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Review Article

The Essentials in Tourette Syndrome

Sacristán HE[1]*, Galati AS[2], Canestrari L[3] and Gómez Forero AG[3]

[1]Department of Neurology, Anselmo Marini Rehabilitation Institut, Professor of Neurology, School of Medicine, University of Morón, Associate Professor of Neurology, School of Medicine, UBA, Buenos Aires, Argentina

[2]Department of Neurosurgery, Cosme Argerich Hospital, Department of Neurosurgery, Bernardo Houssay Hospital, Buenos Aires, Argentina

[3]Hospital Teaching Unit, Bernardo Houssay Hospital, Buenos Aires, Argentina

***Corresponding Author:** Sacristán HE, Department of Neurology, Anselmo Marini Rehabilitation Institut, Professor of Neurology, School of Medicine, University of Morón, Associate Professor of Neurology, School of Medicine, UBA, Buenos Aires, Argentina.

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Abstract

Tourette's syndrome (TS) is a complex neuro-psychiatric disorder that manifests itself in childhood or adolescence. It is characterized by motor and vocal tics, present at least one year prior to the consultation and of a changing nature in number, frequency and complexity. Patients with TS may manifest psychiatric comorbidities: 1-attention deficit hyperactivity syndrome (ADHD), 2-obsessive-compulsive disorders (OCD), 3-impulse control disorders (ICD), 4-anxiety, 5-depression or 6-self-aggressive behaviors, which can affect their personal, social and work life. Some patients with TS progress to a severe and malignant clinical form, which generates disability, usually refractory to medical treatment. In the course of life, motor and vocal tics diminish or disappear with persistence of neuro-psychiatric manifestations. The pathophysiology of TS is unknown, although serotonergic and dopaminergic cortico-strio-pale-thalamic-cortical circuits are postulated, the involvement of which justifies the motor (tics) and behavioral manifestations. Treatment strategies vary depending on the type and degree of severity of symptoms. Treatment must be adapted to the needs and objectives of the individual patient and with respect to her family environment. Patients should be educated about the condition and, if possible, participate in behavioral therapy targeting tics and comorbidities. Various drugs, alpha adrenergic agonists, topiramate, and mono-amine transport inhibitors, are used as first-line therapies in patients with tics refractory to behavior therapy. Botulinum toxin injections are indicated in patients with severe focal tics. Typical or atypical antipsychotics (fluphenazine, aripiprazole, risperidone, and ziprasidone) are another treatment option. These generally effective medications carry the risk of metabolic syndrome, Parkinsonism, tardive dyskinesias, or other side effects. Clinical trials with ecopipam, a D1 antagonist, are promising. Patients with tics refractory to conventional treatment are candidates for neurosurgical treatment. Injury neurosurgery not exempt from sequelae is currently in disuse. Instead, deep brain stimulation surgery has been tried. The Tourette Syndrome Association and the European Society for the Study of Tourette Syndrome have published guidelines that establish the criteria for the selection of patients who are candidates for DBS. DBS constitutes a programmable and reversible modality of neuromodulation on associative or limbic circuits within the basal ganglia and has been used to treat severe forms of TS. Preliminary results of DBS at the level of associative and/or limbic parts of the striatum, thalamus and/or the pallidum in patients with TS, demonstrated a clear decrease in the severity of tics and self-injurious behaviour. Future studies will make it possible to establish the impact of DBS in the motor sphere and in associated neuro-psychiatric comorbidities. In the present work, the clinical manifestations and the various medical and/or surgical treatment options currently available are reviewed.

Keywords: *Tourette; Tics; Cognitive Behavioral Therapy; Drug Therapy; Deep Brain Stimulation*

My Life with Tourette...

"Tourette appeared in my life when I was eight years old. However, I knew her name eighteen years later. My friends asked me why I blinked so hard and I had no answer. Year after year the tics disorder worsened. A psychologist advised me to consult a neurologist. It took a few minutes for him to make the diagnosis. On the way home, distraught and angry, I started screaming… why me!!! Then, when I started taking the medication, the tics disorder improved. This changed my life and now, when the people ask me if I have hiccups or a sore neck, I no longer change the subject, or stammer an answer and introduce them to Mr. Tourette" (MP, with permission).

History

In 1825, Jean-Marc Gaspard Itard (Figure 1), described for the first time a patient with tics, the Marquise de Dampièrre, who manifested involuntary movements in the body, vocalizations and coprolalia from the age of 7. Sixty years later, Georges Gilles de la Tourette (Figure 2), describes 9 patients with a similar clinical picture and includes the initial case described by Itard, establishing his diagnostic criteria: 1-motor and vocal tics, 2-onset in childhood, 3-chronic course, 4-recrudescences and remissions [1].

Figure 1: *Jean-Marc-Gaspard Itard (1775-1838).*

Figure 2: *Georges Gilles de la Tourette (1857-1904).*

Introduction

Tics are recurring, non-rhythmic movements or vocalizations out of context. Any movement or sound that a human being can make can manifest as a tic. The TS is a condition that begins in childhood or adolescence and is characterized by the appearance of motor and vocal tics in a chronic form, present at least one year prior to the consultation. Motor tics can be clonic (rapid and jerky); tonic (isometric contraction of a muscle); dystonic (sustained abnormal postures) or manifest as a temporary cessation of movement (blockages). Motor tics are described as simple or complex. Simple motor tics are fast and nonsensical and usually involve only one area of the body or muscle group. Examples include blinking, wrinkling the nose, facial grimacing, shrugging the shoulders, and abdominal tension. Complex motor tics are slow and involve more than one muscle group. Examples include eye movements, facial expressions, dystonic postures, blocks, copropraxia (obscene gestures), and compulsive behaviors related to tics, such as touching or pairing. Vocal tics are also described as simple or complex. Simple vocal tics are fast, nonsensical sounds. Examples include coughing, clearing, sniffing, snorting, grunting, or animal noises. Complex vocal tics consist of the utterance of syllables, words, phrases, or statements. These include coprolalia (profanity); echolalia (repetition of other words or phrases); palilalia (repetition of terminal segments of a word or sentence); blockages (interrupted speech or stuttering). Coprolalia (obscene or insulting expressions) is the most notorious tic of TS. However, it is observed in less than 50% of the cases in the published series. Obscenity can be limited to thought that does not manifest itself as verbalization, constituting a mental coprolalia. The tics are usually preceded by premonitory, extremely uncomfortable sensations, which are usually located at the site of the tic. Patients frequently report that their tics alleviate these sensations. The tics have been described as "involuntary", however the patient retains some ability to voluntarily suppress his expression, but the impulses and sensations accumulate until a point is reached where the impulse is irresistible and the tics ensue. Patients with TS have multiple types of motor and vocal tics, which vary over time. These tics occur in waves and vary in frequency and intensity from week to week or even month to month (fluctuating time profile). The increase or decrease in the magnitude of the tics is a characteristic of the disease and the exacerbations are not necessarily related to situations of emotional stress [2]. Psychiatric comorbidities are frequent in individuals with TS. ADHD was observed in 54%, OCD in 50% and OCD associated with ADHD in 30% of patients with TS. Mood disorders are also observed (depression or bipolar I and II) present in 30%; anxiety disorders, including generalized anxiety disorder (GAD), panic, agoraphobia, social phobia, and specific phobia by 36%; and disruptive behavior disorders (DBD), including oppositional defiant disorder (ODD), present in 30%. Self-destructive behavioral alterations have been described that include self-mutilations that can put the patient's life at risk (malignant TS). The mean age of TS diagnosis is 8 years. Severity usually peaks between the ages of 10 to 12, and subsequently there is an improvement in the severity of tics between the ages of 14 and 17. The diagnosis of TS is based on the medical history and physical examination. There are no diagnostic tests or biological markers of the disease. Most patients with TS have an intelligence quotient (IQ) within normal values. In 2 out of 3 patients with TS, the tics at the beginning are motor and predominate in the region of the face, shoulders and neck [3].

