OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Brief Reports

Prenatal and Perinatal Morbidity in Children with Tic Disorders: A Mainstream School-based Population Study in Central Spain

Esther Cubo[1*], Montesclaros Hortigüela[2], Sandra Jorge-Roldan[1], Selva Esther Ciciliani[2], Patricia Lopez[1], Leticia Velasco[1], Emilio Sastre[2], Vanesa Ausin[3], Vanesa Delgado[3], Sara Saez[3], José Trejo Gabriel-Galán[1] & Jesús Macarrón[1]

[1] Neurology Department, Hospital Universitario Burgos, Burgos, Spain, [2] Pediatrics Department; Hospital Universitario Burgos, Burgos, Spain, [3] Research Unit, Hospital Universitario Burgos, Spain

Abstract

Background: While current research suggests that genetic factors confer the greatest risk for the development of tic disorders, studies of environmental factors are relatively few, with a lack of consistent risk factors across studies. Our aim is to analyze the association of tic disorders with exposure to prenatal and perinatal morbidity.

Methods: This was a nested case–control study design. Cases and controls were selected and identified from a mainstream, school-based sample. The diagnosis of tic disorders was assigned by a movement disorder neurologist using 'Diagnostic and statistical manual of mental disorders, 4th edition, text revision' criteria, and neuropsychiatric comorbidities were screened using the Spanish computerized version of the Diagnostic Interview Schedule for Children Predictive Scale. Information regarding the exposure to pre-perinatal risk factors was collected by a retrospective review of the birth certificates. Logistic regression analyses were then performed to test the association of tic disorders with pre-perinatal risk factors.

Results: Out of 407 participants, complete pre-perinatal data were available in 153 children (64 with tics and 89 without tics). After adjusting for family history of tics, neonatal respiratory distress syndrome, body mass index, prenatal infection, and coexisting comorbid neuropsychiatric disturbances, tic disorders were associated with prenatal exposure to tobacco (odds ratio [OR]=3.07, 95% confidence interval [CI] 1.24–7.60, p=0.007), and cesarean section (OR=5.78, 95% CI 1.60–20.91, p=0.01).

Discussion: This nested case–control study of children with tic disorders demonstrates higher adjusted odds for tics in children with exposure to cesarean delivery and maternal smoking. Longitudinal, population-based samples are required to confirm these results.

Keywords: Tics, Tourette syndrome, tobacco, cesarean delivery, cohorts

Citation: Cubo E, Hortigüela M, Jorge-Roldan S, et al. Prenatal and perinatal morbidity in children with tic disorders: A mainstream school-based population study in central Spain. Tremor Other Hyperkinet Mov. 2014; 4. doi: 10.7916/D8FN14W9

*To whom correspondence should be addressed. E-mail: esthercubo@gmail.com

Editor: Elan D. Louis, Columbia University, USA

Received: September 10, 2014 **Accepted:** November 11, 2014 **Published:** December 15, 2014

Funding: None.

Financial disclosures: None.

Conflict of interest: The authors report no conflict of interest.

Introduction

While current research suggests that genetic factors confer the greatest risk for the development of tic disorders, there is evidence that these have been identified in less than 1% of patients.[1] Studies of environmental factors are relatively few, and consistent risk factors have not been identified across studies.[2] Of all the risk factors studied, maternal smoking and low birth weight appear to be the only risk factors with a consistent significant association.[2] Existing studies have major limitations, mainly due to the use of clinical rather than epidemiologically derived samples and analytical methods.[2] In contrast, research into pre-perinatal risk factors for common comorbidities associated with tic disorders, such as attention deficit hyperactivity disorder (ADHD) and autism, is more robust, finding higher odds for children exposed to maternal smoking and increased maternal stress during pregnancy, as well as pregnancy and delivery complications.[3] Dysfunction of the dopaminergic system has been implicated in tics and comorbid disorders, and evidence from animal studies suggests that prenatal stress may cause changes in the

dopaminergic system as a result of early brain injury.[4,5] Therefore, when evaluating children with tic disorders, and in order to attempt to minimize risk factors in pregnant women at risk genetically for tic disorders, it is essential to distinguish the specific role of the pre-perinatal risk factors relative to other individual contributing factors. The aim of this study was to analyze the association of tic disorders with exposure to prenatal and perinatal morbidity in a population sample from a mainstream school.

