Title: The association of poor academic performance with tic disorders. A longitudinal, mainstream-school based population study.

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Abstract

Background: Little is known about the academic performance in students with tic disorders (TD). Our aim was to investigate the association of TD and poor academic performance over time.

Methods: Longitudinal, observational study of mainstream schoolchildren comparing grade retention (GR), and learning disorders (LD) in students with vs. without TD between 2010 and 2014. Students with vs. without TD based on DSM-IV-TR criteria, or with vs. without GR and LD were compared in terms of comorbidities, school, and environmental characteristics. The association of TD with GR was analyzed using hazard ratios (HRs) with 95% confidence intervals (CI), and with LD using logistic regression analysis [Odds ratio (OR)].

Results: 258 students were included (mean age 14.0 ± 1.71 years), 143 (55.4%) males. The incident rate for TD and GR was 2.6 and 3.3 per 100 persons-year, respectively. LD found in 21 (9.9%) students was associated with TD (OR= 11.62, 95% CI 2.21-60.90, p=0.004), and attention deficit hyperactivity disorder (ADHD) (OR=6.63, 95% CI 1.55-28.37, p=0.01). Low psychological support (HRs=12.79 95% CI 3.39-48.17) and low sport participation (HRs=6.41, 95% CI 1.54-26.78) were risk factors for GR.

Conclusions: TD was associated with academic difficulties, namely LD in conjunction with ADHD, but not GR. The diagnosis of TD and comorbidities, and the initiation of proper treatment could have a favorable impact on school performance, and social development.

Background

Tic disorders (TD) are neuropsychiatric diseases encompassing a spectrum of neurological, cognitive and behavioral manifestations [1]. They are the most frequent movement disorders in the pediatric population, with an estimated 4-20% of school children experiencing tics during their lifetime [2,3]. An accumulating body of evidence on learning disability (LD) and other specific neuropsychological deficits in TD, suggests that difficulties in these areas are present in a significant percentage of these patients [4]. Comorbid attention deficit/hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD) are likely to further influence the long-term adaptive outcomes of individuals with TD [1].

Children with TD and LD have skills below their age-matched peers in reading, comprehension, spelling, and math [5]. Besides ADHD, other factors contributing to poor academic performance in children with and without TD, include other neuropsychiatric comorbidities, sedative effects of drugs, intellectual disability, and specific socio-cultural and home-environmental characteristics [6,7].

To date, there is little information available on the evolution of academic performance in children with TD over time. We hypothesized that students with TD, and especially those with comorbid disorders such as ADHD, are at risk for poor school performance. The aim of this study was thus to analyze the incidence of academic problems, and assess whether the presence of a TD is associated with an increased risk for developing poor academic performance over time.

Methods

Design and Ethics

This is a two-wave investigation method, mainstream population-based study comparing academic performance in exposed subjects (students with tics) and non

exposed subjects (students without tics). First and second waves of the study were approved by the Ethical Review Board of the Hospital Universitario Burgos (Spain), the director of the Burgos School District and the local school boards, acting as the Ethical Committee for each school. Informed written consents were obtained from parents/guardians, and data were collected only for students whose parents signed the informed consent.

Procedure

First wave of the study was conducted between 2007 and 2009 in the Burgos school district (Spain) including public, urban and rural, state-funded schools (Supplementary figure 1). It was a cross-sectional study of a cohort of 1867 mainstream schoolchildren (mean age, 10.9 $\pm$ 2.9 years; 53.9% males). The methodology has been extensively described elsewhere [8,9] (see supplementary file). Second wave of the study (present study) took place from May 1st 2014 to December 30th, 2014 (figure 1). The students without any history of grade retention (GR), with and without TD identified during the first wave of the study still at school, were contacted again and invited for participation.