Diagnosis diagnostic criteria (according to DSM 5 and TSG) (Table 1)

DSM-V (APA) (1)	TSG (2)
Tourette Syndrome (TS) 1-Have two or more motor tics (e.g. blinking and shrugging the shoulders) and at least one vocal tic (e.g. humming, clearing throat, shouting a word or phrase), although it is possible that not all occur at the same time. 2-Having had tics for at least a year. Tics can occur many times a day (usually in attacks), almost every day, or from time to time. 3- Onset of tics before the age of 18. 4-The condition cannot be attributed to the consumption of drugs and/or medications or to another condition (e.g.: Huntington's disease or encephalitis).	Definitive TS: 1-Age of onset before 21 years 2-tics are witnessed by a reliable examiner or recorded by video. ST by Medical History: 1-Tics are witnessed by a trusted family member or close friend, but not by a trusted examiner.
Abbreviations: (1) APA- American Psychiatric Association-; DSM -Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition; (2) TSG, Tourette Syndrome Group [4].	

Table 1: *Diagnostic criteria for Tourette syndrome.*

The diagnosis of a tic is clinical and is based on the patient's description: 1-premonitory sensation, 2-movement or vocalization, 3-tension relief after the tic has occurred. These three phenomenological criteria do not always take place, although they allow them to be differentiated from other clinical entities characterized by repetitive movements (Table 2). Neuroimaging, EEG and neurophysiological studies will allow a certain diagnosis to be reached. The DSM-5 includes three types of tic disorders and they are differentiated by the type of tic that is present (motor or vocal) or a combination of both, and by the duration of the symptoms: 1-Disorder or Tourette Syndrome: Patients have both types of tics, motor and vocal, and have had symptoms for at least 1 year, 2-Persistent motor or vocal tic disorder (chronic): Patients present with motor or vocal tics, and have had symptoms for at least 1 year, 3-Transient motor or vocal tic disorder: Patients have either motor or vocal tics, or both, but have had symptoms for less than 1 year.

Differential diagnoses of tics should be considered (Table 2).

Myoclonus	Stereotypies Mannerism
Dystonia	Compulsions
Chorea	Akathisia
Paroxysmal dyskinesias	Restless Leg Syndrome
Hemibalism	Epilepsy
Hemifacial spasm	

Table 2: *Differential diagnoses of tics.*

Regarding the etiology, the possibility of primary or secondary tics should be considered (Table 3).

Primary tics	Secondary Tics
Simple transient tics in childhood	Neurodegenerative diseases
Chronic tics in childhood	Developmental disorders
Tourette syndrome	Structural brain injuries
Primary dystonia	Infections
	Drugs-Toxic

Table 3: *Etiology of tics.*

Pathogenesis

TS constitute a neurobiological disorder of a genetic nature, although the responsible gene or genes have not been identified, probably due to clinical and genetic heterogeneity added to bilinear transmission (inherited from both parents). Genetic susceptibility has been postulated, demonstrated through genome-wide association studies. The effective clinical response after the administration of drugs that block dopaminergic transmission (DBRD) lays the foundations for a disorder at the CNS level. A PET study, using flumazenil and magnetic resonance imaging, provided evidence of decreased binding to GABA receptors in patients with TS, suggesting that the GABAergic system plays an important role in TS and this represents a disinhibition disorder. Adult-onset tics usually represent recurrences of childhood tics, either due to the consumption of cocaine or other CNS-stimulating drugs or DBRD, in the latter case, tardive syndromes. A developmental alteration, of a hereditary nature, responsible for the disinhibition of the cortico-strio-pale-thalamus-cortical circuit has been proposed. An alteration in the serotonergic and/or dopaminergic circuits would be linked to the development of tics, although the data are insufficient. In the generation of tics associated with TS, a variety of factors intervene: 1-the premonitory urge, 2-neuro-hormonal imbalances, 3-abnormal activity of neural circuits and 4-the inability to regulate tics. The premonitory urge associated with tics constitutes an uncomfortable sensation that precedes the tic and is relieved after it has resolved. Magnetic resonance imaging (MRI) studies show a loss in asymmetry in the volume of the basal ganglia (considered normal) in TS, suggesting it is a developmental abnormality. Transcranial magnetic stimulation in patients with TS has demonstrated a defect in intra-cortical inhibition, which could explain the decrease in motor

inhibition and the intrusive phenomena of ST and OCD. TS, is linked to a history of group A beta-hemolytic Streptococcus infection, responsible for the appearance of anti-neuronal antibodies. Infection could trigger the appearance of symptoms in a small group of patients with TS. Functional neuroimaging studies demonstrate an increase in metabolism at the level of the prefrontal cortex and in the anterior striatal region during voluntary suppression of a tic, while the opposite occurs during the occurrence of a tic [5].

Phenomenological classification of tics [6]:

- Simple motor tics: Blinking, eyebrow raising, grimacing, mouth opening, tongue protrusion, head jerking, shoulder raising, shoulder rotation or abduction, neck stretching, arm shaking, clenched fists, abdominal tension, thrusting pelvic, buttock or sphincter contraction, hip flexion or abduction, kicking, knee or foot extension, toe flexion.
- Simple vocal tics: Sniff, growl, hawk, scream, howl, bark, huff, cough, whistle, hum, moan.
- Complex motor tics: Head shaking, teeth grinding, hand shaking, finger gnashing, touching, jumping, hitting, squatting, kicking, smelling hands or objects, rubbing, finger fiddling, echopraxia, copropraxia, spitting, exaggerated startles.
- Complex vocal tics: Uttering obscene words or phrases, unintelligible words, whistling, panting, burping, hiccups, stuttering, echolalia, palilalia.

Clinical picture

The diagnosis of TS is made when motor and vocal tics have been present for at least 1 year prior to consultation. TS must be differentiated from chronic motor tic disorder and chronic vocal tic disorder in which there are motor or vocal tics, but not both, characteristic of TS. Tics must be distinguished from compulsions, which are manifested in response to an obsession (washing hands for fear of contamination), according to a certain ritual (the movement is repeated a number of times or following an order). However, tics and compulsions often coexist and have very similar phenomenologies that make it difficult to distinguish between one and the other. Tics often accompany developmental disorders such as mental retardation, autism, and Asperger's syndrome. When these disorders are present, TS is not considered and tics are considered secondary to this disorder. TS, is considered a neuropsychiatric disorder and the diagnosis is clinical. Neuroimaging or laboratory studies are not required to establish the diagnosis. Clinical rating scales that can be used to assess the child for coexisting psychiatric comorbidities include: 1-the Yale-Brown obsessive-compulsive scale, 2-the Conners Parent/Teacher ADHD rating scales, and 3- the childhood depression inventory. In patients with TS, tics are often associated with other comorbidities (OCD and/or ADHD). The combination of tics, OCD, and ADHD is called the "ST triad". Children are more likely to suffer from tics and ADHD; girls, on the other hand, tend to suffer from tics and OCD. Patients with TS may suffer from other psychiatric manifestations including 1-impulse control disturbances (ICD), 2-depression, 3-bipolar disorder, 4-anxiety, 5-self-aggressive behaviors, and 6-oppositional defiant behaviors (ODB) (Figure 3) [7,8].