Methods

This study was performed using a nested case–control study design. This study was approved by the Ethical Review Board of the Hospital Universitario Burgos (Spain); the mother or father, or the legal guardian signed the consent form. Cases and controls were selected and identified from pupils in a mainstream school; the study was originally conducted between March 2007 and December 2009 in the Burgos school district (Spain). This study was aimed at determining the prevalence of tic disorders and associated comorbidities, and its association with school performance.[6,7] Briefly, the original cohort included pupils aged 6–16 years enrolled in primary or secondary education. Special education schools were excluded. This study was carried out in two phases. Phase 1 involved the application of the screening tool for tic disorders, and Phase 2 involved screening for neuropsychiatric comorbidities, and the ascertainment of tic disorders by a neurologist using 'Diagnostic and statistical manual of mental disorders, 4th edition, text revision' (DSM-IV-TR) criteria.[8]

In summary, in the original cohort, out of 2,806 eligible participants, 1,867 pupils, agreed to participate (66.5%) and the tic screening survey was obtained in 1,858 children (99.5%). In phase 2, 799 pupils were invited to participate (those with at least one positive screening for tic disorders, and poor school performance, and unaffected age-, gender-, and matched-classmates). Five hundred and twenty-six pupils were included, and complete data on the tic diagnosis were available for 407 participants (162 with tics, and 245 without tics).

Assessments. Neuropsychiatric comorbidities were screened by trained raters using the Spanish computerized version of the Diagnostic Interview Schedule for Children (DISC) Predictive Scale (DPS).[9] The DPS contains 18 subscales using DSM-IV criteria,[9] including phobia disorders, ADHD, obsessive compulsive disorder (OCD), oppositional defiant disorder, anxiety, major depression conduct disorder, and substance abuse disorder. Verbal and non-verbal intelligence information was measured by an intellectual quotient (IQ) composite score obtained using the Kaufman Brief Intelligence Test.[10] Information regarding the exposures of interest was collected by a retrospective review of the birth certificates signed by a physician. Subjects for whom a birth certificate was not available, and those with an IQ <90 were excluded from this study.

Outcomes. Cases were defined as children in the original cohort fulfilling DSM-IV-TR criteria for tic disorders.[8] Controls were defined as children without tic disorders. Data on risk factors were obtained from birth certificates and included demographic factors and pre-conception status, namely the mother's age and pre-existing medical conditions. For the pregnancy period, data included exposure to tobacco (yes/no), alcohol (yes/no), gestational diabetes, infections, eclampsia, and twin pregnancy. For the perinatal period, data included preterm newborns, intrauterine growth retardation, instrumental vaginal deliveries (forceps or vacuum extraction), cesarean delivery, and perinatal disorders such as neonatal respiratory distress syndrome (NRDS), neonatal jaundice, fever, use of neonatal intensive care unit, Apgar scores at 1 and 5 minutes, newborn anthropometrics, and the presence of any significant newborn medical condition or associated malformations. Follow-up data, such as age, gender, family history of tics, IQ, neuropsychiatric comorbidities, parental education background, body mass index (BMI) at data collection, and handedness, were obtained from the original study.

Analysis

Statistical analyses were performed using IBM-SPSS Version 19.0 (SPSS, Inc., Chicago, IL). All tests were two-tailed with alpha = 0.05. Missing observations were coded as missing data. Children with cesarean delivery because of cephalopelvic disproportion, prolonged second stage, planned, or due to other reasons were coded as cesarean delivery exposure. Children with NRDS (with and without cesarean exposure) were coded as NRDS exposure. Differences between cases and controls (tics vs. no tics) were compared using the Wilcoxon-Mann-Whitney test or Student t test for continuous variables, as required, and the Chi-squared tests, and Cramer's V test for categorical variables.

