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MEDICAL LETTER

2004 Retrospective Summary of TS Literature

Editorial

EPIDEMIOLOGY OF TIC DISORDERS

by **Lawrence Scahill, MSN, Ph.D.**

Several recent studies offer new insight into the epidemiology of TS. Because these studies do not resolve the question concerning the prevalence of TS in school-age children, the controversy continues. Traditionally, the prevalence of Tourette syndrome has been considered relatively rare ranging from 3 to 5 per 10,000 (Burd et al, 1986; Caine et al, 1988; Apter et al, 1993)[1-2-3] In a recent review prepared prior to several of the studies presented in the table below, this estimate was revised to 10 to 30 per 10,000 (Scahill et al, 2001).[4] Tics are considered relatively common in school-age children affecting an estimated 12% in this population (Scahill et al, 2001).[4] A recent study using classroom observers reported isolated or transitory tics to be as common as 24%, though the prevalence of enduring tics was estimated at 6% (Snider et al, 2002).[5] The Table on the next page shows the prevalence estimates for all published studies since 2000. The discrepancies across these studies, as well as differences in prior estimates, are due to several factors.

First, earlier estimates were based on clinically ascertained cases. Reliance on clinically ascertained cases means that some cases—especially mild ones—went undetected. Recent studies have tried to correct this ascertainment problem by moving out of the clinic to community samples. Not surprisingly, this sampling change has resulted in higher estimates of prevalence.

Second, several of the more recent studies have used direct parent interview and/or observation of the child to confirm the presence of tics rather than relying on patient registries to identify cases.

Third, these more recent studies have applied different diagnostic criteria for tic disorders including TS. For example, the study by Lapouse and Monk (1964)[6] included a randomly selected sample of 482 children (between 6 and 12 years of age) and identified 59 children (12.2%) with at least one tic and 0.4% with multiple tics. No cases of chronic tic disorder or TS were identified. In the Isle of Wight study, Rutter and colleagues (1970)[7] evaluated a sample of 3000 children that included all 10- to 12-year-olds in the community. In that study 4.4% of the children were identified as having tics, but no cases of TS were identified. It seems likely that if these early community studies had used current definitions of TS, some cases would have been identified. Using DSM-III-R criteria, Costello et al (1996)[8] reported a prevalence of 4.2% for all tic disorders combined (Transient, Chronic Tic Disorder and TS) in school-aged children. Tourette syndrome was relatively uncommon in the range of 1 per 1000. As shown in the following Table, the prevalence of TS in more recent surveys ranges from 26 to 115 per 10,000. All but the study by Peterson et al (2001) provide higher estimates than the range put forth in the Scahill et al (2001)[4] review. Kurlan et al (2001) set out to ascertain a large randomly selected sample through public school rosters. Unfortunately, only 11% of the randomly selected sample agreed to participate, and there was evidence in the report that those with tics were more likely to participate. There is also evidence that newer studies are including milder cases in the estimate of prevalence. For example, of the 7 TS cases identified by Hornsey et al (2001) only 1 case had a moderate level of tics and 3 cases had minimal tics. Obviously, for disorders that are likely to reside on a spectrum, moving the threshold toward milder cases will result in an increase in prevalence. The study by Khalifa and von Knorring (2003) attempted to deal with this issue by insisting on evidence of impairment in the definition of cases. Their prevalence estimate of 60 per 10,000 is based on a relatively large sample with a respectable participation rate. Nonetheless, the findings from community-based samples suggest that TS is more common in school-age children than previously proposed and apparently goes undetected. Differences across studies are due to differences in methodology; e.g., direct observation versus parent report only, or the difference between

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SUMMARY OF STUDIES ESTIMATING PREVALENCE OF TS IN CHILDREN PUBLISHED SINCE 2000

Author/Year***	N	Source of sample	Age years	Informant	Diagnostic criteria	# of TS Cases	Prevalence
Kadesjo & Gillberg, 2000	435	birth cohort	10-11	parent questionnaire	DSM-III-R	5	115/10,000 TS
Hornsey et al, 2001	918	community	13-14	questionnaires, parent interview, clinician exam	DSM-III-R	7	80/10,000 TS
Peterson et al, 2001	776	community (random)	9-20	parent, subject interview	DSM-III	2	26/10,000 TS
Kurlan et al, 2001	1,596	community	8-17	parent, teacher, trained observer	DSM-IV	not reported	150/10,000 TS* 80/10,000 TS**
Khalifa & von Knorring, 2003	4,479	community all available in a township	6-16	parent & teacher checklist, clinical exam	DSM-IV	25	60/10,000 TS 660/10,000 all tic disorders

***see pages 3-4

* in Special Education classes
** in Regular Education classes

classification of tics versus tic disorders. Integrating these new data with the discussion from the most recent review (Scahill et al, 2001)[4] suggests that the prevalence of TS can be revised to 1 to 10 per 1,000. Thus, there are several important remaining questions: Is the enduring presence of mild motor and phonic tics sufficient to classify a child as a TS case? Should there be evidence that the tics interfere in some way with daily living before the child is classified as a case? Does the presence of tics—even mild tics—place a child at higher risk for other problems with behavior and/or learning? Regardless of how these questions are resolved, the prevalence of tic disorder cases requiring treatment is presumably uncommon.

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EPIDEMIOLOGY

Tourette's disorder: epidemiology and comorbidity in primary school children

Kadesjo B, Gillberg C: J Amer Acad Child Adolesc Psychiatry 2000; 39(5):548-555

Abstract: **Methods:** School-age children in the general population and children attending a county-wide tic disorder clinic were screened and examined by the same doctor. Behavioral-psychometric instruments with demonstrated reliability and validity were used. **Results:** Depending on the sample characteristics, 0.15% to 1.1% of all children had Tourette's disorder. Boys outnumbered girls by 4:1 through 6:1. Attention deficits and empathy/autism spectrum problems (including Asperger's disorder) were very common, each type of comorbidity affecting approximately two thirds of individuals with Tourette's disorder. Overall behavior problem scores were high, and affected children exhibited a marked degree of functional impairment. **Conclusions:** Tourette's disorder is a common disorder with high rates of significant comorbidity. In most cases, attention deficits and empathy problems are likely to cause more suffering than the tics per se.

Prevalence of tics in schoolchildren and association with placement in special education

Kurlan R, McDermott MP, Deeley C, et al: Neurology 2001; 57:1383-1388

Abstract: **Methods:** Direct, blinded (to educational placement) interviews of 1,596 schoolchildren in Monroe County, Rochester, NY, were conducted. **Results:** Twenty-seven percent of 341 students classified as receiving special education (SpEd) had tics compared with 19.7% ($p = 0.008$) of 1,255 students in regular classroom programs (RegEd). The weighted prevalence estimates for tics were 23.4% in SpEd and 18.5% in RegEd. A higher percentage of students in SpEd (7.0%) met diagnostic criteria for TS than students in RegEd (3.8%; $p = 0.01$). **Conclusions:** Although possibly influenced by selection bias, our results indicate that tic disorders are common in children and are highly associated with school dysfunction. Tics may represent an identifiable sign of an underlying brain developmental disorder that contributes to academic difficulties.

Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample

Peterson B, Pine D, Cohen P, Brook J: J Amer Acad Child Adolesc Psychiatry 2001; 40(6): 685-695

Abstract: **Methods:** Structured diagnostic interview information was acquired on 976 children aged 1 to 10 years, who were randomly selected from families living in upstate New York in 1975. Reassessments were acquired in 776 of these subjects 8, 10 and 15 years later. Diagnostic prevalences were estimated at each time point. The associations among tics, OCD and ADHD

were assessed within and across time points, as were their associations with comorbid illnesses and demographic risk factors. **Results:** In temporal cross-section, tics, and ADHD symptoms were associated with OCD symptoms in late adolescence and early adulthood after demographic features and comorbid psychiatric symptoms were controlled. In prospective analyses, tics in childhood and early adolescence predicted an increase in OCD symptoms in late adolescence and early adulthood. ADHD symptoms in adolescence predicted more OCD symptoms in early adulthood, and OCD in adolescence predicted more ADHD symptoms in adulthood. The associations of tics with ADHD were unimpressive in temporal cross-section and were not significant in prospective analyses. Tics, OCD, and ADHD shared numerous complex associations with demographic and psychopathological risk factors. ADHD was associated with lower IQ and lower social status, whereas OCD was associated with higher IQ. **Conclusions:** Tics and OCD were significantly associated in this sample, as were OCD and ADHD.

