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Tourette's syndrome is associated with an increased risk of traumatic brain injury: A nationwide population-based cohort study

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ABSTRACT

Introduction: Violent motor tics or severe self-harm behaviors have been reported in patients with Tourette's syndrome (TS) and leading to traumatic brain injury (TBI). The study aimed to determine the risk of TBI in TS patients, the effects associated with concurrent psychiatric disorders (attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), or depressive disorder), and the effects of medication treatment (antipsychotics, antidepressants, or clonidine) on the risk of TBI.
Methods: Using the National Health Insurance Research Database of Taiwan, 2261 TS patients and 20349 non-TS controls matched by gender and age were enrolled between 2000 and 2012, and followed until the end of 2013. Participants who developed TBI during the follow-up period were identified. Cox regression analysis was performed to examine the risk of TBI between TS patients and non-TS controls.
Results: TS patients were associated with an increased risk of TBI compared to non-TS controls (hazard ratio (HR): 1.59, 95% confidence interval (95% CI): 1.37–1.85). Also, this study revealed TS patients with ADHD, OCD, or depressive disorder predicted a higher TBI incidence rate than those who did not, but the estimate was not statistically significant. Moreover, this study found that TS patients with frequent use of antipsychotics were associated with a lower risk of TBI than infrequent users (HR: 0.76, 95% CI: 0.57–0.99).
Conclusions: This study highlights the need to pay more attention to the risk of TBI in TS patients, and the importance of adequate antipsychotic medication may reduce the risk of TBI.

1. Introduction

Tourette's syndrome (TS) is a developmental neuropsychiatric disorder characterized by multiple briefs, stereotyped but non-rhythmic movements and vocalizations called tics lasting at least one year [1]. The onset of tic symptoms in TS usually occurs in early childhood [2]. The severity and intensity of tics vary [2]. They can be discreet and go almost unnoticed, or they can be persistent, forceful and intrusive. Most patients experience a peak in the severity of tic symptoms at 10–12 years of age, after which the severity gradually decreases [3]. In Taiwan, the prevalence rate of TS in school-age children was approximately 0.56% [4]. Boys are more often affected than girls with a ratio of 9:2 in TS children [4].

Patients with TS typically have comorbid psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and depressive disorder [2,5]. Also, patients with TS may also have other health problems requiring care. An earlier study found that 43% of patients diagnosed with TS also had at least one other chronic health problem, including asthma, hearing or vision problems, bone, joint or muscle problems, and traumatic brain injury (TBI) [6]. Rates of asthma and hearing or vision problems were similar to those without TS, but bone, joint or muscle problems and TBI were higher in TS patients [6]. An earlier study showed that the incidence of fractures (part of the bone, joint or muscle problems) in the TS cohort was 1.28 times that of the comparison cohort, suggesting important implications for future prevention studies [7]. However, to date, the correlation between TS and TBI warrants further investigation.

TBI resulting from TS has been reported in some cases. For example, acute subdural and subarachnoid hemorrhages due to headbanging,

Abbreviations: TBI, traumatic brain injury; TS, Tourette's syndrome

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and many violent neck tics resulted in the dissection of the vertebral artery leading to right pontine and bilateral cerebellar infarctions have been reported in the literature [8,9]. TBI is one of the leading causes of long-term disability in children, adolescents, and young adults, with severe sequels and burdens on the lives of patients, their families, and society [10–12]. Therefore, exploring risk factors for TBI is a prerequisite to developing effective preventive strategies.

In this study, we use the National Health Insurance Research Database of Taiwan (NHIRD), which is a nationally representative database of medical claims data. A longitudinal follow-up study is designed to study the risk of TBI in TS patients, the effects associated with concurrent psychiatric disorders, and the effects of medication treatment on the risk of TBI. To our knowledge, this is the first study to longitudinally evaluate TBI in a national sample of patients with TS.

