TOURETTE'S SYNDROME IN A BLACK WOMAN WITH ASSOCIATED TRIPLE X AND 9p MOSAICISM

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A review of the literature and a rare case of Tourette's syndrome in a black woman in association with triple X and 9p mosaicism are presented.

The Tourette Syndrome Association placed an advertisement in the September 18, 1976, issue of *Saturday Review*[1] looking for people "who twitch, yelp, grimace, and grunt uncontrollably." The advertisement went on to describe a rare, lifelong, psychiatric disorder whose effects can render the person a social misfit and medical mystery. Once described as a "psychotic curse,"[2] it is characterized as a chronic waxing and waning disorder involving multiple motor and vocal tics which usually afflicts the person at an early age. The disease has been recognized for many years and bears the eponym of the individual who sought to clarify and describe its unique course. Various medical and psychological treatment modalities have been attempted and with the exception of a potent dopamine blocking agent have proven equally ineffective. To date this disorder is still often misdiagnosed and improperly treated. Its etiology remains dubious although it appears to have a genetic and neurochemical basis. Reported here is an unusual instance of this syndrome in a young black woman in association with triple X and 9p mosaicism.

HISTORY

The original case report of a person with the disorder, now known as Gilles de la Tourette's syndrome, or generalized tic disorder, appeared in a paper by Itard (1825),[3] who described a young French noblewoman who first manifested her unusual, involuntary motor tics at the age of seven. Later, she began to exhibit the characteristic vocalizations and, despite her well-bred heritage, uncontrollable coprolalia or compulsive, obscene utterances. Her clinical history, later pursued by Charcot,[4] lasted 75 years, testifying to its chronic course. In 1885 George Gilles de la Tourette[5] reported this case along with eight others, six of which he had observed personally. Tourette characterized the disease as a multiple-tic disorder with both verbal and motor disturbances, having an early onset and a fluctuating, chronic course. He noted that the patients he studied did not deteriorate intellectually or become psychotic, and he was impressed that they were able to maintain their sanity despite their dismal and, at that time, insurmountable disease prognosis. Furthermore, he attributed its etiology to heredity. Today, the diagnostic features remain much the same and the diagnosis is still a clinical one.

CHARACTERISTICS

Gilles de la Tourette's syndrome is considered to be a rare neuropsychiatric movement disorder. The symptoms are complex and individualized, consisting of a dynamic array of clinical manifestations. The most widely recognized of these clinical features include an early onset, a waxing and waning lifelong course, and multiple motor and vocal tics. The range of symptom onset generally extends from the ages of 2 to 15 with a mean of seven years[6] but can appear as late as 28[2,7,8] and perhaps even later.

The motor symptoms most often associated with Tourette's syndrome include involuntary

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tics, organized compulsive actions, and more dystoniclike movements.[9] They generally begin with the head region and appear as grimacing and blinking movements, head jerking, and facial spasms. They later generalize to include shoulder and trunk spasms, leg and arm jerking, and can virtually involve contraction of any muscle group. The more organized, stereotypic, compulsive actions may include echopraxia and copropraxia, but more commonly involve movements such as touching, clapping, kicking, finger snapping, object arranging, skipping, jumping, and running. The more dystoniclike movements are comprised of writhing and stretching actions.

Self-mutilating activities have been reported by several authors.[10-15] Aggressive behavior was present in 65 percent of a sample taken by Yaryura-Tobias and associates,[16] and in a questionnaire sent to members of the Tourette Association, Van Woert and associates[17] found a 40 to 50 percent rate of self-destructive behavior. Furthermore, at least one author[18] considers coprolalia, present in about 60 percent of all cases[6] to be a compulsive expression of verbal aggression.

Phonic symptoms, generally considered to be the most annoying to the patient though the most controllable through the use of dopamine blocking agents,[6] involve noises such as hissing, coughing, throat clearing, whistling, spitting, squeaking, barking, grunting, and hawking. Phonic disturbances may also include speech sounds such as stammering, echolalia, explosive exclamations, and sudden interjections of short phrases into ongoing conversations. Coprolalia, the hallmark of Tourette's syndrome, though not necessary for the diagnosis, occurs in approximately 50 to 60 percent of the cases.[6,7] Coprolalia, like the other symptoms, can make its appearance at any time during the course of the disease and may spontaneously disappear in some patients.

