Motor, Behavioral and Pharmacologic Findings in Tourette's Syndrome

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ABSTRACT: We studied 112 patients with Tourette's syndrome (TS); the male-to-female ratio was 3.8, the mean age of onset was 7.3 years, and the average duration of symptoms prior to the initial evaluation was 15.2 years. Seventy-nine percent of the patients had at least one family member with motor or vocal tics, and an additional 10 percent had a family member with marked obsessive-compulsive behavior. Simple motor tics occurred as the presenting symptom in about one-third of patients; one-third had multiple motor tics at the onset, and another third started with vocal tics. During the course of the illness all patients developed multifocal motor tics and 86 percent had vocal tics. Verbal and mental coprolalia was present in 44 percent of the patients. Copropraxia was seen in 19 percent of patients, and both coprolalia and copropraxia were more frequent among the males than expected. Attentional deficit disorder was diagnosed in 36 percent of the patients and 32 percent had obsessive-compulsive personality. Sleep disturbances were reported by 62 percent of the patients and polysomnographs in 34 patients showed motor and vocal tics during all stages of sleep, sleep apnea, abnormal arousal pattern, and other sleep disturbances. Patients with mild symptoms improved with clonidine or clonazepam, but those with more advanced disorder required fluphenazine, pimozide, haloperidol or tetrabenazine.

RÉSUMÉ: Constations motrices, comportementales et pharmacologiques dans le syndrome de Gilles de la Tourette. Nous avons étudié 112 patients atteints du syndrome de Gilles de la Tourette; la proportion homme/femme était de 3.8, l'âge de début moyen était de 7.3 ans, et la durée moyenne des symptômes avant la première consultation était de 15.2 ans. Soixante-dix-neuf pourcent des patients avaient au moins un membre de leur famille qui présentait des tics moteurs ou vocaux et un autre dix pourcent avaient un membre de leur famille qui présentait un comportement obsessif-compulsif très marqué. Le symptôme de début était des tics moteurs simples chez le tiers des patients; un tiers avaient des tics moteurs multiples au début de leur maladie et chez l'autre tiers, la maladie avait commencé par des vocalisations. Au cours de leur maladie, tous les patients ont développé des tics moteurs multifocaux et 86 pourcent avaient des tics vocaux. La coprolalie verbale et mentale était présente chez 44 pourcent des patients. On a observé de la copropraxie chez 19 pourcent des patients, la coprolalie et la copropraxie étant plus fréquentes qu'on aurait été en droit de s'y attendre chez les sujets masculins. Trente-six pourcent des patients présentaient une incapacité de fixer leur attention et 32 pourcent avaient une personnalité obsessive-compulsive. Soixante-deux pourcent des patients ont rapporté qu'ils avaient des troubles du sommeil et des enregistrements polysomnographiques chez 34 patients ont montré des tics moteurs et vocaux pendant tous les stages du sommeil, de l'apnée du sommeil, un pattern d'éveil anormal, ainsi que d'autres troubles du sommeil. Les patients qui présentaient une symptômatologie peu sévère se sont améliorés avec la prise de clonidine ou de clonazepam; cependant, on a dû avoir recours à la fluphénazine, au pimozide, à l'halopéridol ou à la tétrabénazine chez ceux qui présentaient une symptômatologie plus sévère.

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In 1885 Georges Gilles de la Tourette described nine patients with motor tics.[1] Other manifestations of the Gilles de la Tourette's syndrome (TS) included involuntary vocalizations seen in six patients, coprolalia in five, echolalia in five, and echopraxia in two. Two patients had other family members with tics. Since that time, many large series of TS have been reported.[2-6] However, most of the studies were based on a preselected population of patients seen either in a pediatric or a psychiatric clinic. Because of our interest in movement disorders, we have studied 112 consecutive patients with TS, both children and adults, with emphasis on motor manifestations.

