Quality of life and psychiatric comorbidities in pediatric patients with Gilles de la Tourette syndrome

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Introduction. Tourette Syndrome (TS) is a complex neurodevelopmental disorder which is normally associated to psychiatric comorbidity such as attention deficit hyperactivity disorder, obsessive compulsive disorder, anxiety or depression. Quality of life (QoL) in these patients can be affected by tic severity and associated comorbidities.

Aim. The aim of the study was to describe and analyze QoL and psychiatric comorbidities in a sample of pediatric patients, as well as to develop a Spanish version of the questionnaire C&A-GTS-QoL to measure quality of life in this population.

Patients and methods. Single-center, observational, prospective study. Patients aged 6 to 16 years old with TS were included. Demographic, clinical, diagnostic and treatment data were gathered. Questionnaires regarding tic severity, psychiatric comorbidity and quality of life were used.

Results. Twenty-two patients with DSM-5 diagnosis of TS were included (86.4% male, median age 11 years). Of those, 86.4% had been previously diagnosed of psychiatric comorbidities and 72.7% received psychopharmacologic treatment. The prevalence of an ICD-10 current diagnosis of anxiety was 72.7%, depression 50%, ADHD 40.9% and OCD 7.3%. Median QoL score was 59.5 (RIC: 34.8-71.3) for PedsQL, and 55.5 (RIC: 45-65) for C&A-GTS-QoL, with a correlation between scores of $R^2 = 0.83$ ($p < 0.01$). Higher tic severity was associated with poorer QoL (PedsQL R^2: –0.732, $p < 0.01$, C&A-GTS-QoL R^2: –0.501, $p = 0.021$). A higher EDAH score for ADHD was associated with poorer QoL (PedsQL R^2: –0.463, $p = 0.03$, C&A-GTS-QoL R^2-0.534, $p < 0.01$).

Conclusion. Prevalence of psychiatric comorbidities in pediatric TS is high and frequently underdiagnosed. Tics and psychiatric comorbidities affect quality of life. Further studies are needed to validate the Spanish version of C&A-GTS-QoL scale.

Key words. ADHD. Anxiety. Depression. OCD. Quality of life. Tourette Syndrome.

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Introduction

Gilles de la Tourette syndrome, also known as Tourette syndrome (TS) or Tourette disorder [1], is a neuropsychiatric disorder with onset during childhood, which is defined by the presence of motor and phonic tics, lasting for at least one year and appearing before 21 years of age. It is a complex disorder, frequently accompanied by psychiatric comorbidities such as obsessive-compulsive disorder (OCD) and attention deficit and hyperactivity disorder (ADHD), all of which contribute to an impairment of patient's quality of life [2].

Prevalence of TS is estimated to be around 0.8%, being more prevalent in boys (up to 1.06% of male population) [3]. Clinical manifestations of this disorder appear normally before 10 years of age, with a typical age of onset between 3 and 8 years [4].

Quality of life in these patients is determined by the presence and severity of tics, as well as by coexistence of neuropsychiatric comorbidities, which affect their social, emotional and scholar functionality [5]. In fact, some studies [2,6,7] have observed that comorbidities may have a greater impact in quality of life than the presence of tics, even though tics are what define the disorder. Among psychiatric comorbidities, the most prevalent are ADHD and OCD, followed by autistic spectrum disorders, anxiety and depressive disorders [4]. The association of different comorbidities has been reported to worsen quality of life perception [5], however there are few published studies on this topic in pediatric and adult population. Thus, it is essential to perform an adequate screening of psychiatric comorbidities in pediatric TS patients to obtain a proper diagnosis and implement adequate treatment strategies, which may lead to a significant improvement in patients' quality of life.

