

Original Article

The Close Relation of Tic Disorders with Childhood Migraine and Atopic Background of Both Children and Mothers

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ABSTRACT

Objective: This study aimed to evaluate primary headache disorders and other causative comorbidities (e.g., epilepsy, atopic disorders, recurrent abdominal pain, motion sickness, and headache) in children with tic disorders (TDs) and their mothers. **Materials and Methods:** In a multi-center, cross-sectional, familial association study using case-control design, youth (between 7 and 17 years) with TDs (TD, as per Diagnostic and Statistical Manual of Mental Disorders-5 criteria) and age- and sex-matched healthy controls and their mothers were evaluated in the aspect of functional syndromes spectrum including migraine, epilepsy, atopic disorders, motion sickness, and recurrent abdominal pain. **Results:** Seventy-nine youth with TD and 101 controls were included. Causative comorbidities, other than epilepsy and motion sickness were more common in children with TD with an odds ratio (OR) of 2.1 (atopy) and 3.9 (food allergy). Specifically, recurrent abdominal pain and migraine were found in 36.7% and 31.7% of children (vs. 18.8% and 16.8% of controls, ORs 2.5 and 2.3, respectively). Mothers of youth with TDs also have higher rates of atopy, drug allergy and allergic dermatitis (ORs; 3.8, 3.2 and 2.1; respectively). **Conclusion:** Results of recent studies suggest a possible link between atopic disorders, migraine, recurrent abdominal pain and TDs. Our results contribute to those studies and suggest that this relationship may extend to the mothers of children as well.

KEYWORDS: Atopy, headache, migraine, tension-type headache, tic

INTRODUCTION

Tic disorders (TDs) are among the most common movement disorders diagnosed in youth with a wide range of prevalence between 0.2% and 46.3%.^[1-3] TDs may persist to adolescence and adulthood in a subgroup of children and besides motor and/or vocal tics, the affected children also display higher rates of other psychopathologies such as attention deficit/hyperactivity disorder (ADHD), disruptive behavior disorders, anxiety and obsessive-compulsive disorder (OCD) among others.^[1-4] Recent reports suggest that TDs in children may also be associated with headaches, infections, and allergies.^[5-7]

The prevalence of headache is reported to be 10.0%–17.8% in school age children. The prevalence may increase with age with a peak in early adolescence, reaching to 27.0%–32.0%.^[8] Migraine and tension-type

headache (TTH) are reported to be the most common primary headache disorders in children with rates reported to vary between 6.3%–46.3% and 5.5%–53.7%, respectively.^[9-11] Headache disrupts the quality of life physically, mentally and academically especially in children.^[12] Individuals who suffer from migraine or other severe headaches also suffer from other medical conditions such as epilepsy, atopic disorders (asthma, rhinitis, or eczema), sleep disorders, motion sickness, and obesity. This relationship may be especially prominent in those with migraine.^[8,13] A recent study also suggested

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that headache disorders, specifically migraine, may be elevated among youth with ADHD and their parents.^[14]

Previous studies focusing on the relationships between primary headache disorders and TDs suggest that rates of migraine may be elevated in those youth and that this relationship may be mediated by obsessive-compulsive symptoms.^[5,15] Results of studies on the relationship of TDs with recurrent abdominal pain were inconclusive with previous studies reporting elevated rates of anxiety disorders, depression, obsessive-compulsive symptoms, and ADHD in those children, but not TDs.^[16,17]

However, most of the previous studies have focused on Tourette Syndrome rather than the whole spectrum of TDs (i.e., transient TD, chronic motor/vocal TD, Tourette Syndrome) and did not evaluate the symptoms in parents of children. Furthermore, although psychiatric comorbidities of TDs are well known, data on medical comorbidities are still limited. Considering the genetic etiology of TDs, we aimed to evaluate the children and their mothers in terms of medical comorbidities in this study. As far as we are aware; the prevalence of headache subtypes and medical comorbidities in both patients with TDs and their mothers have not been studied before. Therefore, the present study was performed to evaluate rates of headache subtypes, epilepsy, atopic disorders, motion sickness, and recurrent abdominal pain among children and adolescents with TD and their mothers.

