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ORIGINAL ARTICLE

A pediatric cohort with Gilles de la Tourette syndrome

Descripción de una cohorte pediátrica con síndrome de Gilles de la Tourette

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What do we know about the subject matter of this study?

Tourette syndrome (TS) is a disorder characterized by chronic motor and vocal tics that usually begins in childhood and often improves in adulthood. TS is associated with comorbidities such as attention deficit hyperactive disorder, obsesive-compulsive disorders/behaviours , and other psychopathologies.

What does this study contribute to what is already known?

This study explores internationally recommended therapies in the management of tics in pediatric cohorts with TS. Management is described according to severity, type of tics, and associated comorbidity including non-pharmacological options, personalized pharmacological therapies and surgical approaches as deep brain stimulation.

Abstract

Tourette Syndrome (TS) is a common disorder with chronic motor and phonic tics, associated with neuropsychiatric comorbidities. **Objective:** To characterize clinical-demographic variables, comorbidities, and management in a pediatric cohort with TS and compare them according to sex. **Patients and Method:** A retrospective cohort of patients < 18 years old with TS followed up between 2000 and 2018 was evaluated. Clinical records were reviewed obtaining variables of age, sex, reason for consultation, age of onset, type and complexity of tics, follow-up time, family history, obsessive behaviors, neuropsychiatric and psychopathological comorbidity, neurological disorders, and pediatric morbidity. Studies and treatments performed, and management used were also recorded. **Results:** 126 patients were included, aged between 4-18 years, 103 males (sex F:M ratio = 4.5:1), with a follow-up of 4.8 ± 1.9 years. The mean age of tic onset and TS diagnosis was 6.5 ± 2.2 and 9.4 ± 2.7 years, respectively, and a diagnostic latency of 2.8 ± 2.2 years. The first consultation in the total of girls was due to tics, in contrast to the boys of whom 14.6% (n = 15) consulted due to comorbidities. There was 38.9% of tics and 8,7% of TS. Neuropsychiatric comorbidities were frequent, recorded in 69.8%, with Attention Deficit Disorder (43.6%) and Obsessive-Compulsive Disorder (20.6%) standing out.110 cases (87.3%), received pharmacological therapy and 54.4% required three or more drugs at some point in their evolution. Only in 16 cases (12.7%), no pharmacological therapy was required, only psychoeducation in 7 (5.6%) cases, and behavioral therapy in 9 cases (7.1%). **Conclusions:** The clinical characteristics of our children with TS are similar to international descriptions, highlighting that in the group of boys, the first consultation could be due to comorbidity, recognizing later the presence of tics. Although psychoeducation and behavioral therapies are recommended as first-line management, most of the patients in this group required pharmacological therapy.

Keywords:
Tourette syndrome;
Tics;
Psychoeducation;
Neuroleptics;
Pediatrics

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Introduction

Tourette Syndrome (TS) is a neurodevelopmental disorder that begins before the age of 18. It is characterized by at least two motor tics (MT) and one phonic tic (PT) or vocal tic (VT), lasting more than 1 year, in the absence of substance abuse or other medical condition that could explain it[1,2]. It is associated with neurological and psychiatric comorbidities such as attention deficit hyperactive disorder (ADHD), obsesive-compulsive disorders/behaviours (OCD/B), and Autism Spectrum Disorder (ASD), and other psychopathologies such as Mood Disorders, Oppositional Defiant Disorder, and Conduct Disorder[3]. The estimated prevalence is 1% in school children, with a boy/girl ratio of 4:1[4].

Tics are sudden, non-rhythmic, repetitive, rapid movements, or vocalizations involving small muscle groups[5] that usually have remissions and exacerbations with stressors that are not always identifiable. They may be relieved by physical or mental exercises that require concentration[1].

In TS, MTs usually precede PTs. They have their onset in childhood, typically at a median age of 5.6 years (range 3-8 years), are changing, appearing initially on the face (rostrocaudal) to involve more distal parts of the body[6]. Children older than 8-10 years may report somatosensory experiences or "premonitory urge". The worst severity of TS is between the ages 10-12 years, with a decline towards adolescence, but 50% of adolescents maintain some tic of varying intensity[7].

Tics present for less than 1 year was classified within the Transient Tic Disorder (TTD) and was renamed as Provisional Tic Disorder (PTD) by the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013), considering that TTD can only be diagnosed retrospectively. PTD can go to chronicity or TS, so it requires long-term follow-up[8,9].

