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Tourette syndrome and excitatory substances: is there a connection?

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Abstract
Background and purpose The objective of this study is to investigate the relationship between excitatory substances by testing the urine in children with Tourette syndrome (TS).
Methods We performed a control study involving 44 patients with TS and 44 normal children by investigating the children's daily eating habits. We used the gas chromatograph–mass spectrometer and liquid chromatograph–mass spectrometer from Agilent. Substances for detection included 197 excitatory substances prohibited by the International Olympic Committee and other substances with similar chemical structures or biological functions for urine samples.
Results Forty-four patients who did not take any drugs in the past 2 weeks enrolled in the study. The positive rate in the experiment group was three cases, while it was negative in the control group. The level of 1-testosterone increased in one extremely severe TS patient who ate large amounts of puffed food and drank an average of 350 ml of cola per day. Cathine and other substances with similar chemical constitution or similar biological effects increased in one severe TS patient who ate bags of instant noodles daily, according to the high score of the Yale Global Tic Severity Scale.
Conclusion An increase in ephedrine type, testosterone, and stimulants may be related to the pathogenesis of TS. Unhealthy food possibly causes TS. The relationship between excitatory substances and TS needs to be explored with the goal of providing more information on diagnosing and treating TS.

Keywords Tic disorders · Etiology · Excitatory substances

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Introduction

Tourette syndrome (TS) refers to the childhood onset of involuntary, aimless, repeated, and fast motor or vocal tics at one or several parts of the body accompanied by other behavioral symptoms, including attention-deficit disorder, hyperactivity, self-mutilation, and obsessive–compulsive disorder. The cause of tic disorder remains unclear, and there are various courses of the disease. According to studies, ten out of 1,000 individuals may have tic disorders [1]. TS, according to the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III-R) criteria, yields a prevalence estimated at 299 per 10,000 pupils between the ages of 13 and 14 [2]. Genetic and environ-

mental factors play a role in the etiology of TS, but its exact causes are unknown. In a large genealogy study, 35% of 641 TS patients had first-degree relatives with TS [3], and it was revealed that TS can be passed on by multifactorial inheritance [4, 5].

Clinical doctors found that children with attention-deficit hyperactivity disorder may exhibit TS when they take the excitatory drug methylphenidate [6, 7]. Methylphenidate can aggravate TS patients' seizures or tics [8]. Meanwhile, reduced levels of serum 5-serotonin and tryptophan were found in TS patients. These results demonstrate that reduced 5-serotonin NDN functionality and several central neurotransmitter disorders play a critical role in the TS process. While disorders involving dopamine, 5-serotonin [9], and noradrenalin are related to the extremely complicated interaction between the basal ganglion and various neurotransmitters in relevant structures, TS is related to the reduced suppressive function of γ-propalanine, reduced activity of acetylcholine, and excitotoxicity of excitatory amino acids (EAAs) [10].

Some studies suggested that the abnormal development of special components of the basal ganglion and limbic system is possibly related to TS. These developmental anomalies are controlled by sex hormones and indirectly influenced by the neurotransmitters of EAAs [11]. Kurlan considered that in human bodies, areas of the brain with reproductive functions are possibly located at the basal ganglion and limbic system. The development of these brain areas is controlled by sex hormones, with abnormal development possibly caused by TS [12]. Spasms of TS patients, manifested through behaviors such as touching, rubbing, sucking, sniffing, and pelvic thrusting, among others, might be inappropriate expressions of reproductive behaviors. EAAs (L aspartic acid, L aminoglutaric acid, etc.) extensively exist in the central nervous system of mammals. The nerve pathways of EAAs are abundant and are mostly related to the basal ganglion and the limbic system. During the development of the central nervous system, EAA plays different roles for the same brain area at different stages. In the early stage of development, it serves as a neurotrophy, whereas in the late stage, it serves a toxicity-stimulating function. TS patients have a genetic flaw that affects the development of some areas of the basal ganglion and limbic system (related to reproductive behaviors and facilitate basic movements), voice, and emotions. Hence, EAA indirectly affects sex hormones. Therefore, in the early stage of brain development, an improper increase in nerve cells and over-derivation of neuronal synapse in these areas are produced because of excessive neurotrophy. This, in turn, results in multiple tics and coprolalia syndromes in sick children during their infancy [12].

Our hypothesis is that sex hormone action is mediated by excitatory neurotransmitter mechanisms such that an excessive trophic effect occurs early in development and a neurotoxic environment emerges later on. The defective gene in TS is hypothesized to influence these developmental processes [11]. Peterson's double-blind, placebo-controlled, crossover trial study showed that anti-androgen significantly reduced motor but not phonic tic symptom severity for adults with TS [13]. An epidemiological survey of TS in children and adolescents in China showed that the ratio of boys to girls was 10.6:1 [14].

