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Klinikinis atvejis / Case Report

Treatment Challenges in a Tourette Syndrome Patient with Self-Injurious Behaviour: Case Report and Literature Review

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Summary. *Introduction.* Tourette syndrome is known as a combined vocal and multiple motor tic disorder. It is a chronic complex neuropsychiatric disorder characterised by the onset of symptoms in early childhood and the presence of multiple motor tics and one or more vocal tics. In most cases, the symptoms resolve or become less severe in early adulthood. Nevertheless, there are some cases where the syndrome does not follow its typical clinical course.

Case report. We present a 28-year-old patient with Tourette syndrome. The patient was hospitalized for complex motor and vocal tics, as well as tics resulting in self-harm. First tics began at the age of twelve and gradually intensified. The patient was diagnosed with Tourette syndrome at thirteen and has been taking *Haloperidol* 5 mg 3 times a day and *Trihexyphenidyl* 2 mg 3 times a day for the past 15 years. His condition worsened 6 months ago with increased tics, self-harm, insomnia, social withdrawal, and weight loss. In the hospital, *Haloperidol* was gradually replaced with 20 mg of *Aripiprazole* daily. The patient underwent twenty-six transcranial magnetic stimulation procedures. During hospitalization, insomnia was resolved, whereas motor tics and self-harm decreased.

Discussion. The pathogenesis of Tourette syndrome emphasizes the dysfunction of neuronal networks in the basal ganglia. It leads to impaired inhibition in the sensorimotor cortex of the brain, which results in motor and vocal tics. Their characteristics are individual to each patient. The course of illness and the severity of symptoms are influenced by various stressors, intense emotional experiences, and environmental factors. Tourette syndrome is commonly treated with psychotherapy, pharmacological treatment, or a combination of these methods. The case we present shows that the conventional treatment methods are not always effective, and that the clinical course of Tourette syndrome may deviate from the usual expressions of the syndrome.

Key words: Tourette syndrome, self-injurious behaviour, aripiprazole, transcranial magnetic stimulation

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Tureto sindromo, pasireiškiančio savižala, gydymo sunkumai – klinikinio atvejo aprašymas ir literatūros apžvalga

Santrauka. *Įvadas*. Tureto sindromas yra žinomas kaip kombinuotas vokalinių ir daugybinių motorinių tikų sutrikimas. Tai lėtinis kompleksinis neuropsichiatrinis sutrikimas, kuriam yra būdingas pirmųjų simptomų pasireiškimas ankstyvoje vaikystėje bei daugybiniai motoriniai ir vienas ar daugiau vokalinių tikų. Daugumai pacientų pasiekus suaugusiojo amžių simptomai sušvelnėja – tikų pasitaiko rečiau ar visai nebepasitaiko. Nepaisant to, yra atvejų, kai ši liga nesilaiko būdingos klinikinės eigos, o įprasti gydymo metodai simptomų nesuvaldo.

Atvejo aprašymas. Pristatome klinikinį 28-erių metų paciento, kuriam yra Tureto sindromas, atvejį. Pacientas buvo hospitalizuotas dėl kompleksinių motorinių ir vokalinių tikų bei savižalą sukeliančių tikų. Tikai jam prasidėjo 12-os metų, palaipsniui tikų kiekis ir intensyvumas didėjo. 13-os metų diagnozuotas Tureto sindromas, nuo to laiko pacientas gydytas haloperidoliu 5 mg 3 k./d. ir triheksifenidiliu 2 mg 3 k./d. Prieš pusę metų tikai paūmėjo, atsirado pirmieji savižalą sukeliantys motoriniai tikai – nosies spaudimas, pacientas patyrė nemigą, socialiai atsiribojo, sumažėjo jo kūno masė. Kelios dienos iki hospitalizacijos atsirado naujas tikas – lūpos kramtymo. Ligoninėje haloperidolis palaipsniui nutrauktas, paskirtas aripiprazolis palaipsniui didinant dozę iki 20 mg/d. Taip pat taikytos 26 transkranijinės magnetinės stimuliacijos procedūros. Hospitalizacijos metu išnyko nemiga, sumažėjo motorinių ir savižalą sukeliančių tikų intensyvumas ir kiekis.

Aptarimas. Tureto sindromo patogenezė apima pamatinių branduolių neuronų tinklų disfunkciją, dėl kurios sutrinka slopinimas sensomotorinėje galvos smegenų žievėje. Dėl slopinimo disfunkcijos ištinka motoriniai bei vokaliniai tikai, kurių išraiška ir charakteristikos kiekvienam pacientui yra skirtingos. Ligos eigai ir simptomų stiprumui įtakos turi patiriami intensyvūs emociniai išgyvenimai, įvairūs stresogeniniai veiksniai. Tureto sindromas gydomas taikant psichoterapiją, farmakologinį gydymą ar šių metodų derinius. Mūsų pristatomas atvejis rodo, kad įprasti gydymo metodai ne visada yra veiksmingi, o klinikinė Tureto sindromo eiga gali nukrypti nuo įprastos, dažniausiai pasitaikančios Tureto sindromo išraiškos.
Raktažodžiai: Tureto sindromas, savižala, aripiprazolis, transkranijinė magnetinė stimuliacija.