There are difficulties in the diagnosis of TS and diagnosis is delayed with the initiation of the necessary support at a critical developmental age. Mol et al.[10] report a lack of knowledge of the normal course of TS, both in health professionals, education, and in the community in general, with a diagnostic delay of 0-16 years (median 5.5) and a range of 1-16 (median 2.00, IQR 1.00 - 3.25) professional consultations before diagnosis[11].

The genetic base of TS is complex and heterogeneous. Bilineal transmission of tics (paternal and maternal side simultaneously) has been described in 26-41% compared with 15% for unilineal families, associated with pre and postnatal environmental risk factors and autoimmune mechanisms triggered by infections[12].

Due to its high prevalence, up to 1%[4], neuropsychiatric comorbidities, psychopathologies, and the clinical relevance of early diagnosis, we present this observational study in a retrospective cohort. Unlike other national studies[13,14], it is focuses on a pediatric population of a pediatric neurology unit. The objective is to describe a cohort of children with TS and to provide clinical information in a common pathology, but that is little described in the Chilean literature.

Patients and Method

Descriptive study of a retrospective cohort of pediatric patients with TS seen at a university Pediatric Neurology Center between January 2000 and June 2018. Clinical records were reviewed, with a predesigned format for the collection of clinical history. The diagnosis of TS was made according to DSM-IV-TR criteria, used since 1994 and DSM-5 since 2013[9]. Although its denomination changed to Tourette's Disorder, but in this study the name Tourette Syndrome (TS) has been used, considering that the community has recently integrated this pathology. Patients with ASD were excluded, even though the DSM-5 includes it as comorbidity, trying to homogenize the data of the cohort started in 2000 (where ASD was not included as comorbidity). Motor tic disorders or persistent vocal disorders and those who had follow-up visits for less than 1 year were excluded.

The variables to analyze were sex, presenting symptoms (tics, ADHD, conduct disorder), age at TS diagnosis (years), and the onset of tics, type, and complexity (motor, phonic, simple, complex, coprolalia, and copropraxia), follow-up time, family history of TS and tics, personal history of ADHD, obsessive behaviors and OCD/B, neurological, psychiatric and pediatric comorbidity, studies, and treatments.

The variables of the treatment used were psychoeducation (by the neurologist or psychologist), behavioral therapy for tics (habit reversal training carried out by the psychologist), and pharmacological treatment. Drugs of continuous use were considered those if were used for a period longer than 3 months and of intermittent use those used for ≤ 3 months.

Tic severity was defined by functional impairment associated with tic complexity (e.g., coprophenomena), tic intensity (self-harm risk), school dysfunction (grade retention, prolonged absences, or early academic year closure), and social dysfunction (exclusion from social activities, bullying through social networks).

The IBM SPSS Statistics version 15 (SPSS) software was used for data analysis. Variables were expressed as mean ± standard deviation (SD) or as median and interquartile range (p25-p75) and were compared with $\chi 2$ test or Fisher's exact test and to compare means or

medians, we used the t-test or Mann-Whitney test, establishing a p-value ≤ 0.05. Categorical variables were expressed as frequency and percentages.

The Institutional Ethics Committee authorized the Project (N° 180827048).

Results

We included 126 pediatric patients with TS monitored for more than one year in our center. The mean age at diagnosis was 9.4 ± 2.7 years, with a diagnostic latency of 2.8 ± 2.2 years. The 81.7% were boys, with a difference in the boy/girl ratio of 4.5/1 (p 0.001), and with a follow-up of 4.8 ± 1.9 years.

The reason for consultation in most cases was an MT (88.1%). In 15/103 boys, the reason for consultation was due to comorbidity and TS diagnosis was established when simple motor tics or vocal tics were observed. It is noteworthy that in all girls the first consultation was due to tics (Table 1).

The initial tics were simple MT in all cases, with an age at the onset of 6.5 ± 2.2 years. Subsequently, PT appeared, with an average age at the onset of 7.7 ± 2.4 years, without significant differences according to sex (Figure 1). Complex tics were added to simple MT and PT in 13.4% and 10.3%, respectively. There were coprolalia and copropraxia in 12 and 9 cases, respectively.

In 49/126 patients had a family history of tics in the extended family and 11 cases of first-degree relatives with TS (8 siblings).

Psychiatric comorbidities were observed in 69.8% of the children, ADHD in 55, and OCD/B in 26 cases. Table 2 shows other comorbidities. Neurological comorbidity was diagnosed in 10 cases (7 cases of migraine, 2 of parasomnias, and one case of epilepsy), and pediatric comorbidity in only 7 cases, highlighting malnutrition by excess and obesity in 6 cases and Diabetes Mellitus type 1 in one case.

