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Pre- and perinatal complications in relation to Tourette syndrome and co-occurring obsessive-compulsive disorder and attention-deficit/hyperactivity disorder

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Abstract

Pre- and perinatal complications have been implicated in the onset and clinical expression of Tourette syndrome albeit with considerable inconsistencies across studies. Also, little is known about their role in co-occurring obsessive-compulsive disorder (OCD) and attention–deficit/hyperactivity disorder (ADHD) in individuals with a tic disorder. Therefore, we aimed to investigate the role of pre- and perinatal complications in relation to the presence and symptom severity of chronic tic disorder and co-occurring OCD and ADHD using data of 1,113 participants from the Tourette International Collaborative Genetics study. This study included 586 participants with a chronic tic disorder and 527 unaffected family controls. We controlled for age and sex differences by creating propensity score matched subsamples for both case-control and within-case analyses. We found that premature birth (OR=1.72) and morning sickness requiring medical attention (OR=2.57) were associated with the presence of a chronic tic disorder. Also, the total number of pre- and perinatal complications was higher in those with a tic disorder (OR=1.07). Furthermore, neonatal complications were related to the presence (OR=1.46) and severity (*b*=2.27) of co-occurring OCD and also to ADHD severity (*b*=1.09). Delivery complications were only related to co-occurring OCD (OR=1.49). We conclude that early exposure to adverse situations during pregnancy is related to the presence of chronic tic disorders. Exposure at a later stage, at birth or during the first weeks of life, appears to be associated with co-occurring OCD and ADHD.

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M.A., G.A.H, P.J.H., and A.D. were involved in the organization, design, and execution of the research project, execution and critique of the statistical analysis; M.A. wrote the first draft of the manuscript, which was critically reviewed by J.A.T., G.A.H, P.J.H., and A.D. who were also involved in the conception of the research project. A.G.L. was involved in the recruitment of participants. The following authors were involved in the review, critique of the manuscript, and recruitment of participants: R.A.K., T.V.H., L.W.B., K.C., B.J.C., S.F.T.M.B., L.E., B.G., D.L.G., D.E.G., J.H., T.H., I.H., H.J.H., C.H., L.I., Y.K.K., Y.S.K., Y.J.K., S.D.K., S.K., A.L., B.L., M.G., A.M. (Maras), M.D.M., P.B., A.M. (Morer), A.M. (Münchau), T.L.M., T.J.C.O., K.J.P., J.J.G.R., V.R., O.F., E.Y.S., D.A.S., D.H.S., J.S., A.S., J.T., E.B., F.V., S.W., M.W., S.H.Z., M.W.S. All authors have approved the final article.

Keywords

Attention-deficit hyperactivity disorder; Delivery; Obsessive-compulsive disorder; Pregnancy; Prenatal; Tourette Syndrome

Introduction

Chronic tic disorders are childhood-onset neuropsychiatric disorders characterized by the presence of multiple motor tics and/or one or more vocal tics persisting for at least one year (American Psychiatric Association, 2000). Tourette syndrome (TS) is the best studied chronic tic disorder. While family and twin studies have consistently indicated a genetic etiology for tic disorders, environmental factors are also involved (Mataix-Cols et al., 2015; Price et al., 1985). Pre- and perinatal complications are particularly important environmental factors associated with many neuropsychiatric disorders (Tomasović et al., 2012) and have also been implicated in tic disorders (Chao et al., 2014; Hoekstra et al., 2013). Pioneering work by Pasamanick and Kawi reported that mothers of children with tics experienced pre- and perinatal complications 1.5 times more often compared to mothers of children without tics (Pasamanick and Kawi, 1956).

Although there has been a steady, albeit slow, increase in the number of studies investigating pre- and perinatal complications in association with TS (see Chao et al., 2014 for a recent review), findings across studies have been remarkably inconsistent. This makes it difficult to draw valid conclusions with regard to the role of pre- and perinatal factors (7). For example, maternal smoking during pregnancy was associated with TS in some studies (Cubo et al., 2014; Mathews et al., 2006), but not in others (e.g., Bos-Veneman et al., 2010; Mathews et al., 2014; Motlagh et al., 2010). Another example is younger maternal age, that was identified as a factor for TS in one study (Khalifa and von Knorring, 2005), whereas other studies reported no association (Burd et al., 1999; Motlagh et al., 2010). This emphasizes the need for additional studies.

Study design limitations and use of small sample sizes most likely contributed to these inconsistent findings. That is, most epidemiological studies of general population samples typically lacked clinician-confirmed diagnosis of a tic disorder and/or included relatively few affected individuals (e.g., Atladóttir et al., 2007; Mathews et al., 2014), whereas clinical samples may have been biased by over-representation of more severe cases (Leckman et al., 1990; Saccomani et al., 2005). Finally, possible confounding variables, such as socio-economic status (SES), parity, and parental age, have not always been taken into account (Bos-Veneman et al., 2010; Mathews et al., 2006; Pringsheim et al., 2009).