Introduction

Tourette syndrome is a neuropsychiatric disorder manifesting in early childhood. It is characterised by multiple motor tics and one or more vocal tics. It was first described by the French physician Georges Gilles de la Tourette in 1885. Tics are short, repetitive, involuntary movements and/or sounds, such as facial grimaces, shoulder jerks or grunts [1]. Tics are often preceded by a premonitory urge to perform them. The manifestation of motor or vocal tics varies widely, ranging from rapid and rhythmless movements and sounds to voluntary-like behaviour, words, or phrases. In patients with Tourette syndrome, symptoms are usually most intense at the age of 10–12 years, whereas, in adolescence, symptoms often improve and become infrequent, of low intensity, and do not require treatment, or disappear altogether [2]. Intense and disabling Tourette syndrome symptoms, and resistance to treatment are quite rare, especially in adulthood [3].

Case Report

A 28-year-old patient was admitted to Republican Vilnius Psychiatric Hospital due to frequent motor and vocal tics, as well as self-injurious behaviour.

The patient was the sixth child in a family of eight children. According to the patient, his birth was complicated. Early psychomotor development was normal; however, the patient cried a lot during infancy. The patient did not attend kindergarten and was brought up by his mother. He started school at the age of seven and finished at the age of eighteen. He did well at school, his grade average was 8 out of 10 (roughly equivalent to B+/B). The first tics started at the age

of twelve, manifesting as occasional involuntary blinking. Gradually, the blinking increased in frequency, and new tics, such as grunting, twisting the neck, tapping the ground with the foot, shouting, and spitting emerged. At that time, the patient's family did not understand his tics or why such behaviour would be occurring. They would become irritated and urge the patient to control himself. At the age of thirteen, the symptoms intensified, thus worrying the patient's family, and prompting them to go to the Emergency Department of Šiauliai Hospital. The patient was then admitted to Šiauliai Hospital for 2 weeks at the Woman and Child Clinic, Neurology Department. The patient was diagnosed with Tourette syndrome. *Haloperidol* 5 mg 3 times a day was prescribed. Following the discharge from the hospital, the patient developed cervical dystonia. The patient's neck was tense, turned to one side, painful. The patient returned to the Emergency Department of Šiauliai Hospital. *Trihexyphenidyl* was administered, and the symptoms subsided within 20 minutes. Since then, for about 15 years, he has been taking Haloperidol 5 mg 3 times a day and *Trihexyphenidyl* 2 mg 3 times a day regularly. For some time, the treatment was effective, thus reducing the intensity of tics. However, the medication has been ineffective for the last 2–3 years.

At school, due to intense tics, the patient briefly experienced bullying and had problems with writing and staying still in class. However, despite these difficulties, he graduated. After graduation, he attended vocational training for several months, frequently changed jobs and lived in several different cities. After a couple of years, the tics subsided. The patient found a long-term job, socialised with other people, and found a girlfriend. A year later, the romantic relationship ended, causing the patient to undergo emotional distress. This resulted in an increased frequency and intensity of tics, hindering the patient's ability to work. At the age of twenty-two, the patient was hospitalised at Vilnius University Hospital Santaros Klinikos. *Haloperidol* was changed to *Risperidone* up to 3 mg a day. However, the patient was on the medication for less than 2 months, as he experienced drying of the mouth and did not feel any reduction in tics. *Risperidone* was discontinued, and *Haloperidol* 15 mg a day and *Trihexyphenidyl* 6 mg a day were restarted. The same year, he also attended the Day Stay Unit at the Vilnius City Mental Health Centre. There, he received psychological counselling and art therapy. However, the patient did not notice any positive effects on the intensity and frequency of the tics. Later, the patient returned to his hometown where he is currently living with his parents. The patient frequently volunteers, engages in social activities, and helps organise events in his city.

Half a year ago, the patient's father was diagnosed with liver cancer. The patient was close to his father, thus the news of the diagnosis caused emotional distress to the patient. The next day, the patient started to exhibit self-injurious behaviour – pressing and rubbing on his nose. The patient experienced motor tics during which he repeatedly pressed on the nose with his finger or palm of the hand. After some time, pressing on the nose resulted in a wound which later became a visible tear on the left ala of the nose. Over the past 6 months, the patient has experienced weight loss of 6 kg, exhibited social withdrawal, narrowed his interests, and faced challenges at work. These symptoms have intensified during the last month. Over the last 3 months, he has been experiencing insomnia. The patient cannot fall asleep for about 1–1.5 hours, wakes up about five times during the night, has difficulty falling back asleep, and frequently presses on his nose. His father's funeral took place 5 days before the hospitalisation. A couple of days later, the patient strongly bit his lip, initiating the start of a new reoccurring self-injurious behaviour – lip biting.