Based on the possible mechanism for hormonal and excitatory neurotransmitter influences in TS, as well the 10-fold occurrence of TS in boys, this study aimed to assess the effects of excitatory substances on TS children by testing their urine through the stimulant test laboratory used for the 2008 Beijing Olympics.

Materials and methods

Eighty-eight children participated in this study. We obtained the consent of all the children and their parents. The trial was conducted in accordance with the international rules of good clinical practice. Informed consent was obtained from each patient's parents before trial-related procedures were initiated.

Study group Forty-four children diagnosed with TS from two children's medical centers in Beijing were tested between October and December 2008. The sample population included 39 boys and five girls. The DSM, 4th ed. (DSM-IV-TR) for TS has the following criteria for diagnosing TS: (1) Both multiple motor tics and one or more vocal tics must be present at the same time, although not necessarily concurrently; (2) the tics must occur many times a day (usually in bouts) nearly every day or intermittently over more than 1 year, during which time there must not have been a tic-free period of more than three consecutive months; (3) the age at onset must be less than 18 years; and (4) the disturbance must not be due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or post-viral encephalitis) [15]. They must not have taken drugs in the past 2 weeks including cough medicines, or medications for colds, fever, and asthma and have been excluded from the possibility of chorea minor, hepatolenticular degeneration, habit spasm, epilepsy, drug-induced disease, and other extrapyramidal system degeneration. They have normal results for skull computed tomography inspection, EEG, blood routine, biochemistry, blood sedimentation, and antistreptolysin-O test. They must also have received Yale Global Tic Severity Scale (YGTSS) evaluation.

Contrast group We selected healthy children of the same age (with an age difference less than 0.5 year) and the same gender (1:1) to form the contrast group. These children were from Beijing.

Criteria Children must be without tic disorder, hyperactivity, obsessive–compulsive disorder, emotional disorder, sleep disorder, epilepsy, encephalitis, and other neural diseases. They must also not have taken any recent medication.

Study design: general information The participants' general information includes the TS child's name, gender, age, residence, age of onset, progress, initial symptoms, and eating habits. This basic information came from the children, their parents, and guardians. In the YGTSS of the American Academy of Child and Adolescent Psychiatry [16], a score of ≤24 indicates a mild case of TS, 25–39 is moderate, 40–59 is severe, and ≥60 indicates extremely severe. TS children were graded using the YGTSS and scored based on their clinical symptoms in the past week. The age of onset for TS children was 8.7+2.88 (years old), from 3 (the youngest) to 16 years of age (the oldest). More boys than girls were in all age brackets, with a ratio of 7.8:1, as shown in Table 1.

Collection and storage of samples: pre-treatment A 50-ml clean centrifugal tube was used to collect 50-ml morning urine of TS children in the experimental group when they were tested for YGTSS and surveyed via questionnaire the next morning. The samples were sent to the Stimulant Test Center of General Administration of Sport of China within 6 h. Pre-treatment of samples were completed by the professional workers in the laboratory, including hydrolysis, extraction, concentration, derivatization, and sampling, among others. All samples were tested in one batch in strict accordance with the operation procedures as specified by the International Anti-Doping Laboratory.

Analysis of final urine samples After pre-treatment, urine samples were analyzed using the gas chromatograph–mass spectrometer and liquid chromatograph–mass spectrometer from Agilent. Substances for detection included 197 excitatory substances prohibited by the International Olympic Committee and other substances with similar chemical structures or biological functions. These chemicals were classified into ten types based on the criteria developed by the International Anti-Doping Center. Table 2 shows the specific concentrations.

Table 1 Comparison of general information

	Case	Average age (years)	Gender	
			M	F
TD group	44	8.7±2.88	39	5
Control group	44	8.69±3.01	39	5
P		>0.05		>0.05

Statistical analysis The ages and genders of the children from both study groups were compared using one-way or two-way analysis of variance. The results were expressed as adjusted means for each treatment group with 95% confidence intervals for the differences between means.

Results

YGTSS distribution A total of 31 cases had initial symptoms of an increased number of motor tics on the head and face (70.4%), including 21 with initial symptoms of blinking (47.7%), three with motor tics on four limbs (6.8%; shrugging and extending arms), and five with only vocal tics or both vocal and body tics (11.4%). Their YGTSS score was 42.66+17.95, ranging from 19 to 85. They were graded based on YGTSS guidelines and were evenly distributed among all levels, as indicated by Table 3.

