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STATE-OF-THE-ART REVIEW ARTICLE

Etiologic Classification of Attention-Deficit/ Hyperactivity Disorder

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ABSTRACT

Attention-deficit/hyperactivity disorder is a neurobiological syndrome with an estimated prevalence among children and adolescents of 5%. It is a highly heritable disorder, but acquired factors in etiology are sometimes uncovered that may be amenable to preventive measures or specific therapy. Early reports have described symptoms similar to attention-deficit/hyperactivity disorder that followed brain trauma or viral encephalitis, and recent MRI studies have demonstrated brain volumetric changes that may be involved in the pathophysiology of the syndrome. The American Psychiatric Association's *Diagnostic Statistical Manual*, introduced in 1968, emphasizes symptomatic criteria in diagnosis. Here, an overview of environmental factors in the etiology of attention-deficit/hyperactivity disorder is presented to encourage more emphasis and research on organic causal factors, preventive intervention, and specific therapies. An organic theory and the genetic and biochemical basis of attention-deficit/hyperactivity disorder are briefly reviewed, and an etiologic classification is suggested. Environmental factors are prenatal, perinatal, and postnatal in origin. Pregnancy- and birth-related risk factors include maternal smoking and alcohol ingestion, prematurity, hypoxic-ischemic encephalopathy, and thyroid deficiency. Childhood illnesses associated with attention-deficit/hyperactivity disorder include virus infections, meningitis, encephalitis, head injury, epilepsy, toxins, and drugs. More controversial factors discussed are diet-related sensitivities and iron deficiency. Early prenatal recognition, prevention, and treatment of environmental etiologies of attention-deficit/hyperactivity disorder may reduce physician reliance on symptomatic modification with medication, a frequent reason for parental concern.

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Key Words
attention deficit, hyperactivity, etiology, environmental, viral, nicotine, thyroid

Abbreviations
ADHD—attention-deficit/hyperactivity disorder
GRTH— generalized resistance to thyroid hormone

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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD), a neurobiological syndrome that affects an estimated 5% or more of school-aged children, has been recognized under different names for more than a century. In the earliest reports, behavioral abnormalities similar to ADHD were described after head injury[1] and as a complication of encephalitis after the influenza epidemic of 1918.[2,3] "Organic drivenness" was a term used to describe the behavior after epidemic encephalitis, and damage to the brainstem was suggested as the cause.[4] This description of behavioral symptoms caused by encephalitis or brain damage was followed by a variety of reports linked to brain dysfunction and described by various terms including "minimal brain dysfunction" in 1966[5] and "hyperkinetic reaction of childhood or adolescence" in 1968. The American Psychiatric Association's *Diagnostic Statistical Manual* and its subsequent revisions[6] omit reference to frequently associated motor perceptual and subtle neurologic signs, favoring symptomatic diagnostic criteria. Similarly, a clinician's approach to the management of ADHD is concerned primarily with symptomatic treatment. The purpose of this critical assessment of our approach to ADHD is to present an overview of organic and genetic causes and reports of environmental factors in the etiology of ADHD. A greater emphasis on etiology might encourage a preventive or specific approach to treatment, with less reliance on symptom modification with medications.

ORGANIC THEORY OF ADHD

Numerous experimental studies of cortical ablation and subcortical lesions in animals and clinical studies of brain-damaged children and adults have correlated the sites of cerebral lesions with the symptoms of hyperkinesia, distractibility, and inattention.[7,8] A cortical-striatal circuit has been proposed to explain the heterogeneous nature of the ADHD syndrome.[9] A decrease in volume of the right anterior frontal region and loss of normal right-to-left

asymmetries in striatal nuclei have been shown on MRI studies. These findings support the involvement of the frontal lobes and striatal connections in the pathophysiology of ADHD.[10] A temporal lobe arachnoid cyst–ADHD syndrome has also been described in patients with coincidental learning and language disabilities.[11] In 1 case report of a patient with this syndrome who presented with headaches after a head injury, surgical intervention with shunt procedure resulted in improved cognitive function and behavior.[12]