The patient denies any history of head injuries and/or psychiatric comorbidities. The patient infrequently consumes alcohol, has been smoking for 8 years one pack a day, and denies the use of any other psychoactive substances. The patient was asked to fill out the *Yale-Brown Obses-*

sive Compulsive Scale. During his childhood, the patient exhibited odd habits, such as frequent showering, discomfort with close face-to-face conversations, a fear of contracting illnesses, and a tendency to touch things multiple times. However, these symptoms are not currently present, and the patient did not indicate any recent compulsions or obsessions. Thus, the scale did not confirm the presence of obsessive-compulsive disorder (OCD) symptoms in the patient. The patient's father had a history of alcohol abuse when he was young. There were no documented mental illnesses in the family. The neurological examination showed no abnormalities except for frequent involuntary movements involving the entire body and head, with vocalizations. CT and EEG showed no clinically significant abnormalities. The patient shows no evidence of depression, psychosis, or suicidal thoughts. There was not enough clinical evidence to diagnose any other psychiatric syndrome, hence the patient is thought to have no other psychiatric or neurologic comorbidities.

Upon hospital admission, the inspection revealed a patch on the nose concealing a wound on the left nasal ala. Additionally, the right side of the lower lip was bitten, swollen, and scabbed. Conversation with the patient was constantly interrupted by frequent complex and simple motor and vocal tics. The tics observed included the patient leaning forward or sideways at the waist, turning his head and making a loud noise, grunting, hitting his thigh several times with his fist, pressing his nose with fingers or wrist, biting his lower lip, taping the floor with the foot, saying "Atsiprašau" (en. *I'm sorry/ I apologize*), and moving the paper with his hand while signing the document. Fine motor tics in the facial area such as blinking, rapid movements of the eyes, nose scrunching, and grimaces, were also observed. The patient finds the tics annoying and frequently swears after tics, he presses on his nose and bites the lip until he feels pain. The patient experiences tension, an unpleasant sensation prior to executing a tic, and engages in the tic to alleviate this discomfort. An attempt to suppress the tic results in the subsequent tic becoming stronger. The patient does not experience tics while asleep. Tics occur in rapid succession, with one tic frequently followed by another. Motor tics are often followed by vocal tics. Tic paroxysm lasts for about 10–15 seconds. The patient tends to press on his nose and bite his lip when thoughts of these tics arise. He presses his nose less when it is covered and bites his lip less when it is coated with ointment. The patient believes that the escalation of symptoms is connected to stress and negative events in life. For instance, the tics intensified in response to his father's cancer diagnosis, during conflicts with his family members, after a breakup with his girlfriend, and while experiencing bullying at school. Nevertheless, the patient is not fully aware of such a connection. Playing the guitar, singing, and taking shower reduce the tic intensity.

As *Haloperidol* was ineffective in treating the tics, it was decided to change medication to *Aripiprazole*. The *Aripiprazole* dose was increased from 3.75 mg a day to the therapeutic dose of 20 mg a day, while *Haloperidol* was gradually tapered off by overlay. *Quetiapine* 50 mg a day for insomnia and anxiety, and *Trihexyphenidyl* 2 mg day for preventing extrapyramidal effects were also prescribed.

During the first week of hospitalization, the patient's symptoms slowly improved. The patient fell asleep faster, woke up less often during the night, and felt well-rested during the day. The patient observed a decrease in the tic intensity, due to biting his lip less and touching his nose with reduced frequency and force. There was an increase in simple vocal tics and a decrease in complex motor tics (less bending at the waist and shouting). During complex tics, shouting was not as loud as previously. The patient pressed on his nose less frequently, but rubbed and touched the nose more often. Simple motor tics such as head turning, blinking, nose scrunching, blowing air through the teeth, and tapping the floor with the feet were more frequently observed than

complex motor tics. During the second week, the patient's condition worsened. He experienced a depressed mood, persistent thoughts about his father's death, and a notable increase in the intensity and frequency of tics.

