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Severe psychosocial stress and heavy cigarette smoking during pregnancy: an examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome

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Abstract

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Attention-deficit/hyperactivity disorder (ADHD) is frequently diagnosed in children with Tourette syndrome (TS). The basis for this co-occurrence is uncertain. This study aimed to determine if specific pre- and perinatal risk factors, including heavy maternal smoking and severe psychosocial stress during pregnancy, were associated with one or both disorders, or neither. We compared maternal report data on pre- and perinatal risk factors on 222 children between the ages of 7 and 18 years including 45 individuals with TS alone, 52 individuals with ADHD alone, 60 individuals with condition of comorbid TS + ADHD, and 65 unaffected control children. Pre- and perinatal histories as well as psychiatric assessments were performed using standardized questionnaires and semi-structured interviews with the mothers and children. Logistic regression was used to determine the odds ratio for each variable of interest. Compared to the mothers of unaffected control children, the mothers of children with ADHD alone reported higher rates of heavy smoking (>10 cigarettes per day) during pregnancy and higher levels of severe psychosocial stress during pregnancy (OR = 13.5, $p < 0.01$ and OR = 6.8, $p < 0.002$, respectively). The TS + ADHD and the TS alone patients also had higher rates heavy maternal smoking and high levels of psychosocial stress compared to the control children, but these differences failed to reach statistical significance (heavy smoking: OR = 8.5, $p < 0.052$, OR = 4.6, $p < 0.19$, respectively; severe psychosocial stress: OR = 3.1, $p < 0.07$, OR = 2.6, $p < 0.11$, respectively). Heavy maternal smoking and severe levels psychosocial stress during pregnancy were independently associated with a diagnosis of ADHD. TS patients also had higher rates of these risk factors, but the ORs failed to reach statistical significance. Efforts are needed to reduce the frequency of these risk factors in high-risk populations. Future studies, using genetically sensitive designs, are also needed to sort out the causal pathways.

Keywords

Tourette syndrome (TS); Attention-deficit/hyperactivity disorder (ADHD); Environmental factors; Obstetric complications; Pre-; perinatal complications

Introduction

Tourette syndrome (TS) and attention-deficit/hyperactivity disorder (ADHD) are common neuropsychiatric disorders of childhood onset, and they frequently co-occur [1–4]. The co-occurrence of TS and ADHD is often associated with academic difficulties, peer rejection, family conflict, and disruptive behaviors such as aggression, explosive behavior, low frustration tolerance, and noncompliance [5–8]. The reasons for the high rate of co-occurrence of tic disorders and ADHD are unclear. Genetic factors may be involved, and the available evidence suggests common neurobiological substrates, in particular fronto-striatal circuits [9, 10].

The potential role of environmental factors contributing to the etiology of TS has not been a major focus of research. The few extant studies suggest that children with tics or TS have higher rates of risk factors, including advanced parental age, maternal smoking, and severe maternal psychosocial stress, during pregnancy, increased rates of pregnancy and delivery complications, as well as low birth weight (LBW) and lower APGAR scores. These findings, however, have not been consistently replicated across studies [11–19]. In contrast, research in ADHD is more robust, implicating pre- and perinatal factors including maternal smoking and increased maternal stress during pregnancy, as well as pregnancy and delivery complications (i.e., toxemia, preeclampsia, poor maternal health, advanced maternal age, long duration of labor, fetal distress, ante partum hemorrhage, and LBW [20–30]).

The objective of this study was to assess the rates of pre-and perinatal risk factors associated with one or both disorders or neither. Our four a priori hypotheses were that: (1) heavy

maternal smoking; (2) high levels of maternal stress; (3) LBW; and (4) acute hypoxic–ischemic events, would be encountered most commonly in the histories of individuals with ADHD, with or without co-occurring TS.

