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Case Report

Two Cases of Gilles de la Tourette Syndrome in One Family

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Abstract

The article presents the cases of two half-brothers with Gilles de la Tourette syndrome and concomitant intellectual disability, manifestation of dysmorphic features (small upward slanting eyes, large low-set dysplastic ear auricles and short neck), and a family history of tics on their mother's side – relatives with tics in their childhood. Tics and Tourette syndrome have been diagnosed only in male members of this family. The genetic screening performed in both patients did not find presence of the fragile X chromosome syndrome.

Key words: Gilles de la Tourette syndrome, intellectual disability, fragile X chromosome.

Introduction

A multitude of motor tics and one or more vocal tics of childhood onset have been diagnosed in Tourette, occurring comparatively frequently with other concomitant mental disorders. Tourette incidence among the population ranges between 0.3 [1] and 1 per cent [2], the ratio males/females being 3:1[1] according to some authors and 4.3:1[3,4] according to others. The results of family studies on patients with Tourette disclose a greater incidence of tics and Tourette among first-degree relatives, as compared to the families of healthy controls. [4, 6, 7]

Materials and methods

A genetic screening (real-time PCR) was carried out in both patients for the fragile X syndrome to find out expansion of the CGG repeat in the 5'UTR of FMR1 gene. The tics were evaluated by the Yale Global Tic Severity Scale (YGTSS) applicable to adults as well. [8]

Results

First case: N. is a 32-year-old male.

Individual development: Born of a normal first pregnancy and delivery. He mastered skills like walking, speaking and controlling pelvic reservoir functions late, had difficulty taking care of himself and needed the support of adults significant to him. He was raised in a family with disharmonious relationship between the parents, who divorced when he was 9. The mother re-married and the members of the extended family aided in raising him. He was a reticent and unsociable child.

Education: At the age of 3 he attended a kindergarten for a short period because he had adaptation difficulties and could not take care of himself (e.g. dress or feed himself without assistance). He went to school at the age of 7. In the first grade he had difficulty mastering the subjects taught and from the second grade he was individually taught at school. He has a completed primary education (4-th grade).

Social history: After leaving school, until he became 18, he helped in the household. He found it difficult to communicate with people his age. He took unqualified jobs at different places for short periods of time but kept leaving because he was frequently ridiculed by his colleagues. In the last 3 years he has been working as a cleaner in a café. He lives with his mother, step-father and younger half-brother in one household. His communication is restricted within the family. He has no friends.

Family history: His father abused alcohol, N. has two relatives on his mother's side with tics in their childhood.

History of present illness: N.'s early mental development was retarded; at the age of 7 he was diagnosed with mild intellectual disability (ID). At the age of 10 he started grimacing and shuffling one of his legs while walking. He was referred to a neurologist, who ruled out a neurological disease. At that time his mother was pregnant with her second child. A consultation with a psychologist was made, since N. had witnessed the frequent rows between his parents, his father's alcohol abuse and physical violence towards his mother. He found it difficult to communicate with children his age, who frequently mocked him for his grimacing. N. was referred to a child psychiatrist.

At the age of 11 he started blinking and squinting, as well as saying involuntarily separate syllables or words. He was physically assaulted by his classmates twice, stopped attending school and completed only primary education. He was repeatedly consulted by a psychologist and a child psychiatrist, received drug treatment, was admitted several times to the Day Care Unit of the Clinic of Child and Adolescent Psychiatry and until the age of 18 he was included in various mental education and rehabilitation programmes.

N. was treated in an outpatient setting for a variety of tics, such as tilting his head to the left or right, shrugging his shoulders, making different movements with his fingers, shouting words or sounds outside the context of the conversation.

When he was 24, he was consulted by a neurologist – the CT and MRI of brain revealed no evidence of disturbance. EEG was also performed, disclosing a low-amplitude disorganized alpha rhythm, for which treatment was applied. At the age of 28 a follow-up EEG was performed

Table 1: Medications prescribed to N. – duration of administration, daily doses, therapeutic effect on tics and side effects.