The prevalence of Tourette syndrome in 13-14 year-olds in mainstream schools

Hornsey H, Banjerjee S, Zeitlin H, Robertson M: J Child Psychology Psychiatry 2001; 42(8): 1035-1039

Abstract: A three-stage ascertainment was used to identify those who had TS. First, all 1012 Year 9 pupils were screened for tics using validated self-report questionnaires, which were completed by parents, teachers, and pupils. Data were available from at least one informant for 918 (90.7%) subjects. Tics were identified in 189 (18.7%) pupils. Second, families were contacted and a semistructured interview was carried out to determine whether they had TS. Finally, to ensure that the diagnosis was correct, all those assessed as having TS were systematically assessed by an expert clinician in the field of TS.

Seven young people were identified as fulfilling the criteria for TS, giving a minimum prevalence rate amongst 13-14-year-olds of 0.76% (95% CI 0.31 to 1.57) and a more realistic estimate of 1.85% (95% CI 1.00 to 2.95). Behavioral problems, in particular hyperkinetic disorder, were frequently associated with the TS group. These findings lend further support to the contention that the prevalence of TS in the community has hitherto been underestimated, though the symptoms may be generally milder than the cases of TS in primary care and in educational settings, so that children with this potentially serious disorder can be identified and assessed and effective management packages can be formulated to address their needs, when necessary.

Prevalence of tic disorders and Tourette syndrome in a Swedish school population

Khalifa N, von Knorring AL: Dev Med Child Neurol 2003; 45(5):315-319

Abstract: The aim of the study was to find the epidemiological distribution of tic disorders and Tourette syndrome (TS) in Swedish school children aged 7 to 15 years. A total population of 4,479 children and their parents were asked to fill in a questionnaire covering both motor and vocal tics. A three-stage procedure was used: screening, interview, and clinical investigation. Two hundred and ninety-seven children (190 males, 107 females) were found to have tics. TS, according to DSM-IV criteria, was found in 0.6% of the total population, another 0.8% had chronic motor tics, and 0.5% had chronic vocal tics. Further, 4.8% of the children had transient tics. All together 6.6% of 7- to 15 year-old children currently had or had experienced some kind of tic disorder during the last year. Prevalence of different tic disorders was higher among younger children and in males, and was highly associated with school dysfunction. The prevalence of TS was higher than was previously thought but other tic disorders were more common in this childhood population.

GENETICS

Genome scan for linkage to Gilles de la Tourette syndrome

Barr CL, Wigg KG, Pakstis AJ, et al: Amer J Medical Genetics 1999; 88(4):437-445

Abstract: Despite clear evidence for a genetic predisposition to TS from family, twin, and adoption studies, there have been no confirmed linkage findings. In this article we test for linkage to TS in multigenerational families segregating TS using a panel of 386 markers with the largest interval between any two markers being 28 cM and an average distance between markers of 10 cM. We tested for linkage using an autosomal dominant model with reduced penetrance and using nonparametric methods. No significant evidence for linkage was found with parametric analysis. A logarithm of the odds (LOD) score of greater or equal to one under the autosomal dominant model was observed in 24 of these markers in at least one of the families tested. No LOD scores greater than two were observed with any of the markers. For the nonparametric analysis, eight markers were observed with a P-value less than 0.00005 for significance evidence of linkage in at least one family. However caution should be used in the interpretation of the nonparametric analyses as this statistic (the affected-pedigree-member method) is known to have a high false-positive rate. Further support for linkage in these regions is required before linkage can be assumed.

Significant linkage for Tourette syndrome in a large French Canadian family

Merette C, Brassard A, Potvin A, et al: Amer J Human Genetics 2000; 67(4):1008-1013

Abstract: Family and twin studies provide strong evidence that genetic factors are involved in the transmission of Gilles de la Tourette syndrome (TS) and related psychiatric disorders. To detect the underlying susceptibility gene(s) for TS, we performed linkage analysis in one large French Canadian family (127 members) from the Charlevoix region, in which 20 family members were definitely affected by TS and 20 others showed related tic disorders. Using model-based linkage analysis, we observed a LOD score of 3.24 on chromosome 11 (11q23). This result was obtained in a multipoint approach involving marker D11S1377, the marker for which significant linkage disequilibrium with TS recently has been detected in an Afrikaner population. Altogether, 25 markers were studied, and, for level of significance, we derived a criterion that took into account the

multiple testing arising from the use of three phenotype definitions and three modes of inheritance, a procedure that yielded a LOD score of 3.18. Hence, even after adjustment for multiple testing, the present study shows statistically significant evidence for genetic linkage with TS.

A family study of Tourette syndrome in Japan

Kano Y, Ohta M, Nagai Y, et al: Amer J Medical Genetics 2001; 105(5):414-421

Abstract: In an effort to evaluate population-based genetic differences, we generated risk estimates for first-degree relatives of TS probands in Japan using methods similar to those utilized in recent Western studies. The subjects were 52 TS probands seen at an outpatient clinic of Tokyo University Hospital and their 165 first-degree relatives. All probands and one or more first-degree relatives in each family were interviewed concerning the presence of tic and obsessive-compulsive symptoms by expert clinicians. The age-corrected rates of TS, chronic motor tics, obsessive-compulsive disorder, and subclinical obsessive-compulsive symptoms in the first-degree relatives were 2.0%, 12.0%, 1.6%, and 7.0%, respectively. Rates of TS and related disorders in Japan appear to be much lower than those in recent Western family studies. If replicated, these data suggest that there may be differences in the nature and frequency of vulnerable alleles for TS and related disorders in the Japanese compared to European populations.

Genomewide scan of hoarding in sib pairs in which both sibs have Gilles de la Tourette syndrome

Zhang H, Leckman JF, Pauls DL, et al: Amer J Human Genetics 2002; 70(4):896-904

Abstract: A genome scan of the hoarding phenotype (a component of obsessive-compulsive disorder) was conducted on 77 sib pairs collected by the Tourette Syndrome Association International Consortium for Genetics (TSAICG). All sib pairs were concordant for a diagnosis of Gilles de la Tourette syndrome (GTS). However, the analyses reported here were conducted for hoarding as both a dichotomous trait and a quantitative trait. Not all sib pairs in the sample were concordant for hoarding. Standard linkage analyses were performed using GENEHUNTER and Haseman-Elston methods. In addition, novel analyses with a recursive-partitioning technique were employed. Significant allele sharing was observed for both the dichotomous and the quantitative hoarding phenotypes for markers at 4q34-35 (P=.0007), by use of GENEHUNTER, and at 5q35.2-35.3 (P=.000002) and 17q25 (P=.00002), by use of the revisited Haseman-Elston method. The 4q site is in proximity to D4S1625, which was identified by the TSAICG as a region linked to the GTS phenotype. The recursive-partitioning technique examined multiple markers simultaneously. Results suggest joint effects of specific loci on 5q and 4q, with an overall P value of .000003. Although P values were not adjusted for multiple comparison, nearly all were much smaller than the customary significance level f .0001 for genome wide scans.

