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A Twin Study of Tourette Syndrome

R. Arlen Price, PhD; Kenneth K. Kidd, PhD; Donald J. Cohen, MD; David L. Pauls, PhD; James F. Leckman, MD

• In 43 pairs of same-sex twins, in which at least one co-twin had Tourette syndrome (TS), 30 pairs were probably monozygotic (MZ) and 13 were probably dizygotic (DZ). Concordances for TS were 53% and 8% for MZ and DZ pairs, respectively. When diagnostic criteria were broadened to include any tics in co-twins, concordance rates were 77% and 23% for MZ and DZ pairs, respectively. These concordances are consistent with genetic etiology. However, the fact that only 53% of MZ twins were fully concordant indicates nongenetic factors affect expression of TS. Presence of tics in discordant co-twins and timing of onset in partially concordant co-twins support an association between TS and tics in families with TS present. The data are inconclusive on whether some MZ twins with discordant co-twins are etiologically different from those who are concordant.

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Tourette syndrome (TS) is a lifelong disorder characterized by multiple motor and phonic tics. According to *DSM-III* criteria,¹ the syndrome includes both motor and phonic tics, ability to suppress symptoms for minutes to hours, waxing and waning of symptoms over time, and a duration of at least one year. Onset of first symptoms is between ages 2 and 15 years, with a mean of about seven years. There is usually a progression from simple to complex tics, which often have compulsive or ritualistic qualities. Once thought to be extremely rare, estimates of prevalence of TS are as high as one per 2,000, with males outnumbering females by approximately three to one (see Friedhoff and Chase² for a review).

From the earliest description, a familial aggregation of TS and tics has been suggested; however, the frequency of familial transmission has remained uncertain until quite

recently. Reports supporting and challenging this view often relied solely on presence or absence of a family history and did not provide estimates of rates among first-degree relatives. Kidd et al³ and Pauls et al⁴ did indirectly assess first-degree relatives in a national sample and in consecutive clinical cases, respectively. With the use of logistic models, they found that, although the number of first-degree relatives with TS is small, about 2%, this prevalence appears to exceed the population value by as much as an order of magnitude. They also found that rates of other tics that do not meet criteria for TS are elevated in these families, suggesting that this may be a mild form of expression. These articles reported that female probands, less commonly affected than males, confer greater risk on their relatives than do males and that risk to siblings is increased in families in which a parent as well as a proband is affected.

While the etiology of TS is not known, these studies suggest familial transmission and are consistent with a genetic diathesis. The overall pattern suggests sex-modified penetrance, with mild tics representing an intermediate level of genetic vulnerability. Multiple threshold models like those described by Reich et al⁵ and Kidd and Spence⁶ have been applied to family data by Baron et al⁷ and by Kidd and Pauls.⁸ Single-major-locus two- and three-allele models and a multifactorial-polygenic model all received some support. Recently, Comings et al⁹ presented a segregation analysis of TS families that is consistent with a major gene effect on TS. Although not modeled specifically, cultural transmission, including vertical and other forms, remains a viable hypothesis as well.

TS IN TWINS

Reports on twins in the literature are scant and have primarily been limited to anecdotal case reports. Ellison¹⁰ reported a case of TS in a man who had a discordant monozygotic (MZ) twin. Escalar et al¹¹ reported on a pair of single placental male twins who were concordant for TS. Frost et al¹² reported on a case of a male with TS whose mother was an MZ twin. The mother and her co-twin were concordant for tics but did not have TS. Eldridge et al¹³ reported on 21 pedigrees that included three sets of twins. However, only one pair had an affected member, a discordant, opposite-sex pair. Wassman et al¹⁴ reported on 14

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additional families that included two more sets of twins. One opposite-sex pair was unaffected. A like-sex pair, which appeared to be MZ, was concordant for TS. Shapiro et al¹⁵ reported three twin cases. In one of these pairs, which was reported as being probably MZ, one twin had TS and the co-twin had a diagnosis of probable TS. Two opposite sex pairs were discordant. Bachman¹⁶ reported a case of a pair of DZ twins in which one boy developed TS after treatment with pemoline. Recently, Jenkins and Ashby¹⁷ and Waserman et al¹⁸ reported two additional concordant MZ pairs.

