Psychiatry Research 219 (2014) 609–616

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Differential perinatal risk factors in children with attention-deficit/hyperactivity disorder by subtype

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ARTICLE INFO

Article history:
Received 2 August 2013
Received in revised form
16 May 2014
Accepted 18 May 2014
Available online 28 May 2014

Keywords:
Attention-deficit hyperactivity disorder
subtype
perinatal risk factors

ABSTRACT

We compared the attention-deficit/hyperactivity disorder(ADHD) combined subtype (ADHD-C) to the ADHD inattentive subtype (ADHD-I) in terms of genetic, perinatal, and developmental risk factors as well as clinical and neuropsychological characteristics. A total of 147 children diagnosed with ADHD between the ages of 6 and 15 years participated in this study. The parents of the children completed the structured diagnostic interview, the ADHD Rating Scale-IV, the Children's Behavior Checklist, and structured questionnaires on perinatal risk factors, and the children underwent a neuropsychological test and were genotyped. A total of 502 children without ADHD were recruited from the community as a healthy control group. The ADHD-C children showed more severe externalizing symptoms, showed more deficits in a continuous performance test, and were more likely to have comorbid disorders. Maternal stress during pregnancy, postpartum depression, and changes in the primary caretaker during first 3 years were significantly associated with both ADHD-I and ADHD-C. The ADHD-I group was less likely to have received regular prenatal check-ups and more likely to have had postnatal medical illness than the ADHD-C group. There were no significant differences in the genotype frequencies of the dopamine transporter (DAT1) and the serotonin transporter –linked polymorphic region (5-HTTLPR) polymorphisms between ADHD-I and ADHD-C groups. This study shows that the inattentive subtype of ADHD is different from the combined subtype in many parameters including severity of symptoms, comorbidity, neuropsychological characteristics, and environmental risk factors.

1. Introduction

The worldwide-pooled prevalence of attention-deficit hyperactivity disorder (ADHD) is reportedly 5.29% (Polanczyk and Rohde, 2007). ADHD presents with symptoms of inattention, hyperactivity/impulsivity or both. The consequences of this disorder are well recognized and include the inability to thrive in both school and social settings. The genetic heritability of ADHD is reported to be approximately 75% (Faraone et al., 2005), and environmental factors such as perinatal risk factors are estimated to account for 25% of the development of ADHD (Ben Amor et al., 2005).

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) classifies ADHD into three subtypes, inattentive [ADHD-I], hyperactive/impulsive [ADHD-H], and combined [ADHD-C]), based on clinical phenomenology. In the last decade, a heated debate has emerged regarding whether ADHD-I is a separate disorder rather than a subtype of ADHD (Milich et al., 2001). Although ADHD-C and ADHD-I patients both have problems with inattention, the type of inattention suffered by these two groups may be different. In particular, the truly inattentive type of ADHD (ADHD-I without hyperactivity) has been proposed as a potentially separate condition from ADHD, which includes hyperactivity (Diamond, 2005). In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (AmericanPsychiatricAssociation, 2013),), subtypes have been replaced by the similarly defined "specifiers" in the current presentation.

Many comorbidities are associated with ADHD, including conduct disorder (CD)(Rhee et al., 2008), oppositional defiant disorder (ODD)(Gadow et al., 2007), anxiety disorder (Bowen et al., 2008), and depression (Blackman et al., 2005). Faraone et al. (1998) found that children with ADHD-C had more ODD and CD than children with ADHD-I or ADHD-H. They also found that although all three

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http://dx.doi.org/10.1016/j.psychres.2014.05.036
0165-1781/

subtypes presented with the same level of anxiety disorders, both ADHD-C and ADHD-I were significantly associated with increased rates of depressive disorders compared to ADHD-H. Gaub and Carlson (1997) found that children with combined and hyperactive subtypes have more externalizing behaviors than those with the inattentive subtype and controls. However, they also found that ADHD-C and ADHD-I patients have higher levels of internalizing disorders than ADHD-H patients and controls.

The current phenotypic classification of ADHD subtypes raises the question of whether ADHD-I and ADHD-C are different at a more fundamental level, i.e., whether differences may be present at the neuropsychological measurement levels that are not present at the level of clinical psychiatric measurements. Deficits in executive functioning and attentional processes are supposed to be the central pathophysiology of ADHD. When subtypes are taken into account, the inhibition deficit seems to be uniquely linked to ADHD-C (Barkley, 1997; Houghton et al., 1999; Klorman et al., 1999; Nigg et al., 2002), although contradictory findings have emerged regarding other EFs, such as visual working memory, planning, cognitive flexibility, and verbal fluency (Paternite et al., 1996; Klorman et al., 1999; Lockwood et al., 2001; Nigg et al., 2002). Although previous research has often failed to find significant differences in attentional performance as measured by a continuous performance test (CPT) between ADHD-I and ADHD-C (Paternite et al., 1996; Barkley, 1997), a study by Collings(Collings, 2003) produced more subtle findings; the performance of an ADHD-C group deteriorated much faster than that of an ADHD-I or control group, which led to the conclusion that only the former subtype displays a sustained attention deficit.

