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Article title: Perinatal risk factors in Tourette's and chronic tic disorders: A lesson from epidemiology.

Veronica Bruno, MD, MPH[1]

Julieta E. Arena, MD[1]

1. Movement Disorders Section, Neuroscience Department, Raul Carrea Institute for Neurological Research (FLENI), Montañeses 2325, 1428, Ciudad Autónoma de Buenos Aires, Argentina.

Corresponding author:

Dr. Veronica Bruno

Movement Disorders Section, Neuroscience Department

Raul Carrea Institute for Neurological Research (FLENI)

Montañeses 2325, 1428, Ciudad Autónoma de Buenos Aires, Argentina.

Telephone: 54(11) 3667-8141

Email: veubru@gmail.com

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Perinatal risk factors in Tourette's and chronic tic disorders: A lesson from epidemiology.

Brander G, Rydell M, Kuja-Halkola R, Fernández de la Cruz L, Lichtenstein P, Serlachius E, Rück C, Almqvist C, D'Onofrio BM, Larsson H, Mataix-Cols D. Perinatal risk factors in Tourette's and chronic tic disorders: a total population sibling comparison study. Mol Psychiatry. 2017 Mar 28. doi: 10.1038/mp.2017.31. [Epub ahead of print]

The role of perinatal factors in the pathophysiology of TD/CTD has been repeatedly suggested but never systematically analyzed. The recently published article by Brander et al [1] proposes a relationship between the occurrence of TD/CTD and several adverse perinatal events. The study cohort consisted of all live singleton births over a 30 year period in a single country. Follow up was done over a 40 year period. It included a total of 3,026,861 individuals, 5,597 of which were diagnosed with TD/CTD during the study period. The main results showed that impaired fetal growth, preterm birth, breech presentation and cesarean section were associated with a higher incidence of TD/CTD. A dose–response relationship was also found, by which the higher the number of perinatal events, the higher the risk for TD/CTD. Maternal smoking during pregnancy was also suggested to be associated with the risk of TD/CTD in a dose-response manner; however this could not be verified after sibling comparison analysis.

During the current era of continuous genetic cause findings, evidence places TD/CTD as one of the most heritable, non-Mendelian neuropsychiatric diseases [2]. Different studies found high population-based heritability estimates for this disorder [3, 4]; however, no unique monogenic cause or ultimate associated risk gene of major effect has been identified, suggesting a polygenic origin for the disease or the possibility that epigenetic factors, such as

perinatal hazards, may be accounting for the substantial heterogeneity and complexity of TD/CTD [5].

This study is particularly relevant due to its methodological design. It was designed as a population-based study, allowing for exclusion of potential biases, and also allowing for sibling comparisons and posterior sensitivity analyses to minimize confounders.

The first consequence of this study´s interesting findings is clinical, and related to the need of addressing the presence of modifiable risk factors to prevent or reduce the occurrence of TD/CTD. This particular aspect also raises the question whether these perinatal events are actually risk factors or the result of an ongoing process that generates such events that happen in the perinatal period, considering that impaired fetal growth, preterm birth, breech presentation, and the need of cesarean section can be a result of multiple hazards to the normal fetal development.

The second learning point from the study by Brander et al, is how relevant epidemiological studies are to help clinicians and researchers clarify controversial hypothesis that aroused from results from smaller studies or retrospective case series, such as those about the pathophysiology of TD/CTD.

To conclude, this interesting study increases our knowledge about perinatal risk factors for TD/CTD, creates the need of developing strategies to improve those events during the perinatal period in order to reduce the occurrence of TC/CTD, and serves as an excellent example of how epidemiological studies with clear and simple designs and analysis can add extremely important information to clinical practice.

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Veronica Bruno: 1.A, 1.B, 1.C, 3.A, 3.B

Julieta E. Arena: 1.A, 1.B, 1.C, 3.A, 3.B

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