Human dopamine transporter gene: coding region conservation among normal, Tourette's disorder, alcohol dependence and attention-deficit hyperactivity disorder populations

Vandenbergh DJ, Thompson MD, Cook EH, et al: Molecular Psychiatry 2000; 5(3):283-292

Abstract: The dopamine transporter (DAT) provides major regulation of the synaptic levels of dopamine and is a principal target of psychostimulant drugs. Associations between DAT gene polymorphisms and human disorders with possible links to dopaminergic neurotransmission, including attention-deficit/hyperactivity disorder (ADHD) and consequences of cocaine and alcohol administration, have been reported. We now report approximately 60000 bp of genomic sequence containing the entire DAT gene. This sequence was used to amplify each of the 15 DAT gene exons and several introns and analyze these amplification products by single-stranded sequence conformation (SSCP) and/or direct sequencing. These results define silent allelic single nucleotide sequence variants in DAT gene exons 2, 6, 9 and 15. Rare conservative mutations are identified in amino acids encoded by DAT exons 2 and 8. Analyses of the common nucleotide variants and the previously reported VNTR in the non-coding region of exon 15 define the pattern of linkage disequilibrium across the DAT locus. These comprehensive analyses, however, fail to identify any common protein coding DAT sequence variant in more than 150 unrelated individuals free of neuropsychiatric disease, 109 individuals meeting City of Hope criteria for Tourette's syndrome, 64 individuals with DSM-IV diagnoses of ethanol dependence, or 15 individuals with ADHD. These data are consistent with substantial evolutionary conservation of the DAT protein sequence. They suggest that gene variants that alter levels of DAT expression provide the best current candidate mechanism for reported associations between DAT gene markers, ADHD and other more tentatively associated neuropsychiatric disorders.

Further evidence for linkage of Gilles de la Tourette syndrome (GTS) susceptibility loci on chromosomes 2p11, 8q22 and 11q23-24 in South African Afrikaners

Simonic I, Nyholt DR, Gericke GS, et al: Amer J Medical Genetics 2001; 105(2):163-167

Abstract: Utilizing DNA samples from 91 Afrikaner nuclear families with one or more affected children, five genomic regions on chromosomes 2p, 8q, 11q, 20q, and 21q that gave evidence for association with GTS in previous case-control association studies were investigated for linkage and association with GTS. Highly polymorphic markers with mean heterozygosity of 0.77 were typed and resulting genotypes evaluated using single marker transmission disequilibrium (TDT), single marker haplotype relative risk (HRR), and multi-marker "extended" TDT and HRR methods. Single marker TDT analysis showed evidence for linkage or association, with p-values near 0.05, for markers D2S139, GATA28F12, and D11S1377 on chromosomes 2p11, 8q22 and 11q23-24, respectively. Extended, two-locus TDT and HRR analysis provided further evidence for linkage or

association on chromosome 2 with p-values of 0.007 and 0.025, and chromosome 8 with p-values of 0.059 and 0.013, respectively. These results provide important additional evidence for the location of GTS susceptibility loci.

Association between homozygosity at the COMT gene locus and obsessive compulsive disorder

Schindler KM, Richter MA, Kennedy JL, et al: Amer J Medical Genetics 2000; 96(6):721-724

Abstract: A functional polymorphism in the coding region of the catechol O-methyltransferase (COMT) gene has been reported in previous studies to be associated with obsessive compulsive disorder (OCD), particularly in males [Karayiorgou et al, 1997, 1999]. Using a family-based population analysis, we attempted to replicate these findings in a group of 72 OCD patient/parent trios collected from Buffalo, New York, and Toronto, Canada. Analysis of allele and genotype frequencies using the haplotype relative risk (HRR) and transmission disequilibrium test (TDT) did not identify an association between a particular allele and OCD as had been previously reported. Furthermore, no evidence was found to support the findings of a gender-based association for COMT when the patients and the parents of the same gender were compared. However, our genotype results (n = 72) demonstrate a tendency for association between homozygosity at the COMT locus and OCD (homozygosity analysis: chi(2) = 5.66, P = 0.017; genotypic analysis: chi(2) = 5.78, P = 0.056). Although these findings do not replicate the previous reports, they do provide limited support to demonstrate a trend for homozygosity at the COMT locus in the OCD patients and, in turn, further implicate a potential role for COMT in the genetic etiology of OCD.

Association between the COMT locus and obsessive-compulsive disorder in females but not males

Alsobrook JP 2nd, Zohar AH, Leboyer M, et al: Amer J Medical Genetics 2002; 114(1):116-120

Abstract: A polymorphism in the coding region of catechol-O-methyltransferase gene (COMT) was previously reported to be associated with obsessive-compulsive disorder (OCD), particularly in male probands. We attempted to replicate the previous finding using a family-based genetic design in haplotype relative risk (HRR) and transmission disequilibrium (TDT) analyses. Fifty-six OCD probands and their parents were genotyped for the COMT locus using established methods. Analysis of allele and genotype frequencies between the proband genotypes and the control (parental nontransmitted) genotypes failed to replicate the previous finding of gender divergence, gave no evidence of overall association, nor was linkage detected by TDT. However, further analysis of the COMT allele frequencies by proband gender gave evidence of a mildly significant association with the low-activity COMT allele in female probands (P=0.049), but not in male probands. These findings indicate that COMT may be etiologically relevant to OCD in a gender-specific manner opposite to that shown in previous studies.

Comment: Given the accumulated evidence for a genetic contribution in TS, there is continued effort to map the chromosomal location of the susceptibility genes. Linkage is an approach that tries to identify an association between a genetic marker of a known location and a certain trait. This search for an association may be done by selecting a specific candidate gene or by genome scanning. The genome scanning approach used by Barr et al (1999) may ultimately result in the identification of candidate genes, which might then inform future study. Failure to demonstrate linkage in this and previous studies may be due to locus heterogeneity (i.e., different susceptibility loci in different families), misclassification of affected status within the pedigree (false negative or false positive determination of affected individuals), or incorrect assumptions about the mode of inheritance (e.g., autosomal dominant transmission). The study by Merette et al, (2000) which showed linkage to chromosome 11 replicates one of the findings observed in the Afrikaner population (Simonic et al, 2001). This region may provide a basis for selecting a candidate gene. Candidate genes may also emerge from case reports (Kroisel et al, 2001)[1] or leads from other disorders (Bottini et al, 2002).[2] Newer statistical techniques such as the affected-pedigree-member method, affected sibling-pair and the transmission disequilibrium test (TDT) are being actively pursued in TS. These approaches are less vulnerable to locus heterogeneity and less vulnerable to assumptions concerning the mode of transmission. The study by Zhang et al (2002), which used the sib pair method with genome scanning, focused on a specific phenotypic feature (hoarding). This study showed allele sharing at 4q, 5q and 17q. The finding of shared alleles at 4q was also reported by the Tourette Syndrome Association International Genetics Consortium (see Pauls, 2001 for a review).[3] The TDT approach was used in the study of OCD by Schindler et al (2000) and showed an association between homozygosity at the COMT gene and OCD. The COMT gene codes for the enzyme that breaks down catecholamines (e.g., dopamine and norepinephrine). Attempts to replicate this finding have been unsuccessful (Alsobrook et al, 2002). Similarly, Cavallini et al (2000)[4] failed to find an association between a specific polymorphism (variation of the DNA sequence) of the COMT gene and TS.

References: 1. Kroisel PM, Petek E, Emberger W, et al: Candidate region for Gilles de la Tourette syndrome at 7q31; Amer J Medical Genetics 2001; 101(3):259-261. 2. Bottini N, MacMurray J, Rostamkani M, et al: Association between the low molecular weight cytosolic acid phosphatase gene ACP1*A and comorbid features of Tourette syndrome; Neuroscience Letters 2002; 330(2):198-200. 3. Pauls DL: Tourette Syndrome Association International Consortium on Genetics. Update on the genetics of Tourette syndrome; Advances in Neurology 2001; 85:281-293. 4. Cavallini MC, Di Bella D, Catalano M, Bellodi L: An association study between 5-HTTLPR polymorphism, COMT polymorphism, and Tourette's syndrome; Psychiatry Research 2000; 97(2-3):93-100.