Summarizing twin cases, Shapiro and Shapiro¹⁹ mentioned 14 cases of which they were aware among their clinical cases and in the literature. They noted that seven of nine MZ twin pairs were concordant and four of five DZ pairs were discordant for TS. The article did not document the cases. These concordances were not for TS alone, but also for TS paired with other, milder forms of tics in the co-twins (Arthur Shapiro, MD, oral communication, 1982). When we looked only at published reports, we found only seven cases of same-sex twins in which one or both have TS. Of these cases, (80%) four of five MZ and zero (0%) of one DZ twins were concordant for TS. The pair with uncertain zygosity described by Escalar et al¹¹ was concordant. An additional opposite-sex pair described by Eldridge et al¹³ and two opposite-sex pairs described by Shapiro et al¹⁵ were discordant.

Differences in twin concordances are commonly used to suggest the effects of genes, since MZ twins are genetically identical and DZ twins share on average only half their genes. The twin cases just reviewed appear to fit such a pattern and agree with the evidence of vertical transmission in families. However, it is a very small number of cases, particularly if only same-sex twins are considered, and the cases were accumulated in a fragmented manner.

SUBJECTS AND METHODS

Twin Ascertainment

All but one of the twin pairs reported on in the present study were ascertained as pairs rather than as cases. These were same-sex pairs in which one or both had previously been diagnosed as having TS. All but one of the pairs reported on here were identified through a mailed questionnaire sent to over 8,000 members of the Tourette Syndrome Association. There were 42 pairs that had at least one member with symptoms of TS. Of these, all but two individuals with TS reported having been diagnosed previously. One was reportedly considered probable TS by his physician, and another, who was considered possible TS by the physician's report to the mother, had reportedly had greatly increased symptoms since his last examination and, based on our questionnaire assessment of symptoms, did meet *DSM-III* diagnostic criteria for TS. One individual who had received a definite diagnosis of TS from his physician reported never having had vocal tics. This individual was classified as affected since it was thought that the possibility of a false-positive diagnosis was less likely than the possibility that the parent missed some vocal symptoms. In summary, a diagnosis of TS depended primarily on previous diagnoses, but all diagnoses were confirmed by our questionnaire assessment and phone interviews, which supports the reliability of the diagnosis. Our assessments of individual twins were not blind, since both were made by a single individual (R.A.P.). One additional pair was ascertained as a case through the Child Study Center clinic (as a patient of one of us [D.J.C.]) and was included in the sample, making a total of 43 pairs.

We note that two of these "pairs" were actually triplets. In one set, the opposite-sex triplet was treated as an ordinary sib of the same-sex pair. In another set of same-sex triplets, the two MZ individuals were chosen arbitrarily to form a pair, and the third "DZ" triplet was treated as a sib rather than constructing two additional, overlapping DZ pairs.

The current twin sample may have some overlap with previous

reports. We know, for example, from communication with both subjects and researchers, that the patient described by Jenkins and Ashby,¹⁷ some patients studied by Shapiro,^{15,19} and other cases currently under study by Eric Caine, MD, (oral communication, January 1983) are included in our sample. However, we have not attempted a comprehensive study of degree of overlap, and, because of confidentiality, it has usually not been possible to identify specific instances except when the subjects have volunteered the information.