To assess the possibility of selection bias (differences between included and non-included subjects), data obtained from the original study were compared for gender, presence of tics, parental education background, and self-report by the mother on cesarean delivery and tobacco use. Logistic regression analyses were then performed to test the association of tic disorders with pre-perinatal risk factors. The presence of tic disorders (yes vs. no) was used as the dependent variable, and pre-perinatal risk factors as the independent variables. The selection of variables included in the model was based on the univariate analysis of independent variables, and the clinical decision to adjust for potential confounders was based on biological or epidemiological evidence. To determine if a logistic regression model provided a good fit for the data, the Hosmer–Lemeshow and Nalgerkeke goodness-of-fit tests were used. These analyses generated odds ratios (ORs) with 95% confidence intervals (CIs). Post hoc analysis performed using GPower 3 for variables of interest, such as maternal smoking and cesarean delivery exposure, showed that the statistical power was $\geqslant$95% with a sample size of at least 148 subjects, at a 5% alpha level.

Results

A total of 407 children were eligible for the study, and 153 children, including 103 males (67.3%), were included in this study. Complete pre-perinatal data were available for 64 children with tics (41.8%) and 89 children without tics (58.2%). Two hundred and fifty-two children were excluded: 19 of them (7.5%) had an IQ <90, and for 233 (92.5%)

Table 1. Clinical Characteristics Comparison

	Comparison of Tics		p-Value
	No	Yes	
	N=89	N=64	
Child characteristics			
Gender (male %)	57 (64)	45 (70)	0.41
Age (mean ± SD)	11.81 ± 3.03	10.78 ± 2.84	0.04
Handedness (%)			
Right handed	80 (91)	55 (87)	0.01
Left handed	4 (5)	4 (6)	
Ambidextrous	4 (5)	4 (6)	
Body mass index	18.85 ± 2.89	17.56 ± 0.01	0.01
IQ mean ± SD	100.65 ± 11.48	99.91 ± 10.56	0.68
ADHD (%)	9 (10)	10 (16)	1.00
OCD (%)	3 (3)	2 (3)	0.37
Other medical conditions (%)	12 (14)	8 (13)	0.37
Family history			
Tics (%)	17 (19)	22 (35)	0.03
ADHD (%)	1 (3)	1 (3)	1.00
OCD (%)	1 (3)	0 (0)	1.00
Parental education background			
Primary and secondary studies (%)			
Father	64 (74)	41 (69)	0.95
College and higher studies (%)			
Father	22 (26)	19 (31)	
Primary and secondary studies (%)			
Mother	63 (81)	43 (77)	0.99
College and higher studies (%)			
Mother	25 (29)	21 (23)	
Pre-perinatal neonatal risk factors			
Mother's age (mean ± SD)	30.67 ± 4.42	30.05 ± 4.88	0.37
Healthy mother before pregnancy (%)	75 (88)	48 (76)	0.05
Prenatal smoking exposure (%)	21 (25)	25 (40)	0.05
Prenatal alcohol exposure (%)	0 (0)	1 (1)	0.42