Prefrontal and cingulate brain regions are involved in inhibitory control, a function typically deficient in children with ADHD. A functional MRI study of 17 subjects with ADHD and 15 healthy controls showed that, in relation to control subjects, children with ADHD failed to activate the anterior cingulate cortex and the left ventrolateral prefrontal cortex after unsuccessful inhibition. The patients were treatment-naive, and the findings were unrelated to long-term treatment or abrupt withdrawal of stimulant medications before imaging.[13]

GENETIC AND BIOCHEMICAL BASIS OF ADHD

Genetic factors account for ~80% of the etiology of ADHD.[14] Family, twin, and adoption studies support the theory that ADHD is a highly heritable disorder, with the majority of patients having a first- or second-degree relative with a history of ADHD or learning disorder. Learning disability is frequently associated with ADHD as an interrelated, overlapping problem[15] and is reported in 70% of patients and among their relatives. In a study of 145 children with ADHD, boys outnumbered girls by 3 to 1, and 30% had siblings with learning disabilities compared with only 7% among control children without ADHD. A familial-genetic factor in this group of patients was expressed by the preponderance of boys and the increased frequency of learning disabilities in siblings.[16]

Gender differences in the prevalence of ADHD have been attributed to the sample examined and the increased disruptive behavior of boys. Little is known about the causes of ADHD in girls, because the incidence is relatively infrequent. A study of the familial transmission of ADHD ascertained through girls revealed that proband gender was not an influencing factor, which suggests that the genetic contributions to ADHD are similar in boys and girls.[17] Familial risk factors cannot account for gender differences in prevalence or the clinical variability of *Diagnostic Statistical Manual, 4th Edition*, subtypes. First-degree relatives (parents, siblings, and children) of patients with ADHD have a higher risk of being affected, with a frequency that is five- to sixfold greater than that in the general population.[18,19] Twin studies of children with ADHD have shown 79% concordance in monozygotic twins compared with 32% in same-gender dizygotic twins.[19] A review of 283 adult adoptees divided into 2 groups, with or without behaviorally disturbed biological parents, revealed that those with childhood histories of hyperactivity had both a biological parent affected and a placement in a poor socioeconomic adoptive home.[20] Adoption studies support the role of both genetic and environmental factors in the etiology of ADHD.

Genetic syndromes associated with ADHD include fragile X, Klinefelter, velocardiofacial (22q.11.2 deletion), Williams, Turner, Prader-Willi, and neurofibromatosis type 1, but these disorders are rare among ADHD-clinic patients. The prevalence of cytogenetic abnormalities was assessed in 100 children (64 boys) with combined-type ADHD and normal intelligence. One girl with ADHD had a sex chromosome aneuploidy (47,XXX) and 1 boy had a permutation-sized allele for fragile X, but none of the subjects showed the full mutation. Results of testing for 22q11.2 microdeletion were negative for all children with ADHD screened. In the absence of clinical signs or family history, routine chromosome analysis in children with ADHD is not generally recommended.[21]

Molecular genetic studies support the involvement of the dopamine receptor and dopamine transporter genes. Many ADHD gene studies, most of which have been focused on catecholaminergic candidates, emphasize the role of dopaminergic genes in clinical phenotypes and drug effects.[22] Deficits in dopamine-modulated frontal-striatal circuits are correlated with subtypes of ADHD, and the relation of dopamine deficits to fetal and perinatal stresses may explain the mechanism of environmental etiologies of ADHD.[23] Preterm birth complicated by susceptibility to cerebral ischemia may contribute to increased dopamine receptor availability, deficient dopaminergic neurotransmission, and subsequent development of ADHD.[24] Evidence of environmental mediators in ADHD has been demonstrated in twin studies, with affected twins having greater exposure to risk factors such as maternal smoking, lower birth weights, and delayed growth and development compared with unaffected co-twins.[25] Gene-environment interaction is increasingly recognized as an important mechanism in the etiology and development of ADHD, with some genes (eg, *DAT1*) affecting the individual sensitivity to environmental etiologic factors.[26]