Presence of excitatory substances Among the 44 cases in the experimental group, 41 were negative and only three were positive for excitatory substances. Sample #17 had a higher testosterone content (with a YGTSS score of 68). The boy drank five to six bottles (a bottle of 400 ml capacity) of cola per week and other substances and a bottle of greater than or equal to 400 ml capacity. Sample #26, who ate a bag of instant noodles daily and drank soft drinks (primarily Coke) per day, had a YGTSS score of 53 and was found to have cathine, meclofenoxate, ephedrine, and norephedrine. Sample #43 had a YGTSS score of 41 and was found to have ephedrine. The contrast group's results were all negative. The test results of 197 excitatory substances and substances with similar chemical structures or biological functions are in Tables 4. The level of 1-testosterone increased in one extremely severe TS patient, while cathine and other substances with similar chemical constitution or similar biological effects increased in other two severe TS patients according to the high score of YGTSS.

Discussion

The causes of TS remain unclear, although it is believed to be the result of the joint influence of hereditary and

Table 2 Detectable minimum concentrations of excitatory substances

Substance to detect	Exception	Concentration
Stimulant	Exception	0.5 μg/ml
		0.2 μg/ml
Narcotic	Strychnine	0.2 μg/ml
		10 ng/ml
Anabolic agents (origin-produced substance or major metabolite)	Buprenorphine	10 ng/ml
		2 ng/ml
	Clenbuterol	2 ng/ml
	Methandienone (17β-methyl-5β-andro-1-stene-3α, 17α-diol)	2 ng/ml
	Methylnortestosterone (17α-methyl-5β-androstane-3α, 17β-diol)	1 ng/ml
	Norethandrolone	2 ng/ml
	Stanozolol (3′-hydroxy stanozolol)	2 ng/ml
β-Blocker	Epitestosterone	0.5 μg/ml
Diuretic (thiazide, metabolite or degradation product)		0.25 μg/ml
Glucocorticoid		30 ng/ml
Peptide hormone		30 ng/ml
		5 mIU/ml

environmental factors [10]. Its onset is possibly related to the presence of excitatory substances in children's bodies caused by changes in their external environment. The study found one case of a child with a YGTSS score indicating severe TS and a higher level of testosterone in his urine. This result supports Kurlan's [11, 12] hypothesis that sex hormone action is mediated by excitatory neurotransmitter mechanisms. Some scholars suggested that the abnormal development of special parts of the basal ganglion and limbic system is possibly related to TS. These developmental anomalies are controlled by sex hormones and hence are indirectly influenced by EAAs [11]. The average age of children in this group was 8.7+ 2.88, and their normal level of testosterone should be lower than adult standards. However, this study was based on adult standards as specified by the International Anti-Doping Center. This may explain the low positive rate of this study.

Sharma and Olmedo reported a patient with ephedrine-induced TS in 2003 [17]. Ephedrine is much stronger than adrenalin in exciting the central nervous system. It excites the cerebral cortex and subcortical center, the midbrain, the respiratory center of medulla oblongata, and vasomotor center; lifts the spirit; and shortens the hypnosis time of barbitone. It is an ingredient used in synthesizing benzedrine, the major raw material for amphetamine chloride. In this study, two children with severe cases of TS had levels of ephedrine substances (cathine, meclofenoxate, ephedrine, and norephedrine) higher than those recommended for adults. Children eating unhealthy food would have multiple risk factors for cardiovascular diseases, type 2 diabetes, and other co-morbidities before or during early adulthood [18]. The severe cases of TS, namely children who ate bags of instant noodles and drank soft drinks daily, had increased risk of developing chronic disease. This suggested that unhealthy food possibly causes TS.

Table 3 YGTSS distribution

Disease severity (YGTSS) [15]	Number of cases	Percentage (%)
Mild (≤24)	11	25.0
Moderate (25–39)	12	27.3
Severe (40–59)	11	25.0
Extremely severe (≥60)	10	22.7
Total	44	100.0