Patients and methods

Subjects

The 222 participants between the ages of 7 and 18 years included 45 individuals with TS alone, 52 individuals with ADHD alone, 60 individuals with condition of comorbid TS + ADHD, and 65 individuals without major neuropsychiatric disorders. Subjects were recruited to participate in one or more studies of childhood neuropsychiatric disorders conducted at the Yale Child Study Center between 1993 and 2003. The TS sample was ascertained through the Tic Disorder Clinic and through the local membership of the Tourette Syndrome Association. Subjects with a primary diagnosis of ADHD were recruited either through the Yale outpatient clinic or through the local membership of Children and Adults with Attention Deficit Disorder (CHADD). Unaffected controls were recruited from a list of 10,000 names purchased from a telemarketing company. The names were identified by the company as representing individuals whose ages were within a specified range and whose residences were within particular ZIP codes (chosen to match the ages and ZIP codes for the subjects with TS). Individuals from the list were selected for contact by the investigators using a random number generator. Introductory letters were followed by screening telephone calls. Approximately 10% of the eligible control families who were contacted ultimately participated.

Participants with TS or ADHD met DSM-IV criteria for one or both of these diagnoses [31]. Exclusionary criteria included another major neuropsychiatric disorder that antedated the onset of TS or ADHD. Children in the comparison group had no current axis I disorder or history of tics, OCD, or ADHD. Additional exclusionary criteria for all groups included epilepsy, head trauma with loss of consciousness, lifetime substance abuse, psychotic disorder, developmental delay, or IQ less than 80, as measured by the Wechsler Intelligence Scale for Children-III [32].

Written informed consent was obtained from all parents, and signed assents were also obtained from the child or adolescent. The institutional review board at Yale University School of Medicine approved the study.

Diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (SADS-PLV) [33] and a “best estimate” consensus procedure in which expert clinicians (JFL, BSP, RAK, and PJL) considered all available clinical and diagnostic information [34]. The severity of ADHD symptoms was assessed by parental report using the DuPaul-Barkley ADHD rating scale [35]; severity of tic symptoms (current and worst ever), excluding the impairment scale, was assessed by expert clinicians using the Yale global tic severity scale (YGTSS) [36]; obsessive compulsive symptom severity was estimated by expert clinicians using the Children’s Yale-brown obsessive compulsive scale (CY-BOCS) [37]; anxiety symptoms were assessed with the revised children’s manifest anxiety scale (RCMAS) [38]; and depressive symptoms with the children’s depression inventory [39]. The RCMAS and the CDI ratings for pre-adolescent subjects were based on maternal report. Socioeconomic status (SES) was estimated using the Hollingshead four-factor index of social status [40].

To evaluate the prenatal, obstetric, and medical risk factors, all mothers were interviewed directly using a semi-structured scale of the modified schedule for risk and protective factors in early development (MSRPFED) [41, 42]. All information concerning pregnancy, labor,

and delivery was collected blindly with regard to the diagnostic status and psychiatric symptom severity. To evaluate our first a priori hypotheses, the mothers were asked if they smoked more than 10 cigarettes per day at any point in their pregnancy. Based on their yes/no response, we created a binary variable heavy maternal smoking to test this hypothesis.

The second specific area of inquiry included the family's life circumstances during the pregnancy. Detailed questions were asked concerning potential psychosocial stressors across a range of areas including the home environment, the parental interpersonal relationship, the availability of emotional supports, parental employment, family's financial status, the parents' physical health, and any legal issues. After completing the MSRPED interviews, two experienced raters (LK and NT), using 5-point ordinal scales (range 1–5), were asked to rate, independently and blind to the subject's diagnoses: the family's level of stress severity (LSS) [14] and the family's coping ability scale (CAS) [14]. These raters also independently and blindly assessed pregnancy complications using the pregnancy complication scale (PCS) [14]. The Spearman correlation coefficients for the two raters was 0.91 for the LSS, 0.85 for the CAS, and 0.88 for the PCS indicating excellent inter-rater agreement for each scale ($p < 0.001$). Any discrepancies were resolved by consensus (LK, NT, and JFL). Next, we examined the distribution of ordinal scores for all subjects. Given the small number of subjects reporting severe levels of psychosocial stress, scores of 4 and 5 were collapsed into a single group. The LSS was used to test our second a priori hypothesis.