The waxing and waning of symptomatology is periodic and appears related to environmental stress, emotional levels, and ongoing activities.[19-26] For instance, the manifestation of symptoms is almost totally absent during coitus, sleep, or during a nonanxious activity requiring mental attention such as problem solving, reading, or television viewing. There is also some recent evidence which indicates that therapeutic effectiveness may be somewhat dependent upon the patient's current state of anxiety.[22]

DEMOGRAPHICS

Tourette's syndrome has been found in many parts of the world, within most races, and across all socioeconomic barriers. It occurs three times as frequently in males as in females and has an average age of onset of approximately seven years.[6,7,10,11,13,25,27,32] The incidence of this disorder has yet to be determined, but the combined total number of reported cases in the world literature is probably less than 1,000.

Very little importance has previously been given to the ethnic or racial background of Tourette patients, and many reports fail to mention these demographic data. It has been noted, however, that this disorder has a higher incidence in patients of Jewish, Italian, or northeastern European background[10,22,31-33] and that it rarely occurs among the black population.[34] It has been suggested, however, that the greater incidence found among the Jewish and northeastern European groups may represent a geographical selection bias.[35] One recent study, in pooling a different regional area, did not find a higher incidence of those ethnic groups.[36] The reported incidence among the black population is very low. Shapiro and his associates[6] in their review of the literature revealed only four black patients, including two of their own. Golden[37] reports an additional six black/Hispanic patients but fails to differentiate between the two ethnic groups. The total number of reported cases with Tourette syndrome in blacks is thus less than ten.

ETIOLOGY

Gilles de la Tourette's syndrome is an enigmatic disorder for which various causes have been proposed. Originally, Tourette believed that the cause may have a genetic character. The genetic disposition soon fell to disfavor, however, as psychogenic theories became increasingly emphasized. The children, it was claimed, were raised in stressful environments, with one of the parents being rigid and domineering. The symptom complex arose as an unresolved and unacceptable hostile reaction toward the parents. The evidence today shows while there is little doubt that the environment, particularly within the home, plays an important role in the frequency and duration of the symptoms, there is little reason to believe that this disorder is primarily the result of parental upbringing or environmental conditioning.

The etiological pendulum is beginning to swing back in favor of the genetic aspect as it is becoming increasingly appreciated.[34] The main impetus of the genetic movement is being generated from the well-known finding that this disorder occurs in males approximately three times as often as in females, that movement disorders tend to be found in the families of Tourette patients and the belief of some authors that this disorder has a higher incidence within Ashkenazic Jews and other Eastern European families.

Interestingly, the only recorded chromosomic analysis of a Gilles de la Tourette patient did reveal an anomaly of the 47, XYY male karyotype.[38] The evidence is not yet conclusive, but some form of genetically determined mode of inheritance will probably be established.[5,11,33,34,39-41]

The discovery that haloperidol, a known dopamine blocking agent, ameliorates the symptoms of this syndrome following ingestion and exacerbates the symptoms following termination has led to the now popular and current concept of an organic etiology for Tourette's syndrome. More specifically, proponents indicate that there exists an over-activity or super-sensitivity of dopaminergic neurons. Tangential evidence supporting the neurotransmitter approach is the observed exacerbation of symptomatology following administration of medications that augment dopaminergic activity such as methylphenidates[32,42] and dextroamphetamine;[43-46] exacerbation with tricyclic antidepressants which augment noradrenergic, as well as serotonergic activity;[47,48] the similarity of behavior following chronic, long-term ingestion of amphetamines that release catecholamines and promote dopaminergic over-activity; the stereotypic and ticlike behavior elicited in animals treated with amphetamines; and the ticlike symptoms often seen in children following amphetamine treatment.[10,49-52] Furthermore, the recognition that other movement disorders, eg, Huntington's chorea and Parkinson syndrome, reflects an imbalance of neurotransmitters lends additional credibility to the idea.[13]

Recently some lines of investigation have attempted to implicate the direct role of dopamine in Tourette's syndrome by measuring levels of homovanillic acid (HVA), the principal metabolite of dopamine in the cerebrospinal fluid of Tourette patients. This research has, however, produced inconsistent results.[9,13,17,43,53-56]