Most studies designed to evaluate quality of life in pediatric patients with TS are have been based on

generic quality of life scales such as the PedsQL scale [8]. In consequence, they do not take into account specific aspects of the disease such as tics or stereotypical behaviors and may thus underestimate the impact of these symptoms in patient's quality of life. In 2008, Cavanna et al. developed the Children and Adolescents Gilles de la Tourette syndrome Quality of Life test (C&A-GTS-QoL), a specific questionnaire to measure quality of life in TS patients, which was initially validated in adults [9] and later in children and adolescents [10,11]. This questionnaire assesses four different areas regarding quality of life: psychological impact, physical and daily living activities, obsessive-compulsive symptoms and cognitive domains. However, so far, this test is only validated and available in Italian and English [10,11]. Currently there are no published studies about quality of life in Spanish TS pediatric patients, and neither is there an available nor validated Spanish version of the C&A-GTS-QoL questionnaire either, which could help clinicians and researchers to delineate and measure quality of life in this population.

The aim of this study is to measure quality of life and prevalence of psychiatric comorbidities in a Spanish sample of pediatric patients with TS and to evaluate the impact of tics and psychiatric comorbidities in their quality of life. Secondary objectives are to provide a Spanish version of the C&A-GTS-QoL which measures quality of life specifically in this population and to compare the obtained scores with this tool with those obtained with the generic PedsQL scale.

Patients and methods

This is a prospective, observational, single-center, descriptive and analytic was designed. We included patients between 6 and 16 years of age with Tourette syndrome and who were followed-up between October 2018 and January 2020 in a neuropediatric outpatient clinic of a tertiary hospital and being the reference center for movement disorders in Madrid (Spain). Exclusion criteria were: patients younger than 6 years or older than 17 years old or those whose cognitive function did not allow to evaluate psychiatric comorbidities or quality of life. The study was approved by the hospital research ethics committee, and all parents/legal guardians signed an informed consent.

Demographic and epidemiological information was gathered, as well as clinical data related to TS, psychiatric comorbidities and ongoing treatments. A set of questionnaires was handed to caregivers aiming to evaluate tic severity, screen for psychiatric diseases and analyze quality of life. Specifically, tic severity was measured with the Yale Global Tic Severity Scale (YGTSS) [12], which evaluates motor and phonic tic severity and also related disability; for this study we used both the motor and phonic tic severity score alone as well as a total score which includes the degree of disability. Psychiatric comorbidities studied were: a) anxiety disorder and obsessive-compulsive disorder (OCD), which were evaluated using a semi-structured interview (MINI-KID [13]), b) attention deficit hyperactivity disorder (ADHD), that was evaluated using the Spanish EDAH test [14] (based on the Conners scale [15]); and c) depression, that was evaluated using the CDI inventory test [16]. Quality of life was initially measured with the PedsQL questionnaire [8]. Patients who screened positive for a psychiatric comorbidity but had not been previously identified were referred to the Child Psychiatry Unit of our hospital for further assessment.

Patients also fullfilled the Spanish version of the Gilles de la Tourette syndrome-Quality of Life Scale or C&A-GTS-QoL [10]. For translation of this test, a forward-backward translation procedure was conducted by two translators: initially, the questionnaire was translated from English to Spanish and then inversely translated again to English by a second translator who was blind from the original English version. Both translators later compared the final versions together with other researchers, solving possible conflicts or imprecisions that could have emerged during the translation process and reached final consensus.

Statistical analysis was performed using SPSS inc. software, version 23.0. Percentages for qualitative variables and mean and standard deviation or median with interquartile range (IQR) for quantitative variables were computed, depending on normality of distributions. For proportion comparisons, χ^2 and Fisher's exact tests were used depending on sample size and normality of distribution; for quantitative variable comparisons Student's *t* test or Mann-Whitney *U* test were used depending on normality of distributions. For association between different quantitative variables, univariate and multivariate linear regression models were fitted, computing adjusted R^2 for all models and predictors. The alpha level was set at $p < 0.05$.

Results

Between October 2018 and January 2020, 22 pa-

Table I. Psychiatric comorbidities diagnosed prior to the study and diagnosed by the study screening questionnaires.