TABLE 1 **Etiologic Classification of ADHD**

Group	Timing	Etiologic Factors
Genetic		Dopamine deficit, idiopathic
Acquired	Prenatal	Developmental cerebral abnormality, chromosome anomaly, viral exanthema, alcohol, nicotine, lead, cocaine, anemia, hypothyroidism, iodine lack
	Perinatal	Prematurity, low birth weight, anoxic-ischemic encephalopathy, meningitis, encephalitis
	Postnatal	Viral meningitis, encephalitis, cerebral trauma, iron deficiency,[a] fatty acid deficiency,[a] thyroid dysfunction, otitis media[a]

[a] Significance is controversial.

ENVIRONMENTAL FACTORS IN ETIOLOGY

Environmental factors may be classified as prenatal, perinatal, and postnatal in origin, as shown in Table 1. Pregnancy- and birth-related risk factors include maternal smoking, exanthema, maternal anemia, breech delivery, prematurity, low birth weight, hypoxic-ischemic encephalopathy, small head circumference, cocaine and alcohol exposure, and iodine and thyroid deficiency. Childhood illnesses associated with occurrence of ADHD include viral infections, meningitis, encephalitis, otitis media, anemia, cardiac disease, thyroid disease, epilepsy,

and autoimmune and metabolic disorders. Other causative factors include head injury involving the frontal lobes, toxins and drugs, and nutritional disorders, the involvement of many being controversial (eg, food additives, food allergies, sucrose, gluten sensitivity, and fatty acid and iron deficiencies). Of all the factors implicated during pregnancy, maternal smoking has attracted the greatest attention in the recent literature.

Maternal Smoking

In a population-based sample of twin pairs, genetic influences accounted for most of the variance in offspring with ADHD, but maternal smoking during pregnancy showed a significant environmentally mediated association.[27] A systematic search of the literature found 24 studies on maternal tobacco smoking published between 1973 and 2002, all of which indicated an increased risk of ADHD in the offspring.[28] One study that used data from the National Health and Nutrition Examination Survey of 1999–2002 found that of 4704 children 4 to 15 years of age, 4.2% were reported to have ADHD and be taking stimulant medication treatment, equivalent to 1.8 million affected children in the United States. Prenatal tobacco exposure was significantly associated with ADHD and accounted for 270 000 excess cases of ADHD.[29]

Prenatal Exposure to Alcohol

In contrast to the risk of ADHD with prenatal nicotine exposure, the results of studies that have linked alcohol with ADHD are less uniform, and the findings reported from 9 alcohol studies have been contradictory.[28] Studies with a positive association include 26 children whose mothers abused alcohol during pregnancy. When examined at 11 and 14 years of age for neuropsychiatric problems, of 24 alcohol-exposed children seen at follow-up, 10 had ADHD, 2 had Asperger syndrome, and 1 had mild mental retardation. The severity of the disorder was correlated with the degree of alcohol exposure in utero. Children whose mothers discontinued alcohol consumption by the 12th week of gestation developed normally and had no learning problems in school.[30]

A retrospective, case-control study of the effects of in utero exposure to alcohol and nicotine found that among 280 patients with ADHD and 242 controls without ADHD, patients with ADHD were 2.5 times more likely to have been exposed to alcohol in utero ($P = .03$) and 2.1 times more likely to have been exposed to cigarettes ($P = .02$) than the controls. Alcohol is considered a risk factor for ADHD that is independent of prenatal exposure to nicotine and other familial risk factors.[31] Analysis of a large Australian twin cohort showed that offspring of twins with a history of maternal alcohol-use disorder were significantly more likely to exhibit ADHD than offspring of nonalcoholic controls. Maternal smoking probably contributes to the association of alcohol and ADHD, but with adjustment for the nicotine risk factor, a significant genetic correlation exists. Genes that influence the risk of alcohol use also influence vulnerability to ADHD.[32]