The child's birth weight was obtained by maternal reporting at the time of interview. A birth weight of less than 2,500 g is defined as LBW in a binary variable to test our third a priori hypothesis. In addition, a summary index of adverse events that were judged to place a child at a higher risk of transient perinatal hypoxia or ischemia was also created to test our fourth a priori hypothesis. This summary index included 16 risk factors that were judged to be typically associated with hypoxia including: an emergency intervention other than C-section during a vaginal delivery due to fetal distress, an emergency C-section, prolonged labor (>24 h), an unusual presentation, the umbilical cord around baby's neck, a knotted cord, a prolapsed cord, cyanosis, delayed breathing or crying, aspiration, stained amniotic fluid, decreased or increased fetal heart rate, placenta previa, and placenta abruption or infarction.

In addition to our four a priori hypotheses, we also conducted a number of exploratory analyses. These included examining the association of the CAS and PCS with ADHD and TS diagnoses. We also examined the rates of other reported obstetric and perinatal complications; however, in many instances there were too few specific pregnancy complications to warrant multiple separate analyses. As a result, in our exploratory analyses, we only examined the rates of those events which had a rate of 10% in the total population. Exposure to eight variables were examined: excessive maternal weight gain (18.0%), edema (26.6%), vaginal bleeding (13.5%), severe nausea and vomiting (23.9%), more than one pregnancy complication (38.7%), drinking more than three cups of coffee per day (10.0%), using antibiotics (15.3%), and a limited ability to cope with psychosocial stress during pregnancy (based on the CAS scores, 11.3%).

Data analysis

Statistical analyses were performed using SPSS, version 16. Demographic and clinical variables were described as relative and absolute frequencies. Continuous demographic variables were compared using ANOVA, and categorical demographic variables were compared using Pearson's chi-square test.

To test our four a priori hypotheses, we used logistic regression to compute the odds ratio (OR) for each of the risk factors (maternal smoking, level of maternal stress, LBW, and the presence of >1 hypoxic–ischemic risk factor) in the unaffected control population versus the

three patient groups, with gender as a covariate. We then completed a series of exploratory analyses in which we compared each of the three groups of affected children to the unaffected control group. Additional univariate exploratory analyses were run for each of the remaining eight risk factors. Next, we performed a logistic regression in which each of the significant variables (from the univariate analyses) was simultaneously evaluated. Variables with a non-significant p value were sequentially removed by using a backward stepwise regression until the model parameters were maximized. In this analysis, we compared the rates in each mutually exclusive diagnostic category (AHDH alone, TS alone, and ADHD + TS) to the rates observed in the unaffected comparison group.

In a final set of exploratory analysis, we examined the associations of total worst ever YGTSS scores and total scores from the ADHD rating scale with each of the risk variables using general linear models in which “gender” was included as a covariate.

Results

Group characteristics

Demographic and clinical characteristics of the four diagnostic groups are presented in Table 1. The percentage of boys in the TS/ADHD groups (71–85%) was greater than in the control group (46%). We found no significant differences among the diagnostic groups regarding their age, race, socioeconomic status, parental age at the time of delivery, or parental years of education. No significant differences were found between the TS alone and the TS + ADHD groups on the variables of tic severity or age at tic onset. None of the clinical groups differed from the others in the rates of co-morbid OCD or on measures of anxiety or depression.

Primary analysis

Individuals with ADHD alone had the highest rate of heavy maternal smoking during the pregnancy (17.3%), followed by ADHD + TS (11.6%) and TS alone (6.6%) (Tables 2, 3). The lowest frequency of heavy maternal smoking (1.6%) was reported by the unaffected control population. The odds of heavy maternal smoking during pregnancy were significantly higher in the children with ADHD alone compared to the unaffected control children (OR = 13.5, 95% CI 1.6–113.2, $p < 0.01$; Table 3). The rate of heavy maternal smoking in the group of children with ADHD + TS was also elevated at a trend level of significance (OR = 8.5, 95% CI 0.97–75.2, $p = 0.052$; Table 3). The TS alone group also had a higher rate of heavy maternal smoking, but despite a substantial OR of greater than 4.5, this result was not statistically significant (Table 3).