	% with previous diagnosis	% diagnosed by the study screening tests
ADHD	14 (63.6%)	9 (40.9%)
OCD	10 (45.5%)	6 (27.3%)
Anxiety	2 (9.1%)	17 (72.7%)
Depression	1 (4.5%)	11 (50%)

ADHD: attention deficit and hyperactivity disorder; OCD: obsessive-compulsive disorder.

tients with TS were included in the study. Of these, 19 patients (86.4%) were male and the median age was 11 years (IQR 10-12.8). Previous psychiatric comorbidities had been diagnosed in 19 children (86.4%), whereas prevalence of current psychiatric comorbidities found by the study screening questionnaires was 90.9% (20 patients). Prevalence of previously diagnosed psychiatric comorbidities as well as the prevalence of current disorders assessed with screening questionnaires are detailed in Table I.

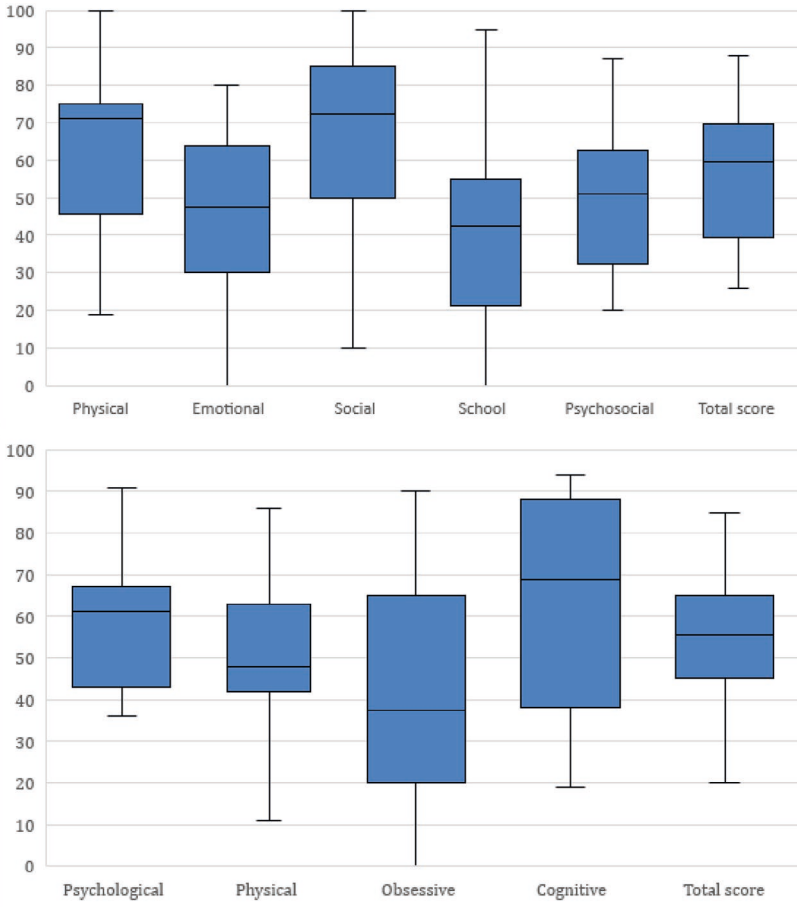
A total of 16 patients (72.7%) received psychopharmacological treatment at the moment of study enrollment. Specifically, 9 patients (40.9%) were treated for ADHD, 6 (27.3%) were treated with antidepressants, 6 (27.3%) with antipsychotics, and 3 patients (13.6%) with benzodiazepines.

Median age at the start of TS symptoms was 6.5 years (IQR: 4.8-7.3) and median age at diagnosis of TS was 10 years (IQR: 7.8-12). Regarding tic severity, median YGTSS score at study enrollment was 24 (IQR: 18.5-25.75) for motor and phonic tics, and 45 (IQR 35.5-60.7) for the global scale including disability.