Definition of poor academic performance

Poor academic performance, the main outcome was operationally defined as current or any grade retention from September 1st 2010 to December 30th, 2014. Academic data included information on GR, presence of LD, need for academic support at school and at home, school characteristics (urban/suburban, educational level, public/state-funded school, teacher/student ratio, and availability of academic team support), and teacher characteristics (number of years of experience). Data were collected by a trained rater. LD (reading, writing, mathematics) was assessed using psychoeducational assessments validated in the Spanish population, conducted in

participants with an intelligence quotient (IQ) > 70. LD was assessed using the Luria Nebraska test for mathematics [10], the Emla-Prolect test for writing [11], and the Prolec-R test for reading [12], using established cutoff values. Second outcome measure for LD was tutor´s judgement based on DSM-IV TR criteria [13], dichotomized into unimpaired/ impaired.

Ascertainment of TD

The diagnosis of TD since 2010 was directly established based on the telephone interview by the neurologist (EC) with the parents. Based on our previous reliability analysis for 37 teenagers with TD [9], the intra-rater reliability of the telephone-based interview versus in-person neurological interview for TD has shown a kappa coefficient of 0.83. A historical diagnosis of TD was made if all essential criteria of tics were fulfilled, including presence of repetitive movements or vocalizations, preceded by urge and followed by relief, fluctuating in severity and variety over time, not due to medicine/drug administration or any medical condition [9]. If some of the essential criteria were not fulfilled, a diagnosis of possible TD was established. Therefore, a student was diagnosed with TD based on the information obtained from the first (2007-2009), and second (2014) wave of the study. Students not fulfilling the full criteria for TD between 2007 and 2014 were diagnosed as not having TD. Students diagnosed with possible TD during the first "and/or" second wave of the study, were excluded from analysis. TD was furthermore classified into TS, vocal/motor chronic tics, transient tics and non-specific tics, based on DSM-IV TR criteria (excluding impairment criteria) [13], by the neurologist (EC). Missing observations were encoded as missing data.

Comorbidities

Screening for comorbidities was performed by the trained rater (blinded to the tic assignment), using validated clinical scales and semi-structured questionnaires. We

included scales screening comorbidities previously associated with TD including: 1) Autism Spectrum Disorders (ASD), using the autism domain of the Autism-Tics ADHD and other Comorbidities Inventory (A-TAC) scale [14]; 2) Psychiatric disorders, using the Spanish computerized version of the Children Predictive Scales (DPS) [15], which contains 18 subscales including phobia disorders, ADHD, OCD, oppositional defiant disorder, anxiety disorders, major depressive disorders, conduct disorder, and substance abuse. Specific psychiatric disorders were diagnosed using the individual DPS cutoff scores for each subscale [15]. Screening estimates of verbal and non-verbal intelligence plus a composite IQ were obtained in the first wave of the study, using the Kaufman Brief Intelligence test (KBIT) [16], based on a mean of 100 and standard deviation of 15, scores >130 indicating very high abilities, scores 120-129 high abilities, scores 110-119 average-high abilities, scores 90-109 average abilities, and scores $\leq$ 90 below average abilities. Additionally, structured questionnaires were administered to parents to elicit information on presence of students´ sleep complaints (yes/no).

Environmental characteristics and quality of life.

Parents/guardians provided information regarding treatments, sociodemographic factors, parental education background, extra-curricular sport participation (yes vs.no), TV and electronic games exposure (number of hours a day), using a semi-structured questionnaire administered by the trained rater. Quality of life (QoL), psychosocial domain, was assessed using self-administered PEDS-QL4 [17], validated for the Spanish population with higher scores indicating better quality of life.

Data management:

Students were classified based on the diagnosis of tics (yes vs. no), GR (yes vs. no), and the presence of any LD (yes vs. no). The main outcome measure for poor academic achievement was GR and secondary outcome measure was the presence of

LD. Data were expressed in terms of mean (standard deviation), median (range, interquartile range), and frequency (percentages, %).

Analysis

Statistical analyses were performed using IBM-SPSS Version 21.0 (SPSS, Inc., Chicago, IL). Comparisons between students with/without TD, GR, and LD were conducted, using the Mann–Whitney U or Student t tests for continuous variables, as needed, and, the Chi Square or Phi and V Cramer tests for categorical variables. A significance level of α=0.002, two sided tests was applied after post-hoc Bonferroni multiple comparisons adjustments.