In the social and school context, 21.4% reported low of quality of life with social interference, including exclusion in extracurricular activities or messages through social networks, and school dysfunction with 13 cases of grade retention and 16 cases with prolonged absences due to tics exacerbation and early academic year closure with special exams

Secondary causes of tics were excluded in all cases. A complete blood count with blood smear, anti-streptolysin O, and ceruloplasmin was requested in all patients. Other tests were included in specific cases.

Figure 2 details the treatment algorithm used in this cohort. Psychoeducation was performed in all children and caregivers during the first or second consultation and reinforced in subsequent follow-up visits. In 16 cases no drugs were used. In this group, 7 patients received only psychoeducation, and 9 children older than 8 years with mild functional impairment due to tics, Behavioral Therapy (BT) was included.

Exclusive or mixed pharmacological therapy (pharmacological and BT) was used continuously or intermittently in most cases (87.3%) (Table 3). The drugs of continuous use were alpha-2 adrenergic agonists (clonidine) in all drug-treated cases. Antiepileptics (levetiracetam or topiramate), typical benzamide-type antipsychotics (sulpiride and tiapride), and atypical antipsychotics (aripiprazole, ziprasidone) were also used. Antidepressants (clomipramine, fluvoxamine) were added when psychiatric comorbidity (obsessive-compulsive disorder or behavior) was diagnosed. Benzodiazepines (clonazepam) were used intermittently in some patients. For ADHD management, methylphenidate was added in low doses or during periods of high academic demands. A significant group of cases (54.5%) received 3 or more drugs at some time during their evolution.

Discussion

The prevalence of TS is at least 1% in the general pediatric population in the UK, rising to 6.8-8.1% in children with ASD and school children with learning disabilities, behavior disorders, and emotional problems[15].

The biodemographic variables (boy/girl ratio of 4.5/1), latencies between the onset of MT and PT, and diagnostic latency of TS in our cohort are similar to those described in the international literature[16]. Even so, the age at the onset of tics, recorded by the parents, was 6.5 ± 2.2 years, 11 months later than the 5.6 ± 2.3 years reported by Leckman[7]. In our sample, 14.6% of the children were diagnosed when observing their tics, in consultations due to ADD or behavior disorder. These tics were attributed to chronic respiratory or ophthalmologic pathologies (coughing, throat clearing, sniffing, blinking) or to other movements such as mannerisms/stereotypies, similar to that reported by Mol et al.[10]. Some parents reported these as bad habits. On the other hand, in the group of girls, the first consultation was due to tics in all cases, which we attribute to the lower tolerance of the girls and their parents to facial or phonic motor tics, and the lower frequency of ADHD in this group.

MT and PT are not recognized as such in the general population and health professionals, who usually wait for the appearance of coprolalia for diagnosis[11,17]. Coprophenomena represents severe complex motor and vocal tics and has an age bias (they start 5-7 years after the first tic and are more frequent in adults), a specialty bias (more frequent in movement disorder

Table 1. Clinical features in 126 children with Tourette Syndrome (ST) (2000-2018)

Characteristics	Total	Boys	Girls	p value
	126 (100)	103 (81.7)	23 (18.2)	0.0001
Presenting symptoms (first visit) n, %				
Motor Tic	111 (88.0)	88	23	
ADHD*	11 (8.7)	11	0	
Behavioural problems	2 (1.5)	2	0	
Other	2 (1.5)	2	0	
Mean age at symtoms onset				
Onset of motor tics ($\bar{x}$, SD)	6.5 (2.3)	6.4 (2.3)	6.9 (2.1)	0.5
Copropraxia (n, %)	9 (7.1)	8 (88.8)	1 (11.1)	0.3
Onset of vocal tic ($\bar{x}$, DE)	7.7 (2.4)	7.5 (2.5)	8.2 (2.4)	0.6
Coprolalia (n, %)	12 (9.5)	12 (100)	0	
Mean age at the time of diagnosis ($\bar{x}$, SD)	9.4 (2.7)	9.4 (2.7)	9.3 (2.6)	0.6
Delay(years) diagnosis ST ($\bar{x}$, SD)	2.8 (2.2)	2.9 (2.3)	2.7 (1.5)	0.4
Family history of tics or TS (n, %)				
Tourette Syndrome	11(8.7)	8 (7.7)	3 (13)	0.3
Tics	49 (38.9)	39 (37.8)	1 (43.4)	0.4
Obsesive-compulsive disorders/behaviours	9 (7.1)	6 (5.8)	3 (13.0)	0.3
ADHD*	7 (5.5)	6 (5.8)	1 (4.3)	0.6

*Attention Deficit hyperactive disorder

specialists), and a cultural one. Robertson and Eapen (18–21) specialists in movement disorders, describe 18-35%, lower than the 16% of our sample and the 9-11% described by Shilon[11] in general pediatric neurology consultations. According to Cardoso et al.[22], the low frequency described in Japan by Nomura and Segawa could reflect a distinctive feature of their millenary culture.

