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Original Article

Diagnosis of children's attention deficit hyperactivity disorder (ADHD) and its association with cytomegalovirus infection with ADHD: a historical review

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Abstract: As the most common mental disorder identified in children and teenagers, attention deficit hyperactivity disorder (ADHD) affects millions of children and their families, making it a critical health issue worldwide. This article reviewed the historical opinions about the diagnosis of ADHD and defined different subtypes of this disorder. It also summarized the current diagnostic criteria and available medications. After re-visiting the etiology of ADHD in the sense of both genetic and environment factors, it was further hypothesized that viral infection might be involved in ADHD pathogenesis. Human cytomegalovirus (HCMV) infection may be associated with ADHD, although both clinical observations and animal studies need to be performed for validation.

Keywords: Attention deficit hyperactivity disorder (ADHD), human cytomegalovirus (HCMV) infection, mental disorders childhood mental disorder

Introduction

Attention deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood and adolescents [1-8] with clinical manifestations including learning disabilities [13], making it a major public health issue [9]. Over the last two decades, advances have been made in both etiological and clinical understandings of ADHD [10]. However, no treatment can reverse the disease progression and completely cure all symptoms, a timely and appropriate primary care for ADHD patients is, therefore, of critical importance [11].

ADHD compromises the life quality of children and causes heavy burdens for the family [14]. ADHD patients are also predisposed to other mental dysfunctions including stigma, prejudices, and discrimination [2]. Due to lack of definitive clinical manifestation and variable etiological factors, the diagnosis of ADHD currently can only be achieved by observations of behavior symptoms, thus seriously compromising the consistency and sensitivity. The cognitive profile of ADHD had been studied by various clinicians [15], leading to several available guidelines for the patient care of ADHD children [16]. A simplified and practical guideline for ADHD diagnosis, however, is still lack.

The history of ADHD diagnosis

To improve the care of ADHD children, the American Academy of Pediatrics developed practice guidelines for primary care clinicians regarding the diagnosis and treatment of ADHD among children between 6 to 12 years old [12, 17, 18]. Optimal diagnostic thresholds for attention deficit hyperactivity disorder were determined in "Diagnostic and Statistical Manual of Mental Disorders, fourth edition" (DSM-IV) by comparing the psychometric properties to alternative definitions [19]. Since the 19th century, it has been recognized that many children suffered from hyperactive-like symptoms, which were described as mental retardation and severe nervous system damage such as "no peace, impulsivity, inattention and hyperactivity". Some of those symptoms were found to be associated with brain damage, raising the "brain injury syndrome" concept in 1940s. The

meeting of the International Child Neurology expert seminar (Oxford, UK, 1962) named these symptoms as "minimal brain dysfunction" (MBD). Later studies found that the primary mental disorder of hyperactive children was attention disorder, which occurred since early childhood in various occasions and persists until puberty. Other studies in past 30 years suggested that this condition is not only manifested as hyperactivity and attention disorders, but also includes other behavioral abnormalities such as not obeying the rules, poor self-control and poor social skills.

The first edition (ICD-10) using the name of DSM (DSM-1, 1957) failed to address the ADHD issue, but DSM-II for the first time introduced the "hyperactive response" concept. DSM-III renamed it as attention deficit disorder (ADD), which is defined as a cluster of three symptoms, namely, distractibility, impulsivity and hyperactivity. This criterion further divided ADD into two sub-types: attention disorder with hyperactivity; and those without hyperactivity. The revised DSM-III criterion further combined those two syndromes into one, named ADHD, whose diagnosis can only be satisfied with at least 8 out of 14 total symptoms as described. The updated DSM-IV standard further listed 18 symptoms of this disorder of ADHD, which was divided into three subtypes, namely, predominantly inattentive type (PI), predominantly hyperactive/impulsive type (HI) and combined type (CT) [19].

The self-awareness of ADHD may be difficult for adults who have lived with these symptoms since childhood [20]. Currently, there are two widely used diagnostic criteria for ADHD: the International Classification of Diseases (ICD) by WHO and the Diagnostic and Statistical Manual of Mental Disorders (DSM) by American Psychiatric Association. ICD-10 uses the name "hyperactivity disorders" to emphasize the two major symptoms, attention disorder and hyperactivity (impulsivity), which occur simultaneously and in multiple occasions such as home and school. This standard excludes other mental dysfunctions including anxiety disorder, mood disorder, pervasive developmental disorder and schizophrenia.