Methods

All patients were examined by one neurologist (JJ). The motor and vocal tics were videotaped, and family members were questioned about other manifestations that were not evident during the clinic visit. Psychological evaluations and overnight polygraphic sleep studies were performed in 27 and 34 patients, respectively. The family history was obtained by detailed questioning of the spouse or parents, and whenever possible by examining the family members. All patients met the DSM III (Diagnostic and Statistical Manual of Mental Disorders, 3rd

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edition) criteria for TS, but we did not exclude patients if their onset was before 2 or after 15 years of age. The criteria for the diagnosis of TS are discussed further elsewhere.[7] If the motor and behavioral manifestations were controlled with the current medication, then that medication was continued and was considered to be "the best medication." If the symptoms were not satisfactorily controlled, the patients were treated with clonidine, clonazepam, fluphenazine, pimozide, haloperidol, or tetrabenazine, usually in that order. The response from each drug trial was rated according to the following scale: 1) excellent 2) moderate, or 3) poor control of motor and vocal tics. For a rating of 1, the patient or his family members had to demonstrate not only a subjective improvement in the tics, but also an improvement in overall function, school or work performance, and an improvement in social interactions. The data was analyzed using the DBASE III plus program (Ashton-Tate).

RESULTS

One hundred and twelve patients were included in the study. The male-to-female ratio was 3.8, the mean age at onset was 7.3 years (range: 1-28), and the average duration of symptoms prior to the initial evaluation was 15.2 years (range: 0-53). There were eight patients who clearly had the onset of symptoms prior to age 2 and five with onset after age 15. Seventy-nine percent of the patients had at least one family member with motor and vocal tics and additional 10 percent had relatives with marked obsessive-compulsive behavior. As expected, fathers, brothers, and sons were reported more frequently to be affected than the female members of the family (Table 1). Simple motor tic was the most frequent presenting symptom of TS, occurring in over a third of the patients at the onset of the disease. A third of the patients had multiple motor tics at the onset, and another third started with either simple or multiple vocal tics. Decreased attention span and learning difficulties occurred as initial symptoms in 8 percent of TS patients, and only 3 percent had coprolalia as the first manifestation of the disorder (Table 2).

During the course of the illness, all patients developed motor tics, usually involving the face and head region. Blinking was the most common motor tic, seen in more than half of all patients, followed by facial grimacing , head jerking, shoulder, arm and neck jerks, oculogyric deviations, tongue protrusion, and trunk and pelvic movements (Table 3). One-third of the patients had various movements of the shoulder varying from an occasional simple shrug to bizarre, dystonic, rotatory movements of the scapula. In addition to simple motor tics, many patients exhibited complex movements including hitting, kicking, whole body twisting, jumping, tapping, self-scratching, "stretching" or "cracking" of fingers, shaking of hands, compulsive touching, and other complex movements (Table 3) . The most common vocal tic was throat clearing, occurring in about half of the patients, often prompting a referral to otolaryngologists; a third of the patients had sniffing which was often attributed to "allergies." Involuntary vocalizations also included grunting, humming, squeaking, coughing, barking, screaming, various expiratory sounds, whistling, snorting, blowing, and other noises (Table 4).

While often emphasized as a typical feature of TS, coprolalia was present in only 39 percent of the patients, although an additional five patients had mental coprolalia (obscene thoughts).

Table 1: Family Occurrence

(N = 110)

	Number of Probands
FAMILY HISTORY OF TICS OR OBSESSIVE-COMPULSIVE BEHAVIOR*	98 (11)
Father	33 (8)
Mother	17 (2)
Brother	13
Sister	7 (1)
Son	4
Daughter	2
Others	28 (1)

*( ) Obsessive-compulsive behavior

Table 2: Initial Symptoms

(N = 112)

	Number of Patients
Simple motor tics	41
Multiple motor tics	39
Simple vocal tics	20
Multiple vocal tics	15
Attention deficit or learning disability	9
Coprolalia	3
Echolalia	3
Echopraxia	2

Table 3: Motor Tics

(N = 112)