MATERIALS AND METHODS

Study center, patients, and protocol

The protocol was designed as a cross-sectional, case-control, multi-center, family association study. The evaluation of both parents was planned at the initial stage. However, lack of attendance of fathers for evaluations precluded their analyses and the study was commenced by the evaluation of children and their mothers.

This study was performed at the Mersin and Baskent University Medical Faculties as a collaborative study by the Departments of Child and Adolescent Psychiatry (GG, MOK) and Neurology (AO). Children, between 7 and 17-year-old diagnosed with TDs according to Diagnostic and Statistical Manual of Mental Disorders-5 criteria without mental retardation/intellectual disabilities (MR/IDD) and/or autism spectrum disorders (ASD) and healthy controls matched for age and sex were included in the study. Medical comorbidities may be more frequent among children with MR/IDD and ASD diagnoses. Therefore, MR/IDD were ruled out with clinical examination and Turkish version of the Wechsler Intelligence Scale for Children-Revised^[18] while children were diagnosed with the Turkish version of the

Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL).^[19] ASDs were ruled out by developmental history and clinical examinations. Healthy controls were selected from youth attending routine health control visits at the pediatrics departments of the study centers within the study period and they should be free of any infections/chronic medical disorders requiring treatment.

There are various definitions of recurrent abdominal pain in the literature. For the purposes of this study, “recurrent abdominal pain” as defined as abdominal pain lasting more than a month and reported at least once per week.^[17] Atopy refers to the genetic tendency to develop allergic diseases. For this study, atopy is screened by interviewing the children and the mothers for the presence of a diagnosed allergic disorder. After initial screening, follow-up questions evaluated the presence of asthma, allergic rhinitis, epidermal reactions, food/drug allergies, and others.^[20,21] Offending agents were also evaluated for food/drug allergies but reduced cell sizes prevented further analyses. Motion sickness was evaluated by questioning the presence of nausea, vomiting, dizziness, loss of balance, headache, as sweating by a form of travel.^[22]

Written informed consent of the parents and legal guardians were procured prior to study entry and the children provided verbal assent for participation. All the patients and parents underwent a neurological examination following a complete psychiatric evaluation. Headache diagnoses were made according to the third edition of the International Classification of Headache Disorders (ICHD-3) criteria for children and their mothers by a headache specialist (AO).^[23]

Ethics

The study protocol was approved by the local ethics committee of the study center with a protocol number of 0.01.00.06/265. All study procedures were in accordance with the Declaration of Helsinki and local laws and regulations.

Statistics and power analysis

A priori power-analysis for Chi-square tests revealed that a sample size of 460 will achieve 95.0% power for an alpha level of 0.05 (two-tailed) at 45° of freedom to detect a medium effect size ($w = 0.3$) difference.^[24] A priori analysis for *t*-tests revealed that 484 participants will be required to detect a difference at a similar effect size. Within the study period 180 youth (41.6% with TDs) could be enrolled leading to 48.8% power for Chi-square and 65.0% power for *t*-tests. Data were entered into a database prepared by IBM SPSS Statistics Software version 23 (IBM Corp, Armonk,

NY). Quantitative variables were summarized as means and standard deviations (SDs) while nominal variables were summarized as numbers and frequencies. Bivariate comparisons of quantitative data were conducted with *t*-tests for independent groups or Mann–Whitney U-tests depending on normality. Comparisons of nominal variables between groups were conducted with Chi-square tests with Yates' or Fisher's corrections as needed. Odds ratios (ORs) were calculated from contingency tables with 95% confidence intervals (CI). *P* was set at 0.05 (two-tailed).

RESULTS

Within the study period, 105 patients with TDs presented to the study centers. Eleven were excluded due to comorbid MR/IDD and one patient due to comorbid ASDs. Three of the patients could not be enrolled due to refusing enrollment and two of the patients did not attend the neurological evaluations leading to 79 patients with TDs and 101 controls.