Due to an insufficient therapeutic effect, transcranial magnetic stimulation (TMS) using continuous theta burst stimulation of premotor cortex area over the linea mediana (pre-supplementary motor area (pre-SMA)) was implemented. Before TMS, the patient was given the Yale Global Tic Severity Scale (YGTSS). This is a questionnaire assessing the number, frequency, and intensity of tics, and the impairment that these tics may have on the quality of life, social and domestic functioning. As the patient is fluent in English, the questionnaire was provided to him in English. During the 'worst ever' episode, on the day of hospitalization, the patient scored 80 out of 100 on the scale. Throughout the TMS procedures, the patient did not carry out tics and kept his head still. In total, the patient underwent 26 TMS procedures. At the end of the hospitalisation, the YGTSS questionnaire was repeated, and the patient scored 47/100. At the end of the hospitalization, following 4 weeks of treatment, the patient reported symptom relief, quicker sleep onset, no longer woke up during the night, and felt rested. Although paroxysms of tics persisted, they were comprised of fewer tics and were shorter in duration, lasting 2–3 seconds. Objectively, during the interview, the patient no longer repeated "Atsiprašau" (*Sorry*), did not turn his neck, press on his nose, lean forward, or shout. Occasionally, he stuttered, blinked, rubbed his nose, chewed his lip, or moved his hand while writing. Towards the end of the hospitalization, the patient was more distressed by vocal tics than motor tics. According to the patient, the number of vocal tics remained similar to that of the beginning of the hospitalisation, including grunting, mumbling, repeated utterances of "Atsiprašau", and occasional stuttering. The patient feels like his vocal tics disrupt fluent speech and communication, and he is concerned that these tics might be bothersome to others. According to the patient, the number of motor tics decreased significantly. Simple motor tics are predominant, such as opening his mouth, twisting lips to one side, and scrunching the nose. Additionally, the frequency of self-injurious behaviour decreased. The wound on the nose healed, but the tissue defect remains. The patient can refrain from pressing on his nose for approximately 1 hour. However, the lip scabs and swelling are still present, and the patient can avoid biting it for 15–20 minutes. As indicated in **Table 1** and **Table 2**, both the quantity and the intensity of motor tics decreased during the treatment period. However, the reduction in the quantity and intensity of vocal tics was less prominent

Table 1. Tics of the patient and their progression throughout the treatment course

Tics	'Worst ever' level at the start of hospitalization	At the end of hospitalization
Simple Motor Tics		
Eye blinking	✓	
Eye movements	✓	
Mouth movements	✓	✓
Nose movements	✓	✓
Facial grimace	✓	
Head jerks/movements	✓	
Arm movements	✓	
Hand movements	✓	✓
Leg, foot, or toe movements	✓	

Tics	'Worst ever' level at the start of hospitalization	At the end of hospitalization
Simple Vocal Tics		
Throat clearing	✓	✓
Shouting	✓	
Grunting	✓	✓
Blowing air through the mouth	✓	
Complex Motor Tics		
Facial movements or expressions	✓	
Mouth movements		✓
Head gestures or movements	✓	
Writing tics	✓	✓
Bending or gyrating	✓	
Self-abuse behaviour	✓	✓
Complex Vocal Tics		
Repetition of 'e…erm'	✓	
"Atsiprašau" (*Sorry*, uttered in Lithuanian)	✓	✓
"Sorry" (uttered in English)	✓	✓
Blocking	✓	✓

Table 2. Evaluation of tic intensity by using the YGTSS questionnaire and its progression throughout the course of the treatment

	Motor tics	Vocal tics	Impairment	Total score
'Worst ever' level at the start of hospitalization	25	15	40	80
At the end of hospitalization	13	14	20	47
Maximum score	25	25	50	100

Discussion

Tourette syndrome, also known as combined vocal and multiple motor tic disorder, is a complex neuropsychiatric disorder characterised by the onset of symptoms in early childhood and the presence of multiple motor tics and one or more vocal tics [4]. The prevalence of the syndrome in school-aged individuals (4–18 years) is 0.3–0.9%, whereas the prevalence in adults is significantly lower, with only about 0.002–0.08% of adults having a diagnosis of Tourette syndrome. Boys are about four times more likely to have Tourette syndrome. The first symptoms usually appear in early childhood (at 3–6 years of age), with motor tics preceding vocal tics. The intensity peaks at 10–12 years of age, and, by late adolescence, most cases improve [2]. The presented clinical case is unique in that the first symptoms of Tourette syndrome started late, at around 13 years of age, and the symptoms remained intense, even tending to worsen, and significantly impaired the quality of life in adulthood. Tourette syndrome is also characterised by comorbidity with certain psychiatric disorders, in particular obsessive-compulsive disorder (OCD) and attention deficit and hyperactivity disorder (ADHD), although the presented clinical case had no diagnosed co-morbidities [5, 6].

The most common motor tics are blinking, head, shoulder or trunk twisting or jerking, and facial grimacing, while vocal tics are most often accompanied by grunting, nose twitching and,

less frequently, repetition of a word or a phrase. The diagnosis of Tourette syndrome is based on ICD-10 criteria which include current or former multiple motor tics and vocal tics of one or more types, not necessarily occurring simultaneously, with the disorder worsening in adolescence and persisting into adulthood [4, 7].

