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Associations between urinary cotinine and symptoms of attention deficit/hyperactivity disorder and autism spectrum disorder

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ABSTRACT

Background: The present study investigated associations between urinary cotinine levels as a biomarker of secondhand smoke exposure and symptoms of attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).

Methods: A total of 520 child participants (200 with ADHD, 67 with ASD, and 253 normal control subjects) were assessed using the Korean version of the ADHD rating scale (K-ARS), Autism spectrum screening questionnaire (ASSQ), and Behavioral Assessment System for Children, second edition (BASC-2). The Korean version of the computer-based continuous performance test was used to assess cognitive function. Urinary cotinine was evaluated as a biomarker of secondhand smoke exposure.

Results: Urinary cotinine levels were significantly and positively associated with K-ARS score (B = 4.00, $p < 0.001$), ASSQ score (B = 1.71, $p = 0.030$), the behavioral problem subscales of the BASC-2 (B = 1.68–3.52, $p < 0.001$–0.045), and omission and commission errors in the continuous performance test (B = 6.21–8.42, $p < 0.001$–0.019). Urinary cotinine levels were also associated with the increased odds ratio of ADHD (OR = 1.55, 95% CI 1.05–2.30, $p = 0.028$) and ASD (OR = 1.89, 95% CI 1.12–3.21, $p = 0.018$).

Conclusion: Urinary cotinine levels were associated with lower behavioral adaptation and cognitive function and increased odds ratios of ADHD and ASD, indicating a negative effect of secondhand smoke exposure on the symptomatic manifestation of ADHD and ASD.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are 2 major neurodevelopmental disorders in the field of child and adolescent psychiatry. The prevalence of ADHD and ASD in children are estimated to be 5% and 1%, respectively (American Psychiatric Association, 2013; Polanczyk et al., 2007). Although hyperactivity, impulsivity, and inattention are core symptoms of ADHD, ADHD is also associated with emotional dysregulation (Shaw et al., 2014), anxiety (Schatz and Rostain, 2006), deficits in executive function (Willcutt et al., 2005), and learning disability (Semrud-Clikeman et al., 1992). Similarly, ASD is characterized by impairments in social communication and restricted interest, but is otherwise a heterogeneous disorder that can include intellectual disability (Matson and Shoemaker, 2009), hyperactivity (van Steijn et al., 2012), and emotional dysregulation (Samson et al., 2014).

Although the prototype symptoms of ADHD and ASD are quite different, the diagnostic criteria in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) prohibit the comorbid diagnosis of ADHD and ASD, attributing hyperactivity and impulsivity to ASD in patients with an ASD diagnosis (American Psychiatric Association, 2000). Yet, recent studies indicate a high comorbidity of ADHD and ASD (van Steijn et al., 2012), with reported prevalence ranging widely from 14% to 78% (Jang et al., 2013). Rommelse et al.

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ASSQ, Autism spectrum screening questionnaire; BASC-2, Behavioral Assessment System for Children, second edition; CPT, Continuous performance test; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; SHS, Exposure to secondhand smoke; K-ARS, Korean version of the ADHD rating scale

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(2010) reported that 20–50% of children with ADHD also meet the criteria for ASD, and that 30–80% of children with ASD meet the criteria for ADHD. Thus, the DSM-5 allows the comorbid diagnosis of ADHD and ASD (American Psychiatric Association, 2013).

Both ADHD and ASD are highly heritable, with heritability estimates of 0.76 (Faraone et al., 2005) and > 0.90 (Rutter, 2000), respectively. ADHD and ASD are also reported to share 50–72% of contributing genetic factors (Rommelse et al., 2010). Yet, the exact etiologies of each disease are unknown. Environmental factors associated with ADHD and ASD include various bioactive chemicals, such as bisphenol A, lead, mercury, phthalate, and organochloride pesticides (De Cock et al., 2012; Symeonides et al., 2013).

Exposure to secondhand smoke (SHS) is another important environmental risk factor for ADHD (Cho et al., 2013; Kaur, 2014; Langley et al., 2005; Rückinger et al., 2010; Tiesler et al., 2011). Although there is some controversy regarding the effect of prenatal SHS on ADHD (Thapar et al., 2009), Tiesler et al. (2011) reported that SHS during both the pre- and post-natal periods increased the likelihood of hyperactivity/inattention problems in children (odds ratios of 1.67 and 1.97, respectively). Rückinger et al. (2010) also reported that pre- and post-natal SHS increased the risk of hyperactivity by 2-fold.

In contrast, a possible association between prenatal SHS and ASD is plausible, but is backed by inconsistent findings (Lee et al., 2012). Tran et al. (2013) reported that maternal smoking was associated with an increased risk of pervasive developmental disorder, not including childhood autism or Asperger's syndrome. Other meta-analyses reported that maternal smoking during pregnancy was not associated with ASD in children (Rosen et al., 2015; Tang et al., 2015). In contrast, studies supporting an association between SHS and ASD were potentially confounded by parent socio-demographic characteristics such as age, education, income, and occupation (Kalkbrenner et al., 2014; Lee et al., 2012).