Cox´s regression models were conducted to test the value of TD on the incidence of GR after adjusting for variables associated with GR in bivariate analyses. These analyses generated hazard ratios (HRs) with 95% Confidence Intervals (CI). Secondary analyses included logistic regression models to analyze the association of study variables significantly associated with LD in bivariate analyses. These analyses generated odds ratios (OR) with 95% CI. The number of variables included in the Cox and logistic regression analysis took into account the number of observations in our dataset.

Results

Subjects. Two hundred and fifty eight students, 143 males (55.4%), with a median age of 14 years (range:11-17) were included out of 418 eligible mainstream students (Figure 2). There were no differences between participants and non participants in terms of carrying the diagnosis of TD in the first wave study (Chi square test, p=0.36), but males were more likely to be part of the second-wave study [OR=1.99 (95% CI 1.46-2.71, p<0.0001)].

Data quality: Tic information was available in 217/258 subjects (84.1%), 23/32 (71.8%) of the students with GR, 192/219 (78.2%) of the students without GR, 13/21 (61.9%) of the students with LD, and 156/191 (81.7%) of students without LD. GR information was available in 251/258 subjects (97.3%), and LD in all 212 subjects (100%). Comorbidity information was available in 85/156 (54.4%) students without tics, 31/61 (50.8%) of students with tics, 102/156 (65.3%) of students without GR, 14/32 (43.7%) of students with GR, 12/21 (57.1%) of students with LD, and 118/191 (61.8%) of the students without LD.

Prevalence and incidence of tics and poor academic performance: Sixteen students (6.2%) diagnosed with possible TD between 2007 and 2014 were excluded from analysis. Between 2007 and 2014, the 7-year cumulative prevalence of TD was 61/258 (23.6%, 95% CI 18.8-29.1). The incident rate for TD was 2.6 per 100 persons-year. Based on the information provided by the parents, TS was diagnosed in 12/217 (5.5%), chronic motor tics in 13/217 (5.9%), chronic vocal tics in 1/217 (0.4%), transient tics 1/217 (0.4 %), unspecified TD in 1/217 (0.4%), and unknown in 33/217 (15.2%).

GR was identified in 32/258 (12.42%) students, with a GR incident rate of 3.3 per 100 persons-year. After excluding 52/258 (20.1%) students with an IQ < 70, LD data were available in 212/258 (82.1%). One or more LD was found in 21/212 (9.9%) including mathematics in 4/212 (1.9%); reading in 14/212 (6.6%); and writing in 10/212 (4.7%) students. According to tutors´ judgement, the prevalence of LD was lower in the second wave compared to the first wave of our study [51/212 (24.0%) vs. 29/212 (13.6%), $p<0.0001$].

Comorbidities. Our results for comorbidities are summarized in Table 1. After adjusting for multiple comparisons, only TD was associated with LD ($p=0.001$). There was a trend for higher frequency of panic attacks, and sleep complaints in students with TD,

ASD in students with TD and GR, generalized anxiety disorder in students with GR, and depression and ADHD in students with LD.

Clinical, demographic, school/teacher, and environmental characteristics of the cohort stratified by tic and academic performance status. Comparisons of students with/without TD, with/without GR and with/without LD are summarized in Table 2. Overall students with poor academic performance including GR and LD had more academic support, and a trend for lower quality of life in the psychosocial domain compared to those with regular academic performance. Instead, students with GR had a trend for having teachers with higher number of years of experience, higher frequency of parents with poor academic achievement, lower psychological support and lower sports practice compared to students without GR. On the other hand, students with LD had a trend for a family history of tics and higher exposure to electronic games and TV.