Clinical Features

The main symptoms of Tourette syndrome are motor and vocal tics; however, the type, intensity, frequency, and complexity of the tics vary from patient to patient [8]. Tics can be divided into simple tics and complex tics (any combination of movements or vocalisations). Simple motor tics are short and repetitive movements involving a single muscle group or part of the body (e.g., blinking, snapping fingers, jerking a limb), while complex motor tics are coordinated combinations of movements that may resemble a voluntary action, involving multiple muscle groups (e.g., facial grimacing with a tilt of the head, a shrug of the shoulders, chewing, jumping). Simple vocal tics describe vocalisations without words, such as grunts, single syllables, or sounds, while complex vocal tics include phrases, and/or sound combinations. Several types of tics (e.g., abdominal tensing combined with grunting) often occur together and may occur in predetermined orchestrated sequences; such orchestrated sequences were also observed in the presented clinical case. Obscene or socially inappropriate gestures and vocalisations (coprophenomena) occur in 28.1% of individuals with Tourette syndrome [4, 5]. It has been observed that tics become stronger while experiencing stress, fatigue or excitement, and symptoms tend to improve when the patient is engaged in mental or physical activity, when focusing attention [1, 7]. This was also observed in the presented patient – certain emotional stress and life events had a considerable influence on the severity of his symptoms.

According to a retrospective study of patients with Tourette syndrome, approximately 17% of patients express self-injurious behaviour (SIB). Self-injurious behaviour can be categorized into two types: one resulting from self-injurious tics, as observed in this case, and another involving deliberate self-harm, which the patient did not exhibit. A term 'malignant GTS' (malignant Tourette syndrome) was introduced, defined as two or more emergency room visits or one or more hospitalizations for Tourette syndrome symptoms or its associated behavioural comorbidities. Hospital admissions are for tic-related injuries, self-injurious behaviour, uncontrollable temper or suicidal ideations/attempts. Compared with patients with non-malignant Tourette syndrome, those with malignant Tourette syndrome were more likely to have a personal history of OCD, complex phonic tics, coprolalia, copropraxia and a poor response to medication. Taking into account that the presented patient has been hospitalized a couple of times for his symptoms, presents with self-injurious behaviour and has a poor response to pharmacotherapy, malignant Tourette syndrome could be used to describe his symptoms [9]. A positive correlation was found between SIB and the YGTSS score, so severe tics may be associated with an increased risk of self-harm. The most common tics with a self-injurious behaviour component include hitting the chest, head, legs, arms, rubbing or hitting the wall with one's head, as well as pulling, scratching skin, gnashing teeth, and biting. Patients who experience tics with a self-injurious behaviour component are not only in physical pain, but they may also feel severe anxiety because of the tics they perform [4, 9]. The presented patient expressed self-injurious behaviour, such as lip biting and pressing on his nose, resulting in lip wounds and a tissue defect on his nose. Tics with a self-injurious component resulted in the patient feeling anxious about such behaviour (as he would perform the tic until he was in pain) and the appearance of the affected area.

It is of interest that the age of onset of self-injurious behaviour for the majority of cases is in childhood, and only a few cases had the onset manifested in adulthood. The average age of the

onset is 11 years of age, and coincides with the worst tic severity period, which usually occurs between 10 and 12 years of age. The onset of self-injurious behaviour in adulthood is rare, usually related to other psychiatric conditions, such as depression, OCD, and anxiety disorders. The presented case did not express self-injurious behaviour until he was 27 years of age, which is uncommon, considering that there are no psychiatric comorbidities. In this case, the self-injurious behaviour could have manifested alongside his severe tics, as tic severity is also seen as a risk factor for current (not very long-lasting) self-injurious behaviour [9].

The tics may be preceded by a premonitory urge, which can be described as a desire to perform tics, it can be a feeling, an emotion (e.g., excitement, anxiety), and a substantial proportion of patients feel that they "just need to do it." Sometimes tics can be partially or completely suppressed for a period of time. Voluntary suppression of a tic causes 'build-up', and, when the tic is finally performed, it is performed with greater intensity, and there is a feeling of relief afterwards [10].