Family Studies in OCD

A family study of obsessive-compulsive disorder

Nestadt G, Samuels J, Riddle M, et al: Arch Gen Psychiatry 2000, 57(4):358-363

Abstract: **Methods:** Eighty case probands were identified in 5 specialty OCD clinics and 73 community control probands were identified by random-digit dialing. These probands and their first-degree relatives (343 case and 300 control relatives) were blinded to group and evaluated by psychiatrists and doctoral-level clinical psychologists using semistructured instruments. Final diagnoses were assigned by a blinded-consensus procedure. The results were analyzed using logistic regression by the method of generalized estimating equations. **Results:** The lifetime prevalence of OCD was significantly higher in case compared with control relatives (11.7% vs 2.7%) (P<.001). Case relatives had higher rates of both obsessions and compulsions; however, this finding is more robust for obsessions. Age at onset of obsessive-compulsive symptoms in the case proband was strongly related to familiality (odds ratio, 0.92; confidence interval, 0.85-0.99) (P = .05); no case of OCD symptoms was detected in the relatives of probands whose age at onset of symptoms was 18 years or older. Probands with tics or obsessive-compulsive personality disorder were not more likely to have relatives with OCD than those without these features. **Conclusions:** Obsessive-compulsive disorder is a familial disorder. Obsessions are more specific to the phenotype than are compulsions. Age at onset of OCD is valuable in characterizing a familial subtype.

Complex segregation analysis provides compelling evidence for a major gene underlying obsessive-compulsive disorder and for heterogeneity by sex

Nestadt G, Lan T, Samuels J, et al: Amer J Human Genetics 2000; 67(6):1611-1616

Abstract: The purpose of this study was to test whether a major gene is implicated in a proportion of families with OCD. Complex segregation analyses of 153 families (80 case and 73 control), ascertained in the Johns Hopkins OCD Family Study, provided strong evidence for a major gene. A Mendelian-dominant model, with significant sex effects and with residual familial effects, best explained the observed data. Stratification of the sample by the sex of probands provided further evidence of heterogeneity with respect to familial aggregation. Segregation analyses of 86 families with a female proband and of the 67 families with a male proband suggested that a Mendelian-dominant model with familial residual effects was the most parsimonious model explaining the inheritance of OCD in both subgroups.

The familial phenotype of obsessive-compulsive disorder in relation to tic disorders: the Hopkins OCD family study

Grados MA, Riddle MA, Samuels JF, et al: Biological Psychiatry 2001; 50(8):559-565

Abstract: **Methods:** Eighty case and 73 control probands and their first-degree relatives were examined by experienced clinicians using the Schedule for Affective Disorders and Schizophrenia-Lifetime Anxiety version. DSM-IV psychiatric diagnoses were ascertained by a best-estimate consensus procedure. The prevalence and severity of tic disorders, age-at-onset of OCD symptoms, and transmission of OCD and tic disorders by characteristics and type of proband (OCD + tic disorder, OCD – tic disorder) were examined in relatives. **Results:** Case probands and case relatives had a greater lifetime prevalence of tic disorders compared to control subjects. Tic disorders spanning a wide severity range were seen in case relatives; only mild severity was seen in control relatives. Younger age-at-onset of OCD symptoms and possibly male gender in case probands were associated with increased tic disorders in relatives. Although relatives of OCD + tic disorder and OCD—tic disorder probands had similar prevalences of tic disorders, this result is not conclusive. **Conclusions:** Tic disorders constitute an alternate expression of the familial OCD phenotype.

The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study

Nestadt G, Samuels J, Riddle MA, et al: Psychological Medicine 2000; 31(3):481-487

Abstract: **Methods:** Eighty case and 73 control probands, as well as 343 case and 300 control first-degree relatives of these probands, participated in the study. Subjects were examined by psychologists or psychiatrists using the Schedule for Affective Disorder and Schizophrenia-Lifetime Anxiety version (SADS-LA). Two experienced psychiatrists independently reviewed all clinical materials, and final diagnoses were made according to DSM-IV criteria, by consensus procedure. **Results:** Except for bipolar disorder, all anxiety and affective disorders investigated were more frequent in case than control probands. Substance dependence disorders were not more frequent. Generalized anxiety disorder (GAD), panic disorder, agoraphobia, separation anxiety disorder (SAD) and recurrent major depression were more common in case than control relatives. These disorders occurred more frequently if the relative was diagnosed with OCD. Only GAD and agoraphobia were more frequent in case relatives independent of OCD. **Conclusions:** GAD and agoraphobia share a common familial aetiology with OCD. The other anxiety and affective disorders, when comorbid with OCD, may emerge as a consequence of the OCD or as a more complex syndrome.

The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study

Bienvenu OJ, Samuels JF, Riddle MA, et al: Biological Psychiatry 2000; 48(4):287-293

Abstract: Methods: Eighty case and 73 control probands, as well as 343 case and 300 control first-degree relatives, were examined by psychiatrists or Ph.D. psychologists using the Schedule for Affective Disorders and Schizophrenia-Lifetime Anxiety version. Two experienced psychiatrists independently reviewed all diagnostic information and made final consensus diagnoses using DSM-IV criteria. **Results:** Body dysmorphic disorder, hypochondriasis, any eating disorder, and any grooming condition occurred more frequently in case probands. In addition, BDD, either somatoform disorder, and any grooming condition occurred more frequently in case relatives, whether or not case probands also had the same diagnosis. **Conclusions:** These findings indicate that certain somatoform and pathologic grooming conditions are part of the familial OCD spectrum. Though other "spectrum" conditions may resemble OCD, they do not appear to be important parts of the familial spectrum.

Comment: This series of reports by Nestadt and colleagues provides strong support for vertical transmission of OCD and some support for the OCD spectrum. The recurrence risk of obsessions appear higher than compulsions in the families of OCD probands. In addition, the familial form of the disorder is associated with age of onset younger than 18 years in the proband. Tic disorders, agoraphobia, and generalized anxiety disorder recurred in the families of OCD probands whether or not the proband had these disorders or not. Pathological grooming behaviors also recurred in the families of OCD probands, but hypochondriasis, eating disorders and skin picking (Cullen et al, 2001)[1] did not. Strengths of this research include the detailed interviewing of the adult probands and controls as well as a high percentage of family members in each group. Interviewers were trained clinicians and diagnoses were established by a panel of psychiatrists blind to the diagnostic status of the proband.

Reference: 1. Cullen BA, Samuels JF, Bienvenu OJ, et al: The relationship of pathologic skin picking to obsessive-compulsive disorder; J Nervous Mental Disease 2001; 189(3):193-195.

TREATMENT

Atypical Antipsychotics in the treatment of tics

Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study

Sallee FR, Kurlan R, Goetz CG, et al: J Amer Acad Child Adolesc Psychiatry 2000; 39(3):292-299

Abstract: Methods: Twenty-eight patients aged 7 to 17 years were randomly assigned to ziprasidone or placebo for 56 days. Ziprasidone was initiated at a dose of 5 mg/day and flexibly titrated to a maximum of 40 mg/day. **Results:** Ziprasidone was significantly more effective than placebo in reducing the Global Severity (p = .016) and Total Tic (p = .008) scores on the Yale Global Tic Severity Scale. Compared with placebo, ziprasidone significantly reduced tic frequencies as determined by blind videotape tic counts (p = .039). The mean (+/- SD) daily dose of ziprasidone during the last 4 weeks of the trial was 28.2 +/- 9.6 mg. Mild transient somnolence was the most common adverse event. No clinically significant effects were observed on specific ratings of extrapyramidal symptoms, akathisia, or tardive dyskinesia. **Conclusions:** In this limited sample, ziprasidone (5-40 mg/day) appears to be effective and well tolerated in the treatment of Tourette's syndrome. Ziprasidone may be associated with a lower risk of extrapyramidal side effects in children. However, additional studies are necessary to evaluate more fully its safety and efficacy in children with tic disorders.

Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study

Bruggeman R, van der Linden C, Buitelaar JK, et al: J Clinical Psychiatry 2001; 62(1):50-56

Abstract: Methods: In a 12-week, multicenter, double-blind, parallel-group study, 26 patients were treated with risperidone (mean daily dose = 3.8 mg), and 24 patients were treated with pimozide (mean daily dose = 2.9 mg). **Results:** There was significant improvement of tics with respect to the Tourette's Symptom Severity Scale (TSSS) for both groups. Forty-one patients completed the study. At endpoint, 54% (14/26) of the risperidone patients and 38% (9/24) of the pimozide patients had only very mild or no symptoms on the global severity rating of the TSSS. Both treatment groups had improved significantly at endpoint in regard to Global Assessment of Functioning and Clinical Global Impressions scale outcomes. Symptoms of anxiety and depressive mood improved significantly from baseline in both groups. Obsessive-compulsive behavior improvement reached significance only in the risperidone group. Although the severity of extrapyramidal side effects was low in both groups, fewer patients in the risperidone group reported extrapyramidal side effects (N = 4) compared with the pimozide group (N = 8). Depression, fatigue, and somnolence were reported as the most prominent side effects in both treatment groups. **Conclusions:** Both drugs were efficacious and well tolerated in patients with Tourette's disorder. Risperidone may become the first-line drug in the treatment of Tourette's disorder owing to a more favorable efficacy and tolerability profile.