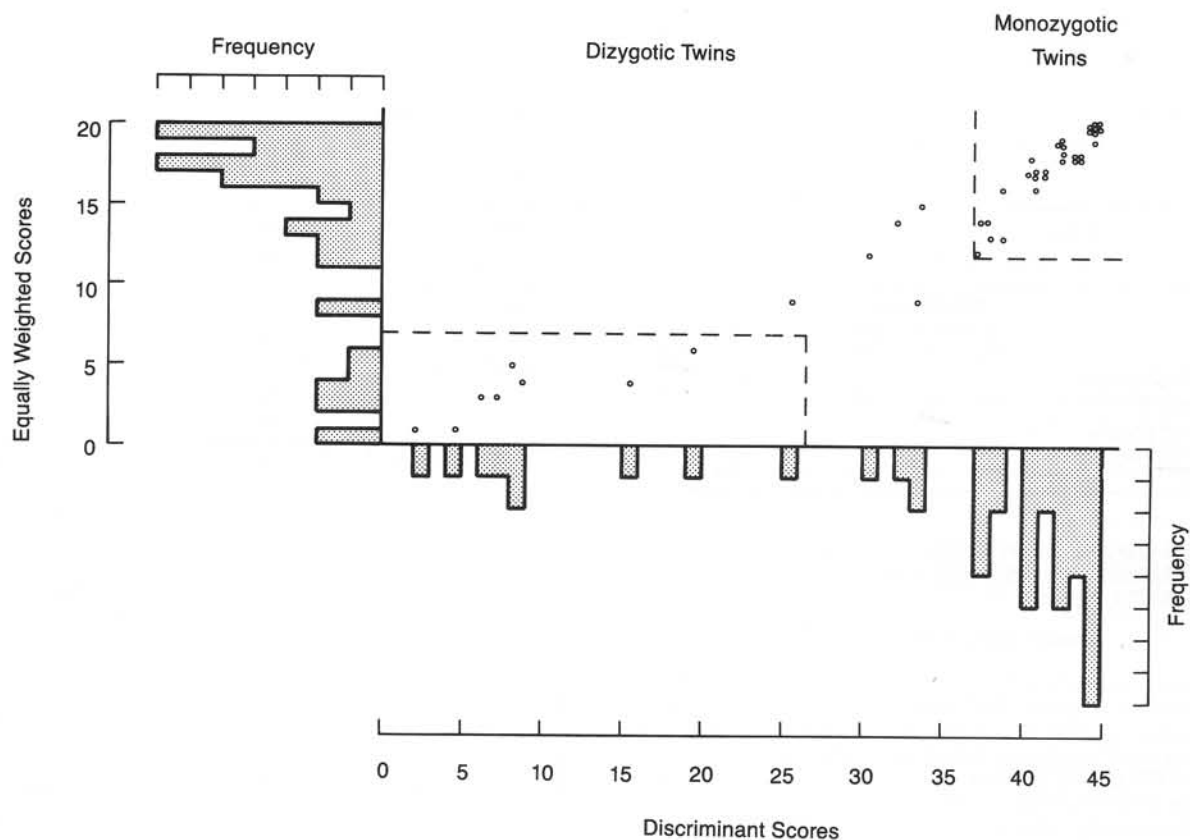
Assessment

Of the total sample of 43 pairs, 36 were first contacted by a mailed questionnaire using standard procedures for informed consent. All 43 were contacted by telephone, at which time both the initial and follow-up questionnaires were covered in detail. All subjects had previously given their consent to being contacted about possible participation in research projects, either to the Tourette Syndrome Association or directly to us. In addition, procedures to assure informed consent were followed verbally in the phone conversation. Usually the contact was with the mother and in a small minority of cases there were two or more respondents, in which case responses were pooled. The questionnaire (available on request from us) assessed presence, onset, suppressibility, and severity of motor and vocal tics. Duration of symptoms and previous diagnosis were also determined. In addition, presence of symptoms was recorded for all first-degree relatives. History of drug treatment was assessed, and presence of obsessive/compulsive (O/C) behaviors were also reported. The assessment of O/C was based on the *DSM-III*. However, duration and impairment were not measured. As with TS, diagnoses were made by the interviewer (R.A.P.). A questionnaire on physical similarity and confusability was also included.

Diagnosis of Zygosity

All but two of the twin pairs, or parents of the twins, were contacted only by mail and/or telephone. Therefore, it was not possible to use genetic markers to assess zygosity. Instead, a ten-item questionnaire was used that is based on physical similarity and confusability during childhood. The questionnaire method has been shown by Cohen et al^{20,21} as well as by others²²⁻²⁵ to have high validity in diagnosing zygosity. The questionnaire was scaled by two methods: by an approximately equal weighting procedure and by using discriminant weights. The distributions of these two sets of scores are shown in the Figure. The equal weighting method yielded a distribution with a large number of values in the intermediate range. This result is to be expected for a mixed distribution of MZ and DZ twins and normal siblings, who vary greatly in similarity. The only natural breaks in this distribution occurred at locations that were inappropriate for separating MZ from DZ pairs, seven for high probability of DZ and 12 for high probability of MZ.²⁰ On the other hand, there were two natural breaks in the distribution of discriminant scores; these exactly bracket the intermediate range of uncertain zygosity described by Cohen et al,²⁰ viz, 26 to 37. Only four pairs fell within this range. On the basis of individual physical similarity/confusability items, eg, hair color, one of these pairs is probably DZ. The other intermediate pairs reported physical dissimilarities but were less clearly DZ. Because the questionable pairs overlapped those who are probably DZ in overall physical appearance as well as discriminant and equally weighted scores, these pairs were all retained in the analysis and classified as DZ.