Another largely unresolved issue, due to the scarcity of studies, is the role of pre- and perinatal factors in relation to the expression of the disease, i.e., tic symptom severity and the presence and/or severity of co-occurring conditions (Chao et al., 2014). Preliminary evidence has indicated maternal smoking as a possible risk factor not only for the diagnosis of a tic disorder but also severity of tics (Bos-Veneman et al., 2010; Mathews et al., 2006). Two of the most frequent co-occurring conditions are attention–deficit/hyperactivity disorder (ADHD; present in 40–60% of cases, Roessner et al., 2007) and obsessive-compulsive

disorder (OCD; present in 30–50% of cases, Wanderer et al., 2012). In co-occurring OCD, older paternal age (Mathews et al., 2006) and forceps delivery (Santangelo, 1994) have been implicated, whereas low birth weight, premature birth, and maternal smoking were associated with co-occurring ADHD (Leivonen et al., 2015a; Pringsheim et al., 2009), but these findings have not been replicated (Chao et al., 2014).

The aim of the present study was to investigate the role of a broad set of pre- and perinatal complications in relation to diagnosis and symptom severity of TS and other chronic tic disorders, and to the presence and severity of co-occurring OCD and ADHD within the Tourette International Collaborative Genetics (TIC Genetics) study (Dietrich et al., 2015). This study used a large, well-characterized sample of children and adults with a wide range of symptom levels and unaffected family controls. We first distinguished presence of any pregnancy, delivery, and neonatal complication, and subsequently investigated the roles of specific complications and an overall adversity score (cumulative score of all 38 complications).

Materials and Methods

Sample description

Prior to matching on age and sex, our study sample included 1,113 participants (586 cases with a chronic tic disorder; mean age = 23.6, SD = 17 years, range = 3–79 years, 66.7% males; and 527 unaffected family members as controls; mean age= 43.9, SD = 13.2 years; range = 2–83 years, 47.6% males) as part of the TIC Genetics study (Dietrich et al., 2015), recruited between September 2011 and June 2014 across 24 sites in the USA, Europe, and South Korea. We addressed these age and sex differences by applying propensity matching (see statistical analyses section below). This study was established as a comprehensive gene discovery effort for TS by focusing on rare genetic variants within parent-child trios and multiply-affected family pedigrees including both patients and unaffected family members, as described in more detail elsewhere (Dietrich et al., 2015). Investigating the role of environmental factors is a secondary aim of the study. Inclusion criterion of cases was presence of TS or another chronic tic disorder according to the Diagnostic and Statistical Manual of Mental Disorders Fourth edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000); controls were family members of cases without the presence of any type of tic disorder, while other disorders or symptoms were allowed. Subjects were not excluded based on age, gender, race, ethnicity, or IQ. All adult participants and parents of children provided written informed consent along with written or oral assent of their participating child. The Institutional Review Board of each participating site approved the study.

Diagnostic assessment and instruments

Each site followed the same standardized assessment procedures including completion of adult self-report or parent-on-child questionnaires to assess subjects' demographics, medical history, psychopathology, selected environmental factors, and family members' psychiatric history (Dietrich et al., 2015). These questionnaires were subsequently reviewed during a semi-structured clinical interview by clinicians who assigned a lifetime clinical diagnosis of

a tic disorder, OCD, and/or ADHD based on the DSM-IV-TR (American Psychiatric Association, 2000). To ensure consistent application of diagnostic criteria for both within and across sites, all clinicians were in continuous dialog with a Phenotype Assessment Sub-Committee that provided training and guidance to resolve and reach consensus in ambiguous cases (Dietrich et al., 2015).

Assessment of tic severity was based on a modified version of the Yale Global Tic Severity Scale (YGTSS, Leckman et al., 1989; Storch et al., 2005), excluding the sections relating to the number and complexity of tics (Dietrich et al., 2015). The tic severity dimensions (i.e., frequency, intensity, and interference) were each rated from 0 to 5 for "worst ever" motor and phonic tics, and then combined into a sum score of total "worst ever" tic severity (range 0–30).

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, Goodman et al., 1989a, 1989b) or the children's version (Scahill et al., 1997), as appropriate, was used to assess severity of obsessions and compulsions across five severity dimensions (time spent, interference, distress, resistance, and level of control), each rated from 0 to 4. Obsessive-compulsive severity was based on the sum score of "worst ever" obsessions and compulsion scores (range 0–40).

The number of ADHD symptoms (range 0–18) was used as a rating of ADHD severity. Clinicians assessed the presence of ADHD symptoms by reviewing parent-based Swanson Nolan and Pelham-IV (SNAP-IV, Bussing et al., 2008; Swanson, 1992; Swanson et al., 2001) rating scale, capturing each nine DSM-IV items of inattention and hyperactivity-impulsivity symptoms; symptoms had to be present during childhood when the child was not taking medication for ADHD. In adults, it was based on a review of SNAP-IV self-report of their situation as a child when not taking medication for ADHD; often the recall of this information was aided with input from their parents. Finally, as a proxy for SES we used the mean of both parents' education level (1= less than 7 years of schooling to 7= graduate/professional degree).

Pregnancy, delivery, and neonatal complications

We used the Modified Schedule for Risk and Protective Factors Early in Development (Walkup and Leckman, 1988) self-report or parent-on-child report questionnaire, capturing 38 possible adverse situations (see Table 3), which we sub-divided into three categories, i.e., pregnancy (14 items); delivery (8 items); and neonatal complications (16 items). For the adult participants, this information was aided with input from their parents.

