ADHD is reported in association with resistance to thyroid hormone, a disease caused by a mutation in the thyroid hormone receptor B (TRB) gene. Investigators at the National Institutes of Health, Bethesda, MD, evaluated the presence and severity of ADHD in 18 families with a history of generalized resistance to thyroid hormone. Among the children, 19 of 27 subjects resistant to thyroid hormone (70%) and 5 of 25 unaffected subjects (20%) met criteria for ADHD ($P<0.001$). The odds of having ADHD were 3.2 times higher for affected male subjects than for affected females and were 2.7 times higher for unaffected male subjects than for unaffected female subjects. The mean symptom score was 2.5 times higher in the affected group than in the unaffected group (7.0 vs 2.8, $P<0.001$). The frequency of other psychiatric diagnoses was similar in the two groups. In this study sample, ADHD is strongly associated with generalized resistance to thyroid hormone [1]. In a later Australian study, the prevalence of thyroid hormone abnormalities in children with ADHD attending the State Child Development Centre in Perth was 2.3%, and none had generalized resistance to thyroid hormone [2]. Routine screening for thyroid hormone abnormalities in children with ADHD is supported by the NIH study but not by the Australian study. We recommend screening of patients with a family history of thyroid dysfunction [3].

References.

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2. Valentine J, et al. J Paediatr Child Health. 1997 Apr;33(2):117-20.
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ROLE OF COPY NUMBER VARIANTS IN ADHD

Investigators from Brazil determined if copy number variants (CNVs) in glutamate metabotropic receptor genes (GRM) were overrepresented in 1038 individuals with ADHD compared to 1057 subjects without ADHD. No significant difference in the total number of CNVs was found in the two population samples (P=0.326). The presence of CNVs was associated with lower IQ scores in ADHD samples (P=0.026) but not in the sample without ADHD. CNVs in GRM5 were associated with anxiety disorders in ADHD cases (P=0.002), but not in subjects without ADHD. CNVs in the glutamatergic genes were associated with cognitive and clinical characteristics of ADHD. (Akutagava-Martins GC, et al. Glutamatergic copy number variants and their role in attention-deficit/hyperactivity disorder. **Am J Med Genet B Neuropsychiatr Genet** 2014 Jul 2).

COMMENTARY. The results of this study suggest a role for glutamate in ADHD. In an investigation of the association between metabotropic glutamate receptor subtype 7-gene polymorphism and treatment response to methylphenidate, children with the G/A genotype had a more pronounced response rate than children with the G/G genotype [1].

References.

1. Park S, et al. J Child Adolesc Psychopharmacol. 2014 May;24(4):223-7.

DIAGNOSTIC CRITERIA FOR ADHD

IMPACT OF THE DSM-5 CRITERIA ON PREVALENCE OF ADHD

Investigators at the National Institute of Mental Health, Bethesda, MD, compared the prevalence and clinical correlates of DSM-IV-TR versus DSM-5-defined ADHD and subtypes in a nationally representative sample of US youth based on age-of-onset criterion. Extension of the age-of-onset criterion from 7 to 12 years led to an increase in the prevalence rate of ADHD from 7.38% (DSM-IV-TR) to 10.84% (DSM-5). Severity of ADHD and patterns of comorbidity were not changed by the later age-of-onset, but the group with later age of onset was more likely to be from lower income and ethnic minority families. (Vande Voort JL, He JP, Jameson ND, Merikangas KR. Impact of the DSM-5 attention-deficit/hyperactivity disorder age-of-onset criterion in the US Adolescent population. **J Am Acad Child Adolesc Psychiatry** 2014 Jul;53(7):736-44).

COMMENTARY. The DSM-5 edition released in May 2013 replaces the DSM-IV-TR edition and the changes are as follows: symptoms can now occur by age 12 rather than by age 6, and for adults and adolescents age 17 or older, only 5 symptoms are needed instead of the 6 needed for younger children.

Unchanged is the requirement that symptoms must be present for at least 6 months and they are inappropriate for developmental level; several symptoms were present before age 12 years; several symptoms are present in two or more settings (e.g., at home, school or work; with friends or relatives; in other activities); symptoms interfere with or reduce the quality of social, school, or work; and the symptoms are not better

explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder. A patient may have both ADHD and ASD. Symptoms are now referred to as "presentations": Combined, predominantly inattentive, and predominantly hyperactive-impulsive presentations.