Mean ages of children with TDs and controls were 11.4 (SD = 2.2) and 11.2 (SD = 2.2) years; respectively while those of their mothers were 37.3 (SD = 5.4) and 38.5 (S.D. = 5.5) years with no significant difference between groups (Mann–Whitney U-test). Most of the children with TDs and controls were male (79.7% and 83.2%; respectively) with no significant difference between groups (Chi-square test, *P* = 0.69). Forty-seven of children with TDs (59.5%) had psychiatric comorbidity. Most common comorbidities, in order of decreasing frequency, were ADHD (85.1%, *n* = 40), Generalized Anxiety Disorder (17.0%, *n* = 8), conduct disorder (6.4%, *n* = 3), phonological disorders (6.4%, *n* = 3), trichotillomania and major depression (one patient each, 2.1%).

Within the whole sample, the rate of headache was found 47.2% (*n* = 85). Migraine without aura was found to be the most common type (37.6%, *n* = 32). Migraines were significantly more common among children with TDs (OR = 2.3, 95% CI = 1.1–4.6). Furthermore, photophobia accompanying headache was significantly more frequent among children with TDs (OR = 4.9, 95% CI = 1.7–14.0). Rates and features of headache disorders according to the groups are displayed in Table 1.

Recurrent, functional abdominal pain was significantly more frequent among children with TDs (OR = 2.5, 95% CI = 1.3–5.0). Characteristics of abdominal pain and motion sickness according to diagnostic groups were summarized in Table 2.

Rates of epileptic seizures and febrile convulsions in the whole sample were 1.7% (*n* = 3) and 11.7% (*n* = 21), respectively. All children with epileptic

Table 1: Primary headache disorders and their characteristics between children with tic disorders and healthy controls

	TDs (<i>n</i> =79), <i>n</i> (%)	Controls (<i>n</i> =101), <i>n</i> (%)	<i>P</i> *	χ^2
Type of headache				
Migraine	25 (31.7)	17 (16.8)	0.02	0.35
TTH	22 (27.9)	21 (20.8)	0.27	-
Trigger				
Stress	31 (39.2)	28 (27.7)	0.10	-
Insomnia	13 (16.5)	11 (10.9)	0.39	-
Relieved by				
Sleep	24 (30.4)	19 (18.8)	0.10	-
Drug	14 (17.7)	12 (11.9)	0.37	-
Rest	15 (19.0)	12 (11.9)	0.27	-
Accompanied by				
Photophobia	16 (20.3)	5 (5.0)	0.00	0.24
Phonophobia	12 (15.2)	9 (8.9)	0.29	-
Sleep disorders	9 (11.4)	9 (8.9)	0.76	-

*Chi-square test and if necessary, Yates and Fisher corrections were used. TTH: Tension type headache, TDs: Tic disorders

seizures were diagnosed with TDs while no difference between groups was found for febrile convulsions. In the whole sample, rates of asthma, allergic rhinitis, allergic conjunctivitis, and allergic dermatitis were 7.8% (*n* = 14), 23.9% (*n* = 43), 17.2% (*n* = 31), and 15.6% (*n* = 28), respectively. Food allergy, drug allergy, and atopy were reported in 8.3% (*n* = 15), 5.0% (*n* = 9), and 39.4% (*n* = 71) of the whole sample, respectively. Food allergy and atopy are significantly more common in TDs with ORs being 3.9 (95% CI = 1.2–12.8) and 2.1 (95% CI = 1.1–3.9), respectively. Characteristics of epileptic and febrile convulsions and allergic disorders according to diagnostic groups are summarized in Table 3.

The rate of mothers diagnosed with headaches was 75.9% (*n* = 132) in the whole sample. The most common type was migraine without aura (42.4%, *n* = 56). TTH was significantly more common in the mothers of children with TDs (OR = 2.1, 95% CI = 1.1–4.3). Headache diagnoses and their features in mothers of children according to diagnostic groups are summarized in Table 4.