Prenatal Exposure to Lead

Data obtained from the 1999–2002 National Health and Nutrition Examination Survey found higher blood lead concentrations in mothers of children with ADHD, with lead exposure accounting for 290 000 excess cases of ADHD in US children, equal to the number of cases related to prenatal tobacco exposure.[29] A study that reviewed blood lead screening in 102 children with ADHD revealed a mean level of 2.29 μg/dL, with only 1 child having a mildly elevated lead level.[33] In contrast, 2 studies that evaluated the relationship between hair lead levels and attention-deficit disorders in the classroom revealed positive correlations. Scalp hair specimens obtained from 277 first-grade pupils had lead concentrations that ranged from 1.0 to 11.3 ppm (μg/g). A dose-response relationship between lead levels and negative teacher ratings remained significant after controlling for age, ethnicity, gender, and socioeconomic status. The relationship was even stronger between physician-diagnosed ADHD and hair lead levels. No "safe" threshold for lead concentration was apparent as a risk factor for ADHD.[34] In 43 boys aged 8 to 12 years attending schools for learning disorders in the Netherlands, those with relatively high concentrations of lead in their hair reacted slower in reaction-time tasks and were less flexible in changing focus of attention than those with relatively low lead levels.[35] Although the results of these studies have been variable, lead, and particularly prenatal exposure to lead, seems to be a risk factor for ADHD.

INFECTIONS AND ADHD

Reports of a seasonal pattern of birth for subtypes of ADHD suggest an association with seasonally mediated viral infections. In a study of 140 boys with ADHD and 120 normal controls, September births were significantly correlated with ADHD and learning disability (odds ratio: 5.4). A trend toward an increase in winter births was also evident. Exposure to viral infections during winter months in the first trimester of fetal life or at the time of birth may be a predisposing factor in 10% of subjects with ADHD with comorbid learning disabilities.[36] Viral infections during pregnancy, at birth, and in early childhood have been linked to an increased risk of developing ADHD. In a case-control study in Italy, children born to women who had a viral exanthematous rash during pregnancy had an increased risk of ADHD. Measles, varicella, or rubella was reported by 4 of 71 mothers of children with ADHD and none of the 118 control mothers ($P < .01$). The difference was significant after adjusting for other potential risk factors.[37] Other viral infections associated with an increased prevalence of ADHD and learning disorders included HIV, enterovirus 71, and varicella zoster encephalitis. Herpes simplex virus antibodies showed no significant correlation with ADHD or other neuropsychiatric disorders.[38] Febrile seizures, frequently associated with human herpesvirus 6 in the United States and with influenza A in Asia are a risk factor for subsequent development of hyperactive behavior and ADHD.[39–41]

Influenza Virus

Since the initial report of an influenza-associated postencephalitic behavior disorder,[3] influenza viral infection as a potential cause of ADHD has received little attention.[42] A literature search uncovered only 1 influenza-related ADHD epidemiologic study that showed frequency of health care utilization for influenza and ADHD.[43] Data from the National Ambulatory Medical Care Survey (1996–2001) showed that rural children 5 to 9 years old were seen more frequently than nonrural children for treatment of ADHD ($P = .001$) and influenza ($P = .037$).