ADHD affects about 1-3% of children [1]. Despite its high sensitivity to medication, there is still no consensus on how to evaluate the treatment efficacy or to define the optimal remission in ADHD adults [35]. According to DSM-IV TR and ICD-10, a diagnosis of autism or Asperger syndrome precludes ADHD [36]. Mainly based on clinical symptoms, the predominant time period of ADHD onset is in childhood, followed by the persistence of symptoms as a result of behavioral dysfunctions. Clinicians therefore should integrate all information, including analyzing the clinical manifestations during childhood and considering patient's age and gender, to make a confirmed diagnosis. As one of the most common cognitive disorders, the routine diagnostic procedures of ADHD are still based largely, if not exclusively, on subjective assessments of perceived behavior [37].

Current diagnostic criteria and clinical features of ADHD

Childhood ADHD affects nearly all aspects of mental functions including cognitive, academic, behavioral, emotional, social, and developmental perspectives [21]. The three clinical subtypes of ADHD in DSM-IV have their unique characteristics. Studies have shown that there were poor academic scores, combined with anxiety and depression in PI type patients, which mainly consist of girls and adolescents. Children with HI type generally have no academic problems, but are more likely to be complicated with conduct disorder (CD) and oppositional defiant disorder (ODD). CT represents the most common sub-population of ADHD patients, and have combined higher ODD, CD, anxiety and depression disorders, leading to social dysfunction and poor prognosis [22, 23].

Current diagnostic criteria of ADHD require the impairment in making a diagnosis, although clinical and research definitions of ADHD rely more heavily on reported symptoms [24]. As one of the most common neuropsychiatric disorders with childhood onset, ADHD has a chronic disease course associated with high dysfunction and morbidity rates throughout patient's life [25]. Baumgaertel et al reported a 64% increase of prevalence of ADHD when applying DSM-IV standard instead of DSM-III-R criteria in diagnosing the same group of children [22]. Wolraich's study [23] also showed a higher prevalence when adopting the DSM-IV [23]. Tripp [26] compared the ICD-10 and DSM-IV diagnostic criteria on the same group of chil-

dren and found that the scope of DSM-IV diagnostic standards is broader than ICD-10, as the age range of children diagnosed under both ICD-10 and DSM-IV was younger than those simply met DSM-IV criteria [26]. The double-positive group also had more serious problems in the core symptoms, such as activity level, performance of persistent failure test, teacher evaluation attention disorder, impulse and cognitive impairments compared to DSM-IV group.

Such differentiation between two diagnostic criteria can be explained from their focuses. Attention disorder is a non-specific symptom, which can be found in emotional disorders, learning disability and a variety of other psychiatric disorders. ICD-10 standard emphasizes simultaneous attention disorder and hyperactivity/impulsivity symptoms, excluding the sole attention disorder sub-type. Therefore, the ICD-10 criterion is more rigorous than DSM-IV. In a word, clinical diagnosis of PI-type under DSM-IV should be cautious [27].

Age is one of the influencing factors for hyperactivity: ADHD patients often manifested with hyperactivity since childhood, with gradually alleviating symptoms, and may cause feelings of restlessness in adolescence. Therefore, it is reasonable that the diagnostic standards of ADHD in children should be more rigorous than that in adolescents as the latter obviously have improved conditions [28].

ADHD is highly comorbid with other psychiatric disorders, and physicians thus should consider the possibility of ADHD once there was indicators in adult patients [20]. Wender [28] reported that typical ADHD symptoms of adolescent include poor school performance, and gradually aggravated symptoms with increasing age. May be due to a higher level of intelligence, the child children are failed to be early diagnosis in the primary school stage, and the child children does not appear to have significant learning problems. While in the secondary school stage, the ADHD symptoms would be exhibited cause of the need for required higher level of awareness, more focused and durable attention. In addition, characteristic of ADHD symptoms is inappropriate behavior, such as excessive laughter, excited easily, like to tease other person without regard to the feelings of them, and giving us the “immature” feeling. Therefore, tracing a history of the diagnosis in the primary school has a very important significance.