Other studies have investigated the effects of SHS on cognitive function. Cho et al. (2013) reported that urinary cotinine was negatively associated with scores on the continuous performance test (CPT) and positively associated with ADHD rating scale scores. Llewellyn et al. (2009) reported that SHS was associated with an increased risk of cognitive impairment on neuropsychological testing in non-smokers. Another systematic review reported that SHS was associated with an increased risk of neurodevelopmental delay and poor cognitive performance (Chen et al., 2013).

No study to date has comparatively assessed the effects of smoke exposure on childhood ADHD and ASD. Thus, the goal of this research was to investigate associations among SHS, ADHD, and ASD in comparison to a normal control cohort.

2. Methods

2.1. Participants

This study included elementary school-age (1st to 3rd grade) children who completed ADHD and ASD screening in Cheonan, Korea, which is a medium sized city with a mixture of urban and rural areas. The screening questionnaire was distributed to consenting parents or guardians of 30,227 children and the questionnaire included the Korean version of the ADHD rating scale (K-ARS) and the Autism Spectrum Screening Questionnaire (ASSQ). Among the total population, 523 children were enrolled in this case–control study, based on K-ARS and ASSQ cutoff scores of 19 and 15, respectively. The distribution of the screening questionnaire scores was as follows: 266 with ≥ 19 on the K-ARS; 135 with ≥ 15 on the ASSQ; 97 with both ≥ 19 on the K-ARS and ≥ 15 on the ASSQ; and 219 with both < 19 on the K-ARS and < 15 on the ASSQ. Participating children were assessed by a psychiatrist using a diagnostic interview. Three children were excluded after the assessment for refusing to participate in the study. Of 520 children who were included in the analysis, 200 were diagnosed with ADHD, 67 were diagnosed with ASD, and 253 were normal control subjects. Cases of comorbid ADHD and ASD were categorized as having ASD based on the DSM-IV diagnostic criteria. A flow chart for the selection process of the participating subjects is shown in Fig. S1. The study protocol was approved by the institutional review board of a university hospital. All participating children and their parents or guardians provided informed consent after receiving a complete explanation of the study.

2.2. Assessments of behavior and neuropsychological function

Parents completed a questionnaire about demographics and related factors, including socioeconomic status, secondhand smoking exposure, parental age, parental education, and medical and obstetric histories of the children. Parental educational level was classified as high school graduate or less (≤ 12 years of education) or more advanced than high school graduate (> 12 years of education). Household income was classified as either less or more than 3 million won per month (approximately 3000 USD).

The ADHD rating scale, which was developed to assess the symptom severity of ADHD (DuPaul et al., 1998), consists of 18 items reflecting the DSM-IV diagnostic criteria for ADHD. Each item of the K-ARS is rated on a 4-point Likert scale (0–3 points, total score 0–54) using *never or rarely, sometimes, often,* or *very often* as responses. Our study used a previous validated Korean version of the ADHD rating scale (So et al., 2002). The ASSQ is a screening tool for higher-functioning autism that consists of 27 items scored on a 3-point scale with a score range of 0–54 points; this study employed a previously validated version of the ASSQ in Korean (Ehlers et al., 1999; Lee and Cho, 2009). The Behavioral Assessment System for Children, second edition (BASC-2) was completed by parents as an assessment behavioral and emotional function. The BASC-2 is a multidimensional assessment system that assesses internalizing and externalizing psychopathologies, and is checked by parents or a teacher (Reynolds, 2004). The child version of the BASC-2 consists of 160 items rated on a 4-point Likert scale (i.e., 0 = Never, 1 = Sometimes, 2 = Often, and 3 = Almost Always). Attention and response inhibition were assessed using the Korean version of the computer-based CPT (Greenberg and Waldmant, 1993), the ADHD Diagnostic System (ADS), which includes visual and auditory versions. BASC-2 and ADS scores were converted to standardized T scores (mean = 50; standard deviation = 10). Five children did not have completed BASC-2 assessments (2 in the normal control group, 2 in the ADHD group, and 1 in the ASD group). Thirty children failed to complete the auditory ADS and 17 of these children also failed to complete the visual ADS.

2.3. Measurement of urine cotinine

Urine samples were collected from children during hospital visits and urinary cotinine levels were measured with an enzyme-linked immunosorbent assay kit (Calbiotech, Spring Valley, CA, USA). The intra-assay and inter-assay coefficients of variation were 4.2–8.4% and 5.8–14.7%, respectively. All limit of detection (LOD) values were substituted by LOD/2.

2.4. Statistical analyses

Demographic variables were analyzed by chi-square tests and analyses of variance (ANOVAs). ANOVAs and post-hoc Bonferroni tests were used to compare clinical measurements including K-ARS scores, ASSQ scores, BASC-2 subscales, and ADS scores. Generalized linear models were used to investigate associations between urinary cotinine levels and clinical characteristics, including K-ARS, ASSQ, BASC-2, and ADS scores. A multinomial regression analysis was used to investigate the odds ratios of ADHD and ASD according to urinary cotinine level. The generalized linear model and multinomial regression analysis were adjusted for age, sex, paternal and maternal educational level, and