

Clinical Profile of Tic Disorders in Children and Adolescents from a Tertiary Care Center in India

Utkarsh Karki, Lakshmi Sravanti, Preeti Jacob, Eesha Sharma, John Vijay Sagar Kommu, Shekhar P. Seshadri

ABSTRACT

Background: Tic disorders (TDs) are common neurodevelopmental disorders in children and adolescents. To date, there is very scant literature on TDs in children and adolescents in the Indian setting. **Aim:** The objectives of this study were to characterize the clinical profile, including comorbidities and pattern of medication use in the treatment of TDs, in children and adolescents. **Materials and Methods:** The present study is a retrospective chart review of children and adolescents up to age 18 years diagnosed with TD in a tertiary care center in India. Data were derived from case records of patients with a diagnosis of TD, coded as F 95 according to ICD 10, from 1st January 2014 to 31st December 2017. **Results:** We recruited 85 subjects. The majority (95.29%, $n = 81$) of them were male, and the mean age of onset was 8.4 years. Chronic tic disorder was the most common subtype, followed by Tourette syndrome and provisional or transient tic disorder. Eighty patients (94%) had a comorbid disorder, with attention deficit hyperactivity disorder being the most common, followed by obsessive compulsive disorder. Eighty-two percent of patients received pharmacotherapy. Risperidone was the most frequently used medication, followed by clonidine, haloperidol, and aripiprazole. Moderate to significant improvement with medications was seen in 88% of the patients. **Conclusion:** The present study of children and adolescents with TDs highlights very high rate of comorbidity and a favorable short-term course with medication use.


Key words: Adolescent, child, comorbidity, India, tic disorders

Key message:

- Ninety-four percent of children with tic disorders had comorbidities.
- Risperidone was the most frequently used medication, followed by clonidine, haloperidol, and aripiprazole.
- Favorable short-term outcome is seen with medication use.

Tic disorders (TDs) are one of the neurodevelopmental disorders seen in children in every part of the world. For many, the experience of tics may only be transient

— but for those with Tourette syndrome (TS), it may be a debilitating mental health problem.

Access this article online	
Website: www.ijpm.info	Quick Response Code 
DOI: 10.4103/IJPSYM.IJPSYM_324_19	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Karki U, Sravanti L, Jacob P, Sharma E, Kommu JV, Seshadri SP. Clinical profile of tic disorders in children and adolescents from a tertiary care center in India. Indian J Psychol Med 2020;42:262-7.

Department of Child and Adolescent Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence: Dr. Utkarsh Karki

Department of Child and Adolescent Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India.

E-mail: karkiutkarsh@gmail.com

Submitted: 08-Aug-2019, **Accepted:** 26-Dec-2019, **Published:** 25-Apr-2020

As with other neurodevelopmental disorders, boys are more commonly affected than girls with tics. Tic symptoms typically have an onset around the age of 5–7 years and reach their peak severity around 10–12 years of age.^[1] In the majority, symptoms subside during adolescence.^[2] According to DSM-5 and ICD-10, primary tic disorders include TS (= combined phonic and motor tic disorder), persistent (or chronic) motor tic disorder (CMTD), persistent (or chronic) phonic tic disorder (CPTD), and provisional (or transient) tic disorder (PTD). Primary tic disorders are much more common than secondary tic disorders,^[3] which are caused by other conditions, such as certain neurodegenerative disorders, stroke, or substances.^[4]

The prevalence rate of TS in children in the general population ranges from 0.3 to 0.9%,^[5] whereas the prevalence rate of CMTD ranges from 0.5 to 1.65%.^[6] Due to the additional criterion regarding the added presence of phonic tics, TS in the community is rarer in comparison to CMTD.^[7] Accordingly, the prevalence for PTD – the mildest form of all primary TDs – is much higher, ranging from 5 up to 47%.^[8] In a population-based study^[9] from India, the prevalence rate was estimated at 35.34 (95% confidence interval, CI 12.96–76.92) per 100,000 [males: 56.19, 95% CI 18.21–131.15; females: 12.37, 95% CI 0.37–68.93].