Table 1. Continued

	Comparison of Tics		p-Value
	No	Yes	
	N=89	N=64	
Normal pregnancy (%)	58(79)	38 (70)	0.23
Prenatal infection (%)	2 (2)	7 (11)	0.03
Eclampsia (%)	0 (0)	1 (2)	0.42
Gestational diabetes (%)	11 (15)	3 (6)	0.09
Gestational age (mean ± SD) weeks	39.27 ± 1.38	38.89 ± 1.58	0.12
Twin birth (%)	2 (3)	3 (5)	0.64
Vaginal delivery presentation (%)			
Vertex	66 (90)	46 (87)	0.21
Transverse	5 (7)	2 (4)	
Breech	2 (3)	5 (9)	
Cesarean section (%)	8 (9)	23 (37)	<0.0001
Cause of cesarean section (%)			
Unknown	1 (13)	1 (4)	0.31
Cephalopelvic disproportion	0 (0)	3 (13)	
At risk for NRDS	3 (38)	10 (43)	
Planned	4 (50)	5 (22)	
Prolonged second stage	0 (0)	4 (17)	
Instrumental vaginal delivery (%)	13 (59)	9 (40)	0.51
Perinatal hypoxia (%)	5 (6)	6 (9)	0.52
Apgar at 1 minute (mean ± SD)	8.65 ± 1.18	8.56 ± 1.01	0.19
Apgar at 5 minutes (mean ± SD)	9.82 ± 0.76	9.76 ± 0.53	0.07
NRDS (%)	11 (12)	14 (25)	0.03
Birth weight (g) mean ± SD	3197 ± 443	3129 ± 473	0.53
Birth length (cm) mean ± SD	50.24± 1.73	49.92± 2.45	0.34
Cephalic perimeter (cm) mean + SD	34.65 ± 1.34	34.8 ± 2.31	0.88
Need for incubator (%)	6 (7)	8 (16)	0.13
Intrauterine growth retardation[1] (%)	6 (7)	5 (8)	1.00
Prematurity[2] (%)	4 (4)	6 (9)	0.32
Jaundice (%)	9 (10)	4 (6)	0.39
Other significant co-existent medical conditions[3] (%)	4 (6)	4 (6)	1.00

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; IQ, Intellectual Quotient; NRDS, Neonatal Respiratory Distress Syndrome; OCD, Obsessive Compulsive Disorder; SD, Standard Deviation.
[1]Intrauterine growth retardation was determined by taking the birth weight and gestational age of the baby and comparing the value to a population-based Spanish reference for small for gestational age cut-offs (10th percentile).
[2]Prematurity was defined as <36-week pregnancy.
[3]Other significant medical conditions included heart disorders, transient tachypnea, pneumomediastinum, malformations, and hydronephrosis.

birth certificates were not available at our center. Cesarean section was performed in 31 children (20.2%). There were no differences between included and non-included subjects in terms of gender (p=0.56), parental (mother and father) education background (p=0.95, p=0.63, respectively), and tics and cesarean delivery frequency (p=0.60, p=0.80, respectively). In contrast, the included subjects were more frequently exposed to maternal smoking than the non-included group (30.9% vs. 19.1%, p=0.01). Table 1 compares the demographic and clinical characteristics of children with tics vs. no tics.

Presence of prenatal infection, NRDS, cesarean delivery, and exposure to maternal smoking were included in the regression model (Table 2). This model was adjusted for BMI, family history of tics, and the presence of any neuropsychiatric comorbidity. Overall, tic disorders were associated with prenatal exposure to tobacco (OR=3.07, 95% CI 1.24–7.60, p=0.007), and cesarean section (OR=5.78, 95% CI 1.60–20.91, p=0.01).

Discussion

This nested case–control study of children with tic disorders demonstrates higher adjusted odds for tics in children with exposure to cesarean delivery and maternal smoking. In agreement with our results, Mathews et al.[11] also identified prenatal exposure to tobacco as a strong risk factor for increased symptom severity in Tourette syndrome (TS). In contrast, in one study evaluating psychological stress and heavy maternal smoking during pregnancy, Motlagh et al.[12] found that maternal smoking was more strongly associated with comorbid ADHD than with TS. In the Avon Longitudinal Study of Parents and Children prospective longitudinal pre-birth cohort, low socioeconomic status, maternal alcohol and cannabis use, and inadequate maternal weight gain and parity were associated with TS/chronic tic disorder, but prenatal maternal smoking was not associated with TS.[13] Of note, in our study, no differences were found in terms of maternal alcohol exposure and socioeconomic status (marked as parental education background) when children with tics vs. those without tics were compared. Although we do not have a compelling explanation for these discrepancies, methodological and sample characteristics differences should be taken into account. Firstly, the frequency of maternal smoking was higher in our study (30.9%) than in the study by Motlagh et al.[12] (up to 17% in the group of children with ADHD alone). Secondly, we cannot exclude a selection bias, since we have included children with a higher frequency of exposure to maternal smoking than the non-included children. Thirdly, the lack of association between socioeconomic status and tic disorders in our study is unlikely to be a result of bias, since the parental education background was similar between participants and non-participants. In addition, in our study, there was a failure to demonstrate any association between maternal consumption of alcohol and tic disorders, most likely due to the low frequency of consumption, or possibly related to under-reporting.