Age in years	Drug dose per day in mg	Therapeutic effect on tics	Side effects
From 11 to 15	Clonazepam - 1,5	Partial	
From 16 to 18	Haloperidol - 3	Good	Extrapyramidal symptoms
From 19 to 20	Promethazine hydrochloride - 50	Partial	Low blood pressure levels
From 21 to 22	Clozapine - 75	Good	Tendency of decrease in white blood cell count
From 23 to 24	Quetiapine - 200	Partial	
From 24 to 27	Carbamazepine - 400	Partial	
From 28 to 30	Sodium valproate - 1000	Partial	
From 31 until hospitalization	Sodium valproate -1000 and Diazepam -15	Partial	Sedation

that showed mild diffuse non-specific alterations, and his therapy was changed.

The ceruloplasmin blood test and the 24-hour urine copper test were within normal limits; haemoglobin values were at the lower limit of the reference range (acanthocytosis was ruled out following a consultation with a haematologist). He was consulted by a neuro-ophthalmologist; the examination revealed normal ocular fundi, vessels and retina. Nearsightedness was found and glasses were prescribed.

Mental status: Alert, oriented to time, place and personality. Gives short answers to the questions asked, using a comparatively limited vocabulary. Complies with rules and restrictions. During the examination makes facial grimaces, shrugs his shoulders, turns his body to the left or right, or both, moves his fingers and shouts individual sounds outside the context of the conversation. Emotionally anxious, when the tics appear he starts to cry and needs some time to calm down. Concrete thinking. Intellectual disability.

During his stay at the Day Care Unit his doses of sodium valproate and diazepam were gradually reduced and discontinued. Risperidone up to 3 mg and topiramate up to 150 mg were administered, gradually increasing the dose. These medications had a partial effect on the tics following a 3-week administration, and were subsequently discontinued. Aripiprazole in a morning dose of 15 mg was administered; in the course of treatment the patient's condition was stabilized, and the tics subsided within 3 weeks.

N.'s initial evaluation by YGTSS was 67 points, whereas at the 6-th week of treatment his evaluation was 35 points.

Wechsler Adult Intelligence Scale showed mild ID.

The genetic screening did not find presence of fragile X chromosome syndrome.

The laboratory tests of blood, glucose, liver enzymes and urine were within normal limits. The patient was consulted by an internist and a congenital heart disease was ruled out. ECG was within normal limits.

Second case: S. is a 23-year-old male.

Individual development: A child of a second pregnancy of the mother. Born at the beginning of the 9-th lunar month with low body weight – 2500 g and height 52 cm; had to be kept in an incubator for 7 days following birth. He mastered skills like walking, speaking and controlling pelvic reservoir functions late. He was raised in a family with good relationship between the parents. At the age of 3 and a half attended kindergarten for a short period of time, because he could not feed or dress himself without assistance. He was raised at home up to the age of 7. He played mostly with his elder half-brother and was a quiet child.

Education: At school he had difficulty learning the letters, the numbers and could not cope without the support of an adult significant to him. From the first grade until completion of his secondary education he was individually taught at school. He completed secondary education with satisfactory results.

Social history: Following graduation he spent most of the time at home watching television. He found it difficult to perform daily activities without assistance. He lives with his mother, father and elder half-brother in one household. He has a good relationship with his elder half-brother and a close relationship with his grandparents on his mother's side. He has no friends. In the summer of 2014 and 2015 he worked as an unskilled labourer in archaeological excavations for a few months.

Family history: No evidence of mental disorders on his father's side. On his mother's side he has two relatives with tics in their childhood, as well as a half-brother with Tourette's syndrome.

Table 2: Medications prescribed to S. – duration of administration, daily doses, therapeutic effect on tics and side effects.

Age in years	Medication – daily dose in mg	Effect on tics	Side effects
From 10 to 14	Clonazepam - 1,5	Partial	
From 15 to 18	Haloperidol - 3	Good	Extrapyramidal symptoms
From 19 to 22	Quetiapine – 200 and Sodium valproate - 1000	Partial	Sedation
From 23 until hospitalization	Sodium valproate – 1000, Quetiapine – 200 and Risperidone - 2	Partial	Sedation

History of present illness: S.'s early mental development was retarded; at the age of 7 he was diagnosed with mild ID. At the age of 10 he started chattering and grinding his teeth frequently, widening his nostrils as if to smell something, and later on he started making sounds similar to clearing one's throat. He was followed up by a child psychiatrist and a psychologist in an outpatient setting up to the age of 18. After that his condition was followed up by a psychiatrist and he received drug treatment.