TDs are associated with multiple comorbid conditions, which include obsessive compulsive symptoms, attention deficit hyperactivity disorder (ADHD), conduct disorder, oppositional disorder, rage attacks, anxiety, depression, and sleep disturbances.^[10] Tics typically have a waxing and waning course, but the long-term outcome is generally favorable. Many pharmacological and behavioral interventions are available. An effective nonpharmacological approach in the management of tic disorders is the habit reversal therapy (HRT).^[11]

Medications should be considered for CTD patients with moderate to severe tics that cause severe impairment in quality of life. When medication-responsive psychiatric comorbidities are present, medications that target both tic symptoms and comorbid conditions should be considered.^[12] According to the European Child and Adolescent Psychiatry guideline 2011,^[13] haloperidol, pimozide, risperidone, and alpha-2 agonists such as clonidine and guanfacine have level of evidence A for use in tic disorders. Haloperidol and pimozide are the only two FDA-approved treatments for tics, although they are not currently recommended as first-line pharmacotherapy because of their adverse side-effect profile.^[14]

Limited data are available regarding TDs in children and adolescents in the Indian settings, including a

retrospective review of 30 children and a comparison study of obsessive compulsive disorder (OCD) with tics vs. OCD.^[15,16] A recent study^[17] found that the rate of “any” TD was low (9.9%). However, to date, to the best of our knowledge, there is no literature available exclusively on the clinical profile and medication use in children and adolescents with TDs. Therefore, we report the sociodemographic and clinical profile of children and adolescents with TDs who received treatment at the child and adolescent psychiatry Services of National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru between the years 1st January 2014 to 31st December 2017 (four years duration).

MATERIALS AND METHODS

The present study utilized a retrospective chart review design. Ethical approval was obtained from the Institutional Ethical Committee. Data were derived from case records of patients with a diagnosis of tic disorder, coded as F 95 according to ICD 10. The study site is a tertiary care center in India.

The department offers outpatient and inpatient services to children and adolescents up to age 18. There is no definite catchment area for these services, although a majority of the patients hail from the state of Karnataka and the neighboring states. All patients undergo a detailed clinical evaluation in accordance with a prespecified topical format based on an unstructured psychiatric interview with both the child and the parent(s). The topical format includes sociodemographic information, presenting complaints, a history of present illness in chronological order of complaints, developmental history, temperament, family history, treatment details, and a mental status examination. Diagnosis and management plan are confirmed either by a consultant or a senior resident.

Limited information was available about the clinical status of the subjects at follow-up on standard outcome measures like Yale Global Tics Severity Scale (YGTSS) or Clinical Global Impression (CGI). Hence, the response was categorized into three parts based on the researcher’s clinical judgment such as:

- Less than 30 percent improvement - not improved
- 30–60% improvement - moderately improved, and
- More than 60% improvement - significantly improved.

A total of 85 case records with a diagnosis of TD as per ICD 10 were reviewed. Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 21.0 for Windows using descriptive statistics

RESULTS

A total of 12,662 patients attended the out-patient services during this four-year period. We identified 85 patients with a diagnosis of TDs according to the ICD-10 codes (F95-95.9) in the records. Based on the above data, the four-year period prevalence of TDs in the child and adolescent psychiatry outpatient population was 0.67%.

The mean age of presentation was 11.4 (SD: 0.70) years, and 95.2% ($n = 81$) were boys. Majority of the subjects presented with tics either at school-going age (49.4%, $n = 42$) or during the adolescent period (48.2%, $n = 41$). All of the subjects were going to school and 74.11% ($n = 63$) of them were from an urban locality.

Clinical profile of the patients is summarized in Table 1. The, majority (77.6%, $n = 66$) had an onset of tics between 6 and 12 years of age (school-going), with a mean age of onset of 8.4 (SD: 2.5) years. The youngest age of onset of tics was four years presented at seven years of age with chronic motor tic disorder (head jerks, eye blinking) and ADHD with a family history of tic disorder. The majority of patients (64.7%, $n = 55$) had a duration of tics between 1 and 5 years. Psychosocial stressor in the form of bullying was seen in 20% ($n = 17$) of the sample.

A vast majority (94.1%, $n = 80$) of the sample had a comorbid condition [Table 2]. The most common comorbid conditions were ADHD (33.75%, $n = 27$), followed by OCD (21.25%, $n = 17$) and specific learning disorder (SLD) (13.75%, $n = 11$).

The pattern of medication use is summarized in Table 3. The majority (82.35%, $n = 70$) were on both medications and nonpharmacological interventions, resulting in combined treatment. The remaining 17.65 ($n = 15$) exclusively received nonpharmacological intervention in the form of psychoeducation and HRT.