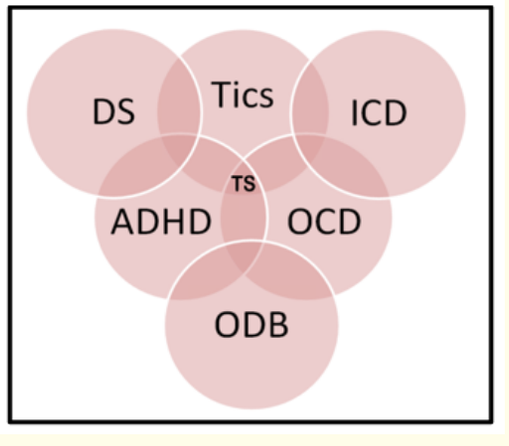

Figure 3: *Comorbidities and Tourette: TS: Tourette syndrome. DS: depressive syndrome; ICD: impulse control disturbances; ADHD: attention deficit hyperactivity disorder; OCD: obsessive-compulsive disorder ODB: oppositional defiant behaviors.*

Symmetry and counting are the most frequent obsessions of seeing in TS. The prevalence of TS in the general child population ranges from 0.5 to 1%, with 4: 1 being more common in males. Family history of tics, OCD, and ADHD are risk factors for TS. Most longitudinal and retrospective studies suggest that as children grow and reach adolescence or adulthood, tics totally remit in 33% of them, partially in another 33%; and in the rest of the cases, TS persists throughout life, without observing a substantial reduction in symptoms. A population study of TS diagnosed in Canadians older than 18 years found a prevalence of 0.1%. Existing data show a more equitable sex distribution in adults [9].

Clinical evaluation

In patients with tics, a medical history should be evaluated, including family history of tics, prescription of medications, developmental disorders, neurological examination, and measurement of the severity of the tics. Secondary causes of tics include neurodegenerative disorders such as Huntington's disease (HD), neurodegeneration with brain iron accumulation (NBIA), and neuro-acantocytosis; infectious or post-infectious conditions such as Sydenham's chorea or PANS; structural injuries; and tics induced by the effect of antiepileptic, psychostimulant or antipsychotic drugs [10]. The patient's medical history may provide evidence of comorbid neuro-developmental delays or disorders. Family history often reveals multiple affected family members. Many patients with TS can be referred by other specialists (ophthalmologists, allergists, otolaryngologists, psychologists and/or psychiatrists). Neurological examination is normal in patients with TS. The detection of deficient neurological, cognitive, behavioral or psychological signs implies the extension of the neurological dysfunction associated with tics. The neurological examination should be exhaustive in those patients with secondary forms of tics, since they may manifest other associated involuntary movements (dystonia, chorea or myoclonus). In the history of tics, the basic clinical characteristics of tics should be obtained. Tics can be suppressed, distracting, and vary in frequency and nature; they can be exacerbated by stress or excitement and are preceded by a premonitory impulse or sensation. The tics result in a voluntary capitulation to this urge and provide a fleeting sense of relief from the urge. At the time of the first interview, the TS patient can control the frequency and nature of the tics. Future interventions are required or family members can record videos that allow their evaluation. Although in the majority of patients with TS, the tics appear from childhood, it happens that they can remit in adolescence and these then reappear during adult life [11]. The most widely used clinical instrument to measure tic severity is the Yale Global Tic Severity Scale (YGTSS). This is a physician-administered interview that assesses the amount, frequency, intensity, complexity, and interference of motor and vocal tics and related impairment. The existence of associated comorbidities should be detected [12]. The American Academy of Neurology (AAN) has issued the following recommendations in patients with TS: 1-The burden of ADHD symptoms should be assessed. There are a number of standardized screening measures for ADHD to aid clinical diagnosis, including the Conners ADHD Rating Scales, the Swanson, Nolan, and Pelham (SNAP) Rating Scale, and the ADHD IV Rating Scale. 2-An evaluation of comorbid OCD should be carried out in people with tics and that the appropriate treatment is provided. Different OCD rating scales are known, including the Yale Brown Obsessions and Compulsions Scale, the Obsession Inventory, and the Leyton Obsession and Compulsion Inventory [13]. The AAN TS guidelines recommend screening for anxiety, mood, and behavior disorders in people with tics. The patient should be questioned regarding the existence of suicidal thoughts or attempts. Patients with TS may have long periods of complete remission of the tics. These usually diminish although they can persist during the different phases of sleep [14].

Treatment general features

The first step in treating TS is to define the degree of disability that TS produces in the patient and how the tics interfere in the educational, family or social spheres. The fluctuating nature of the disease must be recognized, making it difficult to correctly assess the clinical response to different treatment options. The degree of functional impairment that TS generates is also considered, namely: 1-pain, 2-anguish, 3-social shame or 4-interference in activities of daily living. In those patients with tics and functional impairment, behavioral and/or pharmacological therapies can be used. The AAN recommends advising TS patients and their families regarding the natural history of the disease, thus being able to help in decision-making and in the acceptance of treatment. When establishing a treatment strategy, it should be remembered that comorbidities tend to compromise quality of life to a greater extent than tics [15].

Psychoeducation

It consists of the first step of the treatment. The patient, family, teachers or the workplace must be informed regarding the nature of the disease and/or the probable associated comorbidities. This action, added to the outpatient follow-up of the patient and her family, is effective and sometimes makes unnecessary specific therapy for tics. When this is insufficient, the decision to initiate another treatment strategy should be based on the following criteria: 1-tics can affect the social bond (isolation or bullying), 2-can generate emotional problems (reactive depression), 3-produce functional interference (work or study) and 4-generate disagreement (pain or injury). The first three criteria are subjective, while the fourth is objective and involves the physical damage that results from the tics (cervical myelopathy or spontaneous dissection of the neck vessels). Self-mutilations can endanger the life of the patient (fractures, burns or lacerations). The main characteristics of tics and comorbidities associated with patients or close relatives should be discussed, as well as the "involuntariness" of the appearance of tic and its voluntary "suppressibility". The fluctuating nature (increase and decrease) over time and the role of stress and fatigue in moderating these fluctuations must be considered. Provide patients and their families with a clear understanding of the natural history and therapeutic options available for TS. Parents can be instructed about the effects of different emotional reactions on their children's tics and how the excessive emotional burden of family arguments can affect them. The tics impact on the social, academic or work aspects of the patient. Patients and their families should be encouraged to focus on the strengths of the patient as an individual. Parents should become aware of the dynamics of tics as a stigma and discriminatory attitudes created in the school environment. Families should be provided with the knowledge necessary to discuss their children's tics with their fellow students and teachers. Where necessary and feasible, psycho-education should be directed towards the school through focused meetings in order to prevent stigma and discrimination [16].