Regarding quality of life measured with PedsQL, patients showed a median global score of 59.5 (IQR: 34.8-71.3). The median global score when using the specific questionnaire C&A-GTS-QoL was 55.5 (IQR: 45-65). Subscale scores of both questionnaires are shown in figure 1.

Both scales endorsed similar results regarding quality of life in this population. The correlation coefficient between the two global scores was 0.83 ($p < 0.01$). Correlations between parallel subscales were also significant: 0.74 ($p < 0.01$) for physical subscales and 0.54 ($p < 0.01$) for emotional and psychological subscales.

Figure 1. Quality of life scores in the different PedsQL subscales (up) and in the different C&A-GTS-QoL subscales (down). Values are shown in median, interquartile range (box) and maximum and minimum values (whiskers).



In the bivariate analysis, a greater tic severity (measured by YGTSS scale) was associated with worse quality of life measured by both PedsQL (R^2 –0.732, $p < 0.01$) and C&A-GTS-QoL (R^2 –0.501, $p = 0.02$) when disability scored was included, and only with PedsQL scale (R^2 –0.462, $p = 0.04$) but not with C&A-GTS-QoL (R^2 –0.216, $p = 0.36$) when only phonic and motor tics were included. Correlations between global YGTSS scale and both PedsQL and C&A-GTS-QoL are graphically displayed in figure 2.

A higher EDAH score was correlated with greater tic severity (R^2 –0.463, $p = 0.03$) and worse quality of life by both PedsQL and C&A-GTS-QoL (R^2 –0.534 and –0.512, $p < 0.01$ and $p = 0.01$ respec-

Table II. Quality of life scores in patients with and without diagnosis of psychiatric comorbidities by screening tests.

	Quality of life without comorbidity		Quality of life with comorbidity		*p*-value	
	PedsQL	GTS-QoL	PedsQL	GTS-QoL	PedsQL	GTS-QoL
Anxiety	64.8 (SD: 24.5)	65.4 (SD: 23.3)	54.9 (SD: 16.3)	51.8 (SD: 13.7)	0.30	0.12
Depression	60.1 (SD: 16.6)	60.3 (SD: 15.4)	52.3 (SD: 20.4)	48.3 (SD: 16.7)	0.33	0.09
OCD	61.3 (SD: 17.9)	58.4 (SD: 16.2)	45.3 (SD: 16.3)	48 (SD: 19)	0.07	0.23

GTS-QoL: Gilles de la Tourette syndrome Quality of Life test; OCD: obsessive-compulsive disorder; PedsQL: Pediatric Quality of Life Inventory; SD: standard deviation.

tively). Patients in whom anxiety, depression and OCD were diagnosed with the screening questionnaires obtained lower scores in both quality of life tests (PedsQL and C&A-GTS-QoL) in comparison with patients without psychiatric comorbidities, however these results did not reach statistical significance (Table II).

Discussion

The present study describes quality of life in a sample of pediatric patients with Tourette syndrome, the prevalence of psychiatric comorbidities and the repercussion of the association of psychiatric comorbidities and the severity of tics in the quality of life of these patients.

Quality of life in patients with TS has been source of study in the past decades both in adult and pediatric populations [17,18]. The presence of tics has a detrimental effect on physical, psychological and social areas of these patients. In previous studies the relationship between tics and life quality remained unclear [6], however our study proves that tics' severity is inversely associated to life quality, when tics are measured with the YGTSS including the disability score. Life quality is a fundamental parameter when analyzing patients' functional status. Interventional studies have brought light to the fact that despite clinical improvement, functionality and patients' satisfaction do not always improve parallelly [19]. In pediatric population social and education areas [20] are the most affected, having a higher impact in their life quality in comparison with other systemic diseases [21]. Nonetheless, life quality may be difficult to evaluate in this pediatric population.