Pathogenesis

Dysfunction of the cortico-basal ganglia neuronal networks is a widely accepted hypothesis for Tourette syndrome, but the exact pathogenetic mechanisms are still unclear. Functional neuroimaging studies show an increased activity in the premotor cortex, anterior cingulate cortex, supplementary motor area and primary motor cortex, while activity in the premotor dorsolateral cortex and supplementary motor area is associated with the tic severity. At the level of neuronal networks, tics may be a manifestation of inhibitory dysfunction in the sensorimotor cortico-basal ganglia network [11]. The underlying pathogenetic theory is similar to that of parkinsonism, and it involves the cortico-striatal-thalamo-cortical pathway. There exist two basal ganglia pathways: there is one facilitating the movement (the direct one), and one inhibiting it (the indirect one). Glutamate signals from the cortex reach the striatum, and, after processing through these pathways, information is directed to the nucleus accumbens and substantia nigra. The direct and indirect pathways, distinguished by receptors D1 and D2, have different effects on the globus pallidus and brainstem nuclei. Dysfunction in the nigrostriatal pathway can decrease the direct pathway activity, increase the indirect pathway activity, and lead to disruptions in the thalamus-cortex communication, thus potentially causing tics. Dysfunction of GABAergic neurons and GABA receptors is also implicated in the pathogenesis of Tourette syndrome. For example, in an animal study, the injection of a GABA-A receptor antagonist induced stereotypical, tic-like movements [13].

The role of dopamine in the pathogenesis of Tourette syndrome has been observed, with an increase in tonic and phasic dopamine levels influencing the 'learning' of tics and the expression of tics. In some studies, tics are non-adaptive, continuous motor habits that are enhanced by increased phasic dopamine secretion, while tonic dopamine secretion enhances the learning to perform tics. In this context, dopamine antagonists (antipsychotics) may increase the activity of the indirect pathway and thus reduce tics, but they may also increase the tendency to 'learn' tics. Disturbances in the tonic and phasic dopamine release in Tourette syndrome may also explain the premonitory urge to perform the tic. Satisfying the premonitory urge to perform a tic triggers dopamine secretion, thereby reinforcing tic learning [5].

Diagnosis

Diagnosis and assessment of Tourette syndrome can be challenging due to the syndrome's clinical heterogeneity, suppression of tics, and fluctuation of symptoms ('waxing and waning') over

time and in different conditions. Reaching a clinical diagnosis can be delayed by 3–11 years from the onset of symptoms, which indicates that both the general public and the health professionals have difficulties in recognising Tourette syndrome. Behavioural problems, certain personality traits such as shyness, disobedience, emotional lability and frequent anger attacks, or a diagnosis of autism spectrum disorders can all have an impact on the development of tics [3, 6, 7]. At the same time, a family history of Tourette syndrome can be considered, but it is not necessary. The heritability of Tourette syndrome can be quite strong, but, in the presented clinical case, the family history is negative.

It is of importance to perform a neurological examination to exclude other neurological conditions. Electroencephalogram and imaging studies such as head CT do not have significant diagnostic value in Tourette syndrome, but recent studies indicate that imaging studies may show reduced prefrontal cortical thickness. Diffuse cortical thinning has also been observed in patients with complex tics and OCD [4, 12].

Symptoms are assessed by using a number of methods, of which the most commonly used option is YGTSS. YGTSS assesses the type, frequency, and intensity of tics, as well as their impact on the quality of life [3].

Treatment

Patients with Tourette syndrome are usually treated following an individual plan, depending on the specific symptoms that are of most concern. Although tics are often the main feature of Tourette syndrome, it is important to recognise and emphasise the wide range of motor and vocal tics, ranging from simple to complex tics, and the wide variety of comorbidities. For example, some complex motor tics may be accompanied by SIB, which is observed in at least one-third of all patients with Tourette syndrome, especially when there is a comorbidity with OCD. It is important to educate both the patient and the patient's family and to discuss possible behavioural and educational interventions [14]. Observation of self-injurious tics can be accompanied by protective measures such as gloves, helmets, and protective dental caps to reduce the degree of bodily harm [13].

Cognitive behavioural therapy

Cognitive behavioural therapy consists of habit-reversal training (a key component of cognitive behavioural therapy for Tourette syndrome), relaxation training, and more functional interventions to deal with situations that may exacerbate the symptoms. It involves teaching patients to perform opposing behaviours to avoid performing a tic when they feel the premonitory urge to do so [5, 14]. Due to the nature of the therapy, potential downsides of cognitive behavioural therapy include the lack of trained professionals, time and compliance requirements for the family and the patient. Other factors that may be of major importance are the age of the patient and their motivation. As the efficacy of cognitive behavioural therapy is comparable to that of most medications, it is recommended as a first-line treatment approach [15].

Pharmacological treatment

In cases where cognitive behavioural therapy is ineffective, cannot be applied, or offers limited benefits, for example, when the patient is unable to cooperate with the doctor due to age (too young), the next step is pharmacological treatment. When pharmacological treatment of Tourette syndrome is initiated, the potential risks and benefits should be discussed with patients and their family members [16].