Pharmacotherapy

The European Society for the Study of TS (ESSTS) has established guidelines for the treatment of patients with TS, based on clinical trials, case series and case reports. There are differences in the general guidelines of pharmacological treatment, and the beneficial and adverse effects of each drug must be considered. The goal of drug therapy is to reduce the magnitude and frequency of tics. For this, tolerability and adherence to treatment must be adapted. The risk-benefit ratio that each therapy entails must be remembered and the real expectations of the indicated treatment must be analyzed together with the patient and her family. Despite pharmacological intervention, tics may continue to be present or appear alternately (exacerbations and remissions). Currently there is a wide range of drugs available that help reduce the different manifestations of TS, but many of these result in unexpected adverse effects. Consequently, any pharmacological intervention should be subject to a periodic evaluation that indicates the need to continue or discontinue it (Table 4) [17].

Drugs	Initial dose	Therapeutic dose
Haloperidol	0,25-0,5	1-4
Pimozide	0,5-1,0	2-8
Risperidone	0,25-0,5	1-3
Fluphenazine	05-1,0	1,5-10
Tiapride	50-100	150-500
Olanzapine	2,5-5,0	2,5-12,5
Sulpiride	100-200	200-1000
Aripiprazole	2,5-5	2,5-15
Clonidine	0,0025-0,05	0,1-0,3
Guanfacine	0,5-1,0	1-3
Botulinum toxin	30-300 UI/injection	
Tetrabenazine		25-150
Baclofen		40-60
Nicotine Patch		7-21

Table 4: *Pharmacological treatment of tics [36].*

Neuroleptic drugs

Starting in 1959, chlorpromazine was introduced as an effective drug in the treatment of patients with TS. Two years later, haloperidol is tested in patients with severe TS, responding satisfactorily. In a clinical trial carried out in a long series of patients with TS medicated with haloperidol, this drug proved to be highly effective; resulting in the first choice in the treatment of tics. More than half a century after the first report, typical antipsychotics and in the last two decades atypical antipsychotics, represent an effective drug in the treatment of tics [18]. These drugs act like DBRD, due to their affinity for the D2 receptor. Fluphenazine is the drug with the best profile regarding potential adverse effects, generally well tolerated by patients, at doses of 0.25 - 3 mg/d in children and 1.5 to 10 mg/d in adults. Another antipsychotic of choice is pimozide at doses of 2 to 8 mg/d in adults, although it requires ECG monitoring because it prolongs the Q-T interval. Atypical antipsychotics act by blocking 5-HT2A and 5-HT2C receptors and in general have less blocking effect on RD2s. Risperidone has been widely used and is considered the first choice in ST patients. It is prescribed in doses of 0.5 - 3 mg/d. Sedation and fatigue have been reported, which are usually transient and chronically develop a metabolic syndrome characterized by weight gain, hyperglycemia and dyslipidemia, not without cardiovascular risk. Risperidone depresses serotonergic and dopaminergic transmission and carries the risk of developing depression. Suppression should be done progressively over weeks or months to avoid rebound dyskinesias [19]. Aripiprazole is another drug with good results in the control of tics with special efficacy in patients with TS associated with OCD and with a better profile of adverse effects compared to other atypical neuroleptics. It acts as an RD2 antagonist, RD2 and 5HT1A partial agonist, and 5HT2A antagonist [20]. It has been used widely in the last decade [21]. Antipsychotic drugs should be reserved for patients with severe tics that are difficult to control, due to the adverse effects that can be observed in the acute phase (drowsiness), subacute (weight gain, prolongation of the Q-T interval) or chronic (involuntary movements). The adverse effects in chronic phase (tardive syndromes or Parkinsonism) in patients with TS under a chronic treatment regimen with antipsychotic drugs have been observed only exceptionally, unlike patients with psychosis, where these adverse effects affect 30% of patients. This may be due to the low doses and progressive titration of the neuroleptics prescribed in patients with TS or to greater synaptic plasticity that makes them resistant to adverse effects in the context of chronic treatment with DBRD. Careful monitoring should be carried out and the neuroleptic tapering or withdrawing gradually if the patient develops an adverse motor effect.

Non-neuroleptic drugs

Alpha-2 adrenergic agonists have been used in the last two decades and are the drug of first choice in mild cases, with clonidine and guanfacine being the most widely used. Although the results in the control of tics are variable and to a lesser extent than neuroleptics, both drugs are effective in patients with TS associated with various comorbidities such as ADHD [22]. Its prescription results in an improvement in tics and hyperactivity. Clonidine is administered in doses ranging between 0.025 - 0.3 mg/d in children and 0.025 - 0.6 mg/d in adults, in 3 daily doses. In those patients with difficulty in taking the drug orally, transdermal patches can be used, which can even be used in children. Alpha-2 adrenergic agonists activate presynaptic autoreceptors at the locus coeruleus level, decreasing the release of norepinephrine, and consequently possible adverse effects such as orthostatic hypotension, sedation, and bradycardia should be evaluated. Guanfacine stimulates central alpha-2 receptors by decreasing the sympathetic activity of the vasomotor center on the heart and blood vessels. Consequently, both drugs share similar adverse effects and can even prolong the Q-T interval. In the case of abrupt withdrawal of these drugs, rebound arterial hypertension can be generated, which should be done gradually. Benzodiazepines (clonazepam) have a poor response in reducing tics. Serotonin reuptake inhibitors (SIRS) are effective in reducing OCD or anxiety but do not act in the control of tics. The effect of two antiepileptic drugs (levetiracetam and topiramate) in the treatment of patients with TS has recently been reported, although the results are contradictory [23,24]. Other drugs of interest include those that interact on the cannabinoid system and GABA [25]. Baclofen, a GABA auto-receptor agonist, reduces the severity of motor and vocal tics [26]. A reduction in the magnitude of tics was observed using cannabinoid formulations such as dronabinol 2.5 - 5 mg 3/d, through its central nicotinic cholinergic effect, although this treatment carries a risk of chronic addiction [27]. THC (Delta 9-tetrahydrocannabinol) has been tested as an effective drug in the control of tics. Transdermal nicotine patches reduce tics by enhancing the effect of DBRDs [28]. Botulinum toxin has been tested in the treatment of motor and vocal tics limited to a specific region when these are potentially severe and lead to structural damage. Injection of botulinum toxin into the vocal cords can remit vocal tics. A decrease or disappearance of the premonitory sensation has been observed at the site

where the toxin is injected [29]. Ecopipam, an RD1 antagonist, has been shown to be effective in patients with TS, at doses of 50 mg/d in patients weighing less than 34 kg and 100 mg/d in patients weighing more than 34 kg. Future clinical trials are required to objectify its efficacy [30].