HIV Infection

Among 274 previously treated HIV-infected children aged 2 to 17 years, the most common behavioral problems, as measured by the Conners' Parent Rating Scale, were learning (25%), hyperactivity (20%), impulsive-hyperactive (19%), conduct (16%), and anxiety (8%) problems. Mean Wechsler Intelligence Scale for Children-III scores were less than average norms, and hyperactivity was more frequent in children with a performance IQ of <90.[44]

Enterovirus 71 Infection

Enterovirus 71 infection with central nervous system involvement may be associated with neurologic sequelae, delayed neurodevelopment, and reduced cognitive functioning. Of 47 patients who were recovering from enterovirus 71 aseptic meningitis or encephalitis and attending school, 6 (13%) had ADHD and required medication, and 3 were in special education.[45]

Varicella Zoster Encephalitis

A patient with encephalitis caused by primary varicella zoster infection developed ADHD and a tic disorder. MRI studies localized the encephalitis to the basal ganglia.[46]

Borrelia burgdorferi Infection

B burgdorferi is the spirochete that causes Lyme disease; it has numerous psychiatric and neurologic presentations, including ADHD.[47]

Streptococcal Infections

Pediatric autoimmune neuropsychiatric disorders associated with group A β-hemolytic streptococcal infections, in addition to obsessive-compulsive disorder and tic disorders, include hyperactive behavior, cognitive deficits, and oppositional behaviors. Symptom onset and exacerbations of ADHD seem to be triggered by streptococcal infection according to some reports.[48,49] In contrast, a more recent study that examined the temporal relationship between newly acquired streptococcal infections and acute exacerbations of tic and obsessive-compulsive disorders revealed no clear correlation.[50] A possible relation between ADHD and streptococcal infection requires confirmation.

Otitis Media

In preschool-aged children, otitis media was linked to hyperactive behavior and/or inattention, independent of learning disability, in 21 of 138 children evaluated in a child development clinic. Children with ADHD had significantly more complaints of earaches during the preceding 3 months and year of observation.[51] My analysis of a total of 7 articles obtained through PubMed and published between 1978 and 1999 revealed a positive association between a history of recurrent otitis media and subsequent development of typical ADHD in only 1 study; hyperactive behavior was reported in 4, combined with language and/or learning disorders in 2, and speech, language, and learning deficits in 2 patient groups. The studies were retrospective in design, and each involved between 18 and 507 children. Although typical ADHD seems to have a weak association with otitis media, some researchers consider a history of significant middle-ear disease in early childhood to be a risk factor for hyperactivity and especially speech and language disorders in children who present with learning problems in school.[52]

PERINATAL AND EARLY-LIFE RISK FACTORS

The roles of prematurity and perinatal hypoxic-ischemic encephalopathy in the pathophysiology of ADHD have been reviewed by researchers at the John F. Kennedy Institute in Glostrup, Denmark.[53] Up to one third of premature infants with birth weights of <1500 g have ADHD when examined at 5 to 7 years. The striatum and cingulate-cortical loop are vulnerable to the ischemia-induced release of glutamate, which results in hyperactive behavior, impulsivity, and inattention. The magnitude of this cause of ADHD increases with the advances in NICU nursing care and improved survival rates among premature infants.

A case-control study of 305 children with ADHD at the Mayo Clinic revealed that pregnancy and labor characteristics, low birth weight, and twin birth were not associated with ADHD. Positive risk factors included male gender and low parental education levels.[54] In contrast to the findings in this US study, a retrospective analysis of parental questionnaires regarding birth history of 196 children with ADHD followed in Iceland showed a statistically significant increased risk associated with low birth weight, young age of mother, and cesarean delivery.[55]

POSTNATAL RISK FACTORS

Cerebral trauma, meningitis, encephalitis, metabolic and endocrine disorders, toxins and drugs, and nutritional deficiencies, additives, and sensitivities are some of the factors known to be associated with ADHD. In a high proportion of these cases, a genetic factor is a likely basic cause, and the environmental factor in etiology is probably secondary, acting as a trigger. The relative importance of acquired etiologies of ADHD requires additional study. The following are some of the potentially preventable ADHD etiologic factors, although studies have provided variable results, and their significance is controversial.