No significant difference was found among the mothers of children with TDs and controls in terms of abdominal pain, epilepsy, and its characteristics (*P* > 0.05, for all). Among the whole sample of mothers, atopy was found in 46.7% (*n* = 84). Allergic dermatitis (OR = 2.1, 95% CI = 1.1–4.1), drug allergies (OR = 3.2, 95% CI = 1.2–8.2), and atopy 3.8 (95% CI = 2.0–7.0) were significantly more frequent among mothers of children with TDs. Characteristics of atopic disorders in

Table 2: Recurrent, functional abdominal pain and motion sickness in children with tic disorders and healthy controls

Functional syndromes	TDs (n=79), n (%)	Control (n=101), n (%)	P*	χ^2
Recurrent abdominal pain	29 (36.7)	19 (18.8)	0.01	0.20
Recurrent abdominal pain with vomiting	14 (17.7)	16 (15.8)	0.89	-
Recurrent abdominal pain in the past (>1 year)	26 (32.9)	21 (20.8)	0.10	-
Motion sickness	34 (43.0)	39 (38.6)	0.55	-
Motion sickness in the past (>1 year)	31 (39.2)	39 (38.6)	0.93	-

*Chi-square test and if necessary, Yates and Fisher corrections were used. TDs: Tic disorders

Table 3: Epileptic and febrile convulsions and allergic disorders in children with tic disorders and controls

	TDs (n=79), n (%)	Control (n=101), n (%)	P*	χ^2
Epileptic seizure	3 (3.8)	0	-	-
Febrile convulsion	7 (8.9)	14 (13.9)	0.42	-
Family history of epilepsy	9 (11.4)	6 (5.9)	0.30	-
Asthma	9 (11.4)	5 (5.0)	0.16	-
Allergic rhinitis	23 (29.1)	20 (19.8)	0.20	-
Allergic conjunctivitis	17 (21.5)	14 (13.9)	0.25	-
Allergic dermatitis	15 (19.0)	13 (12.9)	0.36	-
Food allergy	11 (13.9)	4 (4.0)	0.03	0.18
Drug allergy	4 (5.1)	5 (5.0)	1.00	-
Atopy	39 (49.4)	32 (31.7)	0.02	0.18

*Chi square test and if necessary Yates and Fisher corrections were used. TDs: Tic disorders

Table 4: Primary headache disorders and characteristics in the mothers of children with tic disorders and those of controls

	TDs (n=79), n (%)	Control (n=101), n (%)	P*	χ^2
Type of headache				
Migraine	42 (53.2)	48 (47.5)	0.45	-
TTH	25 (31.7)	17 (16.8)	0.02	0.35
Trigger				
Stress	55 (69.6)	59 (58.4)	0.12	-
Insomnia	15 (19.0)	23 (22.8)	0.67	-
Drugs	0	2 (2.0)	-	-
Relieved by				
Sleep	27 (34.2)	33 (32.7)	0.83	-
Drug	31 (39.2)	30 (29.7)	0.18	-
Rest	25 (31.6)	18 (17.8)	0.05	0.16
Accompanied by				
Photophobia	28 (35.4)	31 (30.7)	0.50	-
Phonophobia	25 (31.6)	30 (29.7)	0.78	-
Nausea	20 (25.3)	20 (19.8)	0.48	-
Sleep disorders	10 (12.7)	9 (8.9)	0.57	-
Vomiting	3 (3.8)	6 (5.9)	0.73	-
Sensitivity to smell	2 (2.5)	5 (5.0)	0.47	-

*Chi-square test and if necessary are Yates and Fisher corrections were used. TTH: Tension type headache. TDs: Tic disorders

mothers of children according to diagnostic groups are summarized in Table 5.

Finally, we evaluated the effects of psychiatric comorbidity in children with TDs on headache types, abdominal pain, and atopic disorders. None

of the bivariate comparisons reached significance (Chi-square test).