Vesicular monoamine transporter inhibitor drugs

Tetrabenazine (TBZ), a monoamine-depleting agent that includes dopamine and to a lesser extent norepinephrine and serotonin, has been shown to be an effective drug in controlling hyperkinetic involuntary movements, including tics [31]. Its effect is restricted at the central nervous system (CNS), unlike reserpine, another monoamine-depleting drug with action at the central and peripheral level, which was formerly used as an antihypertensive drug. TBZ inhibits the vesicular monoamine transporter (VMAT) and consequently inhibits the reuptake of monoamines within the presynaptic vesicles, these remaining in the cytoplasm, where they are degraded by the enzyme monoamine oxidase (MAO) (Figure 4). Two types of VMAT are known, namely: type 1 located at the peripheral level and encoded by the 8p21.3 gene and VMAT type 2, located at the central level and encoded by the 10q25 gene [32]. TBZ has a higher affinity for VMAT2 to which it binds reversibly. Reserpine, on the other hand, binds irreversibly to peripheral VMAT1 and central VMAT2. This pharmacodynamic difference exempts TBZ from cardiovascular and gastrointestinal adverse effects compared to reserpine. TBZ preferentially depletes presynaptic dopamine. It is a drug that potentially does not induce tardive syndromes or weight gain, unlike antipsychotic drugs with neuroleptic effect, frankly reducing tics in patients with TS, even reaching its complete abolition [33]. Adverse effects such as sedation and dose-dependent depression have been reported and it is contraindicated in patients with TS and depression as comorbidity. TBZ exerts its effect for 12 hours, consequently requiring two doses/d. Treatment is started with a dose of 25 mg/d and then 50 mg/d of maintenance in adults and initial doses of 12.5 mg/d and then 25 mg/d of maintenance in adolescents and children [34].

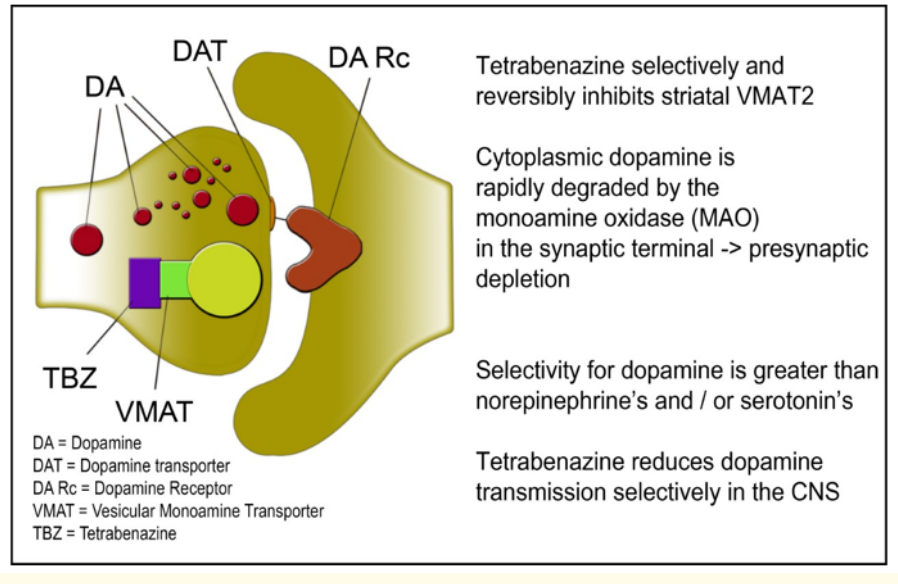

Figure 4: *Mechanism of action of TBZ. Dopaminergic transmission model [35].*

Psychotherapy

All cognitive-behavioral strategies are based on the negative association between a feeling of discomfort (need to do) and the performance of the tic that will alleviate the discomfort. Two types of cognitive-behavioral therapy were developed in TS: 1-Habit reversal training (HRT) in order to prohibit tic realization by habit reversal and 2-Exposure response prevention (ERP) prohibiting tic realization by suppressing negative reinforcement. HRT was introduced as a treatment option in patients with TS [37]. It is a multicomponent

therapy which can be divided into five phases: 1-description of the tics, 2-tic awareness (self management), 3-the principal phase called habit reversal, 4-motivational reinforcement and psychosocial support, 5-generalization; being phases 2 and 3 the most important. The underlying physiological mechanism is unknown although it can be attributed to a disruption between stimulus and response. Eight to fifteen hour-long sessions are required, spaced one week apart. ERP is recommended in patients with a limited number of tics and the clear presence of the premonitory sensation. Two clinical trials carried out in adults and children with TS, demonstrating a better clinical response in children compared to adults. In these studies, an improvement of 31% in children and 26% in adults was observed in the YGTSS scale, showing a stable clinical response 6 months after completing treatment [38,39]. ERP forces patients to gradually accept premonitory sensations while retaining the tics. The underlying mechanism is therefore extinction. In a study carried out in patients with TS, comparing HRT and ERP, an improvement was observed in 58% of the patients treated with ERP vs 28% with HRT. The advantage of ERP is that it allows treating all tics simultaneously [40].

Comorbidities and TS ADHD

When the severity of the ADHD associated with TS does not resolve with psychotherapy, it can compromise the interpersonal, school, social and/or work relationship, consequently requiring pharmacological therapy. There is a high prevalence of ADHD in the pediatric population in general (4 million children with ADHD in the USA), a situation that makes primary schooling difficult for these children compared to those without ADHD. Consequently, those children with medicated ADHD improve their school performance. Drugs that stimulate the CNS (methylphenidate, dexmethylphenidate, methamphetamine, dextroamphetamine, levamfetamine and pemoline) have been tested in various formulations (tablets, oral solutions and transdermal patches) that have demonstrated their beneficial effect in this type of patients. These drugs are characterized by a rapid onset of action but a very short half-life, for which reason extended release systems have been developed in an attempt to prolong the therapeutic effect. Various adverse effects have been observed (nervousness, irritability, anorexia, abdominal pain and insomnia). The effect of drug treatment can be quantified through the ADHD-RS-IV scale. However, CNS stimulants can exacerbate or precipitate tics, so the lowest effective dose should be prescribed [41]. If one CNS-stimulating drug is not tolerated, another can be tried. The therapeutic effect of CNS stimulants in ADHD patients is achieved through their effect on dopaminergic and/or serotonergic transmission. Presynaptic alpha 2 adrenergic agonists and tricyclic antidepressants are another therapeutic option in patients who cannot tolerate CNS stimulant drugs. Clonidine lowers plasma levels of norepinephrine and improves symptoms of ADHD associated with impulse control disorders (ICD). It is available as oral tablets or transdermal patches that must be replenished weekly. Clonidine and guanfacine are useful in the management of patients with ADHD associated with ICD and oppositional defiant behaviors (ODB). As adverse effects, dry mouth, sedation and orthostatic hypotension are described. Selegiline (MAO B inhibitor), has been effective in controlling ADHD without exacerbation of tics [42]. Atomoxetine has been approved by the FDA for the treatment of ADHD in adults and children. It has a half-life of 5 hours, begins with a dose of 25 mg/d and is titrated up to 50 mg x 2/d [43]. This drug has been tested in patients with TS and ADHD, with improvement in ADHD symptoms being observed, although patients may develop changes in heart rate, decreased weight, and appetite [44].

OCD

Cognitive behavioral therapy added to pharmacological therapy constitutes the treatment of choice in patients with TS and OCD [45]. Cognitive behavioral therapy associated with an antidepressant drug (SIRS) achieves an excellent clinical response in children and adolescents with OCD [46]. Fluoxetine, clomipramine and sertraline, especially the latter, are included within the spectrum of SIRS drugs that are effective in the treatment of patients with TS and OCD. Several clinical trials establish that fluoxetine and sertraline in the long term are the best tolerated by patients. It is estimated that 25% of patients do not respond to the SIRS scheme as monotherapy and can be associated with other drugs (clonazepam, lithium or even neuroleptics). There is the possibility of developing a serotonin syndrome characterized by confusion, hypomania, agitation, diarrhea, sweating, and fever [47].