Similarly, severe maternal psychosocial stress during pregnancy was judged to be present in 27% of the offspring with ADHD alone. TS patients also had high rates of maternal stress (TS alone 22%; ADHD + TS 20%) compared to a rate of 8.1% in the unaffected control group. The odds of severe maternal psychosocial stress during pregnancy were significantly higher in the children with ADHD alone compared to the unaffected control children (OR = 6.8, 95% CI 2.0–23.3, $p < 0.002$; Tables 2, 3). At a trend level both the offspring with TS alone and the offspring with ADHD + TS also had higher levels of severe maternal psychosocial stress during pregnancy compared to the unaffected control children (OR = 2.6, 95% CI 0.08–8.7, $p < 0.11$ and OR = 3.1, 95% CI 0.9–11.1, $p < 0.07$, respectively; Tables 2, 3). However, neither the proportion of children with LBW nor the children with >1 indicator of transient hypoxia differed across the groups (Tables 2, 3).

Exploratory univariate analyses of the remaining pre- and perinatal risk factors

In the exploratory analyses, the distribution of three of the eight additional pre- and perinatal risk factors differed across the groups. The children whose families had only a limited ability to cope with psychosocial stressors were more likely to fall in the ADHD alone group compared to the unaffected control children (OR = 9.17, 95% CI 2.9–29.4, $p < 0.0002$). At a trend level, this association was also true of the ADHD + TS group (OR = 3.00, 95% CI 1.0–10.0, $p < 0.06$) and TS alone group (OR = 2.9, 95% CI 0.91–9.52, $p < 0.07$). The mothers of ADHD alone offspring were also more likely than the mothers of the unaffected controls to report more than one pregnancy complication (OR = 3.2, 95% CI 1.6–8.3, $p < 0.0002$). This was also true for the ADHD + TS patients (OR = 3.1, 95% CI 1.4–7.2, $p < 0.006$). At a trend level, this was also true for the TS alone group (OR = 2.2, 95% CI 0.92–5.1, $p < 0.07$). Finally, the mothers of children with TS alone were more likely to report the use of an antibiotic during the pregnancy compared to the unaffected control children (OR = 4.8, 95% CI 1.4–16.5, $p < 0.02$). At a trend level, this was also true of the ADHD + TS group (OR = 3.2, 95% CI 0.9–11.4, $p < 0.06$).

Exploratory multivariate analyses

Before performing an exploratory step-wise logistic regression, we examined the interrelationships across the five identified risk factors (maternal heavy smoking, severe psychosocial stress, limited coping abilities, more than one pregnancy complication, and antibiotic use). The LSS and the CAS were found to be co-linear (Spearman's rank correlation coefficient = 0.92, $p < 0.0001$). Therefore, in the multivariate analysis, we combined the scores from the LSS and the CAS into one binary variable such that only those subjects who scored 4 on *both* the LSS and the CAS were identified as having experienced "severe maternal stress with poor coping" (SMSPC). When each of the four remaining variables were included in a simultaneous logistic model, the best-fit model indicated that the children with ADHD alone had elevated exposures to both heavy maternal smoking (OR = 18.6, 95% CI = 2.1–164.4, $p = 0.008$) and SMSPC (OR = 16.3, 95% CI = 1.5–135.1, $p = 0.01$) compared to the unaffected control subjects. The offspring with ADHD + TS also had higher rates of exposure relative to the unaffected control subjects for both heavy maternal smoking and SMSPC, but the ORs were not significant.

Symptom severity

In a series of exploratory analyses, no association was found between current or worst-ever tic severity and heavy maternal smoking during pregnancy nor with any other pre- or perinatal risk factors or expert ratings (LSS, CAS, and PCS). Likewise, none of the risk factors were associated with current ADHD severity, except in the ADHD alone group, where the children of mothers who had experienced *marital* stress (marital conflicts, physical abuse, separation, divorce, reconciliation, a new relationship or an affair, or a new marriage) had higher scores on the DuPaul-Barkley ADHD rating scale compared to those children whose mothers did not report marital stressors (33.3 ± 10.9 vs. 25.0 ± 8.9 , respectively; $F = 5.06$, $p = 0.03$).