Risperidone in the treatment of Tourette syndrome: a double-blind, placebo-controlled trial

Dion Y, Annable L, Sandor P, Chouinard G: J Clin Psychopharmacol 2002; 22(1):31-39

Abstract: A double-blind, placebo-controlled trial was performed to determine the efficacy and tolerability of 8 weeks of treatment with risperidone in the management of 48 adolescent and adult patients with Tourette syndrome. Twenty-four patients

were randomly assigned to treatment with risperidone in doses of 0.5 to 6.0 mg/day, and 24 were assigned to placebo. The dosage of medication was increased in fixed increments during the first week of double-blind treatment and thereafter in a flexible dose regimen according to clinical response. Risperidone, at a median dose of 2.5 mg/day (range, 1 to 6 mg/day), was found to be significantly ($p < 0.05$) superior to placebo on the Global Severity Rating of the Tourette Syndrome Severity Scale. The proportion of patients who improved by at least one point on this seven-point scale was 60.8% in the risperidone group and 26.1% in the placebo group. Treatment with risperidone was accompanied by an improvement in global functioning in patients with average to above-average impairment at baseline as measured by the Global Assessment of Functioning scale. With respect to extrapyramidal symptom scores measured on the Extrapyramidal Symptom Rating Scale, hypokinesia and tremor increased in the risperidone group, but the effect on tremor was largely confined to subjects with higher baseline tremor scores. There were no significant differences in dystonic reactions, dyskinetic movements, subjective parkinsonism, or akathisia. Risperidone did not increase obsessive-compulsive symptoms. Fatigue and somnolence were the most common adverse events associated with risperidone.

A placebo-controlled trial of risperidone in Tourette syndrome

Scahill L, Leckman JF, Schultz RT, et al: Neurology 2003; 60(7): 1130-1135

Abstract: Methods: This was an 8-week, randomized, double-blind, placebo-controlled trial. The primary outcome measure was the Total Tic score of the Yale Global Tic Severity Scale (YGTSS). **Results:** Thirty-four (34) medication-free subjects (26 children and 8 adults) ranging in age from 6 to 62 years (mean = 19.7 + 17.0 years) participated. YGTSS Total Tic scores were similar at baseline (26.0 + 5.1 for risperidone versus 27.4 + 8.5 for placebo). After 8 weeks of treatment (mean daily dose of 2.5 + 0.85), the 16 subjects on risperidone showed a 32% reduction in tic severity from baseline, compared to a 7% reduction for placebo (N=18) ($F [2,64]=6.07$; $p=.004$). The 12 children randomized to risperidone showed a 36% reduction in tic symptoms compared to an 11% decrease in the 14 children on placebo ($F[2,48] =6.38$; $p= .004$). Two children on risperidone showed increased social phobia, which resolved with dose reduction in one subject but resulted in medication discontinuation in the other. A mean increase in body weight of 2.8 kg was observed in the risperidone group compared to no change in placebo ($F[2,64]=10.68$; $p=.0001$). No extrapyramidal symptoms and no clinically significant alterations in cardiac conduction times or laboratory measures were observed. **Conclusions:** Risperidone appears to be safe and effective for short-term treatment of tics in children or adults with Tourette syndrome. Longer-term studies are needed to evaluate the durability of efficacy and safety over time.

Comment: Risperidone and ziprasidone are atypical antipsychotics with potent D2 and 5HT2 blocking properties. The atypical antipsychotics are a class of chemically unrelated compounds including clozapine, risperidone, olanzapine, quetiapine and ziprasidone. Sulpiride, tiapride and amisulpiride, which are not available in the United States, are often classified with the atypicals as well. Finally, aripiprazole is a recently released compound in the US with features in common with the atypicals, but potentially important differences as well. To date, only clozapine, ziprasidone, and risperidone have been evaluated in randomized clinical trials in TS. Using a cross over design, Caine and colleagues (1979)[1] observed no difference between clozapine and placebo. In a sample of 28 children and adolescents, ziprasidone was superior to placebo showing about a mean 35% improvement in tics compared to 9% in placebo (Sallee et al, 2001). The two placebo controlled studies cited above both showed a significant improvement in risperidone treated subjects versus the placebo group (Dion et al, 2001; Scahill et al, 2003). The study by Bruggeman et al, (2001) showed similar efficacy to pimozide.

Perhaps the most important difference across the atypicals is the relative potency of the D2 and 5HT2 blockade. For example, clozapine and quetiapine have low affinity for D2 receptors and, therefore, little or no D2 blocking properties. Given that both risperidone and ziprasidone have much higher affinity for the D2 receptor, these findings suggest that D2 blockade is important in tic suppression. Although there is continued debate concerning the capacity of the atypicals to improve the so called negative symptoms of schizophrenia (low motivation, poverty of thought and language), there is general agreement that the neurological side effect burden (dystonia, parkinsonism, akathisia) is lower with the atypicals compared to the traditional D2 blockers such as haloperidol and pimozide. It has been proposed that the 5HT2 blocking property of the atypical antipsychotics protects against the neurological side effects associated with the traditional agents, but other explanations have been offered (Kapur, 2001).[2]

An emerging concern with the atypicals is weight gain (Taylor & McAskill, 2000).[3] In the 8-week risperidone study by Scahill et al, (2003) the mean weight gain was 6 pounds, which is similar to the average of 8 pounds for the risperidone group in the 12-week study by Bruggeman et al, (2001). Dion et al, (2002) did not provide change in weight in their report. A recent study of risperidone in 101 children with autism also reported a 6-pound weight gain in 8 weeks compared to no change in the placebo group (RUPP Autism Group, 2002).[4] A meta-analysis of studies in adults with schizophrenia by Taylor and McAskill, (2000)[3] ranked ordered the atypicals according to magnitude of weight gain as follows: clozapine, olanzapine, quetiapine, risperidone, ziprasidone (insufficient information is available to rank aripiprazole). Taken together, these data suggest that risperidone and ziprasidone are reasonable choices for treating moderate or greater severity of tics. Clozapine and quetiapine seem unlikely choices given the negative results from Caine et al (1979)[1] and the

low D2 blocking ability for these two compounds. Olanzapine has only been evaluated in small open-label trials in TS (Stamenkovic et al, 2000; Budman et al, 2001).[5-6] The absence of controlled data and the meta-analytic data showing the risk of substantial weight gain argues against the use of olanzapine in TS. Aripiprazole warrants careful study.

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Non-antipsychotic medications for the treatment of tics

Botulinum Toxin

Botulinum toxin in the treatment of tics

Kwak CH, Hanna PA, Jankovic J: Archives of Neurology 2000; 57(8):1190-1193

Abstract: Methods: Thirty-five patients (30 male, 5 female) were treated with BTX in the sites of their most problematic tics. Response to botulinum (BTX) was based on a 0 to 4 scale (0, no improvement, to 4, marked improvement in both severity and function). Questionnaires were administered to evaluate patients' impressions of overall efficacy and degree of benefit with premonitory sensations. **Results:** Mean duration of tics prior to initial injection was 15.3 years (range, 1-62 years) and mean duration of follow-up was 21.2 months (range, 1. 5-84 months). The mean peak effect response in 35 patients treated in 115 sessions was 2.8 (range, 0-4); the mean duration of benefit was 14.4 weeks (maximum, 45 weeks); and the mean latency to onset of benefit was 3.8 days (maximum, 10 days). Twenty-one (84%) of 25 patients with premonitory sensations derived marked relief of these symptoms (mean benefit, 70.6%). Total mean dose was 502.1 U (range, 15-3550 U); mean number of visits, 3.3 (range, 1-16); and mean dose per visit, 119.9 U (range, 15-273 U). Sites of injections were as follows: cervical or upper thoracic area (17), upper face (14), lower face (7), vocal cords (4), upper back and/or shoulder (3), scalp (1), forearm (1), leg (1) and rectus abdominis (1). Complications included neck weakness (4), dysphagia (2), ptosis (2), nausea (1), hypophonia (1), fatigue (1), and generalized weakness (1), which were all mild and transient. **Conclusions:** Botulinum toxin A injections are an effective and well-tolerated treatment of tics. In addition to improving the motor component of tics, BTX also provides relief of premonitory sensations.

Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial

Marras C, Andrews D, Sime E, Lang AE: Neurology 2001; 56(5):605-610

Abstract: Methods: Patients with suitable simple motor tics were randomized to receive botulinum toxin and placebo in a double blind, crossover design. All outcomes compared week 2 to baseline measurements. The primary outcome measure was the number of treated tics per minute on a videotape segment. Secondary outcome measures were number of untreated tics per minute, the Shapiro Tourette Syndrome Severity Scale score, a numerical assessment of the urge to perform the treated tic (0 to 4), the premonitory sensation associated with the treated tic (0 to 4), and the patient's global impression of change. **Results:** Eighteen patients completed the study. The median relative change in treated tics per minute with botulinum toxin was -0.39 (or a 39% reduction) versus 0.058 (or a 5.8% increase) with placebo (net effect -0.37, p = 0.0007). The average change in urge scores (score range 0 to 4) was -0.46 in the treatment phase and +0.49 in the placebo phase (net effect 0.94, p = 0.02). Other secondary outcome measures were not significantly different between the two groups. **Conclusions:** Botulinum toxin reduced treated tic frequency and the urge associated with the treated tic. Despite these changes, patients did not report an overall benefit from the treatment. Careful consideration of the contribution of the target tic to the patient's disability is needed before making treatment decisions.

Comment: These two studies extend the data base on the use of BTX for the treatment of tics in TS. Based on these results and results from previous case reports and open-label studies, BTX appears to be a potentially useful intervention for specific and interfering tics. Issues such as optimal dose and frequency of injection have not been completely resolved.

Nicotine and Mecamylamine

Transdermal nicotine and haloperidol in Tourette's disorder: a double-blind placebo-controlled study

Silver AA, Shytle RD, Philipp MK, et al: J Clinical Psychiatry 2001; 62(9):707-714

Abstract: Methods: Seventy patients with DSM-IV Tourette's disorder were treated with either transdermal nicotine (7 mg/24 hours) or placebo patches in a 33-day, randomized, double-blind study. Each patient received an individually based optimal dose of haloperidol for at least 2 weeks prior to random assignment to nicotine or placebo treatment. A new patch was worn each day for the first 5 days. On the sixth day, the dose of haloperidol was reduced by 50%. Daily patch applications were then continued for an additional 2 weeks (through day 19), at which time the patch was discontinued, but the 50% dose of haloperidol was continued for an additional 2 weeks (through day 33). **Results:** Patients who completed all 19 days of nicotine (N = 27) or

placebo (N = 29) patch treatment were used in efficacy analyses. As documented by the Clinician- and Parent-rated Global Improvement scales, transdermal nicotine was superior to placebo in reducing the symptoms of Tourette's disorder. The Yale Global Tic Severity Scale was less sensitive in detecting a placebo/drug difference than were the global improvement scores, suggesting that some of the improvement may not have been related to treatment-related changes in tic severity, but to the emotional and behavioral symptoms. The side effects of nausea and vomiting were significantly more common in the nicotine group (71% [N = 25] and 40% [N = 14]) than in the placebo group (17% [N = 6] and 9% [N = 3]) (nausea, p = .0001; vomiting, p = .004). **Conclusions:** Transdermal nicotine was superior to placebo in reducing behavioral symptoms when patients were receiving an optimal dose of haloperidol, when the dose of haloperidol was reduced by 50%, and when the patch had been discontinued for 2 weeks. These findings confirm earlier open-label findings and suggest that combining nicotinic receptor modulation and neuroleptics could be a therapeutic option for the treatment of Tourette's disorder.

Multicenter, double-blind, placebo-controlled study of mecamylamine monotherapy for Tourette's disorder

Silver AA, Shytle RD, Sheehan KH, et al: J Amer Acad Child Adolesc Psychiatry 2001; 40(9):1103-1110

Abstract: Methods: Eligible subjects included subjects with TD (DSM-IV), with a naturalistic mix of comorbid diagnoses, nonsmokers, aged 8 to 17 years, whose behavioral and emotional symptoms (according to parents) were more disturbing than tics. After a washout period of all psychotropic medication, subjects were randomly assigned to either mecamylamine (n = 29) or placebo (n = 32). Mecamylamine doses ranged from 2.5 to 7.5 mg/day. Primary efficacy measures included the Tourette's Disorder Scale-Clinician Rated (TODS-CR) and 21-point Clinical Global Improvement scale; secondary efficacy measures included the Yale Global Tic Severity Scale and a rage-attack scale (RAScal). **Results:** Of the 61 subjects who were randomized, 50 (82%) completed at least 3 weeks on medication and 38 (62%) completed the full 8-week trial. Study withdrawals included 12/29 on mecamylamine and 11/32 on placebo. For the total sample, mecamylamine was no more effective than placebo on any of the outcome measures. However, an item analysis of the TODS-CR suggested that mecamylamine may have reduced sudden mood changes and depression in moderately to severely affected subjects. Except for a slight increase in heart rate during the 1st week in both the mecamylamine and the placebo groups, there where no significant mecamylamine-related changes in vital signs, electrocardiogram, complete blood cell count, or blood chemistry values. **Conclusions:** Mecamylamine, in doses up to 7.5 mg/day, is well tolerated in children and adolescents, but as a monotherapy it does not appear to be an effective treatment for tics or for the total spectrum of symptoms associated with TD. However, further studies should be conducted to investigate its possible therapeutic effects in subjects with comorbid mood disorders and as an adjunct to neuroleptic medication.

Comment: Nicotine in the form of gum or the transdermal patch has been proposed as an adjunctive treatment for TS for several years (Sandberg et al, 1988; McConville et al 1991). The results of the nicotine transdermal patch trial by Silver et al (2001) are difficult to interpret. First, seven subjects in the nicotine group were removed from the analysis because their tics worsened. Given that tic severity was put forth as the primary outcome, this exclusion is a major threat to the fair comparison of the treatments. Second, it is not clear which time point is being used to test the concept of combined treatment. For example, on Day 5, when the subjects were on optimal doses of haloperidol and either the nicotine patch or placebo, the nicotine group showed greater reduction in motor tics than the haloperidol only group, suggesting that the nicotine patch exerted additive effects on haloperidol. At Day 19, however, 2 weeks after the haloperidol dose was cut in half, there was no difference between combined haloperidol and nicotine patch compared to haloperidol alone. This observation suggests that the tic suppressing effects of nicotine are not stable even over a brief period and not sufficient to permit a reduction in the dose of haloperidol. At Day 33, when all children were maintained on 50% of the optimal dose of haloperidol only (nicotine treatment was discontinued at Day 19), there was no difference in tic severity across randomized groups, but the nicotine patch group showed improvement on global measures. The authors note that the Clinician and Parent Global Improvement scales include: "motor and phonic tics, inattention, restlessness, irritability, obsessions and compulsions, temper outbursts and aggression." How a treatment discontinued two weeks previously could have some global benefits in the absence of enduring positive effects on tics is not clear. Thus, the authors conclusion that the results support the use of the nicotine patch on an "as needed" seems unjustified. Nicotine treatment was associated with nausea, vomiting and dizziness.

Based on encouraging open-label data in 24 patients (daily dose ranging from 2.5 to 6.25 mg [Silver et al 2000]), the investigators undertook this randomized control trial of mecamylamine. The active medication was not better than placebo in reducing tic symptoms. The authors claim some evidence of benefit for mood instability is unconvincing.