Statistical analyses

We conducted (i) case-control analyses regarding differences in the frequencies of pre- and perinatal factors; and (ii) analyses within cases, looking at differences in clinical characteristics (i.e., tic severity and presence and severity of co-occurring OCD and ADHD) in cases exposed and unexposed to a pre- and perinatal complication. Given the wide age range of individuals included in this sample and to control for sex and age differences, we created subgroups of individuals propensity-matched on age and sex, for both the case-control analyses as well as the within-case analyses, using the SPSS plugin psmatching3

(Thoemmes, 2012). The matched case control dataset was obtained from the total pool of available participants (N=1,113) allowing us to create a well-matched comparison. We did not include controls under the age of 8 as younger control subjects might still develop a tic disorder. The propensity scores were calculated using logistic regression followed by nearest neighbor matching. The matching algorithm was set to a maximum 1:5 ratio (of cases versus controls and exposed versus unexposed cases, respectively) to increase power and reduce bias (Thoemmes, 2012). To avoid potentially false-positive results due to testing of a large number of exposure variables, we chose a two-stepped approach in which we only investigated individual complications when there was an indication of involvement of any pregnancy, delivery, or neonatal complications, respectively. That is, as first steps, we compared the age- and sex-matched cases and controls on the presence of at least one versus no pregnancy, delivery, and neonatal complication, respectively using Pearson's chi-square test or the Fisher's exact test when the number of exposed cases or controls was less than 5, and additionally investigated the number of complications for each category. As second step, we performed follow-up analyses into underlying individual complications when any of the investigations with regard to the three categories yielded a $P < 0.10$. Third, we investigated the overall adversity score (i.e., cumulative score of all 38 complications) using Mann-Whitney test and a logistic regression.

Within cases, we used a similar two-stepped approach. Here, for each type of exposure under investigation (i.e., presence of at least one pregnancy, delivery, or neonatal complication, respectively), exposed cases were matched on age and sex with unexposed cases using propensity scores, again to a maximum 1:5 ratio. The matched dataset for each type of exposure was obtained from the total pool of available cases (N=586), resulting in datasets with differing sample sizes, ranging from the largest dataset that included 557 cases to the smallest dataset that included 86 cases (see supplemental information). Then, severity scores between exposed and unexposed cases were compared with Student's t-tests and presence of a co-occurring diagnosis with a Pearson's chi-square test. Again, when the investigations into any one of the three categories (i.e., at least one pregnancy, delivery, or neonatal complication) yielded a $P < 0.10$, this was followed up with additional analyses into underlying individual complications, for which we also created exposed and unexposed groups propensity-matched on age and sex. For all analyses we present both unadjusted and results considering SES (Miller et al., 2013), parity (Leivonen et al., 2015b), and paternal age (Leivonen et al., 2015a) as potential confounders if they were associated with clinical ratings and presence of pre- and perinatal complications. All statistical analyses were performed using SPSS, version 22 using a significance level of $P < 0.05$ (two sided); given the seven case-control comparisons the significance level corrected for multiple testing of the case-control comparisons would be 0.05/7 = 0.0075; the significance level corrected for multiple testing for the analyses within cases would be 0.05/15 = 0.0038.

Results

Age- and sex-propensity matched groups

The demographic and clinical characteristics of the age- and sex-propensity matched cases and controls can be found in Table 1 and the demographics of the matched groups of

exposed versus unexposed cases in Table 2. For presentation purposes, the frequencies of the individual pre- and perinatal complications in matched cases versus controls are shown in Table 3. Note that propensity matching resulted in a reduced sample size of cases in our case-control analyses because of a higher proportion of children in cases than controls, and therefore no suitable age-matches were found for a number of cases. Similarly for the within-case analyses, finding age- and sex-matched unexposed cases for each exposed case was not possible, which resulted in a reduction of the number of case-control comparisons. Parity and paternal age were not related to pre- and perinatal complications and the clinical variables (all *P* values >0.05) and therefore did not meet criteria for a confounder; thus, in the following, we present unadjusted results and results adjusted for only SES.

Comparisons between cases and controls

As shown in Table 4, we found that significantly more cases than controls had been exposed to at least one pregnancy complication and, additionally, that the number of pregnancy complications was significantly higher in cases than controls. Both premature birth and morning sickness requiring medical attention were significant individual factors in the follow-up analyses. These results remained significant after SES adjustment. In addition, the result found for at least one pregnancy complication (SES adjusted Wald=7.72, degrees of freedom=2, P=0.005) remained statistically significant after correction for SES and multiple testing. Of note, we did not find a difference between cases and controls with regard to maternal smoking (SES unadjusted χ^2=0.01, degrees of freedom=1, P=1.0; SES adjusted Wald=0.02, degrees of freedom=2, P=0.89).

Cases and controls did not differ regarding the presence of at least one delivery or neonatal complication, and neither on the number of delivery and neonatal complications. However, the total number of complications was significantly higher in cases than controls both before and after SES adjustment.