The zygosity assessment is explicitly based on perceived physical similarity and confusability during childhood. The effect of the appearance of TS symptoms on the perception of physical similarity is not known. However, marked symptoms of TS are not present from birth and severe symptoms often do not appear until late childhood or even later on in adolescence. This feature should minimize any possible effect of tics on the perception of physical similarity. We cannot exclude the possibility of some misclassification of zygosity, which, if present, might inflate MZ concordances relative to those for DZ twins. However, whatever bias is present in our data, our concordance rates (see below) are considerably lower than the rate estimated from previously published uncontrolled reports. Moreover, in our own data, physical similarity and con-



Joint plot and marginal distributions of equal and discriminant weighted zygosity scores. Dashed lines enclose areas in which no errors in zygosity estimation occurred when verified with serological markers.^{19,20} Intermediate area includes five twin pairs with uncertain zygosity.

fusability of twins classified as MZ was not related to concordance. Discordant, partially concordant, and fully concordant pairs (see below for category definitions) had discriminant scores that overlapped completely. The mean values were 41.4, 42.0, and 41.8, respectively, and did not differ significantly.

Although it is not possible to be entirely certain of diagnosis without examining a number of genetic markers, based on the results of Cohen et al^{20,21} it seems likely that we have misclassified no more than one or two pairs. Moreover, based on the placement of the cutting point, it is improbable that pairs we have classified as MZ are in fact DZ. Any misclassifications are likely to have been in the other direction, and, hence, would tend to be conservative from the standpoint of testing genetic hypotheses.

RESULTS

Twin Sample

The total number of twin pairs divided by sex and probable zygosity is presented in Table 1. There were 30 pairs who are probably MZ and 13 who were classified as DZ. The excess of MZ twins may reflect a volunteer bias common to twin studies,²⁶ but it could also be due to other factors, eg, a higher probability of ascertainment of concordant pairs combined with a lack of independence in diagnoses of MZ twins. The smaller number of female pairs must reflect to some degree the lower population prevalence of TS among females.

Since the twins were ascertained as pairs in which at least one of the twins was affected, there is no proband per se. Because of this, pairwise rates will be presented in the paper. It seems probable

that concordant pairs have a higher probability of ascertainment than discordant pairs and that individuals from concordant pairs were not ascertained completely independently. Thus, the observed pairwise rate may be inflated relative to the pairwise concordance rate in the population.

The proband concordance rate, which is an estimate of the segregation frequency, is probably higher than the observed pairwise rate, although it is possible to imagine the proband rate being lower if the probability of ascertaining concordant pairs were much higher than twice the probability of ascertaining two affected twins as individuals. In addition, because the ascertainment probability is much lower for DZ twins, it is possible that DZ concordances are decreased relative to rates in MZ twins. It is simply not possible for us to make precise estimates of the probability of ascertaining MZ or DZ twins as individuals. This uncertainty imposes limitations on the interpretation of the concordances in terms of genetic parameters like penetrance and heritability (see Lykken et al,²⁶ Allen et al,²⁷ Hrubec,²⁸ and Smith²⁹ for a discussion of these issues). Because of this limitation, we have chosen not to make any specific parameter estimates at this time.