Other behavioral problems

Patients with TS can manifest other behavioral alterations associated with ADHD and OCD. Treatment of ADHD usually improves the ICD. In patients with TS, sudden attacks of rage that respond to paroxetine have been observed [48]. In the future, treatment strategies must be developed; limited not only to the control of symptoms, but that can modify the biological course of the disease [49].

Surgical treatment

Various lesional neurosurgeries were tried, which resulted in serious sequelae and consequently, they have been discontinued. Deep brain stimulation (DBS) surgery is another neurosurgical treatment option. The Tourette Syndrome Association and the European Society for the Study of Tourette Syndrome have established criteria for the selection of patients who are candidates for DBS. This constitutes a programmable and reversible modality of neuromodulation on associative or limbic areas at the level of the nuclei of the base. DBS surgery at the level of the striatum, thalamus or globe pallus in patients with TS has shown a clear decrease in the severity of tics. Before considering a patient with TS as a candidate for DBS surgery, the diagnosis must be confirmed using strict criteria, as well as addressing all psychiatric comorbidities and non-motor manifestations. The patient must be evaluated by a multidisciplinary team, which includes different specialties: neurology, neurosurgery, psychiatry and neuropsychology. Potential candidates must be evaluated independently by each of the team members, taking into account the inclusion and exclusion criteria. Subsequently, the real scope, benefits, risks and proposed surgical approach should be discussed together (Table 5).

Inclusion Criteria	Exclusion Criteria
1. DSM-V Diagnosis of TS by an expert clinician. 2. Age is not a strict criterion. Participation of the ethics committee for cases involving persons less than 18 years of age and for cases considered "urgent". 3. Severity of tics: YGTSS> 35/50. 4. Tics are the leading cause of disability. 5. Tics are refractory to conservative treatment (failed trials with at least three different clases of drugs, including CBIT). 6. Psychiatric, medical or neurological comorbidities treated and stable for 6 months. 7. Stable and containing psychosocial environment. 8. Demonstrated ability to meet the prescribed treatments 9. The neuropsychological profile of the patient and family indicates that the candidate can tolerate surgery, postoperative control to the possibility of complications.	1. Active suicidal or homicidal ideation for 6 months. 2. Active substance abuse or recent abuse. 3. Examination by MRI of the brain demonstrates the existence of structural lesions. 4. Psychiatric, medical or neurological comorbidities that Increase the risk of the procedure and/or post-operative follow-up of DBS. 5. Fictional disorder or psychogenic tics.

Table 5: *Inclusion/exclusion criteria for patients who are candidates for DBS surgery.*

Surgical targets

Thalamus

Visser-Vandewalle., *et al*. (1999) published the first case of DBS surgery in the thalamus for the treatment of TS. The authors postulate that stimulation of the nucleus ventralis oralis internis (Voi) would lead to a decrease in motor and vocal tics by inhibiting projections towards the facial representation of the pre-motor and motor cortex. Stimulation of the intralaminar nuclei of the thalamus would reduce the activity of the dorsal motor-sensory regions of the striatum, while stimulation of the thalamic nuclei of the midline would reduce the activity of the ventral striatum. The initial surgical target was located 5 mm lateral to the line of the anterior white commissure (AC) and posterior white commissure (PC), 4 mm posterior to the midpoint of the commissure, and at the level of the AC-PC plane, approaching

the median center nucleus-periventricularis substance-internal ventro-oralis nucleus (CM-Spv-Voi). Intra-operative stimulation was performed with a Radionics probe with a 2 mm exposed tip, using a frequency of 100 Hz and a pulse width of 200 ms; a pleasant sensation reported by the patient supported proper electrode position. During the initial follow-up of 3 patients implanted with this technique, the authors report a 90% decrease in the frequency of tics at 5 years of follow-up in patient 1, a decrease of 72.2% at one year of follow-up in patient 2 and reduction of 82.6% at 8 months of follow-up in patient 3. The authors shared the long-term follow-up of patient 1 and patient 3. At 10 years of follow-up, patient 1 maintained a reduction in the frequency of tics of 92.6%. At 6 years of follow-up, patient 3 maintained a significant benefit with a 78% improvement from baseline [50]. Maciunas., *et al*. (2007) conducted a blind trial of thalamic stimulation for ST in 5 adult patients. The authors followed the model of Visser-Vandewalle and chose the same stereotactic target to stimulate the anterior extension of the CM-Pf complex. Intra-operative micro electrode recording (MER) was used during the implantation of the DBS electrodes and intra-operative stimulation through the same DBS electrode. During the blind randomization phase of the study, patients were evaluated in four states: 1- both stimulators on, 2- left on-right off, 3-right on-left off and 4- both off, for 1 week each. This was followed by an open-label evaluation with a 3-month follow-up. Clinical improvement based on the modified Rush video-based rating scale was 4.2 points during the randomized power-on state, 5.4 points at the beginning of the open-label period, and 2.6 points at 3-month follow-up. Unilateral DBS showed no clinical benefit. Three of the 5 patients improved at all times assessed using the modified Rush video-based rating scale or simple tic counting [51]. Bajwa., *et al*. (2007) report on an implanted patient with the target described by Visser-Vandewalle., *et al*. The patient was implanted under general anesthesia and at baseline, the total tic score on the Yale Global Tic Severity Scale (YGTSS) was 33 and the Yale Brown Obsessive Compulsive Scale (YBOCS) score was 29. At 24-month follow-up, the YGTSS score decreased by 66% to 12, and the YBOCS score decreased to less than 10 [52]. Servello., *et al*. (2008) reported their experience with DBS of the thalamus in patients with TS. The surgical target for all patients in their series was the anterior nucleus of the CM-Pf-ventralis oralis complex. The stereotactic coordinates of its target were determined from the Schaltenbrand-Wahren atlas. The target used was similar to that chosen by Visser-Vandewalle. The cortico-striatum-pale-thalamic circuit was extensively modulated. The patients were operated on using intra-operative MER. Stimulation was performed using a frequency of 100 Hz, and a pulse width of 60 ms, and amplitude between 1 and 5 mA. Intra-operative stimulation determined the optimal trajectory to locate the DBS electrode [53]. Porta., *et al*. performed thalamic DBS in 18 patients with TS and reported the results of the 2 years clinical follow-up. During the follow-up period, 2 patients no longer wanted to have the pulse generator (IPG); one patient had to be re-operated with a GPi implant for unspecified reasons. In the remaining 15 patients, the mean baseline YGTSS score of 76 improved significantly to 36 after two years of follow-up [54]. Ackermans., *et al*. (2011), presented a series of 6 patients who participated in a prospective, randomized, double-blind study of DBS directed at the CM-Spv-Voi complex. Its coordinates were those described by Visser-Vandewalle. Intra-operative MER was used and the test stimulation was performed at a frequency of 130 Hz and a pulse width of 60 ms and amplitude between 1 and 6 mA. In the postoperative period, a significant improvement was observed in the YGTSS in the state of active stimulation (IPG on) compared to the state of inactive stimulation (IPG off). The improvement in the YGTSS was maintained at one year of follow-up, with an improvement of 49% [55]. Savica., *et al*. (2012) reported the results of the one-year follow-up of 3 patients operated on for DBS in the CM-Pf complex. Its surgical target was 5 mm lateral and 8 mm posterior to the midpoint of the commissure, which is a more posterior target than that suggested by Visser-Vandewalle. A mean reduction in YGTSS of 70% was observed [56].