DISCUSSION

This multi-center, cross-sectional case-control, familial association study evaluated headache, recurrent abdominal pain, motion sickness, epilepsy, and atopic disorders among children with TDs and age- and gender-matched controls and their mothers. We found that migraine, photophobia accompanying migraine, recurrent functional abdominal pain, food allergies, and atopies were significantly more common among children with TDs and that this was not affected by psychiatric comorbidities. On the other hand, mothers of children with TDs reported significantly more frequent TTH which is alleviated by rest and they also reported more frequent allergic dermatitis, drug allergies and atopy.

TDs are known to be accompanied by other psychopathologies, especially ADHD, conduct disorder, anxiety disorder, OCD and sleep disorders.^[4,25] Similar to those reported previously, rates of comorbidity in our sample were also high (59.5%). Furthermore, similar to previous studies ADHD, Conduct Disorder and anxiety were frequently comorbid with TDs in our sample.

In one of the first reports of the association between migraine and TDs, Barabas *et al.* reported that 27.0% of patients with Tourette Syndrome also had a migraine.^[26] In another study, rates of migraine in pediatric and adults patients with Tourette Syndrome

Table 5: Atopic disorders in mothers of children with tic disorders and healthy controls

	Mothers of children with TDs (n=79), n (%)	Mothers of control children (n=101), n (%)	P*	χ^2
Asthma	10 (12.7)	7 (6.9)	0.30	-
Allergic rhinitis	23 (29.1)	22 (21.8)	0.34	-
Allergic conjunctivitis	21 (26.6)	23 (22.8)	0.68	-
Allergic dermatitis	28 (35.4)	21 (20.8)	0.04	0.16
Food allergy	5 (6.3)	5 (5.0)	0.75	-
Drug allergy	15 (19.0)	7 (6.9)	0.03	0.18
Atopy	51 (64.6)	33 (32.7)	0.00	0.32

*Chi-square test, if necessary Yates and Fisher corrections were used. TD: Tic disorders

were reported as 16.0% and 39.0%, respectively.^[11] Another, more recent study reported that 55.0% of their sample with Tourette Syndrome had primary headache disorders.^[5] In this study, rates of migraine and TTH were reported as 17.4% and 28.4%, respectively. Our results support and extend those previously reported and suggest that headache disorders may be elevated across the broad spectrum of youth with TDs, rather than Tourette Syndrome *per se* and that this relationship may also hold for mothers of children with TDs. Although preliminary, our results also suggest that features of headaches (i.e., photophobia, relationship with rest) may differ in families of probands with TDs. The mechanism of the associations between headache disorders and TDs are still unclear and may involve neurobiology, stress, learning and psychiatric comorbidity (especially internalizing disorders).^[5,11,26] Although we could not find an effect of psychiatric comorbidity on headaches observed in children with TDs, those analyses were exploratory and cell sizes may be insufficient to detect statistical significance. Further studies on children with various TDs and enrolling parents of both genders are required to evaluate those relationships.

Although previous studies reported that TDs in children were not associated with recurrent, functional abdominal pain,^[16,17] our results suggest otherwise. This discrepancy may be due to methods of sampling and ascertainment (i.e., depending on children's and mothers' reports for recurrent abdominal pain, etc.) and may be mediated by psychiatric comorbidities. Inclusion of maternal and self-reports of internalizing symptoms may have enriched our results and would allow us to evaluate the role of those symptoms in recurring abdominal pain, rather than binary diagnoses. Regardless, further studies on medical comorbidities and pain symptoms in children with TDs may benefit from the inclusion of self and parent-reports of internalizing and pain symptoms.