The response to medications is summarized in Table 4. Documentation of follow-up and response to medication use was available in 45 case records. The mean duration of follow-up was 9.78 months with one patient having a follow-up of maximum of 34 months. Thirty-three patients out of 37 who were prescribed risperidone had documentation regarding follow-up and response.

A total of 10 out of 16 patients who were prescribed clonidine and six out of eight who received haloperidol had follow-up and response records. The response of the child ($n = 1$) who was on polypharmacy

Table 1: Clinical profile of patients (n=85)

Characteristics	Frequency (n)	Percentage	Mean±SD
Age of onset (years)			
Preschool (<5 years)	8	9.41	8.4±2.50
School-going (6-12 years)	66	77.64	
Adolescence (12-18 years)	11	12.94	
Duration of tics (in years)			
<1 year	14	16.47	
1-5 years	55	64.70	36.09±25.60
>5 years	16	18.82	
Characteristics	Frequency (n)	Percentage	
Type of tic disorders			
Provisional or transient tic disorder	14	16.47	
Chronic tic disorder	43	50.58	
Tourette syndrome	28	32.94	
Family history of tic disorder	3	3.52	

Table 2: Pattern of comorbidity in patients with tic disorders (n=80)

Comorbid disorders (n=80)	Frequency (n)	Percentage
Attention deficit hyperactivity disorders (ADHD)	27	33.75
Obsessive compulsive disorders	17	21.25
Specific learning disorders	11	13.75
Intellectual disability	6	7.5
Oppositional defiant disorder (ODD)	5	6.25
Conduct disorder (CD)	4	5
Generalized anxiety disorders (GAD)	3	2.5
Social anxiety disorder (SAD)	1	1.25
Autism spectrum disorder (ASD)	2	2.5
Psychosis	2	2.5
Dysthymia	1	1.25
Trichotillomania	1	1.25
Expressive speech delay	1	1.25
More than one comorbidity (n=11)		
CTD+ADHD+ODD	3	3.75
CTD+ADHD+CD	3	3.75
TS+ADHD+SAD	1	1.25
CTD+OCD+GAD	1	1.25
CTD+OCD+CD	1	1.25
TS+ADHD+OCD	1	1.25
CTD+ADHD+OCD	1	1.25

Table 3: Pattern of medication use and response to medications (n=70)

Medications (n=70)	Frequency (n)	Percentage
Antipsychotics (n=50) Risperidone	37	52.85
Haloperidol	8	11.45
Aripiprazole	5	7.14
Alpha-2 agonist (n=16) Clonidine	16	22.85
Others: Tetrabenazine	3	4.28

Only one child (1.42%) received polypharmacy in the form of risperidone, clonidine and tetrabenazine

was “not improved”. Mean dose (dose range) was 51.56 mcg/d (25–100 mcg/d) for clonidine, 0.72 mg (0.25–3 mg/d) for risperidone, 0.62 mg/d (0.5–1.5 mg/d) for haloperidol, 8 mg/d (5–15 mg/d)

Table 4: Response to medications (n=45)

	Frequency (n)	Percentage
Response		
Not improved (<30%)	5	11.11
Moderately improved (30-60%)	28	62.22
Significantly improved (>60%)	12	26.66
Risperidone (n=23)		
Not improved (<30%)	4	17.39
Moderately improved (30-60%)	14	60.86
Significantly improved (>60%)	5	21.73
Clonidine (n=10)		
Not improved (<30%)	-	-
Moderately improved (30-60%)	8	80
Significantly improved (>60%)	2	20
Haloperidol (n=6)		
Not improved (<30%)	1	20
Moderately improved (30-60%)	3	60
Significantly improved (>60%)	2	40
Aripiprazole (n=5)		
Not improved (<30%)	-	-
Moderately improved (30-60%)	3	60
Significantly improved (>60%)	2	40
Tetrabenazine (n=1)		
Not improved (<30%)	-	-
Moderately improved (30-60%)	-	-
Significantly improved (>60%)	1	33.3

for aripiprazole, and 41.6 mg/d (25–75 mg/d) for tetrabenazine. No substantial side effects were noted with any of these medications.