Three articles reviewing work comparing ADHD-C and ADHD-I have all underscored the paucity of studies comparing the etiologies of the two subtypes in terms of genetics and environmental factors (Milich et al., 2001; Woo and Rey, 2005; Baeyens et al., 2006). Although environmental factors may have less effect on the development of ADHD than genetic factors, they are important, particularly in public mental health perspectives, because of their preventable nature. Studies on environmental factors have associated the risk for ADHD with low birth weight (Linnet et al., 2006), maternal smoking (Linnet et al., 2003), maternal alcohol consumption (Mick et al., 2002), and maternal stress during pregnancy (Grizenko et al., 2008). Oades (2011) found that in ADHD children more than in controls, a stress-associated perinatal experience was related to the balance of metabolites of the tryptophan/kynurenine pathway and cytokine activity, which are associated with ADHD symptoms and attention-related performance (Oades et al., 2010). These results suggest that certain types of perinatal stress could contribute to the ADHD phenotype by altering certain aspects of the tryptophan/kynurenine pathway and cytokine activity. However, we know of only one study comparing perinatal risk factors for ADHD according to subtype; Grizenko et al. (2010) reported that ADHD-Cchildren are exposed to more moderate to severe stress during their mothers' pregnancies than are ADHD-I children.

In terms of genetics, the fact that ADHD has a high population frequency, that twin studies show clinical heterogeneity, and that linkage analyses in families have proven the heterogeneity of linkage shows that multiple genes must have major or minor effects on a variety of genetic subtypes (Sharp et al., 2009). Genes with dominant effects associated with ADHD-subtype phenotypes have been proposed (Acosta et al., 2004). Some studies linking genetic variants to ADHD provide clues to ADHD subtype differences at a molecular genetic level. For example, Waldman et al. (1998) reported that the number of dopamine transporter (DAT1) high-risk alleles (10 repeats in the variable number of tandem repeats) was directly associated with the number of hyperactive-impulsive symptoms but not with the number of inattention symptoms in a group of 117 probands. They also found a linkage disequilibrium for the 10-repeat allele in the ADHD-C group but not in the ADHD-I group when examining 122 families. Moreover, Grizenko et al. (2010) reported that ADHD-C children showed a higher frequency of L/L genotype for the 5-HTTLPR compared to ADHD-I children in a group of 371 children with ADHD. A meta-analysis of two functional polymorphisms within the DRD4 gene (120-bp duplication in the promoter and 48-bp VNTR in exon 3) in a clinical sample of 1,608 adult patients with ADHD and 2,352 controls of Caucasian origin showed an association of the L-4R haplotype (dup120bp-48bpVNTR) with adulthood ADHD, especially with ADHD-C (Sánchez-Mora et al., 2011).

To overcome the above-mentioned limitations, we compared a comprehensive set of perinatal and developmental risk factors among children with ADHD-I and ADHD-C and healthy controls. We also compared clinical and neuropsychological characteristics and genotype frequencies of the DAT1 and 5-HTTLPR polymorphisms according to subtype of ADHD to reconfirm previous findings in our sample.

2. Methods

2.1. Participants and procedures

We recruited children with ADHD from the child psychiatric clinic of the Seoul National University Hospital in South Korea. The recruited children were aged between 6 and 15 years and had been given a diagnosis of ADHD according to the DSM-IV criteria by a child psychiatrist. The exclusion criteria included the following: 1) a history of pervasive developmental disorder including autism, mental retardation, bipolar disorder, psychotic disorder, obsessive compulsive disorder, or Tourette's syndrome; 2) a history of organic brain disease, seizure disorder, or another neurological disorder; 3) an IQ below 70; 4) the presence of learning disabilities or language disorders; 5) the presence of major depressive disorder, anxiety disorder, or tic disorder requiring drug therapy; and 6) any previous administration of methylphenidate for more than 1 year or within the last 4 weeks. To diagnose ADHD and any comorbid disorders, we used the Korean Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) (Kim et al., 2004).

The non-ADHD control group was composed of participants in the research project titled, "The effects of pollution on neurobehavioral development and future policies to protect our children". Control subjects were recruited from five different administrative regions of Korea: Seoul, Seongnam, Incheon, Ulsan, and Yeoncheon (Cho et al., 2013). We selected two to three elementary schools from each region that best represented the local demographics. We used the parent version of the Diagnostic Interview Schedule for Children version-IV (DISC-IV) ADHD module to diagnose ADHD (Shaffer et al., 2000; Cho et al., 2006). Among the 921 children who participated in the diagnostic interview, the 48 children who met all the DSM-IV criteria for ADHD and the 106 who met the DSM-IV criteria for ADHD except the number of Criterion A symptoms (the presence of at least 3 and no more than 5 inattentive and/or hyperactive/impulsive symptoms) were excluded. Among the remaining 767 children, a total of 389 boys and 113 girls were randomly selected for inclusion in the present study to match the patient group in terms of sex ratio.

For both ADHD and control groups, we assessed intellectual abilities using the abbreviated form of the Korean Educational Development Institute's Wechsler Intelligence Scales for Children (KEDI-WISC) (Park et al., 1996), which tests vocabulary, arithmetic, picture arrangement, and block design. Parents completed the questionnaires on perinatal and developmental risk factors and clinical scales. For the children with ADHD, a neuropsychological test and molecular genotyping were also done. Based on the previous studies (Waldman et al., 1998; Curran et al., 2005; Grizenko et al., 2010), the DAT1 and serotonin transporter (5-HTT) genes were selected as the candidate genes associated with subtype of ADHD.

We gave the parents and children detailed information about the study and then obtained written informed consent before any child entered the study. The study protocol was approved by the institutional review board of the Seoul National University Hospital.

2.2. Perinatal and developmental risk factors

Mothers completed structured questionnaires on perinatal and developmental risk factors for ADHD. The risk factors were grouped into four categories: prenatal factors, postnatal factors, child-rearing factors, and early developmental factors.