Discussion

This is the largest study to date to compare rates of pre- and perinatal risk factors across children with ADHD and/or TS. Two of our a priori hypotheses, exposure to maternal heavy smoking and to severe levels of psychosocial stress during pregnancy, were robustly associated with ADHD. When considered together in the same multivariate model, exposures to maternal heavy smoking (>10 cigarettes per day) during pregnancy and high levels of psychosocial stress with limited ability to cope remained significant only for the children with ADHD alone. The findings replicate earlier prospective and retrospective

studies that have documented that maternal smoking or increased maternal stress during pregnancy are potent environmental risk factors associated with ADHD alone or in combination with TS [17–30]. Systematic meta-analyses have shown a dose relationship with the number of cigarettes smoked during pregnancy, and several biologically plausible mechanisms could account for this association [28, 43–45]. Maternal smoking and smoking in the home after delivery have also been implicated [28]. However, several studies using genetically sensitive designs have suggested that this association, either in whole or part, may reflect the impact of genetic factors [46–49].

Maternal stress during pregnancy has been shown to have enduring epigenetic effects on gene expression that can influence fetal neuroendocrine patterns of stress response, alter cognitive development, and increase the risk of subsequent behavioral problems including ADHD [25–27, 29, 50–52]. Consistent with this perspective, initial neuroendocrine studies of children with TS and ADHD indicate that their hypothalamic–pituitary–adrenal axis response to stressful stimuli may be atypical [53, 54]. In addition, a recent study using a genetically sensitive design has suggested that this association, either in whole or part, may reflect the impact of genetic factors [49].

Our hypothesis regarding the influence of LBW and hypoxic–ischemic factors in ADHD or TS was not supported in this study. Although ADHD and TS patients had a higher prevalence of almost all of these events compared to the unaffected population, no compelling evidence was detected for a statistically significant association. While these results are consistent with an earlier study of pre- and perinatal risk factors in TS [17], these findings contradict earlier reports that found obstetrical complications to be associated with the later development of either ADHD or TS or both [14–16, 18, 19, 25].

The results of our study are also in contrast with the findings of Mathews et al. [17]. They reported an association of prenatal smoking exposure with increased tic severity. Although we have no compelling explanation for this discrepancy, it should be noted that, in contrast to our study that only involved children and adolescents, nearly 30% of patients in the Mathews et al. study were adults with TS. Adults who continue to have tics may form a distinct subgroup in terms of clinical characteristics and causative factors [55].

In our exploratory analyses, we observed a significant association with TS and the use of antibiotics during pregnancy. Although this may be an important observation indicating possible alterations in immune function [56, 57], it did not remain in the best-fit model, suggesting that it may represent a Type I error.

Fundamental limitations of this study include its retrospective nature, the relatively small number of subjects, and the recruitment strategy. First, our pre- and perinatal findings are based on recollections by mothers. Previous studies have suggested that there is a high degree of concordance between the quantitative data recorded in hospital records and the memories of mothers regarding birth weight, as well as many of the pre-, peri-, and postnatal events for many, but not all, of the variables assessed in this study [58, 59]. Fewer data are available concerning the degree of agreement for more qualitative measures such as the level of maternal stress or coping ability. Some degree of recall bias is likely to be present. This may be particularly true for mothers who have a child with a disorder.

Second, compared to many of the ADHD studies, the sample size of the current study is small so that we have limited power to detect even large differences across groups. For example, data from the 1997–2005 National Health Interview Survey (NHIS, $n = 87,578$), found that the prevalence of ADHD was 1.4–2.0 times higher in the group for children with birth weights <2,500 g compared to those whose birth weight was $\geq 2,500$ g [30]. In addition,

there is a significantly larger proportion of females in the control group than in the patient groups which again may have contributed to our failure to replicate some earlier findings.