The diagnosis of TS is clinical. However, its chronic course, with remissions and severe exacerbations in some cases, requires exclusion of secondary causes. Blood count with smear, antistreptolysin O titers, and ceruloplasmin, can exclude neuroacanthocytosis, PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections), and Wilson's disease. Other biochemical, electrophysiological, and neuroimaging studies are requested according to the clinical picture or before administering typical antipsychotics. In our patients, we did not find secondary causes of tics, and 1.5% required additional therapy such as iron, levothyroxine, and antiepileptics, corresponding to one case that had both pathologies.

The management of TS begins with psychoeducation of parents and caregivers in all cases. The first line of treatment is behavioral therapy (BT), with better results than supportive psychotherapy[6,23]. BT includes comprehensive behavioral intervention for tics or CBIT, habit reversal training, and exposure and response prevention. The habit reversal training is restricted by the age (patients older than 8-10 years perceive

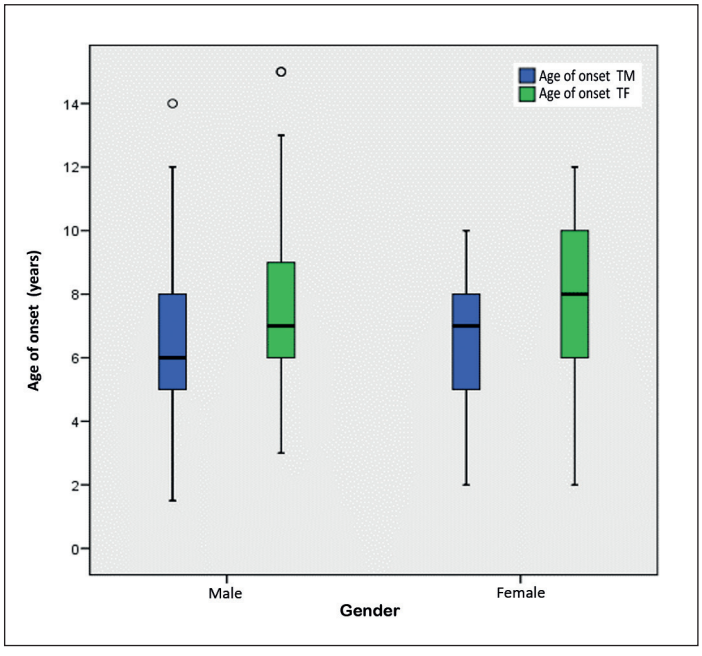

Figure 1. Central tendency and dispersion age of onset motor tics (MT) and phonic tics (PT) according to gender in a cohort of 126 children with TS (2000-2018)

Table 2. Comorbidities in a pediatric cohort with Tourette Syndrome 2000-2018

	Total	Boys	Girls
n (%)	126 (100)	103 (81.7)	23 (18.2)
Neuropsychiatrics comorbidities, n (%)	88 (69.8)	73 (70.8)	15 (65.2)
ADHD* n (%)	55 (43.6)	48 (46.6)	7 (30.4)
Obsesive-compulsive disorders/behaviours, n (%)	26 (20.6)	23 (22.3)	3 (13.0)
Anxiety disorders, n (%)	15 (11.9)	8 (7.7)	7 (30.4)
Learning difficulties, n (%)	11 (8.7)	9 (8.7)	2 (8.6)
Conduct disorder, n (%)	7 (5.5)	5 (4.8)	2 (8.6)
Depression, n (%)	4 (3.1)	4 (3.8)	0
Others: Communication Disorders (3),Personality disorders (2), Elimination Disorders (2), n (%)	7 (5.5)	5 (4.8)	2 (8.6)
Neurological Comorbidities, n (%)	10 (7.9)	13 (12.6)	2 (8.6)
Migraine, n (%)	7 (5.5)	5 (4.9)	2 (8.6)
Parasomnias, n %	2 (1.6)	1(1)	1(0.4)
Epilepsy, n %	1 (1.4)	2 (0.7)	0
Pediatric comorbidities, n (%)	7(5.6)	7(6.8)	0
Malnutrition by excess (Obesity), n (%)	6 (4.7)	6 (5.8)	0
Diabetes type 1, n (%)	1(0.8)	1(1)	0