Research has focused on alpha-2-agonists, such as *Clonidine* and *Guanfacine*. These drugs have a relatively safe profile and are therefore more commonly prescribed as the first-line pharmacological treatment for Tourette syndrome. Evidence suggests that these drugs are more effective in the presence of comorbidity of Tourette syndrome with attention deficit and hyperactivity disorder (ADHD). In the mild forms of Tourette syndrome, treatment with *Topiramate* may be recommended, with studies showing an improvement in tics while using *Topiramate* (a reduction of eight points was observed when comparing YGTSS scores) [17, 18].

Another group of medications prescribed for Tourette syndrome are antipsychotics, also known as dopamine antagonists. Antipsychotics work by blocking dopamine receptors. *Haloperidol* was the first dopamine antagonist to be introduced for the treatment of tics, followed by *Aripiprazole* and *Risperidone*, both of which are now used [18]. Among antipsychotics, *Aripiprazole* is the most commonly used alternative. Its use reduces the intensity and frequency of tics in children and adolescents, but there is a lack of reliable evidence on its effectiveness in adults [19]. *Aripiprazole* is recommended because of its less pronounced adverse effects compared to other antipsychotics: a lower risk of akathisia and other extrapyramidal symptoms, anxiety, dizziness, constipation, and its neutral effect on the body weight and metabolic parameters (no increase in glycaemia, no interference with lipid metabolism). It has also been shown that *Aripiprazole* may have a beneficial effect on psychiatric comorbidities (depression, anxiety, self-harm). In adults, treatment with *Haloperidol* is still the predominant treatment [18, 19]. The presented patient had been receiving a high dose of *Haloperidol* since adolescence and had been taking it daily for 15 years. The patient was taking *Trihexyphenidyl* concomitantly to prevent extrapyramidal symptoms. During the hospitalisation, exhaustion of *Haloperidol*'s effect despite the high dose was being discussed; therefore, *Haloperidol* was switched to *Aripiprazole*, following the recommendations in literature. Although the efficacy of *Aripiprazole* in adult patients with Tourette syndrome is unclear, a beneficial effect was observed in the presented patient. *Aripiprazole* combined with TMS resulted in a significant reduction in motor tics, with fewer and less intense tics being observed.

Although treatment with antipsychotic medication can be effective and achieve good symptom control, many patients may not experience a therapeutic effect, or may experience side effects such as extrapyramidal symptoms, weight gain, an increased risk of metabolic syndrome, hyperprolactinaemia, and a prolongation of the QTc interval. Clinical trials evaluating the efficacy of VMAT2 (vesicular monoamine transporter 2) inhibitors are also underway. VMAT2 inhibitors block the type 2 vesicular transporter of monoamines, such as dopamine, which is required for the 'packing' of monoamines in presynaptic vesicles. VMAT2 inhibitors deplete presynaptic striatal dopamine and reduce the dopamine release. Medications in this class include *Tetrabenazine*, *Deutetrabenazine* and *Valbenazine*, which are most commonly used to treat Huntington's chorea and late dyskinesia but can be used 'off-label' to treat a variety of other hyperkinetic movement disorders, including tics [5, 17, 18].

Transcranial magnetic stimulation (TMS)

TMS delivers repetitive magnetic pulses to a target area of the cerebral cortex. Different parameters of TMS, such as its frequency, intensity, and duration, have been found to modulate the cortical excitability and inhibition, and thus to induce long-lasting changes following the stimulation period. Although TMS has been used most commonly as a treatment for depression, its application in the treatment of tics has recently been explored [19]. The efficacy of TMS in the treatment of Tourette syndrome is still under investigation, and the efficacy has not yet been clarified, with

conflicting data presented in the scientific literature. In certain studies, a positive effect of TMS has been observed when another psychiatric disorder, such as ADHD, has been diagnosed alongside Tourette syndrome. This is thought to be due to abnormal electrical activity in the cerebral cortex, which is characteristic of disorders such as OCD and ADHD. Thus, so far, a beneficial effect has been observed in patients with comorbid psychiatric disorders, also by stimulating the supplementary motor area [20]. Stimulating the premotor cortex or the supplementary motor area increases inhibition in the area, and a decrease in tics is observed objectively. If TMS is found to be an effective treatment for tics, it can be used as an adjunctive therapy for Tourette syndrome as it is well tolerated, and the most common side-effect is a headache [21].