As shown in table 1, the rate of OCD in the controls was clearly higher than the population prevalence of OCD. Therefore, we performed additional analyses within the controls and compared those with and without OCD for differences in pregnancy, delivery, and neonatal complications, but found no significant differences. Thus it is not likely that the higher than expected rate of OCD in controls would have obscured our results.

Role of pre- and perinatal factors within cases (Table 5)

Tic severity—Our analyses did not indicate a role of pregnancy and delivery complications on tic severity, including maternal smoking (SES unadjusted t=−1.01, degrees of freedom=130, P=0.29; SES adjusted t=−0.72, degrees of freedom=2, P=0.47). However, tic severity was significantly lower in cases that had experienced at least one neonatal complication, both before and after adjustment for SES. In our follow-up analyses we found that breathing problems during the first two weeks of life was a significant variable for tic severity after SES adjustment.

OCD diagnosis—Cases that had been exposed to at least one delivery or one neonatal complication had a higher frequency of a comorbid OCD diagnosis than cases without any

of these complications. Follow-up analyses indicated four significant individual complications, i.e., prolonged labor, forceps delivery, suctioning of the airway, and a prolonged hospital stay. Overall, results remained statistically significant after SES adjustment.

OCD severity—OCD severity in cases exposed to at least one pregnancy or neonatal complication was significantly higher than in unexposed cases. While we found no significantly associated individual pregnancy complications, significant neonatal complications were delay in breathing and suctioning of the airway immediately after birth. Results remained significant or yielded a $P < 0.10$ after adjustment for SES.

ADHD diagnosis—Presence of at least one neonatal complication regarding the odds of having a co-occurring ADHD diagnosis yielded a P value < 0.10. Follow-up analyses showed a significant result only for jaundice requiring medical attention, both before and after adjustment for SES. There was no significant result for the presence of at least one pregnancy or delivery complication.

ADHD severity—Cases with at least one neonatal complication had significantly more severe ADHD symptoms than cases without any neonatal complication. Subsequent analyses showed that weak abnormal cry immediately after birth and jaundice requiring medical attention were significant individual complications. Most results were significant before and after adjustment for SES. No significant differences in ADHD severity were found between cases with and without at least one pregnancy or at least one delivery complication.

For presentation purposes, a full listing of the descriptives for all individual pre- and perinatal complications regarding the within-case analyses can be found in supplementary Table S1–3.

Discussion

This study investigated the association of pre- and perinatal complications with lifetime chronic tic disorders and co-occurring OCD and ADHD in clinically well-characterized children and adults matched on age and sex from a large international genetic study cohort (Dietrich et al., 2015). The total number of pre- and perinatal complications was higher in individuals with a tic disorder, mostly due to the higher number of pregnancy complications. Specifically there was a higher frequency of premature birth and morning sickness requiring medical attention. Two previous studies (Motlagh et al., 2010; Pasamanick and Kawi, 1956) also found a higher number of pregnancy complications in individuals with a tic disorder diagnosis, although negative studies have also been reported (Burd et al., 1999; Kondo and Nomura, 1982). In contrast, smoking during pregnancy, implicated by some studies (Cubo et al., 2014) but not others (Leivonen et al., 2015a; Mathews et al., 2014), was not associated with a diagnosis of a chronic tic disorder in our sample. Also, we found no evidence for an association of delivery and neonatal complications with tic disorders. Most of our non-significant findings are broadly consistent with the literature, including the negative findings of maternal smoking and low birth weight (Burd et al., 1999; Leivonen et al., 2015a;

Mathews et al., 2014; Motlagh et al., 2010), thus indicating that these perinatal adversities do not play a role in tic disorders.

Analyses within individuals with a chronic tic disorder showed that co-occurring OCD was associated with pregnancy, delivery, and neonatal complications, notably prolonged labor and forceps delivery and problems relating to breathing, such as delay in breathing immediately after birth and suctioning of the airway. In agreement with our findings, two other studies (Geller et al., 2008; Vasconcelos et al., 2007) found that prolonged labor was associated with OCD diagnosis; also, our finding regarding forceps delivery and OCD diagnosis is in line with one other study (Santangelo, 1994). However, our results regarding co-occurring OCD are in contrast to Mathews et al. (Mathews et al., 2006) who had identified maternal smoking as the most important exposure.

In contrast to our OCD findings, only neonatal complications appeared to be related to ADHD severity. Jaundice requiring medical attention and weak abnormal cry immediately after birth both were significantly associated with ADHD. In a previous study (Bos-Veneman et al., 2010), we did not find a role for neonatal complications affecting ADHD severity in children with tic disorder, most likely due to the small sample size. Our non-significant results regarding pregnancy and delivery complications are in agreement with previous studies (Bos-Veneman et al., 2010; Mathews et al., 2006; Motlagh et al., 2010), except for our negative finding regarding maternal smoking that has previously been implicated in both the presence (Leivonen et al., 2015a; Motlagh et al., 2010; Pringsheim et al., 2009) and severity (Bos-Veneman et al., 2010) of co-occurring ADHD in individuals with a tic disorder. Yet TS with co-occurring ADHD may be etiologically distinct from ADHD as such (Spencer et al., 1998).