	Number of Patients
FACE/HEAD	
Blinking	59
Facial grimacing	57
Head jerks	45
Oculogyric deviations	13
Tongue protrusion	12
Bruxism	9
Blepharospasm	5
HEAD/SHOULDER	
Shoulder jerks	38
Neck jerks	18
UPPER LIMBS	
Arm jerks	21
Finger movements	7
TRUNK	
Truncal movements	11
Pelvic thrusting	11
Abdominal jerks	7
LOWER LIMBS	
Leg jerks	14
COMPLEX MOVEMENTS AND AGGRESSIVE BEHAVIOR	
Hitting/kicking	15
Whole body twisting	7
Biting lips/cheek/tongue	5
Jumping	3
"Cracking" fingers	3
Tapping on things	3
Scratching self	2
Hand shaking	2
Grabbing people	2

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The male-to-female ratio of the patients with coprolalia was 4.4. The most common obscenities among the 43 patients with coprolalia were usually four-letter words describing sexual acts,[18] body function or elimination acts,[13] and organs of reproduction or sexual anatomy.[7] The most common obscenities were "motherfucker," "fuck" and "shit," but many of these words were slurred and only parts of the words were actually pronounced. Profanities with a religious connotation were less common, occurring in only 4 patients. Animals such as "bitch," "bull" and "pig" were used by 6 patients. Copropraxia, an urge to make an obscene gesture, was seen in 19 percent of patients and the male-to-female ratio for this symptom was 20:1. Echolalia, repetition of words, or echopraxia, mimicking of gestures, was seen in less than one-third of the patients. Attentional deficit disorder was present in 36 percent of the patients and 32 percent had definite obsessive or compulsive personality traits. Many patients described various intrusive thoughts, internal fantasies, and compulsive ritualistic behavior. Self-destructive behavior occurred in 9 percent of the patients and ranged from biting nails to more harsh self-mutilating acts: six patients had bitten their lips, cheek, or tongue, and two scratched themselves to the point of bleeding (Table 5) . One patient with congenitally narrowed cervical spinal canal became quadriplegic because of violent uncontrollable neck tics.

Sleep disturbances were reported by 62 percent of patients (Table 6). Enuresis sometimes persisted until the age of 13 years. Twenty-two patients were observed by their parents or their spouse to have motor or vocal tics during sleep. Sleep recordings were performed in 34 patients and showed motor tics during all stages of sleep in 23, reduced REM sleep in 18, abnormal arousal pattern in 10, and sleep apnea in 8 (Table 6).

Most patients required a trial of more than one medication before a satisfactory improvement could be achieved (Table 7). Clonidine and clonazepam were tolerated relatively well except for mild side effects such as drowsiness, fatigability, depression, and anxiety; one patient treated with clonazepam had a rash. However, only a third of the patients treated with either drug had an excellent response. Pimozide, fluphenazine, and tetrabenazine seemed most effective, about half of the patients achieving excellent response, but these medications were also associated with more adverse reactions. About a third of the patients experienced sedation, weight gain, depression, acute dystonic reaction or parkinsonian features. Haloperidol had the highest incidence of these adverse reactions. There were no electrocardiogram abnormalities attributable to pimozide.

Discussion

TS is among the most frequently misdiagnosed neurologic disorders; therefore the true prevalence is unknown. However, the prevalence has been estimated at 0.05 percent.[8] One of the chief reasons for the difficulties in diagnosing TS is the failure to appreciate the full spectrum of the phenomenology of tics.[7] Motor tics consist of involuntary, abrupt, brief, coordinated muscle contractions. Tics can occur as isolated simple events such as eye blinking, facial grimacing, head twitching, or shoulder shrugging. About 51 percent of Shapiro's[3] patients began with a simple tic in a single location, whereas 37 percent of our patients had a simple tic as the presenting symptom (Table 2). Multiple tics were present at onset in 49 percent of Shapiro's[3] patients and in 35 percent of our patients. Only 19 percent of the TS patients in the Shapiro's[3] series had vocalizations at their onset, whereas 31 percent of our patients started with vocal tics. During the course of the illness 83 percent of Shapiro's[3] patients had eye blinking, 79 percent had head jerking, 65 percent had shoulder shrugs, 60 percent arm jerks, and 52 percent had neck tics. The corresponding percentages for our

Table 4: Vocal Tics and Noises

(N = 112)