Nowadays, the evaluation of quality of life is uprising as a key point in the clinical follow-up of children with TS. On this basis, an specific scale has been developed to measure life quality of patients' with Tourette syndrome, namely 'Gilles de la Tourette syndrome-Quality of Life Scale o GTS-QOL', validated in the first place in adult population [9] and lately in children [10,11]. Previously, other generic life quality scales have been used such as YQOL-R [5], PQOL [17], QOLAS [18], EQ-5D [22] and most commonly PedsQL [6]. However, generic scales may not be sensitive to fundamental aspects that influence life quality in these patients and may underestimate their functional impact. Our study opens a pathway towards the validation of the GTS-QOL scale in Spanish, enabling a more accurate assessment of life quality in children with Tourette syndrome in our country as well as the collaboration of our center in other studies and clinical trials which could use this scale as a tool.

In our study, 90% of psychiatric comorbidities were detected using specific questionnaires, being the most frequent comorbidity ADHD followed by OCD. These results are consistent with those obtained by previous studies [2,4,11,23]. However, the percentage of patients in which ADHD or OCD are diagnosed with the use of screening questionnaires is lower than the initial prevalence of these diseases in our sample. This could be due to the wide number of patients which had a former diagnosis of OCD or ADHD. Up to 40.9% of patients with ADHD and 13.9% of those with OCD received medical treatment, therefore a lower score in the scales may due to a correct symptomatic control. Alternatively, we detected a higher number of cases of depression and anxiety with the use of questionnaires in comparison to the initial number of cases reported of these comorbidities, with similar results to those obtained by Eapen et al [24]. Overall, the use of screening questionnaires could be a useful tool to detect underlying undiagnosed psychiatric comor-

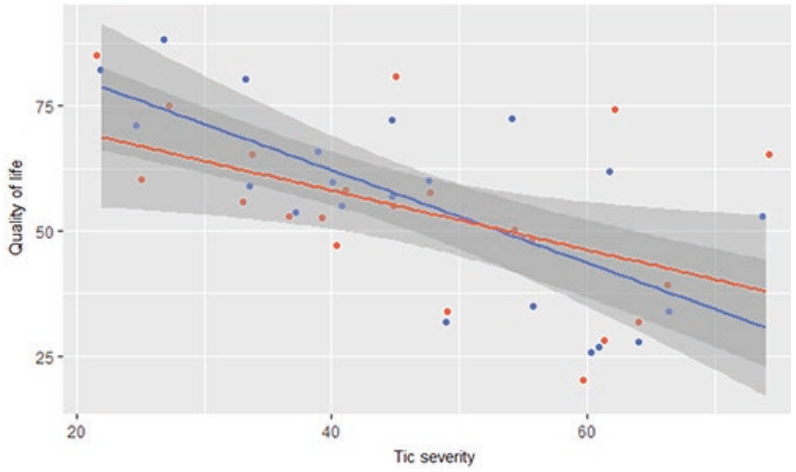
bidities. In addition, they allow monitoring of symptom severity for some of these comorbidities.

The association between psychiatric comorbidities and Tourette syndrome has been widely studied [6,7,10,24] highlighting that the coexistence of psychiatric comorbidities in patients with Tourette syndrome worsens life quality, especially in psychosocial areas. In our study we found an inverse relationship between the ADHD and life quality, as previous studies point out [2,5,24]. Unlike other studies the relationship between anxiety, OCD and depression was not related to a difference in life quality, which is likely to be due to the small sample of the study. Due to the impact of comorbidities in life quality, conducting screening strategies to detect the coexistence of psychiatric comorbidities seems convenient, both at diagnosis and during follow-up of patients with Tourette syndrome, aiming to provide adequate treatment and ameliorate their life quality.