A third limitation is that our patient and control samples may in some respects be “supernormal.” For example, the rate of heavy maternal smoking during pregnancy in our control sample is only 1.5% compared to a rate of 7.0–13.4% for *any* maternal smoking in the State of Connecticut from 1990 to 2001 [60]. While this appears to be large discrepancy in point of fact, the population data are based on birth certificate data that requires health care professionals to check one of five boxes (>21 cigarettes smoked/ day, 11–20 cigarettes smoked/day, 6–10 cigarettes smoked/ day, 1–5 cigarettes smoked/day, and non-smokers) [61]. The rate of 7.0–13.4% is the sum of the first four categories (any smoking) versus the referent category (non-smokers). In most samples, the rate of heavy maternal smoking in the general population is under 5%. For example in a recent German study, an overall rate of any maternal smoking was 11.8% compared with a rate of 4.6% for women who were heavy smokers (>11 cigarettes/day) [62]. Adolescent mothers with low SES also have a higher rate of heavy smoking during pregnancy [59, 60], and this group of mothers was largely absent from this sample. Similarly, the NHIS reported a prevalence LBW of 7.6% compared to our overall rate of just 4.1%, again suggesting that both our patient and control groups are to some degree “supernormal.”

It will be important to follow prospective cohorts from conception to birth to latency age with larger sample size to examine how stress, maternal smoking, and pregnancy complications affect the development of various psychopathologies, and also how these risk factors may influence performance on neuropsychological test results, as well as the expression of specific symptoms in children who may be genetically predisposed to certain psychopathologies.

Conclusion

Maternal smoking and high levels of psychosocial stress during pregnancy were independently associated with a diagnosis of ADHD alone and approached significance for the group of offspring diagnosed with TS. Although public health efforts are needed to reduce the frequency of these risk factors in high-risk populations, future studies using genetically sensitive designs are also needed to sort out the causal pathways for these two closely interconnected disorders.

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Abbreviations

TS	Tourette syndrome
ADHD	Attention-deficit/hyperactivity disorder
OCD	Obsessive compulsive disorder
LBW	Low birth weight
YGTSS	Yale global tic severity scale

CY-BOCS	Children's Yale brown obsessive compulsive scale
MSRPFED	Modified schedule for risk and protective factors in early development
RCMAS	Revised children's manifest anxiety scale
LSS	Level of stress severity scale
CAS	Coping ability scale
PCS	Pregnancy complication scale
SMSPC	Severe maternal stress with poor coping

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Table 1

Demographic and clinical characteristics

Variable	Unaffected control group (N = 65)	TS alone (N = 45)	TS + ADHD (N = 60)	ADHD alone (N = 52)	p value
Mean age, years (SD)	12.2 (2.5)	11.6 (2.6)	12.3 (2.7)	11.8 (2.7)	NS
Male: N (%)	30 (46) ^{a,b,c}	32 (71) ^d	51 (85) ^d	38 (73) ^d	0.0001
Caucasian: N (%)	56 (86)	42 (93)	56 (93)	48 (92)	NS
Mother's age at conception (years, SD)	28.3 (4.1)	28.9 (4.4)	28.1 (5.3)	29.29 (5.2)	NS
Father's age at conception (years, SD)	30.4 (5.0)	30.9 (5.0)	30.2 (6.2)	30.6 (5.2)	NS
Mean years of parents' education (SD)	15.3 (2.0)	15.5 (2.0)	14.9 (1.8)	14.8 (2.1)	NS
Mean socioeconomic status (SD)	48.5 (10.7)	50.4 (2.7)	47.4 (10.6)	46.7 (13.8)	NS
Age of tic onset, years (SD)	—	6.4 (2.2)	5.4 (2.07)	—	NS
Total tic severity, YGTSS ^e (SD)	—	26.5 (7.6)	28.6 (7.7)	—	NS
Motor tic severity, YGTSS (SD)	—	15.3 (4.2)	16.2 (4.2)	—	0.11
Phonic tic severity, YGTSS (SD)	—	11.2 (5.3)	12.5 (4.4)	—	0.11
Age of ADHD onset, years (SD)	—	—	5.0 (2.0)	5.0 (1.7)	NS
Total ADHD severity score ^f	—	6.9 (6.5) ^{a,c}	28.3 (10.1) ^b	27.0 (9.9) ^b	0.0001
Inattentive score	—	4.0 (4.8) ^{a,c}	16.6 (5.5) ^b	15.4 (6.2) ^b	0.0001
Hyperactivity score	—	2.9 (2.9) ^{a,c}	11.6 (5.9) ^b	11.6 (6.1) ^b	0.0001
Comorbid OCD: N (%)	—	14 (31)	12 (20)	13 (25)	NS
OC severity, CY-BOCS ^g (SD)	—	7.7 (10.6)	6.3 (10.4)	7.5 (12.9)	NS
Severity of depression, CDRS-R (SD)	—	25.1 (7.9)	27.5 (6.8)	28.0 (6.6)	NS
Anxiety severity, RCMAAS (SD)	—	45.24 (11.0)	50.91 (11.2)	54.0 (10.6)	NS