References: 1. Sandberg PR, Fogelson HM, Mandersheid, PZ, et al: Nicotine gum and haloperidol in Tourette's syndrome [letter]; Lancet 1988; 1:592. 2. McConville BJ, Fogelson HM, Norman AB, et al: Nicotine potentiation of haloperidol in reducing tic frequency in Tourette's syndrome; Biol Psychiatry 1992; 31:832-840. 3. Silver AA, Shytle RD, Sanberg PR: Mecamylamine in Tourette's syndrome: a two-year retrospective case study; J Child Adolesc Psychopharmacol 2000; 10(2):59-68.

Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial

Singer HS, Wendlandt J, Krieger M, Giuliano J: Neurology 2001; 56(5):599-604

Abstract: Methods: Subjects received, in a randomized sequence, 4-week medication cycles of baclofen (20 mg three times daily) and placebo with a 2-week intervening washout period between the cycles. Outcome measures included the Clinical Global Impression (CGI) scale, and the Yale Global Tic Severity Scale (YGTSS), the latter including subscales for total tics and overall impairment. Measures were assessed at baseline and on days 28, 42, and 70 of the study. **Results:** Ten children (seven boys and three girls, aged 8 to 14) with TS participated. Nine subjects completed the protocol; one dropped out for psychosocial reasons. No major side effects were reported. The mean change in CGI score (-0.9) after 4 weeks of baclofen treatment as compared with placebo treatment showed a significant improvement (95% CI, -1.7 to -0.1; p = 0.04). All subjects showed some amelioration in total YGTSS score during baclofen treatment. The mean change in total YGTSS score (-14.7) approached significance (95% CI, -30.3 to 0.9; p = 0.06). Examination of differences between baclofen and placebo treatment groups expressed as a percent change from baseline showed that baclofen had a statistically significant effect on both outcome measures. Subscales of the YGTSS showed that the reduction in total tic scores was primarily due to a reduction in the impairment score rather than a decrease in tics. **Conclusions:** Children with TS may benefit from treatment with baclofen, although improvements may be related to factors other than tics. Larger studies directly comparing baclofen against other tic-suppressing agents are recommended.

Tourette's syndrome improvement with pergolide in a randomized, double-blind, crossover trial

Gilbert DL, Sethuraman G, Sine L, et al: Neurology 2000; 54(6):1310-1315

Abstract: Methods: The authors enrolled 24 children age 7 to 17 years with Tourette's disorder, chronic motor tic disorder, or chronic vocal tic disorder by Diagnostic and Statistical Manual of Mental Disorders (4th ed.) criteria, plus severity criteria on the Yale Global Tic Severity Scale (YGTSS) of > or = 20, in a double-blind, placebo-controlled, crossover study. Children were randomized to receive either placebo or up to 300 microg/day pergolide for the first 6-week treatment period, with a 2-week placebo washout, followed by crossover to the alternate treatment. The primary outcome measure was tic severity assessed by YGTSS. **Results:** Compared with placebo treatment, pergolide treatment was associated with significantly lower YGTSS scores (42.0 +/- 20.4 versus 23.5 +/- 18.7; F = 12.0, df = 1, 17, p = 0.0011). No patient had a serious adverse event and pergolide was well tolerated. **Conclusions:** In this randomized, placebo-controlled, crossover trial, pergolide appeared to be a safe and efficacious treatment for Tourette's syndrome in children.

Tic reduction with pergolide in a randomized controlled trial in children

Gilbert DL, Dure L, Sethuraman G, et al: Neurology 2003; 60(4): 606-611

Abstract: Methods: The authors enrolled 57 children and adolescents, ages 7 to 17 years, randomizing them in a 2:1 ratio to either pergolide (0.15 to 0.45 mg per day) or placebo. Tic symptoms had to be >30 on the Yale Global Tic Severity Scale (YGTSS). The primary outcome measure was change in tic severity assessed by YGTSS. **Results:** Compared to placebo treatment, pergolide treatment was associated with lower tic severity scores (treatment effect 8.8, pergolide vs placebo; 95% CI 0.1 to 17.6; p = 0.05) and attention-deficit hyperactivity disorder symptoms scores (treatment effect 3.8; 95% CI 0.7 to 6.8; p = 0.02). No patient had a serious adverse event and pergolide was well tolerated. **Conclusions:** In this randomized, placebo-controlled trial, pergolide appeared to be an efficacious and safe medication for tic reduction in children, and may also improve attention-deficit hyperactivity disorder symptoms.

Comment: Concern about the potential adverse effects of the antipsychotics prompts investigators to search for alternative medications to reduce tic symptoms. These three studies provide new information about the use of baclofen and pergolide in children with TS. Each compound offers a plausible mechanism for the treatment of tics and each compound has open-label data showing positive results (Awaad, 1999; Lipinski et al, 1997).[1-2] Baclofen, an analogue of GABA, is presumed to impede the release of excitatory neurotranmitters such as glutamate. Pergolide is a dopamine partial agonist that is presumed to turn down dopamine transmission in the presumably hyperdopaminergic state in TS.

The baclofen and the first pergolide trial used a crossover design with six-week active arms separated by a two-week wash out. Many investigators find the crossover design appealing—especially for small sample trials. Because each subject serves as his/her own control, many investigators are convinced that the crossover design will produce the maximum information from their sample. Unfortunately, however, the results of crossover studies are often ambiguous—especially in small sample trials. For example, in the pergolide study, the difference between active and placebo was only 11% (net change 4 points on the Total Tic Score of the YGTSS in the first arm of the study compared to 36% change in the second arm of the study, and net change almost 7 points on the Total Tic Score in favor of pergolide). These inconsistent results across the two arms of the study present a challenge for interpretation. Thus, clear evidence for benefit for these two agents remains uncertain.

In contrast to the previously described study by Gilbert at al. (2000), this more recent trial with pergolide used a parallel group design (N=36 for pergolide; N=15 for

placebo). Compared to the ziprasidone study (Sallee et al, 2000) and the risperidone study (Scahill et al, 2003) both of which showed a net change score of 7 points (change in active-change in placebo) on the Total Tic Score of the YGTSS, this study showed a more modest net change of 4 points on the same measure. Thus, pergolide was not significantly better than placebo on this measure.

In this study, as in the baclofen trial, active treatment only showed superiority to placebo when the YGTSS Global Score was used. The YGTSS Global Score includes the Total Tic Score (sum of motor and phonic tic severity) and an overall Impairment score. Given the short duration of these trials, it is difficult to understand how such modest effects on tic severity would result in reductions in the overall Impairment score. These results imply that the Impairment Score and the Total Tic Score are not measuring the same clinical phenomenon. Because tic suppression was the goal of these treatment interventions, it seems difficult to justify the Impairment Score in the primary assessment of drug effect.

References: 1. Awaad Y: Tics in Tourette syndrome: new treatment options; J Child Neurology 1999; 14:316-319. 2. Lipinski JF, Sallee FR, Jackson C, Sethuraman G: Dopamine agonist treatment of Tourette disorder in children: results of an open-label trial of pergolide; Mov Disorder 1997; 12:402-407.

Treatment of ADHD in Children with Tic Disorders using Guanfacine and Desipramine

Guanfacine in the Treatment of Children with Tic Disorders and ADHD: A Placebo-Controlled Study

Scahill L, Chappell PB, Kim YS et al: Amer J Psychiatry 2001; 158:1067-1074

Abstract: Methods: Subjects from a specialty tic disorders clinic were randomly assigned to receive 8 weeks of treatment with guanfacine or placebo under double-blind conditions. Follow-up visits occurred every 2 weeks for safety monitoring and dose adjustment. **Results:** Thirty-four medication-free subjects (31 boys and three girls with a mean age of 10.4 years) with ADHD, combined type, and a tic disorder participated. After 8 weeks of treatment, guanfacine was associated with a mean improvement of 37% in the total score on the teacher-rated ADHD Rating Scale, compared to 8% improvement for placebo. Nine of 17 subjects who received guanfacine were blindly rated on the Clinical Global Improvement scale as either much improved or very much improved, compared with none of 17 subjects who received placebo. The mean score on the parent-rated hyperactivity index improved by 27% in the guanfacine group and 21% in the placebo group, not a significant difference. On the Continuous Performance Test, commission errors decreased by 22% and omission errors by 17% in the guanfacine group, compared with increases of 29% in commission errors and of 31% in omission errors in the placebo group. Tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group. One guanfacine subject with sedation withdrew at week 4. Guanfacine was associated with insignificant decreases in blood pressure and pulse. **Conclusions:** Guanfacine appears to be a safe and effective treatment for children with tic disorders and ADHD.