Variables associated with academic underachievement. Different Cox and logistic regression models for GR and LD were analyzed including demographics, clinical and environmental variables. Final models were selected based on clinical judgement and model fitness. The multivariate Cox proportional hazard analyses for GR and the logistic regression model for LD are presented in tables 3 and 4, respectively.

Discussion

In this longitudinal study we found that TD was associated with academic difficulties, namely LD in conjunction with ADHD, but not with GR. In agreement with our previous cross-sectional study [8], GR was independently associated with potentially modifiable environmental factors such as the lack of psychological support at school and low frequency of sport practice.

Students with TD and ADHD were more likely to have LD, in agreement with other studies [4]. Nevertheless, although LD can be lifelong condition, students with LD can still succeed in school. In fact, in our sample, GR was similar in students with and without LD. To explain the association of LD with TD and ADHD, it has been suggested that LD may be specific to executive dysfunction, and impaired fine motor skills [18]. The decision-making and learning process relies on the dopaminergic system projections to the frontal cortico-basal ganglia circuits, which are the neural systems implicated in the pathophysiology of TD [19]. There is no doubt that the coexistence of ADHD in children with tics increase the likelihood of having LD, since the pathophysiology of ADHD is executive dysfunction as well [20].

Interestingly, in our previous focus group study we examined the perceptions of adolescents with TD, their parents and health professionals on tic-related school, social and family problems [21]. Health professionals reported that TD primarily affected learning in school and social adjustment. Adolescents reported a number of difficulties in school including slower learning, attention problems and conflict with teachers. Parents reported that the lack of understanding of TD shown by teachers and peers led to difficulties in school. In fact, in this study, a trend for lower QoL (psychosocial domain) in students with academic underachievement (LD and GR) was found, suggesting conflicts, and low self-esteem in this population [22]. Identifying LD in students with TD and ADHD should then be a priority since there are numerous educational interventions and accommodations available for these students [18].

Our results add a global prospective on academic achievement. Different environmental characteristics such as too much television viewing, and low parental education background were found to be associated with GR and LD in the bivariate analysis, suggesting inadequate study patterns [23, 24]. There is also evidence that

many clinical disorders marked by executive deficits are highly heritable [20], and therefore parental literacy abilities might be then viewed as indicators of offspring's liability for literacy difficulties, since parents provide the offspring with genetic and environmental endowment [25]. Interestingly, low sport practice was strongly associated with GR. It has been reported that participation in sports can improve prefrontal cortex function and executive function due to the need for sustained attention, working memory, and disciplined action [26-28]. Therefore, taking into account the trend for a lower quality of life in students with poor academic performance, the practice of sports can also provide additional benefits such as pride, and social bonding [26].

No comorbidities were statistically associated with tics, GR or LD, except for tics with LD. Interestingly, students with tics and GR had a trend for having ASD, highlighting the need for screening these disorders [29]. In contrast to previous literature [30], we did not observe any significant association of ADHD and OCD with tic disorders likely due to selection bias as a consequence of high drop-out rates in the screening of comorbidities. Circumstances that might contribute to high drop-outs in this population include the requirement that students stay longer at school, possible perception that the study was intrusive, and the lack of incentive to participate for teenagers [31]. On the other hand, adjustments for multiple comparisons have been applied, which have also been argued, because of the danger of erroneous dismissal of meaningful results [32].

Of note, in our study the prevalence of TD was higher compared to previous studies [33]. Besides certain methodological aspects in terms of a historical diagnosis of TD and subsequent recall selection bias, the comparison of point-time prevalence vs.

cumulative prevalence of TD can be controversial for meaningful interpretation of our results.

We would like to highlight the main advantages of this study including the longitudinal design, the sample characteristics (a mainstream school population), encompassing the whole spectrum of TD and eliminating functional impairment from different school settings, and the collection of a large number of variables potentially associated with academic performance.

Conclusions

Education is one of the most important aspects of the development of human being and school underachievement is a major source of distress. The results of this study highlight the need to identify students at risk for school underachievement including students with TD, to proactively target interventions successfully.

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Conflicts of interest:

All authors have no conflicts of interest.

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