DISCUSSION

The prevalence of TDs in our study was 0.67%, whereas other studies, which are epidemiological and community-based studies, reported prevalence of tics (chronic or transient) ranging from 5.9% to 18% for boys and from 2.9% to 11% for girls^[18] and of CTD as 0.5% to 3%.^[5] A population-based Indian study^[19] reported a crude prevalence of 25 (95% CI 15–34) per 100,000, which is lower than that reported from western countries.

Sociodemographic profile

The mean age at presentation was 11.4 years (SD: 0.70 years), and the mean age of onset was 8.4 years (SD: 2.40 years). Other studies have shown a similar age of onset in tic disorders.^[1,20] There may be a delay in the age at presentation due to lack of awareness, mild and transient nature of tic not causing impairment of functioning, or the tics not being noticeable to others.^[21]

The sample was overrepresented by boys (95.2%, n = 81). This finding is similar to that of an earlier study from our center.^[15] Also, in epidemiological studies, the reported male–female ratio varies considerably from 1:1 to 10:1.^[22]

Symptom profile

The majority of patients had a duration of tics of more than one year, with a mean duration of 36.09 (SD: 25.60 months) months, indicating chronic nature of the illness.

Previous findings from our center^[15] and a meta-analysis reported PTD to be more common compared to CTD. However, in our study, the commonest type of TD was CTD, followed by TS and PTD. This difference in findings could be due to the small sample size in the past study from our centre. In addition, reports of PTD being more common than CTD came from a community-based sample.^[23] Another reason for this difference could be an underestimation of PTD prevalence, given that most cases of tics are mild and may be misdiagnosed or unrecognized by medical professionals and may not be impairing to the child or adolescent.

Comorbidity

Comorbidity was found in 94.1% of our sample, which is extremely high and is similar to the finding of a study by Cavanna *et al.*,^[24] in which the rate of comorbidities was approximately 90%.

Other studies that included clinical samples of CTD also report that co-occurring psychiatric disorders are common, and patients with CTD meet the criteria for two or more conditions that are often viewed by the patient and family as more problematic than the tics *per se*.^[25] Symptoms associated with ADHD and OCD have received the most attention in TDs.^[26] Similarly, in our study, the commonest comorbidities were ADHD and OCD. According to a study done by Khalifa *et al.* in both clinical and epidemiological studies, it is not uncommon to see reports of 30–50% of children with TDs diagnosed with comorbid ADHD which is similar to our finding of 33.75% patients with comorbid ADHD.^[27]

Studies have reported 20% to 60% of TD patients meeting criteria for OCD.^[28] Some studies reported the prevalence of OCD in TS as high as 40% to 80%.^[29,30] However, in our study, the rate of OCD as a comorbidity was found to be only 21.25%. However, the association between OCD and TD appears to be bidirectional,^[12] and 20 to 38% of youths with OCD may report comorbid tics.^[28] The third commonest comorbidity was SLD, seen in 13.75% (n = 11) patients. Other studies too have shown that school-related problems and learning disabilities are common (23%) in youth with chronic tics.^[31,32]

It was surprising to see the low rates of mood and other anxiety disorders in our study, which is in contrast to previous studies conducted in the West.^[12]

Medication use and response

Treatment for TDs in our study showed that 70 (82.35%) patients were prescribed a combination therapy of medications and psychosocial interventions, and 15 (17.64%) were provided psychoeducation with HRT exclusively. Despite this large number of patients on medications, behavior intervention in the form of HRT and relaxation was provided to all children and adolescents as a part of the treatment of tics. The use of medications was high, probably due to the chronic nature of the TD, comorbidity associated with it, and distress or impairment in functioning in social, academic, and peer relationships independent of the comorbidities. In our sample, 71.42% ($n = 50$) of patients had received antipsychotics (risperidone being the most commonly used: 52.85%, $n = 37$), followed by the alpha 2 agonist clonidine (in 22.85%, $n = 16$), both of which have level A evidence.^[13] Similar to our findings, a clinician survey found that the most common medications used to treat tics are risperidone, followed by clonidine and aripiprazole.^[13] About half of the patients (48.14%, $n = 13$) with TDs and ADHD in our study were on clonidine. Use of clonidine in TDs with comorbid ADHD has been supported by a recent meta-analysis, which found that trials that enrolled subjects with tics and ADHD demonstrated a medium-to-large effect in reducing tic severity (0.68), whereas trials that excluded subjects with ADHD demonstrated only a small, nonsignificant benefit (0.15).^[33,34] Tetrabenazine was prescribed in 4.28% ($n = 3$) of the patients. It is not a frequently used medication in the child and adolescent population. These patients were already on tetrabenazine at the time of referral from the neurology department of our center. One of the positive and encouraging findings was that polypharmacy was noted only in one (1.42%) patient. None of the subjects had a history of Methylphenidate (MPH)- induced tics or antipsychotic-induced serious adverse effects.