Why are children exposed to maternal smoking at increased risk of tic disorders? Although we cannot give an explanation for this because of the design of our study, there is evidence that nicotine may cause changes in the dopaminergic system. Nicotine is readily transferred to the fetal compartment throughout pregnancy, and fetuses of mothers who smoke are exposed to relatively higher nicotine concentrations than their mothers.[14] Nicotine exposure could impair the function of nicotinic acetylcholine receptors and the regulation of catecholamines during

Table 2. Logistic Regression of Model of Tics vs. No Tics (Dependent Variable)

	Adjusted Odds Ratio (95% CI)	p-Value
Cesarean section	5.78 (1.60–20.91)	0.007
Prenatal smoking exposure	3.07 (1.24–7.60)	0.01
Neonatal respiratory syndrome	1.21 (0.325.61)	0.77
Prenatal infection	2.84 (0.40–19.84)	0.29

Abbreviation: CI, Confidence Interval.
The logistic regression model was adjusted for family history of tics, body mass index, and presence of any coexistent comorbid neuropsychiatric disturbances. The model fitness was adequate (Nagelke R^2, p=0.28; Hosmer–Lemeshow, p=0.67). This model classified 73.4% of the population (55.1% with tics and 85.3% without tics).

brain development. Neuronal nicotinic acetylcholine receptors play a role in neuronal migration, pathfinding, and growth cone direction. Hypoactivity in noradrenergic and dopaminergic projections and fetal exposure to nicotine has also been demonstrated in animal models.[15]

The second question is: Why is cesarean section associated with tic disorders? Possible explanations include the presence of mild fetal hypoxia, the exposure to anesthetics, or the potential influence of oxytocin administered during delivery on child development. Preliminary evidence suggests the possible implication of oxytocin in disorders related to the TS spectrum.[16] The injection of oxytocin in the amygdala of rodents was shown to be able to induce hypergrooming, suggesting the possible involvement of this neuropeptide in the pathophysiology of complex, stereotyped behaviors.[16]

In our study, given the heritability of tic disorders, the presence of a family history of tic disorders was controlled for in the logistic regression model. However, how to control for the genetic risk for tic disorders is controversial. In our study, the genetic risk for tics (family history of tics) was retrospectively obtained from the original study, based on maternal questionnaires. In this regard, we cannot exclude the possibility that maternal questionnaires are more susceptible to recall bias, including false negatives (exclusion of other relatives with mild tics or comorbidities such as OCD related to the tics spectrum), or false positives (inclusion of relatives with other types of repetitive movements/sounds).

This study also has several strengths. Firstly, we analyzed data previously collected from an epidemiologically derived sample, blinded to the current hypothesis. Secondly, we chose rigorous disease definitions with case ascertainment by a neurologist. Thirdly, although there are no standards on how to collect pre-perinatal information for tic studies, in this study, they were exclusively obtained from birth certificates to avoid recall bias. On the other hand, it is recognized that the present study also has several limitations, with a possible over-representation of children with prenatal tobacco exposure and tic disorders, and the fact that the pre-perinatal information was retrospectively ascertained.

In conclusion, this nested case–control study of children with tic disorders demonstrates higher adjusted odds for tics in children with exposure to cesarean delivery and maternal smoking. However, longitudinal, population-based samples are required to confirm these results.