Globus Pallidus

In the treatment of TS, the DBS of the following targets has been tested: 1-posteroventral GPi, 2-ventromedial GPi and 3-GP externus. Van der Linden., *et al*. (2002) publish the first report on the efficacy of pallidal stimulation in a patient with TS. The patient was implanted with electrodes in the posteroventral GPi and in the thalamus as described by Visser-Vandewalle. The coordinates of the GPi were 21.5 mm lateral, 4 mm anterior and 3 mm below the AC-PC plane. The patient reduced tics by 80% with thalamic stimulation and 95% with pallidal stimulation. Consequently, the pallidal electrodes were connected to the pulse generator (IPG). At 6-month follow-up, the benefit of pallid stimulation was maintained [57]. Diederich., *et al*. (2005) reported the result of pallid DBS (posteroventral Gpi) in a 27-year-old patient (target: 17 mm lateral, 4 mm anterior, and 5 mm below the midpoint of the commissure) under general anesthesia. A progressive decrease in the frequency of tics of 73% was observed after 14 months of follow-up. This improvement involved associated comorbidities (depression and anxiety) [58]. Dehning., *et al*. (2008) performed DBS in both posteroventral GPi (3 mm anterior to the mid commissure

point, 20 mm lateral and 4 mm below the AC-PC plane), in a 44-year-old patient with TS. After one year of follow-up, the YGTSS score decreased significantly from 83 (pre-operative) to 10 (post-operative), with no neurocognitive changes being observed [59]. The benefit was stable after 4 years of follow-up [60].

Welter., *et al*. (2008) in another subsequent study compared the efficacy of the CM-Pf complex DBS with the ventromedial GPi DBS in 3 patients with TS refractory to medical treatment [61]. Ackermans., *et al*. (2006) target the ventromedial GPi to more selectively target the limbic and associative fibers of the GPi. The mean coordinates for the ventromedial GPi were 20 mm. anterior to the PC, 12 mm lateral to the midline, and 3 mm ventral to the AC-PC plane. With GPi stimulation, an improvement in the YGTSS score of 65, 96 and 74% respectively was observed in patients 1, 2 and 3. The stimulation of the CM Pf complex led to a reduction of the YGTSS score by 64, 30 and 40% respectively in patients 1, 2 and 3. Simultaneous pallidal and thalamic stimulation did not improve the clinical result, with a reduction in the YGTSS score of 60, 43 and 76%. However, it is interesting that in the last follow-up (60 and 20 months), 2 of the 3 patients used simultaneous pallidal and thalamic stimulation [62]. Filho., *et al*. (2007) reported their results, after stimulating both GPe in patients with TS. The following stereotactic coordinates were used: 3 mm posterior and superior to the AC and 20 mm lateral to the AC. A double-blind evaluation revealed an 81% reduction in tic scores and an 84% reduction in comorbidities (OCD) at 23 months of follow-up [63]. Martinez-Fernandez., *et al*. (2011) reported their experience in 5 patients undergoing 6 surgical implants in the GPi for TS. Three patients were implanted in the posteroventral GPi and 2 patients were implanted in the anteromedial GPi. The anatomical targeting of the anteromedial GPi was based on MR images (proton density sequences), the objective being the stimulation of the limbic GPi as used by Welter., *et al*. At one year of follow-up, the 5 implanted patients showed an improvement in the mean YGTSS score, which decreased from 77 to 54, and the mean YBOCS score, which decreased from 16 to 10. This improvement remained stable in the distant postoperative period. The authors conclude that antero-medial GPi stimulation was most effective throughout the evaluation period [64].

Anterior arm of the internal capsule/nucleus accumbens

DBS of the anterior arm of the internal capsule has become a surgical treatment strategy for OCD refractory to pharmacological and cognitive-behavioral therapies. Due to the frequent association of TS and OCD, case reports have been published using this surgical target [65]. Flaherty., *et al*. (2005) report on a patient with TS operated on for DBS in the region of the anterior arm of the internal capsule. The chosen target was located 12 mm lateral to the AC, 7 mm below the AC and at the midpoint of the anterior branch of the internal capsule. After 18 months of follow-up, the patient experienced a 23% improvement in global severity on the YGTSS [66]. The patient did not experience complete resolution of his tics. When a hardware malfunction occurred, the thalamic target was reviewed with a 46% decrease in global severity in the YGTSS [67]. Kuhn., *et al*. (2007) report a patient with TS and OCD. The following stereotactic coordinates were used: 2.5 mm rostral to the AC, 6.5 mm lateral to the AC, and 4.5 mm ventral to the AC. Post-operative MRI images revealed that contacts 0 and 1 were located within the nucleus accumbens and contacts 2 and 3 were located within the anterior arm of the internal capsule. At 30 months of follow-up, the YGTSS score decreased from 90 to 53 (pre-postoperative) while the YBOCS score decreased from 25 to 12 [68]. Neuner., *et al*. (2009), similarly report the 36-month follow-up in a patient with TS and OCD. The target chosen was the nucleus accumbens and the anterior arm of the internal capsule. The same stereotactic objective was used (2.5 mm rostral to the AC, 6.5 mm lateral and 4.5 mm ventral to the AC). Post-operative MRI images revealed that the two distal contacts were located with the nucleus accumbens and the two proximal contacts in the region of the anterior arm of the internal capsule. At 36 months of follow-up, the YGTSS score decreased from 100 (pre-surgical) to 56 (post-surgical). Likewise, a significant reduction in the YBOCS score from 32 to 15 was observed in this follow-up period [69]. Burdick., *et al*. (2010) reported a patient with mild TS and severe OCD who received DBS in the anterior arm of the internal capsule and the nucleus accumbens. The authors note that, although the patient felt an improvement in the magnitude of vocal and motor tics, objective evaluation did not reveal a significant improvement [70]. Galati., *et al*. (2018) report on a patient with TS with self-harm behaviors, anxiety, severe depression and OCD, who underwent bilateral DBS surgery, combining antero-medial Gpi and Gpe. A 36% improvement was observed in motor tics and 20% in vocal tics. The patient showed an improvement in his comorbidities, going from severe to mild depression during the one-year follow-up and currently ongoing (Figure 5 and 6) [71].