The mean duration of follow-up was 9.78 months, which is definitely not sufficient to draw a conclusion about long term outcome or response to medication. However, from the limited duration of follow-ups, we found that with medication use in general, 62.22% of the patients moderately improved, 26.66% had significantly improved, and only 11.11% of the patients had not improved. Response to different classes of medications was no different, wherein subjects who were prescribed risperidone, clonidine, haloperidol, or aripiprazole showed more than 60% response. With these limited findings, we can consider the use of medications in children and adolescents with tic disorders without hesitation.

Strengths and limitations

The obvious drawback of the study is the retrospective design. One-third of the patients did not have even a

single follow-up, and outcome-based measures such as YGTSS or CGI were not applied on many.

Out of 70 (82.35%) patients who were prescribed medications, case records of 45 (64.28%) had follow-up visits and response documentation. Twenty-five (35.71%) did not have follow-ups. This could be due to various reasons. Being a tertiary care centre, many patients and family turn up only for a second opinion. Many patients, after two or three sessions of psychoeducation, HRT and relaxation, are referred back to psychiatrists or psychologists in their own cities. Lastly, the natural course of the illness itself may result in irregular follow-ups.

Despite all the drawbacks, it is a comprehensive review of available clinical data on tic disorders in children and adolescents, with a good sample size. Although only a short -term favourable outcome, representing a good initial response to medication, could be documented, it is an encouraging finding

CONCLUSION

Given the high prevalence of comorbidities, particularly ADHD and OCD, they should not be overlooked during the assessment and management of tic disorders. Response to medication in tic disorders seems to be promising in combination with nonpharmacological treatment, at least in the short term.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, *et al.* Course of tic severity in Tourette syndrome: The first two decades. *Paediatrics* 1998;102:14-9.
2. Block MH, Leckman JF, Zhu H, Peterson BS. Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. *Neurology* 2005;65:1253-8.
3. Martino D, Leckman JF. *Tourette syndrome*. Oxford: Oxford University Press; 2013.
4. Jankovic JK, Kwak C. Tics in other neurological disorders. In: Kurlan RM, editor. *Handbook of Tourette's Syndrome and Related Tic and Behavioral Disorders*. M D, editor. New York: CRC Press; 2004.
5. Kraft JT, Dalsgaard S, Obel C, Thomsen PH, Henriksen TB, Scahill L. Prevalence and clinical correlates of tic disorders in a community sample of school-age children. *Eur Child Adolesc Psychiatry* 2012;21:5-13.
6. Scharf JM, Miller LL, Gauvin CA, Alabiso J, Mathews CA, Ben-Shlomo Y. Population prevalence of Tourette syndrome: A systematic review and meta-analysis. *Mov Disord* 2015;30:221-8.