In recent years, more and more studies concern female of ADHD. Lahey [19] reported that among girls often exist the main clinical manifestations of attention disorder, but hyperactivity is not obvious, using PI-type standards can bring more girls into the diagnosis of ADHD. Gaub [29] found that girls have little symptoms of hyperactivity and low incidence of extraversion behavioral problems, but have more damage of the cognitive and social functions. Cause of Because girls have less obvious problem of extraversion than boys, this problem cannot easily be found by parents and teachers, but they have more cognitive impairment, clinicians should concern this problem. ADHD is a group of heterogeneous disorders, and is often is associated with other childhood psychological or behavioral problems. Thus physicians should keep alert and integrate all screening results for ADHD once its clinical indicators occur in adult patients [20]. Wender et al reported that the most typical ADHD symptom in adolescents is poor school performance, and gradually aggravating conditions with increasing age [28]. It is interesting that maybe due to their higher averaged levels of intelligence, ADHD children often failed to obtain an early diagnosis at their primary school stage, when no obvious learning problem occurs. However, during the middle school stage, the ADHD symptom raises as the higher level of awareness and long-term focus during the study course. In addition, other characteristics of ADHD including inappropriate behaviors (excessive laughter, easily excited, inappropriate speaking) all endow them “immature” tag. In a word, the retrospective study of the performance in the elementary school can help to make a confirmed diagnosis.

In recent years, ADHD in females has been studied repeatedly. Lahey et al reported that girls often presented the major clinical manifestations of attention disorder except obvious hyperactivity, making them more likely to be classified as PI-type. Gaub et al also found that girls had minor hyperactivity and low incidence of extraversion behavioral problems, but were more predisposed to cognitive and social dysfunctions [29]. As girls usually have less obvious extraversion behavior compared to boys, this cannot easily be pointed by parents and teachers. Girls, however, have more cognitive impairments, which should raise clinicians’ concerns.

Identification and diagnosis of hyperactive-impulsive and attention deficits

ADHD children showed extraordinary hyperactivity and impulsivity, and adults must always take care of them in order to avoid any physical hurt. Such excessive activities of children cause heavy burdens for their parents. Those patients, at their school-age and adolescent, are manifested with higher activity, impulsive behavior, and are more susceptible to the peer pressure. All those behavioral abnormalities affect the normal function of children and adolescents. Hyperactivity, impulsive behavior of children and adolescents affect their learning skills to learn, but are not significant enough to make an ADHD diagnosis. These behaviors may also be associated with adverse emotional and aggressive or oppositional defiant behavior. A common scenario is that teenagers with hyperactivity and impulsivity problems are not peaceful in the classroom, and are easy to annoy others easily [38].

Identification and diagnosis of attention deficit

The time duration of attention in younger children is relatively short, but their focus attention functions mature gradually. Infants' attention depends on the way of the stimulus and the processing capability of auditory sense, visual or sensory inputs. Some children may note the voice of parents; other children may have response of happily facial expressions. Infancy children just only pay attention to a short story book, or a short meditation tasks (such as coloring or drawing). School-age children with attention deficiency may not wish to do works such as reading, homework. Adolescent patients are easy to be distracted. Those abovementioned children may have some of the symptoms of ADHD in attention deficit type, affecting their learning and social abilities. However, these symptoms are not significant enough for a diagnosis of ADHD. Iron and zinc are often used as supplements in patients with known attention deficiencies; they may also enhance the effectiveness of stimulant therapy [39].

Comprehensive diagnosis and medication of ADHD

ADHD is the most commonly diagnosed neurodevelopmental disorder in children and adolescents [21, 40]. There are higher rates of delinquency, incarceration, teenager pregnancy and sexually transmitted diseases associated with inadequate or delayed treatment of ADHD [41]. Obvious symptoms of hyperactivity and impulsivity displayed less frequently than younger children [42]. Despite the different conceptualization, population-based twin studies reported symptom overlap, and a recent epidemiology-based study reported a high rate of ADHD in autism and autism spectrum disorders [36]. Cantwell [43] proposed a comprehensive diagnosis by the following ways: (1) Meets all caregivers, learn of symptoms and extent of when, where and with whom together with children; (2) To assess children's symptoms and signs through observing and talking with children, learning their own interpretation and understanding problems, and most importantly, the exclusion of other disorders, especially anxiety, depression, suicidal ideation, hallucinations and abnormal thinking; (3) Check the general health status appropriately, including feeling defects, neural problems, or other physical issues; (4) Cognitive function evaluation including intelligence and learning ability; (5) Use behavior rating scale such as parent ratings, teacher ratings, or a best estimate diagnostic procedure in children and adolescents; (6) Laboratory tests, including auditory and visual tests; speech or language assessment; fine or gross motor function, continuous performance test (CPT), Wisconsin card Sorting Test, match related learning test (determination of classroom learning) etc., besides certain non-ADHD-specific tests diagnosis.