TS Tourette syndrome, ADHD attention-deficit/hyperactivity disorder, YGTSS Yale global tic severity scale, OCD obsessive compulsive disorder, CY-BOCS children's Yale brown obsessive compulsive scale, CDRS-R children's depression rating scale—revised, RCMAAS revised children's manifest anxiety scale, NS not significant

^aDifferent from TS + ADHD at $p < 0.05$

^bDifferent from TS alone at $p < 0.05$

^cDifferent from ADHD alone at $p < 0.05$

^dDifferent from normal control group at $p < 0.05$

^eTotal tic severity does not include impairment score and is based on the worst-ever tic severity measured at the time of interview

^fBased on Du Paul's parent and teacher ratings of ADHD symptoms. The presented scores are the current ADHD symptom severity at the time of interview

^gOC symptom severity is based on the worst-ever total obsessive compulsive severity measured at the time of interview

Table 2

Pre- and perinatal risk factors (maternal report)

Variable	Unaffected control group (N = 65) (%)	TS alone (N = 45) (%)	TS + ADHD (N = 60) (%)	ADHD alone (N = 52) (%)	p value
Pregnancy complications					
Complication of pre-existing medical condition	4 (6)	1 (2)	4 (7)	6 (12)	NS
Infections	0 (0)	1 (2)	0 (0)	0 (0)	NS
Head injury	0 (0)	1 (2)	2 (4)	0 (0)	NS
Abdomen injury	1 (2)	0 (0)	0 (0)	0 (0)	NS
Excessive weight gain	12 (2)	4 (9)	12 (22)	12 (23)	NS
Anemia	2 (3)	2 (4)	2 (4)	3 (6)	NS
Elevated blood sugar	7 (11)	4 (9)	1 (2)	4 (8)	NS
Elevated blood pressure	5 (8)	2 (4)	6 (11)	5 (10)	NS
Protein in urine	2 (3)	4 (9)	2 (4)	1 (2)	NS
Seizures	1 (1.6)	0 (0)	0 (0)	0 (0)	NS
Edema in face, hands, and legs	15 (23)	10 (22)	19 (35)	15 (29)	NS
Toxemia	2 (3)	2 (4)	2 (4)	3 (6)	NS
Vaginal bleeding	7 (11)	8 (18)	8 (15)	7 (13)	NS
Placenta previa	1 (2)	0 (0)	1 (2)	1 (2)	NS
Placenta abruption	1 (2)	0 (0)	0 (0)	1 (2)	NS
Rh factor	5 (8)	4 (9)	2 (4)	8 (15)	NS
Birth weight, g (SD)	3,519 (755)	3,538 (530)	3,438 (538)	3,382 (585)	NS
Low birth weight (<2,500 g) ^g	2 (3)	1 (2)	3 (5)	3 (6)	NS
Child born before 38 weeks	7 (11)	1 (2)	6 (11)	3 (6)	NS
Child born after 44 weeks	2 (3)	4 (9)	4 (7)	3 (6)	NS
Severe nausea and vomiting	16 (26)	9 (20)	10 (17)	7 (13)	NS
More than one pregnancy complication	16 (25) ^{a,c}	17 (38)	27 (45) ^d	26 (50) ^d	0.01
Exposures during pregnancy					
Heavy maternal smoking during pregnancy (> 10 cigarettes/day) ^g	1 (2) ^{a,c}	3 (7)	7 (12) ^d	9 (17) ^d	0.01
Coffee > 3 cup in 24 h	5 (8)	2 (5)	6 (11)	9 (17)	0.12
> 2 drinks alcohol in 24 h	1 (2)	0 (0)	0 (0)	2 (4)	NS
Anti-hypertensive	1 (2)	0 (0)	0 (0)	0 (0)	NS