Other evidence supporting an organic etiology, though not necessarily one directed toward the dopaminergic hypothesis, is the prevalence of abnormalities on neurological testing, electroencephalogram disturbances, genetic pedigrees, and the frequent association with birth trauma.[6,7,10,11,35,54,57,58]

Another recent line of investigation has attempted to link the Tourette and Lesch-Nyhan syndromes into a common etiological mold. These authors base their research on the similarities between self-mutilating behavior, male predominance, and abnormalities of hypoxanthine guanine-phosphoribosyltransferase (HGPRT).[11,59,60] However, other authors have found no similarity between the two syndromes based on patterns of inheritance, behavioral changes or alterations of purine metabolism.[13,54,61]

We can conclude from the research presented that Tourette's syndrome is neurochemically triggered, genetically determined, and environmentally directed.

TREATMENT

Effective treatment begins, of course, with the correct diagnosis and, in the case of Tourette's syndrome, the diagnostic process may be a very belated one. Shapiro and associates[6] for instance, found that the correct diagnosis follows the initial onset of symptoms an average of ten years with a range of from 0.2 to 54.9 years. Various treatment modalities have been attempted during the interlude between the onset of symptoms and correct diagnosis, and following the diagnosis. This provides us with an unusually rich and varied treatment record.

Abuzzahab and Anderson[7] evaluated the efficacy of various treatments in 430 cases of Tourette's syndrome. They provide an extensive list of "sedatives," "antipsychotic tranquilizers," "antidepressants," "CNS stimulants" and "antiparkinsonian medications." The various medical and psychological regimens attempted have included behavior therapy, shock therapies, hypnotherapy, hydrotherapy, isolation, bed rest, sleep therapy, CO_2 inhalation, and various lobotomies. Other miscellaneous therapies included chiropractic treatment, lysergic acid diethylamide (LSD), fever therapy, hygiene, flogging, strictness, megavitamins, leeches, and muscle relaxants. Most of these regimens proved to be of dubious or harmful value. The highest total percentage improvements was 89

percent achieved with haloperidol, the next being 56 percent and 54 percent with physical therapy and sleep therapy respectively.

Since Seignot first used haloperidol for Tourette's syndrome in 1961, it has remained the treatment of choice.[2,7,10,11,21,22,29,34,53,62-69] Other dopamine blocking agents such as the phenothiazines do not provide relief as successfully as does haloperidol, nor is haloperidol always effective. Up to 180 mg/day may be necessary in controlling symptoms in adults,[10] but most children respond to much lower dosages.[32] The major side effect at lower dosages is sedation, and this is usually the limiting factor in its daily use. At higher dosages extra pyramidal symptoms develop, and patients may require additional treatment with antiparkinsonian drugs.

For the patients who can not tolerate, responded poorly to, or are contraindicated for haloperidol, there are other less used but promising drugs which have been effective. In one recent article,[70] pimozide, a diphenylbutylpiperidine, was hailed as having a more specific antidopaminergic activity than haloperidol and that achieves the same effectiveness as does haloperidol but with fewer, troubling side effects. Other alternatives are clonidine, an imidazoline derivative which acts as a central noradrenergic inhibitor.[9] Clonazepam is a new benzodiazepine with previous usefulness in the treatment of some forms of epilepsy[71]; it acts by modifying the metabolism of serotonin.[72] 5-Hydroxytryptophen, a serotonin precursor, has been used effectively in the treatment of Tourette's syndrome and myoclonic epilepsy[59,73]; corticosteroids were found to be effective in a case of a young boy who developed Tourette's syndrome following a high fever.[74]

Because of the characteristic fluctuations in symptom manifestations, the treatment of choice must be closely monitored. Dose requirement will vary not only due to the intensity of the side effects, but also to the natural cyclical variation in the intensity of the symptoms and the amount of stress perceived by the patient.[62] Caine and associates[75] suggest that some definite but minor signs of Tourette's syndrome be evident throughout treatment as a means of constantly monitoring severity and reducing the possibility of tardive dyskinesia. It has also been suggested that the haloperidol or other neuroleptics be reduced or withdrawn periodically to reassess their need. Furthermore, all patients should be examined regularly for the appearance of dyskinesias, such as choreoathetosis of the extremities, head, and trunk or oral facial dyskinesias. Continued neuroleptic treatment in the presence of such movements may lead to their exacerbation and/or irreversibility.