ADHD is a characterized by persistent pattern of inattention and hyperactivity, affecting multiple aspects such as it can affect motor skills, social relationships, self-esteem and educational success [44]. As the most common neurodevelopmental disorder in children and adolescents, inadequate or delayed treatment of ADHD may cause higher rates of delinquency, incarceration, teenager's pregnancy and sexually transmitted diseases. Typical symptoms including hyperactivity and impulsivity presented less frequently in teenagers than in younger children. There are symptom overlaps between ADHD and autism spectrum disorders, as supported by recent epidemiological study [36].

Stimulant medicines, such as methylphenidate, are effective treatments for ADHD as they can enhance brain dopamine signaling [48]. Pliska

et al, however, reported that the efficacy of methylphenidate in the treatment of ADHD associated with anxiety was unsatisfactory [49], while Galland's findings suggested that methylphenidate can increase sleeping time but not sleep rhythm in ADHD children [50]. Tricyclic antidepressants, on the other hand, can relieve depression and improve children's self-esteem, making it a better choice on children with both ADHD and introversion problems.

Etiology of ADHD and its association of with human cytomegalovirus

Jenson's study tracked a group of children with ADHD for five to seven years and found that ADHD patients associated with misconduct had more antisocial behavior and aggravating reading skills compared to pure ADHD patients [45]. The early onset of antisocial behavior also caused unfavorable prognosis [46], as those children are more vulnerable to school failure, mental illness or substance abuse. Cadoret's research further found that parents with ADHD fostered their children with more criminals [47]. A family study found that the first-degree relatives of ADHD patients have more anxiety and depressive disorders, suggesting that ADHD and mood disorders that share common genetic predisposition [45].

A better understanding of the immune response to certain congenital infections may provide useful information for the pathophysiology and etiology of autism in vulnerable individuals [32]. Various studies showed that ADHD shares the same pathogenesis as autism and other mental disorders in children [33, 34]. Currently there are autoimmune hypothesis and viral infection hypothesis underlying ADHD etiology, the latter of which states that ADHD is associated with lentivirus infection. The viral particle may lurk in the central nervous system by integrating its DNA into the host genome. The viral protein will then be translated under certain stimulus such as the allogeneic antigen which can cause injury of the immune response. Viral activation thus leads to brain damage and results in abnormal regulatory functions, incoordination of neurological-endocrine-immune damaged, and symptoms of ADHD.

Human cytomegalovirus (HCMV), a DNA virus, invades via a long-term latent viral body. Once the body immune system is compromised, the latent HCMV can be activated and replicated quickly, resulting in multi-organ damages, especially in central nervous system. This virus has been reported to have oncogenic roles, possibly via its ability to alter host gene expression [30]. HCMV has been shown to be associated with schizophrenia, bipolar disorder and cognitive deficits in certain populations [30]. Congenital viral infection presents as a neurodegenerative disorder [31].

HCMV infection may be associated with ADHD. HCMV is generally susceptible, highly infectious in human especially in children. Viral body, after infecting body cells, continues to lurk to avoid the host immune attack. When the host body suffers from traumatic conditions such as psychological pressure, the body's resistance to the latent virus may be compromised, causing the activation of HCMV. The virus starts to replicate, causing damages in certain parts of the central nervous system, neuroendocrine changes, leading to various symptoms. HCMV infection somehow alters the body immune function as: (1) B cells will cause immune tolerance, followed by decreased production of antibodies, making the viral body more difficult for clearance; (2) Cytotoxic metabolites of HCMV will activate CD 8+ cytotoxic cells, which change the balance of CD 4+/CD 8+ cells, thus compromising the body's immune function; and (3) HCMV impedes the immune system's regulation on the neuroendocrine system, causing symptoms related to the incoordination with neuroendocrine-immune axis. Currently no direct study has been performed about the association between ADHD and HCMV. However, due to recent findings about its regulation of glutamate uptake and transporter expression in astrocytes [51], HCMV may have certain roles in the pathogenesis of ADHD. Further studies could be pursued in terms of viral expression study in humans, and infections in animal models.

In summary, ADHD is a major concern of the mental health in children and adolescents. Due to its complex subtyping and clinical features, it is probably that multiple factors, including both genetic and environmental influences are involved in the pathogenesis of ADHD. HCMV has the potency to be responsible for at least part of ADHD cases and is worth for further studies as a candidate drug target.

Disclosure of conflict of interest

None.

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