At the age of 20 he was admitted to a psychiatry department because of psychomotor agitation and aggressive behavior towards close relatives. About a week before his hospitalization he had a viral infection and was deeply upset by the hospitalization of his grandfather on his mother's side, with whom he had a strong emotional relationship. After the discharge his condition was followed up in an outpatient setting, but the tics persisted.

At the age of 22 he reported a sensation of heaviness in the abdominal area. He was consulted by a surgeon and operated on for a pseudocyst in the caudal area of pancreas. The patient and his relatives denied alcohol use/abuse.

At the age of 23 he was consulted once again by a surgeon because of general weakness and heaviness in the abdominal area. The laboratory tests revealed diabetes mellitus. An

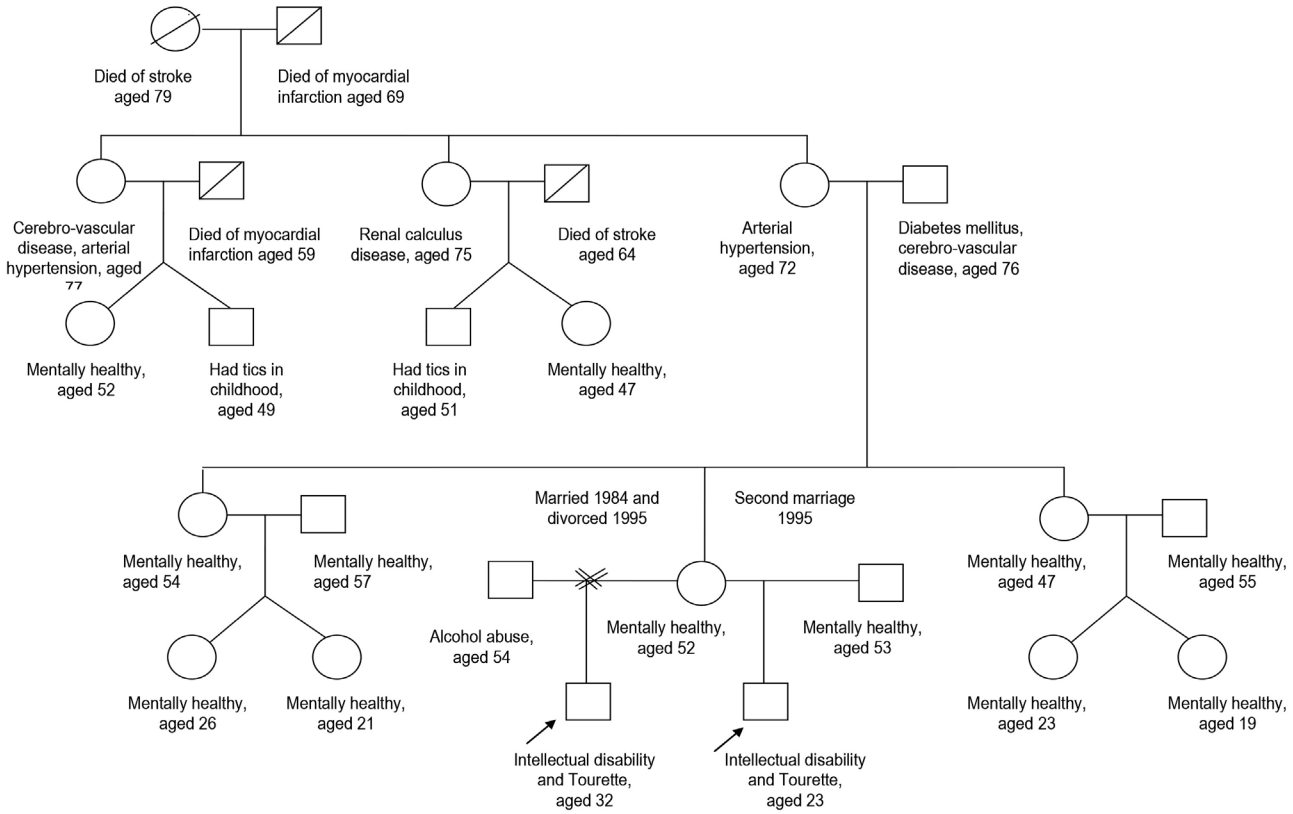

Figure 1: Maternal ancestry of the two half-brothers with ID and Tourette (marked with arrows).