2. Methods

2.1. Data source

The National Health Insurance Program of Taiwan (NHIP) was established in 1995 and provided universal coverage through a single-payer government-mandated insurance scheme to centralize the disbursement of health care financing. As the NHIP covers about 23 million residents in Taiwan, it is one of the largest and most comprehensive population databases in the world. The NHIRD is the entire insurance claims database that includes data on health care > 99% of the population of Taiwan. The database contains comprehensive information on insured persons, including demographic data, dates of clinical visits, disease diagnoses and medical procedures. Diagnostic codes were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Several subsets of data have been created within the NHIRD. One of them: The Longitudinal Health Insurance Database 2000 (LHID2000) was used for this study.

LHID2000 was representative of all of NHIRD. It contained all the original claim data of 1000000 individuals (about 4% of the Taiwanese population) randomly selected from the NHIRD in 2000. There were no statistically significant differences in age, gender, and medical costs between LHID2000 patients and the original NHIRD.

2.2. Inclusion criteria

Children (under 12 years old), adolescents or young adults (aged 12–29) newly diagnosed with TS (ICD-9-CM code: 307.2) between 2000 and 2012 and has no previous history of TBI (ICD-9-CM codes: 800–801, 803–804, 850–854, 959.01) before enrollment were included in the TS cohort. The time of the TS diagnosis was defined as the time of enrollment.

The age-, gender-, and time of enrollment-matched (1:9) control cohort was randomly identified from LHID2000 after the elimination of the study cases, those who had been diagnosed with TS at any time, and those with any TBI before enrollment. Diagram summarizing the enrollment process was present in Fig. 1.

2.3. Incidence of TBI

All TBI included fracture of skull (ICD-9-CM codes: 800–801, 803–804), concussion (ICD-9-CM code: 850), contusion (ICD-9-CM code: 851), brain hemorrhage following injury (ICD-9-CM codes: 852–853), and unspecified intracranial injury (ICD-9-CM codes: 854, 959.01). All patients in the study were followed until the newly diagnosed TBI, withdrawn from the NHIP or on December 31, 2013 (whichever came first).

2.4. Definition of potential risk factors

Baseline demographic characteristics of both cohorts were collected, including gender, age (under 12, and 12–29), and degree of urbanization. The degree of urbanization has been divided into four levels based on population density: Level I refers to the "most urbanized" and Level IV refers to the "least urbanized" communities.

Also, the influence of baseline psychiatric comorbidities before the index date, including ADHD (ICD-9-CM code: 314), OCD (ICD-9-CM codes: 300.9), and depressive disorder (ICD-9-CM code: 296.2, 296.3, 300.4, 311), were evaluated in this study.

Moreover, we also examined the therapeutic effects of antipsychotics (anatomical therapeutic chemical (ATC) code: N05A except for lithium N05AN01), antidepressants (ATC code: N06AB and N06AX), or clonidine (ATC code: C02AC) on the risk of TBI. The frequency of use of these medications was classified as infrequent use (the length of medication use was less than the median duration in this dataset) and frequent use (the length of medication use was equal to or greater than the median duration).

2.5. Statistical analysis

The chi-square test was used to compare distributions of categorical variables, including gender, age groups, the degree of urbanization, psychiatric comorbidities, and frequency of medication use. The Wilcoxon's rank-sum test was used to compare continuous variables, including age and follow-up period, and described by the median. Cox regression analyses with adjustment of all the above variables were performed to calculate the hazard ratio (HR) with 95% confidence interval (95% CI) of all TBI between TS patients and non-TS controls. The survival curve of TS and control cohorts was estimated by Kaplan-Meier analysis with a log-rank test. The significance level of all tests was set at 0.05. We performed the full analysis by SAS 9.4 (SAS Institute Inc., Cary, NC).

2.6. Ethics statement

This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115). All research methods were carried out by the relevant guidelines and regulations. Since the NHIRD only contains anonymized secondary data, the need for informed consent from individual subjects has been lifted.