ADHD: Attention Deficit hyperactive disorder

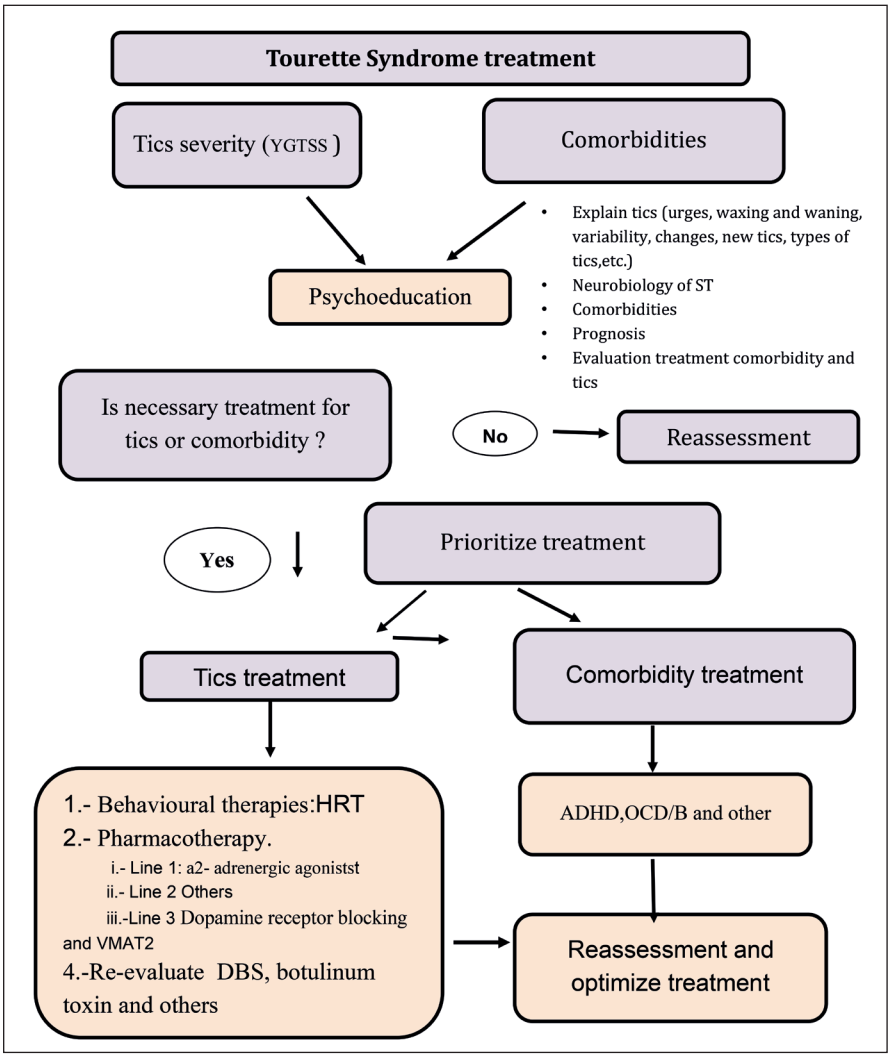

Figure 2. Current Approaches and New proposal in the Management of Tourette Syndrome

Table 3. Registry of pharmacologic treatment in a Chilean cohort with Tourette Syndrome, 2000-2018

	Total	Boys	Girls
n (%)	110 (100)	87 (79.0)	23 (20.9)
Drugs			
One, n (%)	29 (26.3)	23 (26.4)	6 (26.0)
Two, n (%)	21 (19.0)	14 (16.0)	7 (30.0)
Three, n (%)	60 (54.5)	50 (57.4)	10 (43.3)
Continuous Use			
Alpha 2 adrenergic agonists, n (%)	65 (59.0)	54 (62.0)	11 (47.8)
Antidepressant, n (%)	36 (32.7)	28 (32.1)	8 (34.7)
Antiepileptic, n (%)	24 (21.8)	16 (18.3)	8 (34.7)
Intermittent / Continuous use			
Dopamine receptor blocking n (%)	81 (73.6)	65 (74.7)	16 (69.5)
Typical, n (%)	70 (63.6)	57 (65.5)	13 (56.5)
Atypical, n (%)	32 (29.0)	26 (29.8)	6 (26.0)
Methylphenidate , n (%)	36 (32.7)	34 (39.0)	2 (8.6)
Benzodiazepine , n (%)	33 (30.0)	22 (25.2)	11 (47.8)

premonitory urges), the severity of the tic (not indicated for severe tics), and its high cost[24]. The recognition of the premonitory urges that temporarily relieves the tic and feeds back the circle, allows the patients to break this vicious circle[16,25,26]. This therapy was the only treatment in 9 cases, with good results.