Men are presented with squares and women are presented with circles. Their mental condition is stated, as well as the somatic diseases running in the family; the crossed-out circle or square represents a dead person, with the cause of death indicated.

N. is from the mother's first marriage and S. is from her second marriage. N. and S.'s mother has two sisters (one of them elder, and the other one younger), each one having two mentally healthy girls. N. and S.'s maternal grandmother has two elder sisters, each of which has two children – a boy and a girl, and both boys had transient motor tics at the age of 6 or 7.

endocrinologist determined treatment with Insulin Actrapid 6U three times daily and a single dose of Insulatard 8U at 10 p.m., as well as an appropriate diet.

Mental status: Alert, oriented to time, place and personality. Manifests mild psychomotor tension. Gives short answers to the questions asked after a long pause, looking for his mother's support. During the interview complies with rules and restrictions. Emotionally anxious, grinds his teeth, blinks frequently and shouts individual sounds. Concrete thinking. Intellectual disability.

During his stay at the Day Care Unit the administration of risperidone 2 mg daily and quetiapine 400 mg in the evening was continued; sodium valproate was discontinued and replaced by topiramate, gradually increasing the dose up to 150 mg for a period of 3 weeks. A good therapeutic effect on the tics was observed in the course of treatment.

S.'s initial evaluation by YGTSS was 45 points, whereas at the 6-th week of treatment his evaluation was 17 points.

Wechsler Adult Intelligence Scale showed mild ID.

The genetic screening did not establish presence of fragile X chromosome syndrome.

The laboratory tests of blood, glucose, liver enzymes and urine were within normal limits. The patient was consulted by an internist and a congenital heart disease was ruled out. ECG was within normal limits.

Discussion

Tourette's syndrome is manifested most frequently at the age of 5 to 6 [9,10], whereas in the patients studied its first manifestation was around 10, with concomitant ID and dysmorphic signs, as well as family history of tics among the males in the family. This set of manifestations gave us grounds to look for a genetic component in the family studied, associated with the fragile X syndrome. Different authors suggest a possible link between the fragile X syndrome and Tourette – with onset of the disease at a later age, atypical tics and occurrence of a comorbidity involving learning disabilities, speech and language disorders and dysmorphic signs. [11] Other authors studying patients with the fragile X syndrome, have found tics in 16% of them. [12]

Individual cases of co-occurring ID and Tourette have been reported in the specialized publications. In a patient with Tourette and concomitant severe ID, the administration of haloperidol in a daily dose of 10 mg resulted in a considerable reduction in the motor and vocal tics, as well as the hyperactive behavior. [13]

In both patients with Tourette of long standing a good therapeutic effect on the tics was observed with haloperidol administration; however, conventional antipsychotics produced some side effects that were overcome by prescribing atypical antipsychotics. In N. the manifestations of Tourette were more marked (initial evaluation by YGTSS 67 points) and a therapeutic effect was achieved with aripiprazole, whereas in S. the tics were less marked as compared to those of N. (initial evaluation by YGTSS 45 points), but he required a combined therapy involving atypical antipsychotics and an antiepileptic medicament. Various authors share the opinion that atypical antipsychotics, such as risperidone, aripiprazole and others have a good therapeutic effectiveness on tics. [14]

Since both patients had a mild ID and were raised in a common family setting we considered a possible imitation on the part of the younger half-brother. The investigation of the dynamics of motor and vocal tic manifestation in both patients did not reveal superimposition of Tourette symptoms, which was confirmed not only by the parents, but also by the description of their tics as reported in the medical documentation.

By applying YGTSS twice we could assess the effect of drug treatment not only on tics, but also on improving self-confidence, communication and social function.

Conclusion

The results of studies on families with tic disorders suggest a possible genetic cause of these diseases, although the mechanisms are not completely clarified. The application of drug treatment in this group of patients is a challenge, since their individual peculiarities and the co-occurrence of other mental disorders or somatic diseases have to be taken into consideration.

It should be noted that Tourette can acquire a chronic course and may have unfavorable implications on the patients by influencing their relations with people their age

and limiting their opportunities of education and professional realization, but it also stigmatizes the other members of the family.

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