The twins ranged in age from 7 to 61 years, with all but one pair being under 45. The mean age was 18 years. Onset of earliest symptoms ranged from ages 1 to 14 years, with a mean of 7½ years. This distribution is consistent with previous reports concerning the natural history of TS. The reported onset at age 1 year is a little too early to meet strictly *DSM-III* criteria. The onset age was approximated in this case since we arbitrarily took the earlier age of onset whenever we had more than one report on the twins. In

Table 1.—Same-Sex Twin Pairs With at Least One Co-Twin Having Tourette Syndrome

Sex	Monozygotic	Dizygotic	Total
M	25	10	35
F	5	3	8
Total	30	13	43

Table 2.—Twin Concordances for Tourette Syndrome (TS) and Tics

	Monozygotic			Dizygotic		
	M	F	Total	M	F	Total
Fully concordant (both with TS)	.520	.600	.533	.100	.000	.077
At least partially concordant (co-twin with TS or tics)	.760	.800	.767	.300	.000	.231

this particular case, one respondent remembered tics as early as 1 year, while another noticed none until age 5. All other diagnostic criteria for TS were met.

Concordances for TS and Tics

Pairwise twin concordances for TS are presented in Table 2 divided by sex, zygosity, and degree of concordance. The overall concordances in male and female pairs did not differ appreciably, given the small number of female pairs. However, the difference between MZ and DZ pairs was substantial. Fifty-three percent of MZ pairs were concordant, compared with only 8% of DZ pairs. A logistic regression analysis of these concordances was used to facilitate incorporation of zygosity and sex into the same analysis. The effect of zygosity on concordance was significant ($\chi^2 = 5.60$; $P < .05$), while the effect of sex was not.

Since it has been suggested that multiple or chronic tics may be a milder manifestation of TS, we wondered whether discordant co-twins might have motor or vocal tics. Table 2 also presents those pairs who were fully or partially concordant, ie, pairs in which a twin with TS has a co-twin with either TS or only simple tics. This broadening of the diagnostic criteria increases both MZ and DZ concordances. Seventy-seven percent of the MZ pairs were at least partially concordant for TS symptoms, while only 23% of DZ pairs were. In the logistic analysis, the effect of zygosity was significant ($\chi^2 = 8.25$; $P < .01$), but there was no effect of sex on concordance.

TS and Tics in Relatives

In addition to the data on the twins themselves, we collected information on relatives with TS and related behaviors. Three of the twin pairs in our sample, all MZ, were adopted in early childhood, and there was no information on their biological families other than the standard adoption agency assurances of no major familial disease. These cases were excluded from the analysis of relatives.

There were 130 first-degree relatives of the 40 twin pairs who were at risk. The number affected with TS or tics are presented in Table 3, combined by zygosity, sex, and concordance of twin and type of relative. There were only two cases of TS of the total of 130 relatives (1.5%). These were two fathers of fully concordant male MZ pairs. Many more first-degree relatives, approximately 15%, had some form of tics. These rates are comparable to those reported by Kidd et al³ and Pauls et al.⁴ For their combined data, the rates were 2% and 16% for TS and tics or TS, respectively. This comparability of rates across samples suggests that these twin families are not atypical. When analyzed by logistic regression, no significant differences were found in rates of tics or TS as a function of concordance, zygosity, sex of proband, or sex of relative. Because of the sparseness of the table, it was not possible to test these effects in a single analysis. Instead, the two- and three-way

Table 3.—First-degree Relatives With Tics or Tourette Syndrome (TS)

	N*	TS	Any Tics or TS
Total sample	130	.015	.146
Concordance			
Fully concordant	55	.036	.182
Partially concordant	23	.000	.087
Fully discordant	52	.000	.135
Zygosity			
Monozygotic	90	.022	.122
Dizygotic	40	.000	.200
Proband's sex			
M	112	.018	.143
F	18	.000	.167
Relative's sex			
M	65	.031	.200
F	65	.000	.092

*Three adopted pairs are excluded.

Table 4.—Familial Occurrence of Tics or Tourette Syndrome in Monozygotic Twins by Pair Concordance

Pair Classification	No. of First-degree Relatives*	
	Unaffected	Affected
Fully discordant	19	1
Partially concordant	16	2
Fully concordant	44	8

* $\chi^2 = 1.48$; $df = 2$, not significant.

marginal tables were analyzed successively.

Apart from the stable expression of TS across cultures, there is no reason to suppose that there is a single genetic etiology for TS or other tics, and some etiologies may be nonfamilial. Using the genetic "control" of examining only MZ twins, we compared discordant with concordant pairs on the frequency of first-degree relatives with tics or TS. These numbers for the 27 nonadopted MZ pairs are presented in Table 4. There was no significant effect of concordance on affected status of first-degree relatives. The numbers are small, so while these data are consistent with homogeneity in the familial occurrence of tics and TS as a function of concordance, zygosity, or sex of relative and proband, the limited power does not make it possible to exclude heterogeneity.