In severe tics with functional impairment, pain, and risk of self-harm behavior, such as myelopathy or stroke in "whiplash" cervical tics[27], it is suggested to start pharmacological therapy adapted to the patient's needs[28]. The American[29], European[30], and Canadian[31] guidelines consider that combined pharmacological and behavioral therapy have a synergistic effect[32,33], which was used in 87.3% of our children.

Most guidelines describe three levels of oral medications. In the first level are alpha-2 adrenergic agonists, due to their good tolerance except for sedation, dizziness, or dry mouth in some cases. The second level includes a large number of medications with modest benefits, chosen according to the type of tic and the comorbidity, although, according to Billnitzer and Jankovic[34], this is to avoid antipsychotics whose side effects intimidate the family. At this level, there are topiramate, levetiracetam, baclofen, benzodiazepines, among others. Jankovic et al.[35] in a double-blind study with topiramate, reported reduction of tics and migraine, a frequent medical comorbidity in TS. In our group, we use this drug in children with migraine and overweight/obesity, with adequate and well tolerated individual results. Levetiracetam is another antiepileptic drug that is well tolerated and with evidence in the management of TS[32,36,37].

Dopamine antagonists or antipsychotics are the third level of medication. Typical antipsychotics (haloperidol, pimozide, and fluphenazine) have a potency comparable with risperidone, but with greater potential neurological, cognitive, and cardiac effects[32,38,39]. Farag and Robertson in 400 consecutive cases of TS in the UK showed that the most used drugs were aripiprazole, clonidine, sulpiride, and risperidone[28]. In our children, we used sulpiride (considering costs and less sedation) and aripiprazole or ziprasidone (atypical antipsychotics) with adequate results and few side effects. We do not use vesicular monoamine transporter 2 (VMAT2) inhibitors such as tetrabenazine, deutetrabenazine, and valbenazine, nor botulinum toxin due to their cost, although they are suggested as first-line drugs, after clonidine[36].

Regarding comorbidity, a study of 3500 children with TS showed that it is present in most cases[24,40] so that "pure" TS would correspond to only 10-20% of cases[9]. In our cohort, comorbidity was also present in most cases, but it could be underestimated since only neurological consultations were included.

The use of psychostimulants in the treatment of ADHD in TS cases is controversial. While symptoms such as inattention, impulsivity, and hyperactivity decrease with their use, tics may worsen[19,41,42]. However, with low doses of methylphenidate (10 mg) or medication at specific periods of the academic year, some children show benefits, with no increase in tics.

For the management of OCD/B and anxiety disorders as comorbidity, we use clomipramine or fluvoxamine (Table 3), which are more effective than placebo

for anxiety disorders and obsessive-compulsive disorders[43].

This study has limitations since it was conducted in a specialized neurological setting, so psychiatric comorbidity may be underdiagnosed. Standardized scales to measure tic severity, such as the Yale Scale, were not used. In addition, because of its historical cohort design, variables such as premonitory urges, non-obscene inappropriate behaviors, other coprophenomena, impulse control disorders, among others, were not recorded. Additionally, it included a change in the DSM-IV diagnostic manuals, which did not include ASD as comorbidity, unlike the DSM-5. Likewise, due to the design of the research, it is not possible to evaluate the results of the treatment, considering that tics increase or decrease without identified triggers.

Conclusions

TS starts early (4-6 years) and goes through all stages of physical and mental development of children, with a high rate of comorbidity, so it is necessary to recognize the initial symptoms to make an early diagnosis that allows installing the appropriate and timely management. This retrospective cohort shows biodemographic similarities with its international counterparts, as well as the treatments used. We highlight the differences by sex in the first consultation since in all girls the first consultation was due to tics, while in 14.6% of boys the first consultation was comorbidity, and tics were recognized later.

In our sphere, there is a lack of clinical guidelines for the management and studies that evaluate the impact of different therapies considering the evolution towards adulthood.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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