Our study should be evaluated in light of its limitations. In the first place, this is a unicentric study and therefore the sample size is small. It would be convenient to incorporate patients from other centers in order to continue the analysis of the results of the GTS-QOL in Spanish and its validation process. On the second place, this study includes a wide age range, which interferes in the evaluation of the perception of life quality as it modifies with patients' age. The questionnaires used to analyze the prevalence of psychiatric comorbidities are questionnaires used as screening test therefore are unable to analyze the severity of underlying disease.

We can conclude that the prevalence of psychiatric comorbidities in children with Tourette syndrome in our population is high and that there are an important percentage of underdiagnosed comorbidities. Life quality in these patients is affected by the severity of tics and worsen in coexistence with psychiatric comorbidities which justifies the use of screening tests of psychiatric diseases. Studies with a larger number of patients are necessary to confirm our findings and help to validate the specific scale of quality of life in children with Tourette syndrome in Spanish proposed in this study.

Figure 2. Linear correlation models between tic severity (YGTSS scale) and quality of life measured by PedsQL (blue) and C&A-GTS-QoL (red). In grey, confidence intervals for the linear model.



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Calidad de vida y comorbilidades psiquiátricas en pacientes pediátricos con síndrome de Gilles de la Tourette

Introducción. El síndrome de Gilles de la Tourette es un trastorno complejo que se acompaña habitualmente de comorbilidades psiquiátricas, como trastorno por déficit de atención/hiperactividad (TDAH), trastorno obsesivo-compulsivo (TOC), ansiedad o depresión. La calidad de vida de estos pacientes puede verse afectada por la gravedad de los tics y por la presencia de estas comorbilidades.

Objetivos. Describir y relacionar la calidad de vida y las comorbilidades psiquiátricas en una muestra de pacientes pediátricos con síndrome de Gilles de la Tourette, así como proporcionar una versión en español del cuestionario *Gilles de la Tourette Syndrome-Quality of Life Scale for Children and Adolescents* (C&A-GTS-QOL) para medir la calidad de vida en esta población.

Pacientes y métodos. Es un estudio transversal, observacional y unicéntrico. Se incluyó a pacientes entre 6 y 16 años con diagnóstico de síndrome de Tourette, de los cuales se recogieron datos demográficos y clínicos, así como diagnósticos y tratamientos previos. Se entregaron cuestionarios de gravedad de los tics, comorbilidad psiquiátrica y calidad de vida.

Resultados. Se incluyó a 22 pacientes (86,4%, varones; mediana de edad, 11 años) con diagnóstico de síndrome de Gilles de la Tourette (según los criterios del *Manual diagnóstico y estadístico de los trastornos mentales, quinta edición*). El 86,4% tenía comorbilidades psiquiátricas diagnosticadas y el 72,7% recibía algún tratamiento. La prevalencia de ansiedad fue del 72,7%, la de depresión, del 50%, la de TDAH, del 40,9% y la de TOC, del 27,3%. La mediana de calidad de vida medida por el *Pediatric Quality of Life Inventory* (PedsQL) fue de 59,5 (rango intercuartílico: 34,8-71,3), y por la C&A-GTS-QOL, de 55,5 (rango intercuartílico: 45-65) (R^2, 0,83; $p < 0,01$). La gravedad de los tics se relacionó con una peor calidad de vida (PedsQL, R^2: –0,707; $p < 0,01$; y C&A-GTS-QOL, R^2: –0,501; $p = 0,021$). Una mayor puntuación la escala de Conners revisada para el TDAH se relacionó con peor calidad de vida (PedsQL, R^2: –0,463; $p = 0,03$; y C&A-GTS-QOL, R^2: –0,534; $p < 0,01$).

Conclusión. La prevalencia de comorbilidades psiquiátricas en el síndrome de Gilles de la Tourette en nuestro medio es alta y frecuentemente infradiagnosticada. Los tics y las comorbilidades psiquiátricas afectan a la calidad de vida. Son necesarios estudios que validen la C&A-GTS-QOL.

Palabras clave. Ansiedad. Calidad de vida. Depresión. Síndrome de Gilles de la Tourette. TDAH. TOC.