Timing of Onset and Level of Severity

One would expect MZ co-twins who are affected by the same disorder to be related in the timing of onset and in the eventual level of symptom severity, and this was borne out in our data. Concordant twins were correlated in age of onset and, to a lesser extent, in severity of symptom expression.

Age of onset was correlated in both fully and partially concordant pairs, and the values were quite high for onset of motor tics, $r = .93$ ($P < .001$) and $r = .80$ ($P < .05$), respectively. The intraclass correlations for appearance of first symptoms were $r = .93$ ($P < .001$) and $r = .70$ ($P < .05$) for fully and partially concordant pairs, respectively. These results suggest coordination in the timing of onset of symptoms in twin pairs, but the data are not free of diagnostic and reporting bias. For example, onset of severe TS symptoms in one twin may bring relatively mild symptoms in the co-twin to the attention of the family and the physician. Moreover, the ages of onset were not independently reported. From our data, it is not possible to determine how much of the age of onset correlation is due to developmental synchrony and how much is due to diagnostic or reporting bias.

Fully concordant pairs showed a significant intraclass correla-

tion ($r = .70$, $P < .001$) for severity measured as frequency of motor tics. This severity measure is based on discrete scale points, but because of an implied underlying continuum was evaluated by analysis of variance. Severity was based on the period of most frequent symptoms, but twin ratings were not obtained independently. The twin pairs showed no correlation for severity of vocal tics or for a simple sum of frequency ratings of motor and vocal tics. As one would expect, there was no correlation for severity within partially concordant pairs.

We looked at mean onset of MZ twins as a function of sex and concordance to determine whether some subgroups might have, say, milder symptoms or later onset. Either one or both twins may be affected and thus have a separate onset and level of severity. We first pooled all individual twins into a single analysis, so that concordant pairs contributed two observations. In this analysis, there was a significant difference in age of onset as a function of concordance ($F(2,48) = 3.56$; $P < .04$). The mean onset for the fully concordant pairs was 5.9 years ($n = 7$) compared with 9.3 ($n = 13$, from seven pairs) and 8.3 ($n = 32$, from 16 pairs) years for partially and fully concordant pairs, respectively. The full discordant pair mean age of onset differed from the other two means on the Duncan multiple range test ($P < .05$). We next weighted the variance-covariance contributions by the reciprocal of the number of individual twins reporting onset within each pair. The means remained virtually unchanged, but with the reduced sample size the overall difference was not significant ($F(2,24) = 2.89$; $P < .08$). The effect of sex was not significant in either of these analyses.

Both the number of cases and the difference between subgroups are too small to give a definitive indication of whether fully discordant pairs indeed have an earlier onset. However, we make note of the difference because it is an interesting result, especially given the findings of Volkmar et al³⁰ that individuals with early onset TS more often tend to have abnormal electroencephalograms. Of course, the unaffected co-twins who are still young, and thus have co-twins with early onset, continue to be at risk for developing TS or tics at a later time. Given the limited sample size, the observed heterogeneity in onset should be independently confirmed.

Correlated Behaviors

The association of TS with tics, at least within specific families, seems well established by these and previously published results. Rates of tics are elevated in families of individuals with TS.^{3,4} Moreover, the present study has demonstrated a tendency for discordant co-twins to have milder forms of tics. The synchrony of onset in partially concordant pairs, although subject to bias, is also consistent with a common etiology of TS and milder tics.

We wondered whether the twins could help to clarify whether other symptoms might also be associated with TS. We examined O/C behaviors that are features of O/C disorder. The brief assessment was based on *DSM-III* but did not elicit enough information to make a diagnosis of the disorder. These features include repetitive behaviors or thoughts that an individual does not want to engage in and that persist in spite of attempts to resist them or even revulsion over their nature. Impairment was not assessed.