References

1. Bloch M, State M, Pittenger C. Recent advances in Tourette syndrome. *Curr Opin Neurol* 2011;24:119–125, doi: http://dx.doi.org/10.1097/WCO.0b013e328344648c.

2. Chao TK, Hu J, Pringsheim T. Prenatal risk factors for Tourette syndrome: A systematic review. BMC Pregnancy *Childbirth* 2014;14:53, doi: http://dx.doi.org/10.1186/1471-2393-14-53.

3. Bos-Veneman NG, Kuin A, Minderaa RB, Hoekstra PJ. Role of perinatal adversities on tic severity and symptoms of attention deficit/hyperactivity disorder in children and adolescents with a tic disorder. *J Dev Behav Pediatr* 2010;31:100–106, doi: http://dx.doi.org/10.1097/DBP.0b013e3181cc7cbc.

4. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: A comprehensive meta-analysis. *Pediatrics* 2011;128:344–355, doi: http://dx.doi.org/10.1542/peds.2010-1036

5. Latimer K, Wilson P, Kemp J, et al. Disruptive behaviour disorders: A systematic review of environmental antenatal and early years risk factors. *Child Care Health Dev* 2012;38:611–628, doi: http://dx.doi.org/10.1111/j.1365-2214.2012.01366.x

6. Cubo E, Gabriel y Galan JM, Villaverde VA, et al. Prevalence of tics in schoolchildren in central Spain: A population-based study. *Pediatr Neurol* 2011;45:100–108, doi: http://dx.doi.org/10.1016/j.pediatrneurol.2011.03.003.

7. Cubo E, Trejo J, Ausin V, et al. Association of tic disorders with poor academic performance in central Spain: A population-based study. *J Pediatr* 2013;163:217–223, doi: http://dx.doi.org/10.1016/j.jpeds.2012.12.030.

8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.

9. Cubo E, Velasco SS, Benito VD, et al. Psychometric attributes of the DISC predictive scales. *Clin Pract Epidemiol Ment Health* 2010;6:86–93, doi: http://dx.doi.org/10.2174/1745017901006010086.

10. Hays JR, Reas DL, Shaw JB. Concurrent validity of the Wechsler abbreviated scale of intelligence and the Kaufman brief intelligence test among psychiatric inpatients. *Psychol Rep* 2002;90:355–359, doi: http://dx.doi.org/10.2466/pr0.2002.90.2.355.

11. Mathews CA, Bimson B, Lowe TL, et al. Association between maternal smoking and increased symptom severity in Tourette's syndrome. *Am J Psychiatry* 2006;163:1066–1073, doi: http://dx.doi.org/10.1176/appi.ajp.163.6.1066.

12. Motlagh MG, Katsovich L, Thompson N, et al. Severe psychosocial stress and heavy cigarette smoking during pregnancy: An examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome. *Eur Child Adolesc Psychiatry* 2014;19:755–764, doi: http://dx.doi.org/10.1007/s00787-010-0115-7.

13. Miller LL, Scharf JM, Mathews CA, Ben-Shlomo Y. Tourette syndrome and chronic tic disorder are associated with lower socio-economic status: Findings from the Avon Longitudinal Study of Parents and Children cohort. *Dev Med Child Neurol* 2013;56:157–163, doi: http://dx.doi.org/10.1111/dmcn.12318.

14. Luck W, Nau H, Hansen R, Steldinger R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Dev Pharmacol Ther* 1985;8:384–395.

15. Slotkin TA. Fetal nicotine or cocaine exposure: Which one is worse? *J Pharmacol Exp Ther* 1998;285:931–945.

16. Martino D, Macerollo A, Leckman JF. Neuroendocrine aspects of Tourette syndrome. *Int Rev Neurobiol* 2013;112:239–279, doi: http://dx.doi.org/10.1016/B978-0-12-411546-0.00009-3.