Iron Deficiency and ADHD

Iron deficiency has been invoked as a risk factor in a number of neurologic disorders. The report of low ferritin levels in children with cognitive and learning disorders[56] prompted our own investigation of serum ferritin levels in patients with ADHD.[57] The mean serum ferritin level of 39.9 ± 40.6 ng/mL was not different than that of control children without ADHD, but 18% had levels below 20 ng/mL, which was considered abnormal. None had evidence of iron-deficiency anemia. A comparison of the clinical characteristics of 12 patients with the lowest serum ferritin levels (<20 ng/mL) and 12 with the highest serum ferritin levels (>60 ng/mL) disclosed no significant difference in severity or frequency of ADHD and comorbid symptoms or response to medications. In our patient cohort, a causative role for low serum ferritin levels in ADHD was not confirmed.[57] A controlled trial of ferrous sulfate supplementation may be justified for patients with ADHD and abnormally low serum ferritin levels. Supplemental iron therapy does not provide a substitute for medication in the management of ADHD, but given the positive findings in the following report, additional studies are indicated to define a possible adjuvant role.

In a French study, 84% of the patients with ADHD had serum ferritin levels of <30 ng/mL (vs 18% of controls), and 32% had levels of <15 ng/mL (compared with 3% of controls). The iron-storage levels in children in France were generally lower than those in children in Chicago, Illinois, and the results of the studies are not comparable. The authors found supplemental iron to be beneficial, but they agreed that a controlled trial is required.[58]

Role of Zinc in ADHD

In a study at Teheran University (Teheran, Iran), zinc sulfate supplements (55 mg/day), as adjunctive therapy with methylphenidate (1 mg/kg per day) in a double-blind, placebo-controlled trial in 40 children with ADHD, provided significantly greater improvement than methylphenidate/placebo treatment.[59] Several controlled studies have demonstrated a deficiency of zinc in patients with ADHD and a beneficial response to zinc sulfate supplements.[60] The majority of these reports were from Turkey and Iran, countries with suspected endemic zinc deficiency. In a single study of zinc and ADHD in the United States, the median serum zinc level in 48 children with ADHD was at the lowest 30% of the laboratory reference range. Low serum zinc levels were correlated with parent/teacher-rated inattention but not with hyperactivity/impulsivity.[61] Additional trials are recommended.

Omega-3 Fatty Acids and ADHD

The effects of dietary supplementation with fish oil and evening primrose oil were assessed in a randomized, controlled trial in 117 children with developmental coordination disorder, 32 of whom also had ADHD. Significant improvements in reading, spelling, and behavior occurred over a 3-month treatment period, but motor skills were not benefited. Comparing the Conners' Teacher Rating Scale-L/ADHD scores, a reduction and improvement of >0.5 SD were reported for children in the treatment group, whereas no change was seen in those in the placebo group ($P < .0001$). Children who continued treatment during the 3- to 6-month follow-up phase showed improvements in mean reading age of 13.5 months, a mean spelling gain of 3.5 months, and a decrease in the mean Conners' scores from a baseline of 74.7 to 52.6. The gain in reading was 3 times that expected, and spelling advanced twice the normal rate. Fatty acid daily dosages were omega-3 (558 mg of eicosapentaenoic acid and 174 mg of docosahexaenoic acid), omega-6 linoleic acid (60 mg), and vitamin E (9.6 mg of α-tocopherol, natural form). Placebo capsules contained olive oil.[62] These findings confirmed previous reports of abnormally low levels of serum essential fatty acids in hyperactive children with learning disabilities and improvements in reading ability in dyslexic patients treated with omega-3 fatty acid supplements.