However, more recent studies have suggested that previously implicated associations of ADHD with maternal smoking could be attributed to environmental or genetic confounding rather than smoking per se (Langley et al., 2012; Lindblad and Hjern, 2010; Skoglund et al., 2014; Thapar and Rutter, 2009). Our design using family controls may have reduced such confounding (Knopik, 2009; Obel et al., 2015) and suggests no role for maternal smoking with regard to co-occurring ADHD nor presence and severity of tics. While one study had found prenatal maternal smoking to be strongly correlated with increased tic severity, this may have been confounded by not taking SES into account (Mathews et al., 2006). Also in other neurodevelopmental disorders in which a role for maternal smoking had been implicated (Hultman et al., 2002; Kalkbrenner et al., 2012; Stathopoulou et al., 2013), studies conducted with larger sample sizes or with appropriate correction for confounding factors such as SES did not confirm an effect of smoking (Cannon et al., 2002; Knopik, 2009; Larsson et al., 2005; Lee et al., 2012). Still, there may be an effect of heavy maternal smoking (>10 cigarettes per day) on co-occurring ADHD (Motlagh et al., 2010).

Absent evidence for low birth weight with regard to co-occurring ADHD in our study contrasts with studies on ADHD as such (Breslau et al., 1996; Mick et al., 2002). However, as our sample had only a limited number of cases with low birth weight (≤2500 grams at birth), our study may have been underpowered to detect possible associations with low birth weight, especially as the more pronounced effects for birth weight in neurodevelopmental

disorders have often been found for the very low birth weight category (≤1500 grams at birth) (Abel et al., 2010), of which our sample most likely had very few.

A surprising result in our study was the lower tic severity in those with neonatal complications. The literature on neonatal complications in relation to tic severity is limited (see Chao et al., 2014) and the only other study (Bos-Veneman et al., 2010) that evaluated this factor found no association. One possible explanation for this inverse relationship may be that environmental factors are linked to different pathways than genetic factors, leading to a phenotype characterized by milder tics compared to tics that are mainly caused by genetic factors. To confirm this hypothesis replication is required and therefore the inverse association found in this study should be interpreted with caution.

Major strengths of our study included the large sample size of well-characterized individuals and the wide range of tic severities compared to studies with only clinically ascertained individuals (Leckman et al., 1990; Saccomani et al., 2005), spanning individuals typically found in clinical as well as general population-based samples. Unlike most studies (Khalifa and von Knorring, 2005; Mathews et al., 2014; Motlagh et al., 2010; Pringsheim et al., 2009; Saccomani et al., 2005), our study sample consisted predominantly of adults, and because we assessed lifetime history of tics and co-occurring diagnosis, our results have not been influenced by the waxing and waning course of tics and the possibility of late onset OCD remaining undiscovered as in child samples.

We acknowledge that the retrospective collection of worst-ever clinical symptoms and of pre- and perinatal complications is a limitation, although evidence supports accurate maternal long-term recall for the latter (Rice et al., 2007). It should also be noted that our study cohort was a convenience sample including individuals ascertained for a genetic study on TS. Furthermore, our controls were family members (i.e., a mixture of relatives and married-in individuals) that may not be representative of the general population (e.g., by having higher rates of psychopathology); however, this may have had the advantage of controls having a similar background as our cases. Moreover, although we cannot fully rule out potential bias through demographic differences in occurrence of pre- and perinatal complications between cases and controls, we believe that this may have been counteracted by the use of family controls and the large sample size. Finally, most of our findings do not meet the stringent significance level when correcting for multiple testing; however, we believe this would be too stringent since it inflates type II error ruling out potentially important findings especially of modest effect (Rothman, 1990). Despite that we want to highlight that the finding of the presence of at least one pregnancy complication in relation to a chronic tic disorder diagnosis is above the multiple testing threshold.

In conclusion, our study provides evidence for an association of pregnancy complications, but not delivery and neonatal complications with a tic disorder diagnosis; an association of pregnancy, delivery, and neonatal complications with co-occurring OCD; and of neonatal complications with co-occurring ADHD. Overall, our findings suggest that early exposures to adverse situations (during pregnancy) are more prominently associated with tic disorders, and exposures at a later stage (at birth or during the first weeks of life) largely with the presence and severity of co-occurring OCD and ADHD in individuals with tic disorders. In

line with findings from related neurodevelopmental disorders, we found insufficient evidence to implicate any single pre- or perinatal complication (Cannon et al., 2002; Gardener et al., 2011). Underlying biological mechanisms may be the involvement of epigenetic changes that may lead to altered gene expression and/or altered brain development that could result in onset of a tic disorder (Mathews et al., 2006).