Botulinum toxin injections

Botulinum toxin injections can be used as an alternative to other treatment methods for localised and troublesome motor or vocal tics. The duration of the response to the injection is between 12 and 16 weeks, and the injections should be repeated for optimal and sustained symptom control. This method works only at the injection site (e.g., in the case of vocal tics, the injection is administered into the vocal folds), and the side-effects are well tolerated. Side-effects include weakness at the site of injection, which resolves spontaneously after a few weeks [22]. Importantly, botulinum toxin has some effect against the premonitory urge that occurs before tics, suggesting that injections not only 'mask' tics by causing local muscle weakness, but may also alleviate symptoms arising through more complex peripheral mechanisms. This treatment approach is most effective in cases of troublesome single muscle group tics such as blinking, dystonic tics (neck twisting), or troublesome vocal tics (loud screaming, coprolalia), especially in patients who are intolerant to pharmacotherapy [5].

Deep brain stimulation (DBS)

This treatment method for Tourette syndrome is new and experimental, and is used in patients with severe and disabling symptoms or in cases of treatment-refractory Tourette syndrome. In Tourette syndrome, the thalamus (the centromedian parafascicular complex or centromedian nucleus of the thalamus), the inner part of the globus pallidus, or a combination of these target areas, is usually stimulated [23]. Chronic high-frequency stimulation of specific brain regions is associated with sustained and significant improvement in motor and vocal tics, and in the presence of comorbidity with psychiatric disorders such as OCD, the symptoms of these disorders may also be reduced. So far, only short-term effects of DBS have been investigated, with studies lasting up to several years only; hence, the long-term effects are still unclear [24].

Treatment-Refractory Tourette Syndrome

As of now, there are no established criteria for refractory Tourette syndrome, however, it is thought that the most severe clinical phenotype (severe and debilitating tics, coprophenomena, including self-injurious behaviour) could be interpreted as being refractory. In the guidelines published by the *European Society for the Study of Tourette Syndrome* (ESSTS), it was suggested that the following clinical criteria indicate refractoriness (the same criteria could allow a patient to be qualified for experimental treatment with deep brain stimulation): (1) tics should last at minimum five years; (2) tics should be severe for at least a year; and (3) the tic severity should be rated ≥35 according to YGTSS. Treatment refractoriness could also be established after unsuccessful or not well-tolerated pharmacotherapy with three different drugs, including both typical and atypical neuroleptics in adequate dosages over an adequate period of time. Since *Haloperidol* is the only drug licensed for

the treatment of Tourette syndrome in the majority of European countries, the failure of this drug already implicates treatment resistance [25]. If we were to follow these criteria, our presented clinical case could be considered treatment-refractory, as the patient has been experiencing symptoms for over five years, his tics have been severe for over a year, while even manifesting as self-injurious behaviour for the last 6 months. When assessing the patient's YGTSS score, a score of >35 was reached even after initiating treatment with *Aripiprazole* and completing a course of TMS. The presented patient was also treated with Haloperidol, and adequate symptom control was not reached even after increasing the dose. According to a different study, Tourette syndrome should be considered treatment-refractory if several known treatment interventions, including cognitive behavioural therapy (at least 12 sessions), pharmacotherapy, or a combination of these approaches, do(es) not result in adequate symptom control, while comorbid psychiatric illnesses, if present, are being adequately controlled [25]. It is important to emphasise that the goal of treatment for Tourette syndrome is not the complete absence of tics, but rather *sufficient* symptom control to achieve functioning in social and occupational areas. Currently, there is no reliable data on the proportion of patients who are resistant to treatment, and little is known about the mechanisms that contribute to treatment resistance. Apart from comorbidities, there are no clinically useful patient characteristics to predict potential treatment resistance, although some studies have investigated certain traits and features. For example, a greater severity of tics in childhood may predict the severity of tics later on, or their persistence into adulthood, irrespective of the response to treatment [3, 25]. As the criteria for treatment-refractory Tourette syndrome differ depending on the study, it is difficult to assess the presented clinical case, as it can be seen as both treatment-refractory and not treatment-refractory (cognitive behavioural therapy was not applied during the treatment, whereas, in some studies, the failure of psychotherapy is already a criterion). However, the case was difficult to manage, as the patient was resistant to *Haloperidol*, and symptom control was only achieved with the combination of *Aripiprazole* and TMS.

Conclusions

1. Tourette syndrome is characterised by a wide variety of clinical symptoms. The described clinical case is unique because of a late onset of symptoms, symptom progression into adulthood, and intense self-injurious behaviour provoked by psychological stress.
2. The literature describes various treatment options for Tourette syndrome. Despite the proven efficacy of *Haloperidol* for the treatment of tics, it was ineffective in this case, even at high doses. Discontinuation of *Haloperidol* and the addition of *Aripiprazole*, combined with transcranial magnetic stimulation, resulted in a significant reduction in the number and intensity of tics. Therefore, it can be assumed that, when treating patients with Tourette syndrome, it is important to tailor treatment to the individual needs of each patient. The investigation and application of new treatment methods, such as transcranial magnetic stimulation in the treatment of Tourette syndrome, is promising for the treatment of patients who are resistant to pharmacotherapy.

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