References.
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BIOLOGICAL MARKERS IN DIAGNOSIS OF ADHD

BIOLOGICALLY BASED NOSOLOGY FOR ADHD

Investigators at Oregon Health and Science University and other centers attempt to refine subtyping of childhood ADHD by using biologically based behavioral temperament types. Groups were validated using 3 external validators: cardiac measures of respiratory sinus arrhythmia, CNS functioning via functional MRI, and clinical outcomes at 1-year follow-up. Three novel types of ADHD were recognized: mild (normative emotion regulation), surgent (extreme levels of positive approach-motivation), and irritable (extreme levels of negative emotionality, anger, and poor soothability). These types were stable over time and showed unique patterns of cardiac physiological response, resting-state functional brain connectivity, and clinical outcomes. This biologically informed temperament-based typology is thought to provide a superior description of heterogeneity in the ADHD population than any current classification. (Karalunas, et al. Subtyping attention-deficit/hyperactivity disorder using temperament dimensions: toward biologically based nosologic criteria. **JAMA Psychiatry** 2014 Jul 9).

COMMENTARY. The use of a combination of biological markers may help to reduce heterogeneity and to identify homogeneous phenotypes of ADHD. A consensus report of the World Federation of Societies of Biological Psychiatry (WFSBP) task force on biological markers and the World Federation of ADHD determined in 2012 that no reliable ADHD biomarker had been described to date, but some promising candidates (e.g. olfactory sensitivity, substantial echogenicity) exist. The development of ADHD markers is hindered by sample heterogeneity due to etiological and phenotypic complexity and age-dependent co-morbidities [1].

References.
1. Thome J, et al. World J Biol Psychiatry. 2012 Jul;13(5):379-400.

EEG THETA/BETA RATIO IN DIAGNOSIS OF ADHD

Investigators at the Research Institute Brainclinics, Nijmegen, Netherlands, conducted a meta-analysis on the Theta/Beta ratio (TBR) during Eyes Open from location Cz (the electrode halfway between the inion and the nasion) in the EEG of children/adolescents 6-18 years of age with and without ADHD. In nine studies identified with a total of 1253 subjects with and 517 without ADHD, the grand-mean effect size (ES) of the TBR decreased from 0.75 to 0.62 with increasing age, explained by an

increase in TBR for the non-ADHD groups. A substantial sub-group of ADHD patients do deviate on the TBR measure, but excessive TBR is not a reliable diagnostic measure of ADHD. It may have prognostic value. (Arns M, et al. A decade of EEG theta/beta ratio research in ADHD: a meta-analysis. **J Atten Disord** 2013 Jul;17(5):374-83).

COMMENTARY. The FDA approved the Neuropsychiatric EEG-Based ADHD Assessment Aid (NEBA) medical device in 2013 to be used as confirmatory support or to pursue further testing after an evaluation for ADHD, in a child aged 6-17. The device was not to be used as a stand alone method of diagnosis of ADHD.

The AAN, in an Evidence-Based Practice Advisory, concludes that it is highly likely that EEG theta-beta power ratio and EEG frontal beta power correctly identify patients with ADHD (accuracy 89% to 94%) as compared to a clinical evaluation. The AAN recommends that the EEG test should not be used in place of a standard clinical evaluation, because of the risks of misdiagnosis of 6-15% when using the theta/beta ratio. There is neither evidence for, nor against the use of theta/beta EEG power ratio either to confirm a diagnosis of ADHD, nor to support further testing. Whether comorbid disorders such as ODD have similar changes in the theta/beta ratios that mimic the reported finding in ADHD is not known [1].

A recent report of spectral analysis of EEGs on 28 normal and 58 ADHD children, aged 6 to 14 years, found TBR was higher in ADHD subjects, with lower beta but no difference in theta power over Broca's area. Beta-1 power over Broca's area was the best diagnostic test, with sensitivity 0.86 and specificity 0.57. The EEG beta-1 power and TBR assist in confirming the diagnosis of ADHD in a sample with moderate pretest probability of ADHD [2].

The present symptomatic method of diagnosis, based on parent and teacher evaluations, is relatively accurate in children with the hyperactive-impulsive subtype of ADHD but less so with the inattentive type. A more objective test such as EEG if validated could be a valuable aid in the diagnosis and management of ADHD. The significance of seizure discharges in approximately 25% of sleep-deprived EEGs in ADHD children is further evidence of the utility of the EEG in ADHD management [3].

References.

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TREATMENT OF ADHD

EFFECT OF METHYLPHENIDATE ON INATTENTION DURING DRIVING

Investigators at Utrecht University, the Netherlands; and centers in Australia and Detroit, MI, evaluated the lapses of attention during on-road highway driving in 18 adult ADHD patients during treatment with methylphenidate (MPH) or placebo. Driving was significantly better with MPH when compared with placebo, with reduction in weaving, lapses, and inattention. Lapses were common on placebo (11/18 patients), and much less after MPH (5/18). Lapses often go unnoticed by drivers. (Verster JC, Roth T.

Methylphenidate significantly reduces lapses of attention during on-road highway driving in patients with ADHD. **J Clin Psychopharmacol** 2014 Jun 27. [Epub ahead of print]).