Our study highlights the importance of carefully providing optimal pregnancy and perinatal care to families with a history of chronic tic disorders. However, without a clear causal link between the factors investigated in this study and a chronic tic disorder, more studies should be directed towards better understanding of potential mechanisms involved in these complications and the complex interplay between environmental factors and genetic risk factors. The implicated environmental factors in this study could serve as an excellent starting point for these studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics and clinical characteristics of cases affected with a chronic tic disorder and of age- and sex- propensity matched controls

Variable	Cases (N=236)			Controls (N=518)					
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	**df**	**t**	***p***
Age in years	39.2	16.7	3–79	41.2	14.7	9–83	406	−1.56	0.12
SES[a]	4.46	1.49	1–7	4.39	1.49	1–7	703	0.62	0.55
Worst ever total YGTSS rating[b]	12.4	7.88	1–30	0	0				
Worst ever total Y-BOCS rating[c]	11.1	10.5	0–36	4.05	7.5	0–40	599	9.36	<0.001
Total ADHD SNAP-IV symptom count[d]	3.87	4.98	0–18	1.43	3.16	0–18	752	8.11	<0.001
	N	%		N	%	OR	95% CI OR	χ^2	*P*[e]
Participants <18 years old	35	14.8		53	10.2	1.53	0.98–2.41	3.33	0.07
Male	110	46.6		257	49.6	1.13	0.83–1.53	0.59	0.48
Race white	222	94.1		498	96.2	0.64	0.32–1.28	1.61	0.14
Tourette's disorder[f]	145	61.4		0	0				
Chronic motor or vocal tic disorder[f]	91	38.6		0	0				
OCD diagnosis[f]	88	37.3		68	13.2	4.02	2.78–5.80	59.3	<0.001
ADHD diagnosis[f]	44	18.6		20	4.0	6.04	3.46–10.5	48.8	<0.001

df, degrees of freedom; SES, socioeconomic status; YGTSS, Yale Global Tic Severity Scale (Leckman et al., 1989; Storch et al., 2005); OCD, obsessive-compulsive disorder; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale (Goodman et al., 1989a, 1989b; Scahill et al., 1997); ADHD, attention–deficit/hyperactivity disorder; SNAP-IV, Swanson, Nolan and Pelham-IV rating scale (Bussing et al., 2008; Swanson, 1992; Swanson et al., 2001).

[a] Based on parents' education level (1= less than 7 years of schooling to 7= graduate/professional degree)

[b] Sum score of worst ever motor and phonic tics (range 0–30)

[c] Sum score of worst ever obsessions and compulsions (range 0–40)

[d] Number of items scored as "2=quite a bit" or "3=very much" on the SNAP-IV (range 0–18)

[e] Comparisons were done using Pearson's chi-square test with one degree of freedom

[f] Life-time diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR (American Psychiatric Association, 2000)

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Table 2

Demographics of individuals with a chronic tic disorder exposed and unexposed to pre- and perinatal complications[a]

Variable	Exposed individuals			Unexposed individuals						
	N	%		N	%		OR	95% CI OR	χ^2	P^b
Matched sample size										
At least one pregnancy complication	150	100%		150	100%					
At least one delivery complication	170	100%		204	100%					
At least one neonatal complication	203	100%		288	100%					
Participants <18 years old										
At least one pregnancy complication	95	63.3		99	66.0		0.89	0.55–1.43	0.23	0.72
At least one delivery complication	95	55.9		113	55.4		1.02	0.68–1.54	0.01	1
At least one neonatal complication	148	72.9		210	72.9		0.99	0.67–1.49	<0.01	1
Male										
At least one pregnancy complication	103	68.7		102	68.0		0.97	0.59–1.58	0.02	1
At least one delivery complication	106	62.4		133	65.2		1.13	0.74–1.73	0.32	0.59
At least one neonatal complication	143	70.4		204	70.8		1.02	0.69–1.51	0.01	1
Race white										
At least one pregnancy complication	146	97.3		141	94.0		2.33	0.70–7.74	2.01	0.26
At least one delivery complication	161	94.7		193	94.6		1.02	0.41–2.52	<0.01	1
At least one neonatal complication	189	93.1		270	93.8		0.90	0.44–1.85	0.08	0.85
	Mean	SD	Range	Mean	SD	Range		df	t	*P*
Mean age in years										
At least one pregnancy complication	20.3	13.6	6–68	20.3	13.7	6–66		298	−0.04	0.97
At least one delivery complication	24.2	16.8	3–74	24.3	16.9	6–76		372	0.05	0.96
At least one neonatal complication	17.6	12.5	3–65	17.8	12.5	4–66		489	0.14	0.89
SES[c]										
At least one pregnancy complication	5.15	1.36	1–7	5.18	1.32	1–7		289	0.24	0.81
At least one delivery complication	4.95	1.38	1–7	4.83	1.43	1–7		359	−0.81	0.42
At least one neonatal complication	5.31	1.28	1–7	5.12	1.33	1–7		476	−1.52	0.13

df, degrees of freedom; SES, socioeconomic status

[a] Groups were propensity matched on age and sex

[b] Comparisons were done using Pearson's chi-square test with one degree of freedom

[c] Based on parents' education level (1= less than 7 years of schooling to 7= graduate/professional degree)

Table 3

Frequencies of pre- and perinatal complications in cases affected with a tic disorder compared to age- and sex-propensity matched controls