3. Result

3.1. Demographic status at baseline

Table 1 showed the baseline characteristics of patients with TS and non-TS controls. A total of 2261 TS patients and 20349 controls matched by gender and age were included in our analysis. The distribution by gender in both cohorts was higher for male than for female (65.86% vs. 34.14%), and the median age in both cohorts was about 13 years. The distribution of the urbanization degree was not significantly different between the TS and the control cohort. The TS cohort had a higher prevalence of comorbid ADHD (7.70% vs. 1.49%, $p < 0.01$), OCD (4.25% vs. 1.84%, $p < 0.01$), and depressive disorder (5.40% vs. 2.33%, $p < 0.01$) compared to the control cohort.

3.2. Demographic status during follow-up

As shown in Table 1, the median years of follow-up were 7.63 and 7.84 years for the TS cohort and the control cohort, respectively. During follow-up, the frequency distribution of medication use, including antipsychotics, antidepressants, and clonidine, was statistically different between the two cohorts (all $p < 0.01$). At the end of the follow-up, the TS cohort had an increased incidence of developing TBI compared to the control cohort (9.95% vs. 6.93%, $p < 0.01$).

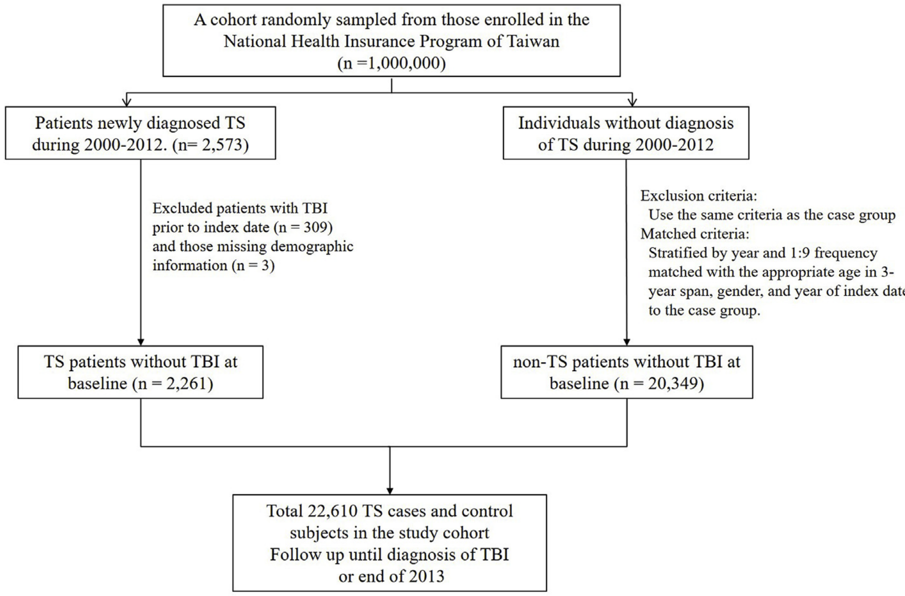

Fig. 1. Summary diagram of the enrollment process.

Table 1
Demographic status of TS patients and comparative controls at baseline and during follow-up.

Variable	TS		Control		p-value
	N = 2261		N = 20349		
	n	%	n	%	
Gender[a]					0.99
Male	1489	65.86	13401	65.86	
Female	772	34.14	6948	34.14	
Age at baseline, years[a]					0.99
< 12	1047	46.31	9423	46.31	
12-29	1214	53.69	10926	53.69	
Median (SD)[b]	12.89		13.31		0.89
Urbanization degree[a]					0.09
I (highest)	724	32.02	6009	29.53	
II	667	29.50	6116	30.06	
III	381	16.85	3630	17.84	
IV (lowest)	489	21.63	4594	22.57	
Psychiatric comorbidities[a]					
ADHD	174	7.70	303	1.49	< .01
OCD	96	4.25	374	1.84	< .01
Depressive disorder	122	5.40	475	2.33	< .01
Follow-up period, years, median[b]	7.63		7.84		0.01
Frequency of medication use[a]					
Antipsychotic					< .01
Frequent	1073	47.46	1998	9.82	
Infrequent	1188	52.54	18351	90.18	
Antidepressant					< .01
Frequent	211	9.33	567	2.79	
Infrequent	2050	90.67	19782	97.21	
Clonidine					< .01
Frequent	125	5.53	36	0.18	
Infrequent	2136	94.47	20313	99.82	
Incidence of TBI[a]	225	9.95	1411	6.93	< .01
Fracture of skull	8	0.35	51	0.25	
Concussion	67	2.96	459	2.26	
Contusion	4	0.18	36	0.18	
Brain hemorrhage following injury	23	1.02	122	0.59	
Unspecified intracranial injury	123	5.44	743	3.65	