Table 4 Test results

	TD group (positive case)	Control group (positive case)
Exogenous anabolic androgenic steroids		
1-Androstendiol (5α-androst-1-ene-3β,17β-diol)	0	0
1-Androstendione (5α-androst-1-ene-3,17-dione)	0	0
Bolandiol (19-norandrostenediol)	0	0
Bolasterone	0	0
Boldenone	0	0
Boldione (androsta-1,4-diene-3,17-dione)	0	0
Calusterone	0	0
Clostebol	0	0
Danazol (17a-ethynyl-17β-hydroxyandrost-4-eno[2,3-d]isoxazole)	0	0
Dehydrochlormethyltestosterone (4-chloro-17-β-hydroxy-17α-methylandrosta-1,4-dien-3-one)	0	0
Desoxymethyltestosterone (17α-methyl-5α-androst-2-en-17β-ol)	0	0
Drostanolone	0	0
Ethylestrenol (19-nor-17α-pregn-4-en-17-ol)	0	0
Fluoxymesterone	0	0
Formebolone	0	0
Furazabol (17β-hydroxy-17α-methyl-5α-androstanol[2,3-c]-furazan)	0	0
Gestrinone	0	0
4-Hydroxytestosterone (4,17β-dihydoxyandrost-4-en-3-one)	0	0
Mestanolone	0	0
Mesterolone	0	0
Metenolone	0	0
Methandienone (17β-hydroxy-17α-methylandrosta-1,4-dien-3-one)	0	0
Methandriol	0	0
Methasterone (2α,17α-dimethyl-5α-androstane-3-17β-ol)	0	0
Methyldienolone (17β-hydroxy-17α-methylestra-4,9-dien-3-one)	0	0
Methyl-1-testosterone (17β-hydroxy-17α-methyl-5α-androst-1-en-3-one)	0	0
Methylnortestosterone(17β-hydroxy-17α-methylestr-4-en-3-one)	0	0
Methyltrienolone (17β-hydroxy-17α-methylestra-4,9,11-trien-3-one)	0	0
Methyltestosterone	0	0
Mibolerone	0	0
Nandrolone	0	0
19-Norandrostenedione (estr-4-ene-3,17-dione)	0	0
Norboletone	0	0
Norclostebol	0	0
Norethandrolone	0	0
Oxabolone	0	0
Oxandrolone	0	0
Oxymesterone	0	0
Oxymetholone	0	0
Prostanozol (17β-hydroxy-5α-androstano[3,2-c]pyrazole)	0	0
Quinolone	0	0
Stanozolol	0	0
Stenbolone	0	0
1-Testosterone (17β-hydroxy-5α-androst-1-en-3-one)	1 (17)	0
Tetrahydrogestrinone (18α-homo-pregna-4,9,11-trien-17β-ol-3-one)	0	0
Trenbolone	0	0

Table 4 (continued)

	TD group (positive case)	Control group (positive case)
Exogenous intake and endogenous anabolic androgenic steroids, their metabolites, and their isomers		
Androstenediol (androst-5-ene-3β,17β-diol)	0	0
Androstenedione (androst-4-ene-3,17-dione)	0	0
Dihydrotestosterone (17β-hydroxy-5α-androstan-3-one)	0	0
Prasterone (dehydroepiandrosterone)	0	0
Testosterone	0	0
5α-Androstane-3α,17α-diol	0	0
5α-Androstane-3α,17β-diol	0	0
5α-Androstane-3β,17α-diol	0	0
5α-Androstane-3β,17β-diol	0	0
Androst-4-ene-3α,17α-diol	0	0
Androst-4-ene-3α,17β-diol	0	0
Androst-4-ene-3β,17α-diol	0	0
Androst-5-ene-3α,17α-diol	0	0
Androst-5-ene-3α,17β-diol	0	0
Androst-5-ene-3β,17α-diol	0	0
4-Androstenediol (androst-4-ene-3β,17β-diol)	0	0
5-Androstenedione (androst-5-ene-3,17β-dione)	0	0
Epi-dihydrotestosterone	0	0
Epitestosterone	0	0
3α-Hydroxy-5α-androstan-17-one	0	0
3β-Hydroxy-5α-androstan-17-one	0	0
19-Norandrosterone	0	0
19-Noreriocholanolone	0	0
Other anabolic agents and similar substances		
Clenbuterol	0	0
Selective androgen receptor modulators	0	0
Tibolone	0	0
Zeranol	0	0
Zilpaterol	0	0
Hormones and related substances and substances with similar chemical structures or biological function		
Chorionic gonadotropin	0	0
Luteinizing hormone	0	0
Aromatase inhibitors		
Anastrozole	0	0
Letrozole	0	0
Aminoglutethimide	0	0
Exemestane	0	0
Formestane	0	0
Testolactone	0	0
Selective estrogen receptor regulators		
Raloxifene	0	0
Tamoxifen	0	0
Toremifene	0	0
Other substances against the function of anti-estrogen		
Clomiphene	0	0
Cyclofenil	0	0
Fulvestrant	0	0

Table 4 (continued)