Atopic diseases such as seasonal rhinitis, conjunctivitis, and asthma are common in migraine patients.^[27] On the other hand, previous studies suggest a bidirectional relationship between neurodevelopmental and allergic

disorders while those on relationships of atopy and TDs are limited.^[20,28,29] Another, nation-wide, community-based study reported that allergic rhinitis (OR = 2.2, 95% CI = 1.8–2.6), asthma (OR = 1.8, 95% CI = 1.5–2.2), dermatitis (OR = 1.6, 95% CI = 1.3–2.0), and allergic conjunctivitis (OR = 1.3, 95% CI = 1.1–1.6) were significantly associated with Tourette Syndrome.^[21] In a recent study, it was suggested that this relationship extended to TDs in general and comorbid ADHD may further elevate the risk.^[6] Similar to those studies we found that children with TDs have elevated odds of atopy and drug allergies and that this extended to their mothers.

The comorbidity of migraine with epilepsy and TD has been stressed in many studies.^[5,11,30,31] In a population-based study, TDs were more common in those with epilepsy (1.7% vs. 0.2%) with an OR of 8.7.^[31] Those results were supported in another population-based case-control study which found that OR of new-onset epilepsy in patients with Tourette Syndrome was 18.4 (95% CI = 8.3–40.9) with a limited effect of psychiatric comorbidity (i.e., adjusted OR = 16.3, 95% CI = 6.3–18.5).^[30] Interestingly, emotional stimuli such as anxiety and stress may be common causes of seizures and tics.^[32] In this study, we found no significant relationships between epilepsy, febrile convulsion, family history of epilepsy, and TDs. This may be due to sampling and/or reporting bias or inclusion of TDs other than Tourette Syndrome may have affected our results. Further studies are required on this issue.

Motion sickness is a common syndrome with a prevalence of 43.4% in school children.^[33] A recent study suggested that rates of motion sickness may be reduced among youth with ADHD and their parents.^[10] In this study, we found no difference in terms of motion sickness rates among children with TDs and their mothers.

There are lots of suggestive data about the changes common pathways both migraine and frontostriatal circuit disorders including anxiety disorders, depression,

TD, and ADHD. There are also some suggestive functional neuroimaging data about abnormalities in anterior cerebral regions, corresponding to frontal/prefrontal cortices and also posterior regions in patients with TD.^[34] It is known that neuroinflammation is a potential part of the mentioned abnormalities that affect both frontostriatal circuits and pain matrix as well.^[35] Comorbidity of migraine and atopic diseases has been reported previously and this comorbidity has been an important point for an immune system dysfunction or potential role of neuroinflammation in migraineurs.^[27,36] An imbalance between pro-inflammatory and anti-inflammatory cytokines has been hypothesized as a possible link between depression, migraine, atopic disorders, fibromyalgia, irritable bowel syndrome, and obesity, with underlying dysfunctions in tryptophan metabolism and serotonergic activation of the HPA axis.^[37,38]

Our results should be evaluated within their limitations. First, they may be valid for treatment-naïve children with TDs applying to the study centers for treatment within the study period and may lack external validity for community samples, those who have received prior treatment or those applying to other treatment centers. Second, the exclusion of MR/IDDs and ASDs may have affected our results. Third, we depended on children's and mothers' reports for motion sickness, recurrent abdominal pain, and atopic disorders although we tried to corroborate the results of allergies, seizures, and febrile convulsions with medical records where available. Dependence on self and parent reports may have introduced reporting and recall bias. Fourth, we could enroll a limited number of subjects within the specified time-frame limiting our power to detect significant differences (48.8% for Chi-square and 65.0% for *t*-tests). Fifth, enrollment of fathers and extended family members may have enriched our results. Despite limitations, our results suggest that previous relationships with headache disorders, allergies and Tourette Syndrome may extend to other forms of TDs and to mothers of index cases.

CONCLUSION

The results of the present study indicate that TDs in children might have a higher risk of migraine, atopy, food allergy, and recurrent abdominal pain. Atopy risk has also been found to be high in the mothers of children with TDs. TDs may be accompanied by other comorbidities and further studies investigating the mechanisms of those relationships are needed.

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Conflicts of interest

There are no conflicts of interest.

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