TS: Tourette syndrome; ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; TBI: traumatic brain injury.
[a] Chi-square test.
[b] Wilcoxon's rank-sum test.

3.3. Risk of TBI

As shown in Table 2, there were a total of 1636 patients with TBI during the follow-up period (225 in the TS cohort and 1411 in the control cohort). The incidence rates of TBI were 13.35 and 9.07 per 1000 person-years in the TS and the control cohort, respectively. After adjusting for all variables, TS cohort was associated with an increased risk of TBI compared to the control cohort (HR: 1.59, 95% CI: 1.37–1.85). The Kaplan-Meier survival analysis with a log-rank test revealed a significant association between the TS cohort and the subsequent risk of TBI ($p < 0.01$) (Fig. 2).

Table 2 also showed the TBI incident rates in two study cohorts stratified by gender and age. After adjusting for all variables, significant risk associations between the TS cohort and the TBI incident were noted in the subgroups of male (HR: 1.62, 95% CI: 1.34–1.95), female (HR: 1.55, 95% CI: 1.18–2.03), those aged under 12 years (HR: 1.40, 95% CI: 1.07–1.82), and those aged 12–29 years (HR: 1.76, 95% CI: 1.45–2.12).

3.4. Psychiatric comorbidities, medication use, and risk of TBI

As shown in Table 3, TS patients with ADHD, OCD, or depressive disorder predicted a higher TBI incidence rate than those who did not, but the estimate was not statistically significant after adjusting for all variables.

As shown in Table 4, after adjusting for all variables, TS patients with frequent use of antipsychotics were associated with a lower risk of TBI than infrequent users (HR: 0.76, 95% CI: 0.57–0.99). Also, frequent use of antidepressants or clonidine was associated with a lower TBI incidence rate than infrequent users, but the estimate was not statistically significant after adjusting for all variables.

4. Discussion

This is the first population-based cohort study using a nationally representative sample that simultaneously determined the risk of TBI in TS patients, the effects associated with concurrent psychiatric disorders, and the effects of medication treatment on risk of TBI. The main finding of this study was that TS patients were associated with an increased risk of TBI compared to non-TS controls. Also, this study revealed TS patients with ADHD, OCD, or depressive disorder predicted a higher TBI incidence rate than those who did not, but the estimate was not

Table 2
Cox regression analyses of risk of TBI among cohorts of TS and control stratified by gender and age.

Variable	TS			Control			Crude[b]	Adjusted[c]
	TBI	Person-years	IR[a]	TBI	Person-years	IR[a]	HR (95%CI)	HR (95%CI)
Total	225	16853	13.35	1411	155504	9.07	1.48 (1.28–1.70)*	1.59 (1.37–1.85)*
Gender								
Male	159	11104	14.32	1020	104497	9.76	1.48 (1.25–1.74)*	1.62 (1.34–1.95)*
Female	66	5749	11.48	391	51008	7.67	1.50 (1.16–1.95)*	1.55 (1.18–2.03)*
Age group, year								
< 12	82	8751	9.37	670	84117	7.97	1.20 (0.95–1.50)	1.40 (1.07–1.82)*
12–29	143	8102	17.65	741	71388	10.38	1.70 (1.42–2.03)*	1.76 (1.45–2.12)*

TBI: traumatic brain injury; TS: Tourette syndrome; IR: incidence rates; HR: hazard ratio; CI: confidence interval.
[a] Per 1000 person-years.
[b] Relative hazard ratio.
[c] Mutually adjusted for gender, age, urbanization degree, psychiatric comorbidities, and frequency of medication use in Cox regression analyses; *$p < 0.05$.