	TD group (positive case)	Control group (positive case)
Agents for the regulation of myostatin functions		
Myostatin inhibitors	0	0
Masking reagents and substances with similar biological functions		
Diuretics	0	0
Probenecid	0	0
Plasma expanders (e.g., intravenous administration of albumin, dextran, hydroxyethyl starch, and mannitol)	0	0
Diuretics and substances with similar biological functions		
Acetazolamide	0	0
Amiloride	0	0
Bumetanide	0	0
Canrenone	0	0
Chlorthalidone	0	0
Etacrynic acid	0	0
Furosemide	0	0
Indapamide	0	0
Metolazone	0	0
Spironolactone	0	0
Thiazides (e.g., bendroflumethiazide, chlorothiazide, hydrochlorothiazide)	0	0
Triamterene	0	0
Nonspecific stimulants		
Adrafinil	0	0
Amfepramone	0	0
Amiphenazole	0	0
Amphetamine	0	0
Amphetaminil	0	0
Benzphetamine	0	0
Benzylpiperazine	0	0
Bromantan	0	0
Clobenzorex	0	0
Cocaine	0	0
Cropropamide	0	0
Crotetamide	0	0
Dimethylamphetamine	0	0
Etilamphetamine	0	0
Famprofazone	0	0
Fencamine	0	0
Fenetylline	0	0
Fenfluramine	0	0
Fenproporex	0	0
Furfenorex	0	0
Mefenorex	0	0
Mephentermine	0	0
Mesocarb	0	0
Methamphetamine(D-)	0	0
Methylenedioxyamphetamine	0	0
Methylenedioxymethamphetamine	0	0
p-Methylamphetamine	0	0
Modafinil	0	0

Table 4 (continued)

	TD group (positive case)	Control group (positive case)
Norfenfluramine	0	0
Phendimetrazine	0	0
Phenmetrazine	0	0
Phentermine	0	0
4-Phenylpiracetam (carphedon)	0	0
Prolintane	0	0
Specific stimulants		
Adrenaline	0	0
Cathine	1 (26)	0
Ephedrine	2 (26 and 43)	0
Etamivan	0	0
Etilefrine	0	0
Fenbutrazate	0	0
Fencamfamin	0	0
Heptaminol	0	0
Isometheptene	0	0
Levmetamfetamine	0	0
Meclofenoxate	1 (26)	0
Nikethamide	0	0
Norephedrine	1 (26)	0
Norfenefrine	0	0
Octopamine	0	0
Oxilofrine	0	0
Parahydroxyamphetamine	0	0
Pemoline	0	0
Pentetrazol	0	0
Phenpromethamine	0	0
Pseudoephedrine	1 (26)	0
Propylhexedrine	0	0
Selegiline	0	0
Sibutramine	0	0
Strychnine	0	0
Tuaminoheptane	0	0
Narcotic substances		
Buprenorphine	0	0
Dextromoramide	0	0
Diamorphine (heroin)	0	0
Fentanyl and its derivatives	0	0
Hydromorphone	0	0
Methadone	0	0
Morphine	0	0
Oxycodone	0	0
Oxymorphone	0	0
Pentazocine	0	0
Pethidine	0	0
β-Blockers and substances with similar biological functions		
Acebutolol	0	0
Alprenolol	0	0

Table 4 (continued)

	TD group (positive case)	Control group (positive case)
Atenolol	0	0
Betaxolol	0	0
Bisoprolol	0	0
Bunolol	0	0
Carteolol	0	0
Carvedilol	0	0
Celiprolol	0	0
Esmolol	0	0
Labetalol	0	0
Levobunolol	0	0
Metipranolol	0	0
Metoprolol	0	0
Nadolol	0	0
Oxprenolol	0	0
Pindolol	0	0
Propranolol	0	0
Sotalol	0	0
Timolol	0	0

Positive sample number in bracket

We used the laboratory that performed stimulant tests for the Olympic Games to test the urine samples of children with TS for 197 excitatory substances. The detected rate of excitatory substance of 6.82% may not be correct since it could have been far from the normal values. Since we do not have the standard values for excitatory substances in normal children, we cannot exclude the possibility that the normal level of excitatory substances in children with TS is higher than that of normal children but lower than that of adults. Our Chinese colleagues investigated the relationship between sexual hormones and children with TS using radioimmunoassay to test the plasma level of testosterone, estradiol, and progesterone in 15 male children with TS and 20 normal children. The TS patient's plasma level of testosterone was significantly higher than that in normal children ($P<0.01$); the plasma level of progesterone was a little lower in TS children ($P<0.01$) [19].

The conclusion may result in children being diagnosed as false-negative patients. Moreover, this study tested only urine samples and excluded blood or saliva samples. Hence, the relationship between excitatory substances and TS needs to be explored, with the goal of providing more information on diagnosing and treating TS.

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