Attention Problems and Attention-Deficit/ Hyperactivity Disorder in Discordant and Concordant Monozygotic Twins: Evidence of Environmental Mediators

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ABSTRACT

Objective: To study familial and nonfamilial environmental influences on attention problems and attention-deficit/ hyperactivity disorder (ADHD) in monozygotic twins discordant and concordant-high and low for these traits. **Method:** Ninety-five twin pairs from The Netherlands Twin Register were selected. Longitudinal survey data were collected at 1, 2, 3, 5, 7, 10, and 12 years from parents, twins, and teachers. Mothers participated in a structured clinical interview when twins were between 10 and 17 years of age. **Results:** Affected twins from discordant pairs scored higher than unaffected cotwins on multiple measures of attention problems, ADHD, and other behavior problems according to mother, teacher, and self. Behavioral discordance was evident at age 2 and all subsequent measurements. Compared with unaffected cotwins, affected twins had lower birth weight and delayed physical growth and motor development. Differences between discordant and concordant groups were reported for maternal smoking, sleeping in different rooms, and living with only one parent. **Conclusions:** Significant markers of ADHD are found in infancy and include low birth weight and delayed motor development. As the knowledge of specific genetic and environmental influences on ADHD increases, future studies may focus on their complex interplay. *J. Am. Acad. Child Adolesc. Psychiatry,* 2007;46(1):83–91. **Key Words:** monozygotic twins, discordant twins, attention problems, attention-deficit/hyperactivity disorder, environmental risk factors.

In the field of developmental psychopathology, there is increasing enthusiasm for the study of specific genetic and environmental influences on attention-deficit/ hyperactivity disorder (ADHD; Kahn et al., 2003). This report presents a powerful method to identify environmental influences on ADHD, namely, the monozygotic (MZ) discordant twin design.

The etiology of ADHD has been studied extensively. Twin, family, and adoption studies provide evidence of significant genetic influences on ADHD (Derks and Boomsma, in press; Faraone and Doyle, 2000) with heritability estimates of at least 60%. This implies that environmental factors may explain as much as 40% of the etiology of ADHD. The search for environmental factors that contribute to the development of ADHD has yielded a number of candidates. These candidates include poor parenting strategies and family dysfunction (Biederman et al., 2002), low parental socioeconomic status (SES) and environmental deprivation (Ornoy, 2003), food additives, (Boris and Mandel, 1994), maternal smoking (Thapar et al., 2003),

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maternal alcohol consumption (Knopik et al., 2005), and traumatic brain injury (Bloom et al., 2001). The strongest evidence concerns insults that occur during the pre- and perineonatal period such as intrauterine exposure to nicotine, which has repeatedly been associated with increased (up to twofold) risk of ADHD (reviewed in Linnet et al., 2003). The relationship between maternal smoking during pregnancy and ADHD in offspring remains significant after controlling for parental ADHD status (e.g., Mick et al., 2002). Children who are born prematurely and with low birth weight are also at increased risk of developing symptoms of ADHD (for meta-analysis, see Bhutta et al., 2002). The relative value of adversity, low birth weight, exposure to intrauterine alcohol, cocaine, nicotine, lead, and viral infections have been hypothesized as potential contributors to the etiopathology of ADHD.

The interaction between environmental mediators and specific genes has been studied by Kahn et al. (2003) who reported that prenatal nicotine exposure and a particular DAT polymorphism (DAT 10 repeat) increase the risk of ADHD only when both risk factors are present. Early findings such as these have increased the need to refine both our molecular genetic and environmental assessment strategies.

A unique application of the twin design, and the focus of this report, is the investigation of specific, unique environmental influences on ADHD through the Monozygotic Twin Difference Method (Martin et al., 1997). Because MZ twins nearly always have identical genomes, most differences in their behavior must be caused by the effects of environmental influences, which may act directly on the phenotype, or, for example, through postgenomic modifications via methylation processes (Fraga et al., 2005). A group of MZ twins discordant for ADHD has previously been described in terms of clinical characteristics (Sharp et al., 2003) and brain anatomy (Castellanos et al., 2003). These MZ discordant twins demonstrated decreased familiality of ADHD in terms of lower symptom scores in fathers when compared with affected singletons. Also, affected twins had lower birth weights, were more likely to present in breech position, and had volumetric reductions in caudate nucleus compared with unaffected cotwins.

This study expands on this prior work by using prospective data to evaluate differences within MZ discordant pairs. We also compare MZ discordant pairs to MZ concordant pairs. We look at a large range of environmental mediators such as maternal smoking and alcohol use during pregnancy, duration of pregnancy, placenta sharing, birth weight and height, time in the incubator, and medical complications. Developmental processes are considered such as rate of maturation, physical health, and medical histories. Environmental factors such as sharing a bedroom or classroom and living with only one parent are also examined.

The aim of this study was to identify and describe environmental mediators of attention problems (APs) and ADHD. MZ twins were selected for discordance in AP symptom scores on the Child Behavior Checklist (CBCL) and ADHD symptom scores obtained with the Diagnostic Interview Schedule for Children (DISC). Two groups of MZ concordant pairs were included: concordant for high APs/ADHD and concordant for low APs/ADHD. All twin pairs were recruited from The Netherlands Twin Register (NTR), which consists of more than 25,000 twin pairs studied prospectively since birth. Their parents and teachers participate in survey studies and provide the data for prospective analyses of AP/ADHD environmental risk factors.

METHOD

Subjects

Twins from the NTR (Boomsma et al., 2002) enroll in longitudinal survey studies that focus on growth, health, and the development of behavior and behavior problems. Surveys are sent to the parents when the twins are 1, 2, 3, 5, 7, 10, and 12 years old and to the teachers from age 7 onward.

Ninety-five MZ twin pairs participated in this study. They were selected from two ongoing studies of the NTR. One study (henceforth referred to as wave I) combines information from multiple informants, time points, and assessment techniques to identify heritable phenotypes for ADHD. The other study (wave II) uses magnetic resonance imaging to trace symptoms of ADHD back to abnormalities in neural structure and processing. The selection procedures employed in both waves are summarized in Figure 1.

For wave I, children were selected from birth cohorts 1989–1992 and for wave II from cohorts 1986–1994. Subjects who were likely to be MZ twins were selected among twins whose mothers had completed the NTR surveys at ages 7, 10, and/or 12 years at least at two time points. Within the remaining sample, discordant and concordant twin pairs were selected for interview participation. A twin pair was initially regarded as discordant if one twin scored high on APs measured with the CBCL ($T \geq 60$ at all available time points and $T \geq 65$ at least once). A twin pair was regarded concordant-low if both twins had low AP scores ($T \leq 55$ at all available time points) and concordant-high if both twins had high scores. Discordant and concordant pairs were matched on gender, zygosity, date of birth, maternal age, and parental SES. For wave II, matching criteria were