Variable	Cases (N=236)		Controls (N=518)	
Pregnancy complications	**N**	**%**	**N**	**%**
a) Assisted reproduction	17	7.20	33	6.37
b) Advanced maternal age (>40 years at conception)	9	3.81	17	3.28
c) Multiple pregnancy (twin pregnancy or more)	5	2.12	19	3.67
d) Maternal smoking	53	22.5	115	22.2
e) Maternal use of alcohol	29	12.3	58	11.2
f) Maternal use of medication	20	8.47	26	5.02
g) Low birth weight (birth weight <2500 grams)	13	5.51	31	5.98
h) Premature birth (gestational age < 37 weeks at birth)	43	18.2	61	11.8
i) Complications of a pre-existing medical problem	11	4.66	13	2.51
j) Maternal illness or infections	7	2.97	12	2.32
k) Morning sickness requiring medical attention	22	9.32	20	3.86
l) Gestational diabetes/elevated blood sugar	5	2.12	10	1.93
m) Preeclampsia	10	4.24	15	2.90
n) Vaginal bleeding	5	2.12	16	3.09
Delivery complications				
a) Prolonged labor	15	6.36	45	8.69
b) Use of labor medication	22	9.32	39	7.53
c) Unusual presentation (e.g., breech)	14	5.93	33	6.37
d) Unplanned caesarean section	13	5.51	23	4.44
e) Cord around the baby's neck	13	5.51	14	2.70
f) Forceps delivery	18	7.63	31	5.98
g) Suction/vacuum delivery	6	2.54	10	1.93
h) Other delivery complications	10	4.24	20	3.86
Neonatal complications				
a) Blue in color immediately after birth	15	6.36	17	3.28
b) Low level activity immediately after birth	8	3.39	8	1.54
c) Floppiness of the muscles immediately after birth	4	1.69	1	0.19

Variable	Cases (N=236)		Controls (N=518)	
Pregnancy complications	**N**	**%**	**N**	**%**
d) Decreased responsiveness immediately after birth	5	2.12	7	1.35
e) Delay in breathing immediately after birth	7	2.97	11	2.12
f) Weak/abnormal cry immediately after birth	6	2.54	11	2.12
g) Oxygen therapy	9	3.81	16	3.09
h) Suctioning of airway immediately after birth	16	6.78	20	3.86
i) Medication given immediately after birth	4	1.69	4	0.77
j) Use of an incubator	8	3.39	26	5.02
k) Stay on intensive care unit	7	2.97	16	3.09
l) Jaundice requiring medical attention	18	7.63	33	6.37
m) Neonatal infection	2	0.85	2	0.39
n) Breathing problems during the first two weeks of life	11	4.66	7	1.35
o) Fever during the first two weeks of life	1	0.42	5	0.97
p) Prolonged hospital stay	21	8.90	42	8.11

Table 4

Comparison of pre- and perinatal complications in cases affected with a tic disorder compared to age- and sex-propensity matched controls

Variable	Cases (N=236)		Controls (N=518)		Unadjusted for SES				Adjusted for SES			
	Exposed N	Exposed %	Exposed N	Exposed %	OR	95% CI OR	χ^2	p^a	OR	95% CI OR	Wald	p^b
At least one pregnancy complication	130	53.5	239	45.5	1.72	1.17–2.50	7.91	<0.01	1.76	1.18–2.62	7.72	<0.01
Premature birth (gestational age < 37 weeks at birth)	43	18.2	61	11.8	1.69	1.10–2.59	5.91	<0.05	1.72	1.11–2.65	5.90	<0.05
Morning sickness requiring medical attention	22	9.32	20	3.86	2.69	1.43–5.06	9.99	<0.01	2.57	1.32–4.75	7.95	<0.01
At least one delivery complication	103	42.4	209	39.6	1.17	0.84 – 1.61	0.85	0.36	1.17	0.83 – 1.65	0.85	0.36
At least one neonatal complication	51	21.0	96	18.2	1.17	0.78 – 1.75	0.59	0.47	1.29	0.87 – 1.96	1.53	0.22
	Mean	SD	Mean	SD			Z	p^c	OR	95% CI OR	Wald	p^b
Total number of pregnancy complications	1.15	1.27	0.94	1.28			−2.21	<0.05	1.13	0.99–1.28	3.78	0.05
Total number of delivery complications	0.55	0.85	0.49	0.85			−1.60	0.11	1.08	0.89–1.32	0.60	0.44
Total number of neonatal complications	0.67	1.70	0.52	1.35			−1.66	0.10	1.09	0.98–1.22	2.68	0.10
Total number of complications	2.36	2.66	1.95	2.57			−3.01	<0.01	1.07	1.01–1.14	5.45	<0.05

OR, odds ratio; CI, confidence interval

[a]Comparisons were done using Pearson's chi-square tests with one degree of freedom

[b]Comparisons were done with a logistic regression with one degree of freedom

[c]Comparisons were done with the Mann-Whitney test

Table 5

Comparison of clinical characteristics of individuals with a chronic tic disorder exposed and unexposed to pre- and perinatal complications[a]