CASE REPORT

This was the second Hubbard Hospital admission for a 24-year-old black woman who had had sporadic spontaneous outbursts of aggressive behavior for the last ten years.

She exhibited motor tics such as eye blinking, facial grimacing, teeth grinding, head nodding, shoulder shrugging, arm waving, and kicking. The motor tics were often accompanied by vocal tics such as coughing, spitting, and blowing. Most striking were her episodes of coprolalia and echolalia. Her symptoms waxed and waned over time and were most noticeable during periods of stress. She became agitated easily, exploding with a violent temper, although generally she was not violent toward others. She exhibited some self-destructive behavior such as hair pulling and slapping. Her aggressive behavior was occasionally associated with grand mal type seizures, of which she had been suffering for the past 15 years. To control the seizure activity, she had been taking 300 mg phenytoin and 60 mg phenobarbital daily. She was also on a daily regimen of haloperidol, 5 mg TID for the amelioration of Tourette symptoms.

The patient is the product of a full-term, low-birth-weight (1279 g), vaginal delivery with breech position. The patient was born with a cleft palate and bilateral inguinal hernias which were repaired at the age of three years. The mother was 37 years of age when the patient was born, and the patient is an only child. The mother had had two previous miscarriages before the patient was born. There was no family history of mental retardation or epilepsy. However, the family medical history did include a grandfather with Parkinson's disease, a grandfather with high blood pressure, and the patient's father dying of a heart attack at the age of 58. The patient walked at the age of two, and had normal speech development. She attained menarche at the age of nine and menstruates regularly. She earlier had been diagnosed as being epileptic, as having Tourette's syndrome, and as of schizophrenia-paranoid type. Interestingly, it was the patient's mother who made the diagnosis of Tourette's

TABLE 1. COMPARATIVE SUMMARY OF THE PATIENT'S CLINICAL FEATURES AND THEIR PLACEMENT WITHIN EACH SYNDROME

Clinical Features	GTS	9p	47,XXX
Aggressive behavior	X		
Compulsive actions	X		
Coprolalia	X		
Echolalia	X		
Seizures	X		X
Motor tics	X		
Poor motor coordination	X		
Vocal tics	X		
Atrophic vagina		X	
Clinodactly		X	X
Flat nasal ridge		X	X
High arched palate		X	X
Inguinal hernias		X	
Low hairline		X	
Low set ears		X	
Scoliosis		X	
Cleft palate			X
Low birth weight			X
Short fifth finger			X
Ataxia			
Bilateral exopthalmus			
Bilateral opthalmoplegia			
Hirsutism			
Hyperkeratosis			
Hypertropic gums			
Interdigital webbing of fingers			
Mild cubitus valgus			
Right facial nerve paralysis			
Right ptosis eyelid sclera			
Right side ectropian			
Short neck			
Short sternum			
Small nipples			
Tapering fingers			
Tapering foot and legs			
Under stature			
Low IQ			
Schizophrenia			

syndrome after reading an article on the disease in a popular magazine.

The patient presented herself as a well-developed and well-nourished female whose height was 134.62 cm and weight 67.95 kg. She had a short neck and a low neck line along with generalized hair over the face, abdomen, thighs, and legs. Pubic hair was of male distribution. There was right facial nerve paralysis, bilateral exophthalmos, opthalmoplegia, and nystagmus. Low set ears, flat nasal ridge, hypertrophic gums, and short sternum were also present. The physical examination also revealed scoliosis, small nipples, atropic vagina, and mild cubitus valgus. Tapering of the legs and fingers was present with mild clinodactyly, and short fifth fingers with interdigital webbing. Also present were poor fine and gross motor coordination with ataxia. A complete listing of the patient's presenting features is included in Table 1.

The patient was functioning at the mild mental retardation level of intelligence, with a full scale IQ score of 61 (Wechsler Adult Intelligence Scale). Her verbal IQ was significantly higher (73) as compared with her performance IQ (50) (Table 2).