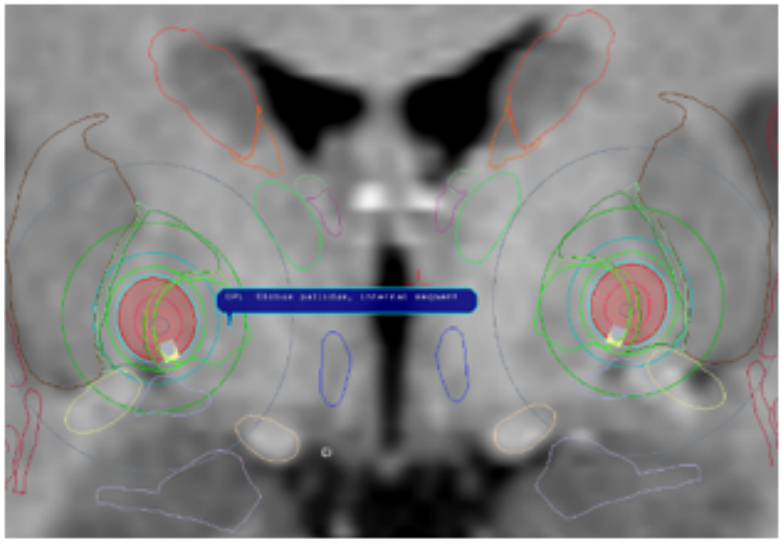

Figure 5: *Coronal. Gpi-Gpe activation- Simulation.*

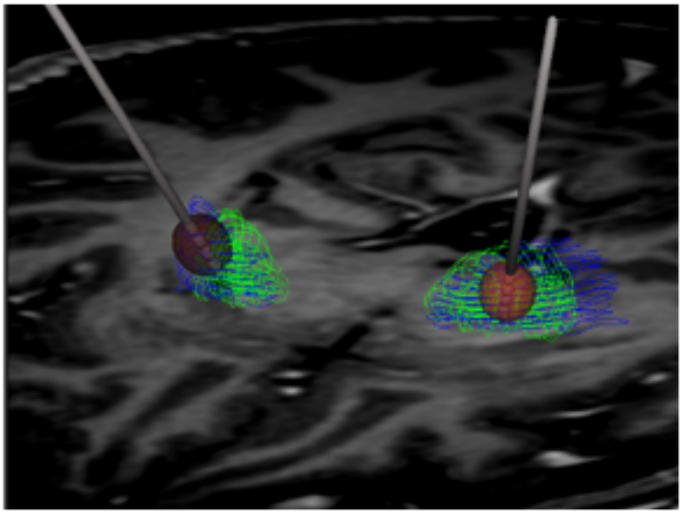

Figure 6: *Axial 3D Gpi-Gpe activation- Stimulation.*

Choice of target

Establishing the optimal target for DBS has been controversial, due to the precise lack of knowledge of the pathophysiology of TS. However, it should be considered that the targets described have a high interconnectivity. The targets most used at present have been the internal globe pallidus and the thalamus, although it is known that these trajectories are also located in the Gpe. For this reason, the authors have presented a case Gpi antero-medial-Gpe that was operated on for DBS in 2018 and in the course of postoperative evaluation with good clinical response. The ultimate goal of the DBS procedure is the re-insertion of the patient in the family, social and work environ-

ment. Consequently, it is crucial to reduce the magnitude of tics, as well as to improve the associated comorbidities (ADHD, OCD, anxiety, or depression), improving activities of daily living and in consequence the quality of life of the patient.

Recommendations

Different treatment strategies should be considered in front of a patient with TS: 1-mild tics do not require treatment, 2-moderate tics can benefit from psycho-education followed by cognitive behavioral therapy; If necessary, a neuroleptic drug (atypical antipsychotic) can be introduced, isolated 3-severe tics can be tested for local application of botulinum toxin, 4-severe tics, evaluate the administration of atypical or typical antipsychotics, associated with alpha 2 adrenergic agonist drugs (according to the comorbidity associated with TS) and/or TBZ. 5-refractory tics to the various treatment schemes tested, consider the option of DBS surgery [72,73].

Coronavirus and Tourette syndrome

According to recent statements by the Tourette Association of America (TAA), the coronavirus pandemic has made the 2020 - 2021 period one of the most challenging in the history of the 21st century. Family members and patients with TS have had to face great challenges related to quarantine, the remote teaching modality, social distancing, isolation, anxiety and depression. After the discovery and development of vaccines for the different strains of COVID 19 and their implementation in the population from vaccination campaigns, the hope arises that the pandemic will come to an end and facilitates the return to a new normal. TS patients and their families inquire as to what exactly these vaccines are, if they are safe for TS patients and if they can exacerbate tics. The speed with which the vaccines were developed should be noted. This new class of RNA vaccines marks a milestone in medical history, and in fact the vaccines were found to be highly effective in preventing COVID-19. Although these RNA vaccines prevent disease, it is possible for a vaccinated individual to carry the virus and infect others, so surveillance and social distancing should continue. While isolated adverse effects have been reported in those who received the COVID-19 vaccines, the dangers of severe COVID-19 illness from not being vaccinated far outweigh the minor risks from the vaccine. The urgent need to have vaccines for COVID 19, meant that when designing clinical trials, they did not include young people and, consequently, only considered the population over 16 years of age. There is a large population of TS patients who are below that age limit and it may really seem worrisome, so vaccines will need to be tried in younger people and even children. Although at present there are no specific data on COVID and TS vaccines, there is no reason to believe that in the long term the vaccine will exacerbate tics or that patients affected by TS will stop receiving the COVID-19 vaccine, except allergy to the components of the vaccine or in immunocompromised patients [74].

Ethical Considerations

The various cognitive-behavioral and/or pharmacological treatment options make possible a remission to a certain degree of the picture of motor and/or vocal tics, as well as stabilize the different associated psychiatric comorbidities. The patient and her family environment witness a true miracle when they note a notable improvement in the patient's quality of life. The desired effects must be considered, but also the adverse effects of the different drugs, which limit their prescription in a child, adolescent or even an adult, such as typical or atypical antipsychotics. An initial pharmacological honeymoon can be interrupted by the appearance of metabolic disorders or motor complications during the course of treatment. Motor complications can remit after the withdrawal of the drug with neuroleptic effect or persist irreversibly (tardive syndromes). The introduction of DBS as a treatment option in refractory patients has allowed them to experience a second bio-electric honeymoon, which significantly improves the motor (tics) and behavioral (psychiatric comorbidities) clinical picture. After DBS surgery, both treatments coexist in the patient and the neurologist must know how to balance the therapeutic effect of pharmacological treatment and DBS, to obtain the maximum benefit. However, only some patients access this last type of treatment. This raises several ethical questions regarding being able to guarantee access to DBS for all those patients who could benefit. The high cost of the devices to be implanted limits their routine use. Most health professionals observe certain ethical principles in their practice, regarding who can and should receive this type of treatment [75].

Discussion

Chronic tic disorders are clinically heterogeneous. The severity and time course of the tics and the comorbidity profile are the main determinants of this heterogeneity. Tics begin in infancy and usually subside within a year (transient infancy tics). In those children who develop TS, the tics tend to worsen at puberty, although they usually remit before 18 years of age. Twenty percent of patients with TS persist with severe tics during adult life, this being a relevant fact. The prognosis of the disease should be considered together with the patient and her family. A comprehensive evaluation is crucial when choosing the best treatment strategy [76].

Conclusion

Future clinical trials should answer several questions: 1-Role of cognitive behavioral therapy associated with pharmacological therapy 2-Pharmacological strategies that combine drugs with different mechanisms of action 3-Implementation of DBS surgery in refractory cases 4-Effects of the various treatment strategies on the patient's quality of life.

Dedication

Dedicated to our loving families, in recognition of their understanding and support.

In Memory

In memory of all the health workers, who lost their lives caring for patients during the COVID 19 pandemic.

Comment

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