Dietary modifications or supplements in the treatment of learning and behavior disorders of children have frequently fallen short of initial expectations after close and more prolonged study. Some etiologic factors invoked in ADHD have been described as myths.[63] They may include the additive-salicylate-free, hypoallergenic, sugar-restricted, megavitamin, and mineral and trace-element diets.[64] Despite the excellent experimental design of the above-mentioned study, additional controlled trials are indicated before advocating fish, with its attendant mercury exposure, or fatty acids as a general substitute for medication. The introduction of a relatively safe and well-tolerated dietary treatment could, if proven successful, serve as a complementary or substitute treatment and offset the increase in concern regarding adverse effects of drug therapies. Initial trials of adjunctive therapy with fatty acids in our attention-deficit disorder clinic have been disappointing.

Iodine Deficiency and ADHD

A prospective study of the neuropsychological development of offspring of 16 women from an iodine-deficient area in Italy found ADHD in 11 (68.7%) of 16 children and no cases from an iodine-sufficient area. The mothers of affected children were hypothyroxinemic at early gestation. Maternal hypothyroxinemia caused by iodine deficiency results in a critical reduction of intracellular triiodothyronine available to the developing fetal brain.[65] Iodine deficiency and hypothyroidism are both prenatal and postnatal risk factors for ADHD in some environments.

THYROID FUNCTION AND ADHD

ADHD has been reported in association with generalized resistance to thyroid hormone (GRTH), a disease caused by mutations in the thyroid receptor β gene and characterized by reduced responsiveness of peripheral and pituitary tissues to thyroid hormone. An evaluation of 18 families with a history of GRTH at the National Institutes of Health in Bethesda, Maryland, found that 19

(70%) of 27 affected children and 5 (20%) of 25 unaffected by GRTH had met the criteria for a diagnosis of ADHD ($P < .001$). ADHD was strongly associated with GRTH.[66] A prospective screening study for thyroid abnormalities in 277 children with ADHD at the University of Chicago found 14 children with thyroid abnormalities, but GRTH could not be demonstrated in a detailed study of 4 of 9 in whom it was suspected. The prevalence of thyroid abnormalities is higher (5.4%) in children with ADHD than in the normal population (<1%). The prevalence of ADHD in subjects with GRTH is reported to be 46%.[67] Despite reports of a lack of association between thyroid function and ADHD,[68] the number of studies that have shown positive associations support the proponents of routine screening for thyroid function, especially for patients with a family history of thyroid dysfunction.

Case reports of thyrotoxicosis and ADHD are rare and sometimes lead to a missed diagnosis when symptoms are subtle and routine testing is not performed. In a center in which thyroid-function tests were a part of the routine evaluation of children with developmental learning disabilities and ADHD, 3 patients were diagnosed with hyperthyroidism, with no systemic signs. Treatment lead to control of hyperactive behavior, increased attention span, and improved language function.[69] Suresh et al recommend thyroid screening in children with ADHD.

In our neurology ADHD clinic at Children's Memorial Hospital, thyroid screening is routine. In the past year we have uncovered 4 cases of hyperthyroidism, 2 with goiter, in patients who presented with ADHD and learning disorders. The relation of thyroid dysfunction to ADHD and learning disorders requires additional study. In pediatric practice, thyroid tests are probably justified in subjects with ADHD and a positive history of thyroid dysfunction. In a specialty clinic, on the basis of personal experience, I consider routine testing for thyroxine and thyrotropin levels justified for a child who presents with ADHD, even with absent family history, goiter, or other physical signs, but with the admission of other dissenting opinions.

CONCLUSIONS

The etiology of ADHD is multifactorial. A genetic cause linked to dopamine deficit is frequent and primary, but various environmental factors, including viral infection, maternal smoking during pregnancy, prematurity, cerebral hypoxic ischemia, alcohol exposure, and nutritional and endocrine disorders may contribute as secondary causes. The etiology is probably a combination of genetic and acquired factors in most cases. The early prenatal recognition, prevention, and treatment of environmental causes may provide more effective management and reduce the reliance on symptom modification with medication. Advice regarding hazards of nicotine and alcohol exposure and monitoring of blood count and thyroid function during pregnancy are particularly important for patients with a family history of ADHD.

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