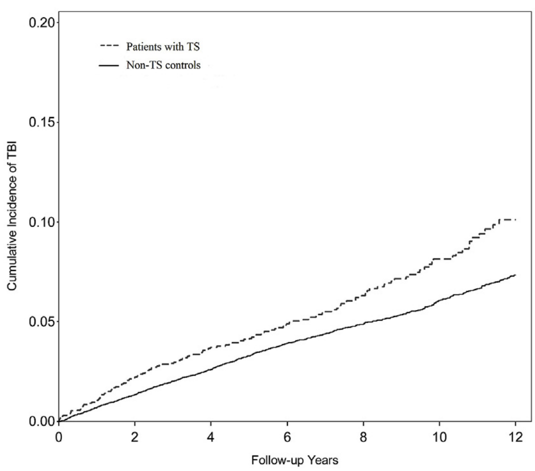

Fig. 2. Cumulative incidence of TBI in TS patients and non-TS controls. Kaplan-Meier survival analysis with a log-rank test revealed a significant association between TS and the subsequent risk of TBI ($p < 0.01$).

Table 4
Cox regression analyses of the frequency of medication use associated with TBI for the TS cohort.

TS cohort	TBI	Person-years	IR[a]	Crude[b]	Adjusted[c]
	n = 225			HR (95%CI)	HR (95%CI)
Frequency of antipsychotic use					
Frequent	97	8556	11.34	0.73 (0.56–0.95)*	0.76 (0.57–0.99)*
Infrequent	128	8297	15.43	1 (Reference)	1 (Reference)
Frequency of antidepressant use					
Frequent	22	1702	12.93	0.96 (0.62–1.49)	0.83 (0.52–1.34)
Infrequent	203	15151	13.40	1 (Reference)	1 (Reference)
Frequency of clonidine use					
Frequent	6	1023	5.87	0.42 (0.19–0.95)*	0.49 (0.21–1.12)
Infrequent	219	15830	13.83	1 (Reference)	1 (Reference)

TBI: traumatic brain injury; TS: Tourette syndrome; IR: incidence rates; HR: hazard ratio; CI: confidence interval.
[a] Per 1000 person-years.
[b] Relative hazard ratio.
[c] Mutually adjusted for gender, age, urbanization degree, psychiatric comorbidities, and frequency of medication use in Cox regression analyses; *$p < 0.05$.

statistically significant. Moreover, this study found that TS patients with frequent use of antipsychotics were associated with a lower risk of TBI than infrequent users.

Several explanations are offered for the mechanisms underlying the relationship between TS and the subsequent risk of TBI. One explanation was that motor tics, the main symptoms of TS, could potentially increase the risk of TBI by direct injury. In most cases, motor tics are mild, but their frequency and intensity can rise sharply, including in cases where violent and uncontrolled movements of the head and neck can result in TBI [8,9,13]. Also, many case reports and studies have indicated that patients with TS may have several types of self-harm behaviors, ranging from benign behavior (e.g., scratching of the skin) to severe behavior (e.g., hitting the head) [14]. Severe self-harm behaviors were observed in 4% of patients with TS [15], possibly explaining this finding. Our study does not indicate whether tic severity or self-harm behaviors are associated with subsequent TBI. However, this study provides strong evidence that in long-term follow-up, patients with TS are associated with an increased risk of TBI.

Table 3
Cox regression analyses of TBI risk among the cohort of TS with or without psychiatric comorbidity.