COMMENTARY. ADHD young adults are twice as likely to be cited for unlawful speeding and have more crashes and more accidents involving bodily injury, when compared to non-ADHD adult control subjects. These findings support a need for continued treatment of ADHD into adolescence and adulthood. Improvement of driving performance of adolescent drivers with ADHD was demonstrated using a driving simulator while taking Concerta compared to placebo [1] or immediate-release MPH [2].

References.

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GUANFACINE EXTENDED RELEASE IN ADHD

Investigators at Massachusetts General Hospital, Boston, MA, performed a multicenter, 9-week, double-blind, placebo-controlled, dose-optimization study of guanfacine extended release (GXR, <4 mg/d) adjunctive to a long-acting psychostimulant for ADHD continued in 461 subjects. Patients were randomized to receive GXR in the morning (GXR AM), GXR in the evening (GXR PM), or placebo.

GXR treatment groups showed significantly greater improvement from baseline compared with placebo plus psychostimulant. Small mean decreases in pulse, systolic, and diastolic blood pressure were observed in GXR treatment groups. Morning or evening GXR administered adjunctively to a psychostimulant showed significantly greater improvement and generated no new safety signals. (Wilens TE, et al. A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. **J Am Acad Child Adolesc Psychiatry** 2012;51(1):74-85).

COMMENTARY. A similar randomized, double-blind trial of guanfacine extended release (Intuniv) administered either in the morning ((n=107) or evening (n= 114) was associated with significant improvements in ADHD symptoms. Once-daily GXR monotherapy is effective, administered AM or PM [1]. The rapid-release guanfacine (Tenex) is often prescribed as an alternative to Intuniv because of cost and insurance denial. Tenex is often effective in the hyperactive/ADHD younger child with sleep disorder or tics, but drowsiness during the day may lessen the ability to focus in school. The effect of Intuniv on school performance and grades requires further study.

References.

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ADVERSE EFFECTS OF MEDICATIONS FOR ADHD

CARDIAC AUTONOMIC DYSFUNCTION AND STIMULANT THERAPY

Investigators at University of Minnesota, Minneapolis, report cardiac autonomic dysfunction and arterial stiffness among children and adolescents with ADHD treated

with stimulants. Compared with controls, ADHD patients had greater resting systolic BP, diastolic BP, and increased sympathetic tone. (Kelly AS, et al. **J Pediatr** 2014 Jul 8).

COMMENTARY. Variable pediatrician attitudes and cardiac screening practices prior to stimulant treatment of ADHD among US-based pediatricians reflect the limited evidence base and conflicting guidelines. In a survey of randomly selected US pediatricians with AAP membership, 25% agreed that the risk of sudden cardiac death (SCD) and 30% that legal liability were sufficiently high to warrant cardiac assessment; 75% agreed that physicians were responsible for informing families about SCD risk; 71% recognized interpreting a pediatric ECG as a barrier; 93% completed a routine H & P; 48% completed an in-depth cardiac H & P; 15% ordered an ECG; and 46% discussed stimulant-related cardiac risks [1].

Several factors influence the risks and cardiac screening practices, including: a cardiac murmur, the patient's sports activities, and an ECG with modifications of uncertain significance. We refer to a cardiologist for an opinion a child with a murmur, especially if engaged in strenuous sports activities, and an ECG abnormality of uncertain significance. Patients with a structural heart defect or prolonged QT interval are excluded from drug therapy for ADHD and are offered behavioral and alternative therapies.

References.
1. Leslie LK, et al. Pediatrics. 2012 Feb;129(2):222-30.

PRIAPISM WITH MEDICATION FOR ADHD

Investigators at Auburn University, Huntsville, AL, and other centers, reviewed reports in the literature (1966-May 15, 2014) of priapism associated with methylphenidate (MPH), amphetamines, and atomoxetine used in treatment of ADHD. MPH is implicated in a recent FDA safety announcement warning as a result of 15 case reports (mean age 12.5 years). Prolonged erections and priapism occurred with immediate- and long-acting products, dose increases, and drug withdrawal periods. Priapism also occurred in 4 patients taking amphetamines and one 11-year-old patient taking atomoxetine for ADHD. Discontinuation is warranted if this adverse drug reaction occurs. (Eiland LS, Bell EA, Erramouspe J. **Ann Pharmacother** 2014 Jun 30).

COMMENTARY. Priapism is a painful, prolonged erection that does not return to a flaccid state within four hours, despite the absence of both physical and psychological sexual stimulation. The duration time of an erection to be called priapism is controversial and some classify priapism as 6 hours. Priapism is a medical emergency that should be treated in the ED. Based on my experience in treating children with ADHD, this adverse effect must be very rare and may not warrant special mention in counseling a young child with parents at the initiation of treatment. Referral of parents to the modified drug package insert should be sufficient warning.

Other drugs known to cause priapism rarely include sodium valproate [1] and risperidone [2], cited as single case-reports in the literature.

References.
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