7. Khalifa N, Von Knorring AL. Prevalence of tic disorders and Tourette syndrome in a Swedish school population. *Dev Med Child Neurol* 2003;45:315-9.
8. Black KJ, Black ER, Greene DJ, Schlaggar BL. Provisional tic disorder: What to tell parents when their child first starts ticcing. *F1000Res* 2016;5:696.
9. Banerjee TK, Hazra A, Biswas A, Ray J, Roy T, Raut DK, *et al.* Neurological disorders in children and adolescents. *Indian J Pediatr* 2009;76:139-46.
10. Srour M, Lesperance P, Richer F, Sylvain C. Pediatric psychopharmacology: Psychopharmacology of tic disorders. *J Can Acad Child Adolesc Psychiatry* 2008;17:150-9.
11. Wilhelm S, Deckersbach T, Coffey BJ, Bohné A, Peterson AL, Baer L. Habit reversal versus supportive psychotherapy for Tourette's disorder: A randomized controlled trial. *Am J Psychiatry* 2003;160:1175-7.
12. Murphy TK, Lewin AB, Storch EA, Stock S; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry* 2013;52:1341-59.
13. Roessner V, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, *et al.* European clinical guidelines for Tourette syndrome and other tic disorders. Part II: Pharmacological treatment. *Eur Child Adolesc Psychiatry* 2011;20:173-96.
14. Schaihl L, Erenberg G, Berlin CM Jr, Budman C, Coffey BJ, Jankovic J. Contemporary assessment and pharmacotherapy of Tourette syndrome. *Neuro Rev* 2006;3:192-206.
15. Eapen V, Srinath S, Devi MG. Descriptive study of tic disorder in children. *J Psychol Med* 1989;12:17-22.
16. Jaisoorya TS, Reddy YC, Srinath S, Thennarasu K. Obsessive-compulsive disorder with and without tic disorder: A comparative study from India. *CNS Spectr* 2008;13:705-11.
17. Deepthi K, Sagar Kommu JV, Smitha M, Reddy YC. Clinical profile and outcome in a large sample of children and adolescents with obsessive-compulsive disorder: A chart review from a tertiary care center in India. *Indian J Psychiatry* 2018;60:205-12.
18. Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 1: The epidemiological and prevalence studies. *J Psychosom Res* 2008;65:461-72.
19. Raina SK, Razdan S, Nanda R. Prevalence of neurological disorders in children less than 10 years of age in RS Pura town of Jammu and Kashmir. *J Pediatr Neurosci* 2011;6:103-5.
20. Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. *Brain* 2000;123:425-62.
21. Pappert EJ, Goetz CG, Louis ED, Blasucci L, Leurgans S. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. *Neurology* 2003;61:936-40.
22. Scahill L, Dalsgaard S, Bradbury K. The prevalence of Tourette's syndrome and its relationship to clinical features. In: Martino D, Leckman JF, editors. *Tourette's Syndrome*. Oxford: Oxford University Press; 2013. p. 121-33.
23. Tabori-Kraft J, Dalsgaard S, Obel C, Thomsen PH, Henriksen TB, Scahill L. Prevalence and clinical correlates of tic disorders in a community sample of school-age children. *Eur Child Adolesc Psychiatry* 2012;21:5-13.
24. Cavanna AE, Servo S, Monaco F, Robertson MM. The behavioral spectrum of Gilles de la Tourette syndrome. *J Neurosychiatry Clin Neurosci* 2009;21:13-23.
25. Scahill L, Sukhodolsky DG, Williams SK, Leckman J. Public health significance of tic disorders in children and adolescents. *Adv Neurol* 2005;96:240-8.
26. Leckman JF, Bloch MH. Tic disorders. In: Thapar A, Pine DS, Leckman JF, Scott S, Snowling MJ, Taylor EA, editors. *Rutter's Child and Adolescent Psychiatry*. 6th ed. Oxford: Wiley Blackwell; 2018. p. 757-73.
27. Khalifa N, Von Knorring AL. Psychopathology in a Swedish population of school children with tic disorders. *J Am Acad Child Adolesc Psychiatry* 2006;45:1346-53.
28. Coffey BJ, Biederman J, Smoller JW, Geller DA, Sarin P, Schwartz S, *et al.* Anxiety disorders and tic severity in juveniles with Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2000;39:562-8.
29. Leckman JF, Bloch MH, Smith ME, Larabi D, Hampson M. Neurobiological substrates of Tourette's disorder. *J Child Adolesc Psychopharmacol* 2010;20:237-47.
30. Gaze C, Kepley HO, Walkup JT. Co-occurring psychiatric disorders in children and adolescents with Tourette syndrome. *J Child Neurol* 2006;21:657-64.
31. Burd L, Freeman RD, Klug MG, Kerbeshian J. Tourette syndrome and learning disabilities. *BMC Pediatr* 2005;5:34.
32. Gorman DA, Thompson N, Plessen KJ, Robertson MM, Leckman JF, Peterson BS. Psychosocial outcome and psychiatric comorbidity in older adolescents with Tourette syndrome: Controlled study. *Br J Psychiatry* 2010;197:36-44.
33. Yang CS, Huang H, Zhang LL, Zhu CR, Guo Q. Aripiprazole for the treatment of tic disorders in children: A systematic review and meta-analysis. *BMC Psychiatry* [Internet] 2015;15:179.
34. Weisman H, Qureshi IA, Leckman JF, Scahill L, Bloch MH. Systematic review: Pharmacological treatment of tic disorders--efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neurosci Biobehav Rev* 2013;37:1162-71.