Comorbidity	TS	TBI	Person-years	IR[a]	Crude[b]	Adjusted[c]
	n = 2261	n = 225			HR (95%CI)	HR (95%CI)
TS with ADHD	174	17	1096	15.51	1.19 (0.73–1.96)	1.55 (0.93–2.58)
without ADHD	2087	208	15757	13.20	1 (Reference)	1 (Reference)
TS with OCD	96	16	657	24.35	1.89 (1.14–3.14)*	1.48 (0.86–2.54)
without OCD	2165	209	16196	12.90	1 (Reference)	1 (Reference)
TS with depressive disorder	122	18	761	23.65	1.84 (1.13–2.97)*	1.49 (0.89–2.51)
without depressive disorder	2139	207	16092	12.86	1 (Reference)	1 (Reference)

TBI: traumatic brain injury; TS: Tourette syndrome; ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; IR: incidence rates; HR: hazard ratio; CI: confidence interval.
[a] Per 1000 person-years.
[b] Relative hazard ratio.
[c] Mutually adjusted for gender, age, urbanization degree, psychiatric comorbidities, and frequency of medication use in Cox regression analyses; *$p < 0.05$.

The psychiatric comorbidity of ADHD or its associated symptoms in TS patients, such as emotional or impulsive dysregulation, particularly with episodic rage or risk-taking behaviors, has been reported to increase the risk of accidents that could also result in TBI [15,16]. Also, the psychiatric comorbidity of OCD or depressive disorder, accompanied by aggressive obsessions, violent compulsions, or suicidal behaviors, has been reported to increase the risk of self-injurious behavior that could lead to TBI [15,17]. This study revealed TS patients with ADHD, OCD, or depressive disorder predicted a higher TBI incidence rate than those who did not, but the estimate was not statistically significant. No matter how TS is considered an independent risk factor for subsequent TBI after adjustment for these comorbidities.

This study found that TS patients with frequent use of antipsychotics were associated with a lower risk of TBI than infrequent users. In the literature review, limited studies have shown an association between the use of antipsychotics and the risk of TBI. This is an observational study that does not deal directly with the mechanism. An explanation for this may be that antipsychotics may reduce the severity and frequency of TS that may protect against TBI [18,19]. Also, self-harm behaviors and accidental injuries have been observed in many individuals with TB, and many of the problems reported in the TS are related to difficulties in controlling impulsivity [15,20–22]. Antipsychotics are known to reduce impulsivity, which may reduce the risk of TBI [23]. Further studies are needed to reveal detailed therapeutic mechanisms.

This study aims to examine whether TS was associated with an increased risk of TBI.

A large gender- and age-matched population-based cohort with many adjusted potential risk factors are the strengths of our study. However, there are several limitations inherent to the use of claims databases that must be considered. First, the diagnoses of TS, ADHD, OCD, depressive disorder and TBI can be underestimated, as only those who sought medical help and consultations were identified in the database. Also, for reliable diagnosis, this study included only patients with at least two outpatient diagnoses or at least one hospitalization for the diseases mentioned above, which might underestimate their prevalence or incidence. Secondly, the NHIRD did not provide information on the severity of the symptoms of TS, ADHD, OCD, and depressive disorder. We, therefore, could not study the association between the severity of these symptoms and the risk of TBI. Finally, the NHIRD did not provide detailed information on various factors such as lifestyle, habits, body mass index, level of physical activity, socio-economic status and family history, all of which are potential confounding factors in this study.

5. Conclusion

This study highlights the need to pay more attention to the risk of TBI in TS patients, and the importance of adequate antipsychotic medication may reduce the risk of TBI and its sequelae.

Author's contribution

S.F. Chen managed the literature searches and wrote the Introduction of the manuscript. Y.C. Su and C.Y. Hsu performed the entire analysis. L.Y. Wang wrote Method and Results of the manuscript. Y.C. Shen conceived the study and wrote the Discussion of the manuscript. All authors have approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Role of funding source

The funding source has no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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