TABLE 2. SUBTEST SCORES FOR PATIENT

Verbal scale	
Information	5
Comprehension	6
Arithmetic	4
Similarities	5
Digit span	4
Vocabulary	8
Performance scale	
Digit symbol	6
Picture completion	4
Block design	1
Picture arrangement	0
Object assembly	1

Inspection of the Bender Visual Motor Gestalt Test revealed several clinically significant errors indicative of organic dysfunction as would be manifested in the perceptual motor area.

Personality tests suggested poor reality contact with a formal thought disorder. She denied having hallucinations although she had been frequently observed acting out bizarre behaviors as if she were arguing with another. Her affect was labile and often inappropriate. Associations were loose. She showed a great deal of hostility and anger. She appeared to have poor control over her impulses and at times, acted out in a violent and aggressive manner. She was very suspicious and distrustful of others. Themes elicited by the Thematic Apperception Test (TAT) revolved around aggressive and hostile acts. Characters in these stories were described as being crippled and helpless in their efforts to change their situations. Furthermore, the patient seemed to flow easily between the reality of the testing session and the unconscious projection provided by the testing materials.

Electroencephalograms taken in June 1978 and May 1979 for both waking and drowsy states were within normal limits.

A dermatoglyphic study revealed ulnar loop patterns on all digits with the exception of an arch on the left thumb and radial loop on the fourth digit right hand. A low total ridge count of 67 was obtained. The axial triradius was in the "t" position bilaterally with an atd angle of 42 degrees in the left and 36 degrees in the right palm. Arch patterns were bilaterally present in the thenar area, with a radial loop in the hypothenar area of the left palm and an arch on the right palm. There was a partial simian crease on the right palm with short fifth fingers bilaterally. Main line formations were 7.7.5'.13 and 7.5'.5'.13 for the left and right palm respectively.

A chromosomal analysis was made from peripheral blood lymphocytes. Thirty metaphase spreads were analyzed by Q and R banding. All cells studied revealed a deletion of the terminal short arm of chromosome number 9. The banding analysis revealed a deletion of the short arm distal to the segment p22. The remaining chromosome consists of the entire long arm of chromosome 9 and part of the short arm lying between the centromere and band p22. In addition, a mosaic pattern of triple X chromosome was found in eight of the cells examined. The resultant analysis revealed a double chromosomal anomaly of a deletion of the short arm of number 9 and a mosaicism of XX/XXX chromosomes. The karyotype therefore was designated 46, XX, del (9) (qter→22)/47, XXX, del (9) (qter→p22).

Chromosomal analysis of the patient's mother revealed a normal karyotype 46, XX, by Q-banding.

A 5-axis diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders (DSM III) using the information provided, psychological testing results, and social/family history is as follows: Axis I: Tourette's disorder, schizophrenia-paranoid type; Axis II: Mild Mental Retardation; Axis III: 9p in association with triple X mosaicism epilepsy; Axis IV: None; Axis V: Poor.

DISCUSSION

This is an unusual case report, considering that the Tourette syndrome occurs rarely in blacks[34] and more commonly in males than in females. In this case, the family history appeared noncontributory to the mode of inheritance, although in the literature, an autosomal dominant mode of inheritance has been postulated. The only other chromosomal analysis reported for a Tourette-like patient found a 47 XYY male karyotype.[38] Merskey[38] suggests that the sex-karyotype may be a predisposing factor for neurological abnormality. It has also been implicated that there may be an association between epilepsy and Tourette's syndrome.[76] The present case analysis revealed two chromosomal

anomalies: one is a deletion of the short arm of chromosome number 9, and the other, a mosaicism of triple X and normal X chromosomes. This patient also presented a history of epilepsy.

Clinically, the present case exhibited several features in common with previously reported cases of 9p,[77] triple X,[78] and Gilles de la Tourette's syndromes (Table 1).

The characteristic dermatoglyphic finding of a radial loop on the fourth right digit, an arch pattern on the left thumb, and a resultant low total ridge count are seen in the present case and also in the triple X female.[79]

It appears advisable to conduct further analysis on all Tourette syndrome patients in order to determine whether this neuropsychiatric disorder is due to chromosomal defects or whether chromosomal anomalies as in the present case occur randomly within this unique population.

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