	Number of Patients
Throat clearing	53
Grunting	45
Sniffing	39
Humming	26
Squeaking	24
Coughing	18
Barking	16
Screaming	11
Expiratory sounds	9
Whistling	7
Snorting	4
Laughing/giggling	4
Blowing	4
Guttural sounds	4
Hyperventilating	3
Sucking	3
Spitting	3
Growling	2
Other sounds	12

Table 5: Associated Symptoms

(N = 112)

	Number of Patients
Coprolalia	43
Attentional deficit disorder	40
Obsessive compulsive trait	36
Echolalia	30
Copropraxia	21
Echopraxia	12
Self-destructive tendencies	10
Mental coprolalia	6

Table 6: Sleep Disturbances

(N = 112)

	Number of Patients
SLEEP COMPLAINTS	69
Tics during sleep	22
Enuresis	19
Restless sleeper	12
Insomnia	12
Somnambulism	9
Nightmares	8
Myoclonus	6
Bruxism	3
POLYSOMNOGRAPHIC STUDIES	34
Motor tics	23
Vocal tics	4
Reduced REM sleep	18
Abnormal arousals	10
Apnea (obstructive)	8 (1-mixed)

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patients were 53, 40, 34, 19, and 16 percent. We cannot explain the difference between the two series, but it is possible that our patients were less severely affected than those in the Shapiro's[3] series. We did not insist on age of onset between 2 and 15 because some patients clearly had their onset out of this range. We also did not insist on multiple motor and verbal tics to be present in each patient because some patients with otherwise typical TS or with typical TS in a family member, have only simple motor or vocal tics when first seen and later developed into the full syndrome. Finally, we did not require that "symptoms always disappear during sleep and orgasm."[3] As discussed later, tics often persist during sleep, although they markedly diminish during sleep and when patients are engaged in sexual activity.

Besides simple or multifocal jerks, tics can also manifest themselves as bursts or sequences of patterned, coordinated, complex movements such as jumping, hitting, touching, tapping, shaking of hands and kissing. Simple or complex tics are sometimes mistaken for voluntary movements. However, the absence of pre-movement cortical potential before a tic suggests that the movement originates in some subcortical structures and, therefore, is not volitional.[9] Some patients, nevertheless, perceive their tics as being intentional because they "satisfy" certain sensations, urges, and compulsions.[10,11] This sensory component helps to differentiate tics from other hyperkinetic movement disorders, such as tremor, chorea, athetosis, ballism, dystonia, myoclonus and focal seizures. Tics fluctuate in response to the emotional state of the patient, increasing with stress, and they may be suppressed volitionally, at least for a few minutes. The suppressibility is another feature that helps to differentiate tics from the other movement disorders.

While most patients with TS have brief, unsustained, repetitive muscle contractions (clonic tics), about one-third also have more sustained, tonic contractions (dystonic tics). The dystonic tics may occur as blepharospasm and oculogyric deviations,[12,13] or as dystonic movements of the neck, shoulders and trunk.[7]

Another feature that helps distinguishing tics from the other hyperkinetic movement disorders is the observation that tics may occur during all stages of sleep.[14] Polysomnographic recordings in 34 patients showed motor tics in 23 and vocal tics in 4 occurring during all stages of sleep. The tics recorded during sleep are similar to those observed during wakefulness. Other disturbed sleep patterns include sleep apnea, enuresis, insomnia, abnormal sleep arousal patterns, nightmares and somnambulism. In one survey of 59 TS patients, 76 percent had sleep disturbance compared to 35 percent of age and sex-matched controls (X^2 = p0.00001).[15] These sleep disturbances seem to be particularly common in patients with a family history of TS or tics.[4,14]

The origin of TS is believed by some to be psychiatric or emotional, but the clinical, physiological and biochemical findings have provided a strong support for a basis in neural dysfunction (organic).[16] However, behavioral disturbances frequently accompany the motor and vocal tics. Among the behavioral disorders, the obsessive-compulsive symptoms are the most prominent,[17] seen in 32 percent of our patients. The percentage of TS patients with an obsessive-compulsive disorder varies between 12 and 74 percent, depending on the diagnostic criteria and other methodologic variables.[18] Some studies have provided evidence for a genetic linkage between TS and the obsessive-compulsive disorder.[18] In contrast, attentional deficit disorder with hyperactivity, seen in 36 percent of our patients, does not seem genetically related to TS.[19] We have noted unusual musical and athletic talents in some of our patients.