Variable	Unaffected control group (N = 65) (%)	TS alone (N = 45) (%)	TS + ADHD (N = 60) (%)	ADHD alone (N = 52) (%)	p value
Thyroid medications	1 (2)	0 (0)	4 (7)	1 (2)	0.13
Tranquilizers	0 (0)	0 (0)	1 (2)	1 (2)	NS
Sleeping pills	2 (3)	0 (0)	0 (0)	0 (0)	0.19
Antihistamines	2 (3)	4 (9)	2 (4)	2 (4)	NS
Antibiotics	6 (6) ^{a,b}	11 (24) ^d	11 (20) ^d	6 (12)	0.02
Severe psychosocial stress during pregnancy ^{f,g}	5 (8.1) ^a	10 (22.2)	11 (20.0)	13 (27.1) ^d	0.05
Delivery complications					
More than one complication potentially associated with hypoxia ^{e,g}	18 (27.7)	17 (38)	18 (30.0)	13 (27.1)	NS

TS Tourette syndrome, ADHD attention-deficit/hyperactivity disorder, YGTSS Yale global tic severity scale, OCD obsessive compulsive disorder, CY-BOCS children's Yale brown obsessive compulsive scale, CDRS-R children's depression rating scale—revised, RCMAS revised children's manifest anxiety scale, NS not significant

^a Different from TS + ADHD at $p < 0.05$

^b Different from TS alone at $p < 0.05$

^c Different from ADHD alone at $p < 0.05$

^d Different from Normal Control Group at $p < 0.05$

^e See text

^f Severe psychosocial stress indicates that the events occurring during the pregnancy were sufficiently severe to disrupt existing patterns of family life such as severe marital conflict with separation or a threat of separation, the death or serious injury to a parent, or brief or extended periods of unemployment [14]

^g A priori variable

Table 3

Odds ratios (OR) for exposure to selected pre- and perinatal risk factors in cases versus controls with gender as covariate

Exposure	n/N cases	n/N controls	OR	95% CI	p value
Maternal smoking		1/62			
ADHD alone	9/52		13.5	1.6–113.2	0.01
TS alone	3/45		4.6	0.45–46.6	0.19
TS + ADHD	7/60		8.5	0.97–75.2	0.052
Severe psychosocial stress		5/62			
ADHD alone	13/48		6.8	2.0–23.3	0.002
TS alone	10/45		2.6	0.08–8.7	0.11
TS + ADHD	11/55		3.1	0.9–11.1	0.07
Low birth weight (< 2,500 g)		2/65			
ADHD alone	3/52		0.48	0.07–3.8	NS
TS alone	1/45		1.3	0.11–15.4	NS
TS + ADHD	3/57		0.55	0.08–3.7	NS
> 1 hypoxic event		18/65			
ADHD alone	13/48		1.2	0.53–2.7	NS
TS alone	17/45		1.4	0.64–3.3	NS
TS + ADHD	18/60		0.9	0.4–2.2	NS

A priori tests for effects of diagnosis (TS/Tourette syndrome, ADHD/attention-deficit/hyperactivity disorder, and ADHD plus TS), NS not significant

Maternal smoking: >10 cigarettes in 24 h at any point in the pregnancy

Severe psychosocial stress: 4 ordinal level of stress severity scale (1–5 ordinal scale) [14]

> 1 hypoxic event: more than one of 16 indicators of transient fetal hypoxia in the perinatal period (see text)