The rate of co-occurrence of TS and O/C features in individual twins was remarkably high. Eighty-three percent of individual TS cases also reported behaviors that exhibit O/C features. Furthermore, concordances for O/C features were about as high as for TS. Considering pairs in which at least one had O/C features, the concordances were 52% for MZ and 15% for DZ pairs. In a logistic analysis with sex and zygosity, the difference in concordance between MZ and DZ twins was only marginally significant ($\chi^2 = 3.72$; $P < .06$). Together these results suggest some continuity of TS and O/C features. On the basis of these data, it is not possible to say whether the continuum necessarily extends to the full O/C disorder. Furthermore, it is likely that some of the very high rate of co-occurrence observed here is due to the fact that it may be difficult at times to distinguish complex motor tics, including the subjective feelings that accompany them, from features of O/C disorder. However, it does seem that O/C features are a part of the TS spectrum, and in co-twins O/C could represent a form of partial concordance.

Response to Haloperidol

The question of drug response in twins is intriguing, but because of the need to subdivide an already small sample size into drug "treatment groups" and the dependency on uncontrolled reports from relatives about unfamiliar drugs, our ability to make inferences from these data is limited and further study is needed. Having begun with this caveat, we would like to make a descriptive note of a few general observations.

As expected, the most commonly reported drug used to treat TS symptoms of the twins was haloperidol. Other drugs, including clonidine, were used by only small numbers of twins and thus these results will not be reported. Data on stimulants will be reported separately, in a later paper.

There were 41 of 60 individual twins with TS who were reportedly treated with haloperidol at one time or another, and 26 of those reported some positive response (at least some improvement in symptoms and side effects that were not severe according to a subjective rating). Both co-twins were treated in only seven of the MZ pairs. In one of these pairs, both had a neutral or negative response, in four pairs both responded positively, and in two pairs one twin responded positively and the co-twin did not respond or responded negatively. Overall, five of seven pairs were concordant for response to haloperidol.

Some investigators have reported that there is a greater familial occurrence of TS or tics in haloperidol responders than in nonresponders.³¹ In our data, response was related to neither other family history nor concordance in MZ twins, although risk to relatives of pairs in which there was at least one responder was somewhat greater than when treated twins were nonresponders.

COMMENT

Differences in MZ and DZ concordances of the magnitude of those observed in our data are suggestive of a substantial genetic etiology of TS. However, the manner in which the twins were ascertained makes it impossible to make precise estimates of genetic heritability from differences in MZ and DZ concordances or to use MZ concordances to estimate penetrance. On the other hand, the twin data are highly consistent with the observation of familial aggregation and with the suggestion of vertical transmission in families.

There is now a considerable accumulation of evidence that simple tics can be considered a mild form of TS, at least in families with a history of TS. Rates of chronic or multiple tics are elevated in families of individuals with TS.^{3,4} Moreover, the present study has demonstrated that discordant co-twins tend to have milder forms of tics. The close timing of onset in partially concordant pairs, although subject to reporting and diagnostic bias, is also consistent with a common etiology of TS and milder tics. When combined with previous reports in the literature, our data on twins appear to establish such a connection.

It is possible that at least some of the cases, particularly those from discordant pairs, are sporadic, ie, cases for which there was no prior vulnerability. However, there were no differences in family history that were associated with concordance, and this pattern seems inconsistent with such an hypothesis. Overall, the concordant and discordant twins were relatively homogeneous, except possibly for age of onset. Positive haloperidol response did not predict twin concordance or morbidity in first-degree relatives of tics or TS. Heterogeneity in some other more specific factors is certainly possible but will require further study.

Finally, it is noteworthy that the difference in MZ and DZ twin concordances and the far from perfect MZ twin concordance are considerably less than one would have expected from the few previous twin cases in the literature. The fact that only 53% of MZ twins were fully concordant for TS, and a total of only 77% were at least partially concordant

strongly suggests that nongenetic factors play an important role in the expression of TS. While the accumulated evidence of the importance of genetic factors in TS is convincing, these findings indicate that a genetic predisposition for TS need not lead deterministically to the full expression of the disorder. Other factors, including specific and cumulative environmental exposures and the possibility of periods of elevated vulnerability during development, appear to determine the pathway that leads to TS, minor tics, related behaviors like O/C, or a complete absence of symptoms in this spectrum. Leckman et al³² have discussed

elsewhere some possible modes of action of stress and stimulants in these pathways.

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