Vocal disturbances in TS patients range from various involuntary noises and sounds to echolalia, palilalia, and stuttering. In our series, throat clearing, grunting, sniffing, humming, squealing, coughing, barking and screaming were the most common vocalizations. Coprolalia may simply represent a linguistic equivalent of a vocal tic.[20] The frequency of coprolalia in patients with TS has ranged from 8% to 64%.[3,6] Verbal coprolalia was seen in 38 percent of our patients while mental coprolalia was reported by only 5 percent. Among Shapiro's[3] patients 56 percent spoke coprolalic words and 8 percent only thought of obscene words. Similar to other studies our data indicate that coprolalia increases with age, but may spontaneously disappear several years later. Words with sexual connotation were used much more frequently than religious profanities. This pattern is also seen in other languages and in other countries, reflecting a strong cultural inhibition of such obscenities (Table 8).[21]

A genetic predisposition was already suggested by Gilles de la Tourette and confirmed by later studies.[1,22,23] Eighty-nine percent of our patients had a first degree relative with tics, TS, or obsessive-compulsive behavior (10 percent). This familial frequency is probably an underestimation because not all family members have been examined. The mode of inheritance is unknown. However, a highly penetrant, sex-influenced, autosomal dominant trait or a major semidominant gene with variable penetrance have been proposed.[23,24] Twin studies have shown higher concordance rates in monozygotic twins when compared to dizygotic twins.[25,26] However, nongenetic factors must account for the fact that not all monozygotic twins are fully concordant and that even when a twin pair is affected, there is a marked phenotypic heterogeneity.[25] A Tourette family was recently identified with all six affected members having 7q22; 18q22 balanced translocation.[27] We found an occasional coexistence between TS and other genetic disorders such as phenylketonuria, neurofibromatosis, congenital myopathy and others. While such associations may be purely coincidental they may provide clues to the genetic mechanisms of TS.

The management of TS is based upon the severity of the symptoms and the impact on school or job performances, fam-

Table 7: Response to Medications

DRUG	Response 1	2	3
Haloperidol (n = 34)	11 (32%)	19 (56%)	4 (12%)
Fluphenazine (n = 28)	15 (54%)	9 (32%)	4 (14%)
Clonidine (n = 27)	9 (33%)	9 (33%)	9 (33%)
Tetrabenazine (n = 15)	7 (47%)	5 (33%)	3 (20%)
Clonazepam (n = 13)	5 (38%)	5 (38%)	3 (24%)
Pimozide (n = 9)	5 (56%)	2 (22%)	2 (22%)

RATING SCALE
1. Excellent response
2. Moderate response
3. Poor response

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ily and peer interrelationships and on other aspects of normal psychosocial interactions.[28] Many patients do not need medications because their symptoms are not disabling. Before initiating pharmacologic therapy the diagnosis should be clearly established. Secondary tic disorders due to anti-psychotic drugs, anticonvulsants, central stimulants, dopaminergic drugs, carbon monoxide intoxication, head trauma and encephalitis should be excluded.[16,29] Blood smear should be examined for evidence of neuroacanthocytosis which is characterized by a variety of findings including motor and vocal tics, lip-biting, chorea, dystonia, parkinsonism, areflexia, amyotrophy, seizures and elevated CK levels.[30]

Based on some indirect evidence from clinical pharmacologic studies, including an improvement of TS symptoms with dopamine blocking or depleting agents, an exacerbation with central stimulants and with dopaminergic drugs, and a low CSF homovanillic acid in some patients, it has been proposed that the underlying mechanism for TS involves "supersensitive" dopamine receptors.[31-33] However, recent PET scan and post-mortem receptor ligand studies have not confirmed this hypothesis.[34] The meaning of low dynorphin found in the striatal system projecting to the pallidum in one autopsied brain is still unclear.[35] The other neuropeptides seem to be present in normal concentrations.