Variable	Exposed		Unexposed		SES unadjusted				SES adjusted			
	N	%	N	%	OR	95% CI	χ^2	p^b	OR	95% CI	Wald	p^c
At least one pregnancy complication	150	100	150	100								
Comorbid OCD	59	39.3	56	37.3	1.05	0.66–1.68	0.05	0.91	1.03	0.64–1.67	0.02	0.89
Comorbid ADHD	39	26	50	33.3	0.70	0.43–1.16	1.93	0.21	0.74	0.45–1.23	1.34	0.25
At least one delivery complication	170	100	204	100								
Comorbid OCD	76	44.7	70	34.3	1.58	1.04–2.41	4.61	<0.05	1.49	0.97–2.29	3.34	0.07
Prolonged labor[g]	34	51.5	121	31.3	1.75	1.02–2.98	4.27	<0.05	1.69	0.98–2.93	3.62	0.06
Forceps Delivery[g]	23	54.8	183	37.9	1.96	1.04–3.71	4.47	<0.05	2.06	1.08–3.91	4.85	<0.05
Comorbid ADHD	60	35.3	61	29.9	1.28	0.83–1.97	1.23	0.32	1.12	0.77–1.88	0.68	0.41
At least one neonatal complication	203	100	288	100								
Comorbid OCD	96	47.3	106	36.8	1.55	1.07–2.23	5.48	<0.05	1.46	1.01–2.12	3.96	<0.05
Suctioning of the airway immediately after birth[g]	41	53.9	123	38.0	1.91	1.16–3.17	6.50	<0.05	1.99	1.19–3.34	6.91	<0.05
Prolonged hospital stay[g]	43	55.8	135	39.0	1.97	1.20–3.26	7.32	<0.05	1.93	1.16–3.20	6.37	<0.05
Comorbid ADHD	83	40.9	95	32.9	1.45	0.99–2.11	3.82	0.06	1.40	0.95–2.03	3.06	0.08
Jaundice requiring medical attention[g]	43	48.9	124	34.7	1.80	1.13–3.01	6.10	<0.05	1.86	1.15–3.01	6.34	<0.05
	Mean	SD	Mean	SD	Mean difference	df	t	*P*	Beta	95% Beta	t	p^c
At least one pregnancy complication												
Tic severity[d]	15.6	7.80	17.1	8.33	−1.50	264	−1.44	0.15	−1.68	−3.64–0.28	−1.69	0.09
OC severity[e]	13.3	11.5	10.5	10.8	2.80	247	1.96	0.05	2.70	−0.13–5.54	1.89	0.06
ADHD severity[f]	4.85	5.53	5.93	5.93	−1.08	296	−1.63	0.10	−1.02	−2.34–0.31	−1.51	0.13
At least one delivery complication												
Tic severity[d]	15.8	7.94	15.9	7.80	−0.10	321	−0.08	0.94	−0.08	−1.80–1.65	−0.09	0.93
OC severity[e]	12.5	11.5	10.9	10.7	1.60	304	1.27	0.20	1.32	−1.21–3.85	1.02	0.31
ADHD severity[f]	5.72	6.08	5.20	5.37	0.52	340	0.87	0.39	0.35	−0.83–1.53	0.58	0.56
At least one neonatal complication												

Variable	Exposed		Unexposed		SES unadjusted				SES adjusted			
	N	%	N	%	OR	95% CI	χ^2	p^b	OR	95% CI	Wald	p^c
Tic severity[d]	16.3	7.31	17.6	7.78	−1.30	434	−1.65	0.10	−1.49	−2.97– −0.02	−1.99	<0.05
Breathing problems during the first two weeks of life[g]	14.9	6.87	17.5	7.26	−2.60	153	−1.58	0.12	−3.55	−6.94– −0.16	−2.07	<0.05
OC severity[e]	13.7	11.5	11.1	11.1	2.60	408	2.34	<0.05	2.27	0.02–4.52	1.98	<0.05
Delay in breathing immediately after birth[g]	16.0	11.5	11.1	11.6	4.90	162	2.06	<0.05	4.47	−0.34–9.29	1.84	0.07
Suctioning of airway immediately after birth[g]	15.8	11.3	12.0	11.3	3.80	325	2.38	<0.05	3.52	0.39–6.65	2.21	<0.05
ADHD severity[f]	6.67	5.76	5.49	5.93	1.18	489	2.19	<0.05	1.09	0.01–2.16	1.99	<0.05
Weak abnormal cry immediately after birth[g]	8.51	5.27	5.89	5.92	2.62	184	2.29	<0.05	2.39	0.02–4.76	1.99	<0.05
Jaundice requiring medical attention[g]	7.39	5.56	5.77	6.04	1.62	141	2.41	<0.05	1.82	0.40–3.24	2.52	<0.05

SES, socioeconomic status; OR, odds ratio; CI, confidence interval; OCD, obsessive-compulsive disorder; ADHD, attention–deficit/hyperactivity disorder; df, degrees of freedom; OC, obsessive-compulsive

[a] Groups were propensity matched on age and sex as per pre- and perinatal risk factor

[b] Comparisons were done using Pearson's chi-square test with one degree of freedom

[c] Comparisons were done with a regression analysis with two degrees of freedom

[d] Sum score of worst ever motor and phonic tics based on the Yale Global Tic Severity Scale (Leckman et al., 1989; Storch et al., 2005) (range 0–30)

[e] Sum score of worst ever obsessions and compulsions based on the Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989a, 1989b; Scahill et al., 1997) (range 0–40)

[f] Symptom count of items scored as "2=quite a bit" or "3=very much" on the Swanson, Nolan and Pelham-IV rating scale (Bussing et al., 2008; Swanson, 1992; Swanson et al., 2001) (range 0–18)

[g] Follow-up analyses on individual risk factor, only significant results shown