Haloperidol, first tried for TS in 1961, is probably the most frequently used drug in the treatment of TS.[36,37] Although a satisfactory improvement can be achieved with haloperidol in about two-thirds of patients, less than a third can continue the drug for an extended period of time.[37] Even when the drug is increased slowly (0.5 mg/week) about a third of the patients experience such problems as irritability, depression, lassitude, loss of motivation, mental dullness, hypersomnia, parkinsonian symptoms, akathisia and weight gain. We have not observed serious allergic reactions, hepatotoxicity, or agranulocytosis, but these adverse reactions may also occur with haloperidol. We, and others,[38,39] have observed tardive dyskinesia, in some cases permanent, in Tourette's patients treated with haloperidol and with other dopamine receptor blocking agents. Tardive dyskinesia may be difficult to detect in patients with facial tics and may partly account for the low incidence of this complication reported in the literature.[37,40]

We use fluphenazine[41,42] or pimozide[43,44] if dopamine blocking drugs are needed to control disabling symptoms. Fluphenazine, a piperazine phenothiazine, seems to have an efficacy superior to haloperidol (Table 7) and has a lower incidence of sedation. Pimozide, a diphenylbutyl piperidine derivative, also seems to be more effective than haloperidol and has fewer adverse effects. While monitoring for potential cardiotoxicity has been recommended, none of our patients have had any ECG changes during the pimozide therapy.

Tetrabenazine, a benzoquinoline derivative which depletes monoamines and blocks presynaptic and postsynaptic dopamine receptors has also been studied in TS.[45] Despite some side effects, including drowsiness, depression, irritability and parkinsonism, about eighty percent of the patients show a marked or moderate improvement in the intensity and frequency of their tics with tetrabenazine.

Clonidine, an imidazoline derivative, has a central agonist effect on the presynaptic alpha2-adrenergic receptors, thereby reducing noradrenaline turnover.[46] Plasma free levels of methoxy-hydroxy-phenylethylene glycol (MHPG), a metabolite of norepinephrine, are reduced in TS patients who improve with clonidine.[47] Some patients feel "calmer" after a few days of taking clonidine and often notice an improvement in their behavioral problems.[48] Clonazepam may have a similar behavioral effect.[49]

Although our study is retrospective and open label, it provides some insight into the differential efficacy of the various drugs (Table 7). Fifty-six percent of patients treated with pimozide achieved "excellent" response, but the number of patients was small (N = 9). Second most effective drug was fluphenazine, with 54 percent of the 28 treated patients having "excellent" response. Tetrabenazine produced "excellent" result in 47 percent of the 15 patients. Since tetrabenazine was used as the last drug, after all the other drugs failed to control the symptoms, our results may be somewhat biased against this drug. Clonazepam produced "excellent" improvement in 38 percent of 13 patients, clonidine in 33 percent of 27 and haloperidol in 32 percent of the 34 treated patients. In some patients refractory to single medications, a combination of pimozide or fluphenazine with tetrabenazine seemed particularly helpful.

Although recognized over a 100 years ago, the greatest advances in the understanding of TS and its clinical, behavioral, genetic and neurochemical complexities have been achieved only in the last two decades.[50] A combined pharmacotherapeutic[28] and behavioral approach[51] should improve the functioning of most, if not all, patients with TS.

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Table 8: Coprolalia in Patients with TS in the United States and in Three European Countries

USA (PRESENT)	USA (3)	ENGLAND (21)	DENMARK (21)	SPAIN (21)
Mother-fucker	Fuck	Fuck	Fisse (vulva)	Puta (whore)
Fuck(er,-off)	Shit	Cunt	Kusse (vulva)	Mierda (shit)
Shit	Cunt	Bastard	Kaeft (shut-up)	Coño (cunt)
Bitch	Mother-fucker	Piss	Pik (prick)	Joder (fuck)
Pussy	Prick, dick	Sod	Rov (arse)	Maricon (queer)
Asshole	Cocksucker	Cock	Gylle (animal shit)	Cojones (balls)
	Nigger	Shit		Hijo de puta (son of a whore)
	Bull	Prick		Hostia (holy bread)
	Damn	Wank		Cabron
				Jillipolla

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