A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder

Spencer T, Biederman J, Coffey B, et al: Arch General Psychiatry 2002; 59(7):649-656

Abstract: Methods: Forty-one children and adolescents with chronic tic disorders, including Tourette disorder and comorbid ADHD, were studied in a 6-week, double-blind, placebo-controlled, parallel trial. Desipramine was titrated weekly up to 3.5 mg/kg per day. We rated ADHD and tic symptoms weekly and monitored adverse effects, laboratory findings, and cardiovascular parameters. **Results:** Treatment with desipramine (mean total daily dose, 3.4 mg/kg per day) was well tolerated without meaningful adverse effects. Desipramine significantly reduced core symptoms of ADHD (ADHD Rating Scale; 42% decrease from baseline relative to placebo, P<.001), with equal response in inattentive symptoms and hyperactive/impulsive symptoms (P<.001 for both). The ADHD response rate was robust (71% vs 0%; desipramine vs placebo, P<.001). Likewise, desipramine significantly reduced tic symptoms (Yale Global Tic Severity Scale; 30% decrease from baseline relative to placebo, P<.001), with equal response in motor and phonic tic symptoms (P<.01 for both). The tic response rate was substantial (58% vs 5%; desipramine vs placebo, P<.001). There were small but statistically significant differences between desipramine and placebo in heart rate and blood pressure. **Conclusions:** Treatment with desipramine was well tolerated and was associated with robust clinically significant reductions in tic and ADHD symptoms in children and adolescents with chronic tic disorders and ADHD diagnoses.

Treatment of ADHD in children with tics: a randomized controlled trial

Tourette's Syndrome Study Group: Neurology 2002; 58(4): 527-536

Abstract: Methods: The authors conducted a multicenter, randomized, double-blind clinical trial in which 136 children with ADHD and a chronic tic disorder were randomly administered CLON alone, MPH alone, combined CLON + MPH, or placebo (2 x 2 factorial design). Each subject participated for 16 weeks (weeks 1-4 CLON/placebo dose titration, weeks 5-8 added MPH/placebo dose titration, weeks 9-16 maintenance therapy). **Results:** Thirty-seven children were administered MPH alone, 34 were administered CLON alone, 33 were administered CLON + MPH, and 32 were administered placebo. For our primary outcome measure of ADHD (Conners Abbreviated Symptom Questionnaire—Teacher), significant improvement occurred for subjects assigned to CLON ($p < 0.002$) and those assigned to

MPH ($p < 0.003$). Compared with placebo, the greatest benefit occurred with combined CLON + MPH ($p < 0.0001$). CLON appeared to be most helpful for impulsivity and hyperactivity; MPH appeared to be most helpful for inattention. The proportion of individual subjects reporting a worsening of tics as an adverse effect was no higher in those treated with MPH (20%) than those being administered CLON alone (26%) or placebo (22%). Compared with placebo, measured tic severity lessened in all active treatment groups in the following order: CLON + MPH, CLON alone, MPH alone. Sedation was common with CLON treatment (28% reported moderate or severe sedation), but otherwise the drugs were tolerated well, including absence of any evident cardiac toxicity. **Conclusions:** Methylphenidate and clonidine (particularly in combination) are effective for ADHD in children with comorbid tics. Prior recommendations to avoid methylphenidate in these children because of concerns of worsening tics are unsupported by this trial.

Comment: The studies by Scahill et al (2001) and Spencer et al (2002) show similar results. In general, the magnitude of effect is lower than the level of improvement typically observed in stimulant studies. Both studies also observed improvement in tic severity.

The Tourette Syndrome Study Group (2002) conducted a multi-site, randomized trial with four groups using clonidine alone, methylphenidate alone, clonidine and methylphenidate, and placebo. The 136 subjects with a tic disorder and ADHD ranged from 7 to 14 years. The clonidine alone group showed a 40% improvement on the Conners' teacher rating scale compared to 38% for the methylphenidate group and 59% for the combined treatment group. The average dose of methylphenidate in this study was approximately 26 mg per day. The level of improvement observed in the methylphenidate only group and the average stimulant dose in this study were both lower than the results and doses observed in the MTA study (MTA Cooperative Group, 1999).[1] The MTA study was a mulitsite trial involving 579 children with ADHD. Children with tics were excluded. In the MTA study, the average dose was 38 mg per day for methylphenidate and the average improvement ranged between 50% to 60% on teacher measures of ADHD. The lower doses used in the TACT study may explain the more modest improvement observed in the methylphenidate alone group.

Approximately a quarter of the subjects in the clonidine only and the methylphenidate only groups showed an increase in tics, which was only slightly higher than the rate observed in the placebo group. In general, the tics improved across all treatment groups. This is a landmark study showing the efficacy and safety of monotherapy with stimulants in children with TS and ADHD, though perhaps the magnitude of effect maybe lower than that observed in children with ADHD without tics. In addition, the results provide empirical evidence for the commonly used combination of methylphenidate and clonidine in children with TS and ADHD. This is especially noteworthy given the previous concerns about the potential for adverse health effects from the combination (Swanson et al, 1995).[2]

References: 1. The MTA Cooperative Group: Multimodal Treatment Study of Children with ADHD: A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder; Arch Gen Psychiatry 1999; 56(12):1073-1086. 2. Swanson JM, Flockhart D, Udrea D, et al: Clonidine in the treatment of ADHD: questions about safety and efficacy; J Child Adolesc Psychopharmacology 1995; 5:301-304.

Pimozide and Drug Interaction

Studies on the mechanism of a fatal clarithromycin-pimozide interaction in a patient with Tourette syndrome

Flockhart DA, Drici MD, Kerbusch T, et al: J Clin Psychopharmacol 2000; 20(3):317-324

Abstract: The authors report in detail the case of a 27-year-old man who experienced sudden cardiac death 2 days after coprescription of the neuroleptic pimozide and the macrolide antibiotic clarithromycin after the documentation of a prolonged QT interval. To determine the prevalence of this interaction, the authors referred to the Spontaneous Reporting System of the Food and Drug Administration and identified one similar case in which clarithromycin was coprescribed with pimozide and sudden cardiac death occurred shortly thereafter. In addition, the search identified 39 cases of cardiac arrhythmia associated with pimozide, 11 with pimozide alone, and 6 with clarithromycin alone, 1 of which had a positive rechallenge. The mechanism of the interaction between clarithromycin and pimozide seems to involve the inhibition of the hepatic metabolism of pimozide by the macrolide. The authors demonstrated that clarithromycin is able to inhibit the metabolism of pimozide in human liver microsomal preparations (K(i) = 7.65 +/- 1.18 microM) and that pimozide, but not clarithromycin or its primary metabolite, is able to prolong the electrocardiac QT interval in a dose-dependent manner in the isolated perfused rabbit heart. The increase was 9.6 +/- 1.1% in male hearts (N = 5) and 13.4 +/- 1.2% in female hearts (N = 4) ($p < 0.05$).

Comment: In an earlier *Medical Letter* (1999), we described a similar case of sudden death in a 27-year-old man treated with pimozide and clarithromycin. In that issue, we also published a statement from the Medical Advisory Board of the TSA regarding the contraindication of combining pimozide and macrolide antibiotics such as erythromycin and clarithromycin both of which are potent inhibitors of hepatic CYP 3A4 enzyme activity. Because pimozide relies on the 3A4 pathway, inhibition of this pathway results in a rapid increase in the pimozide level. This investigation by Flockhart and colleagues provides support for the view that the increase in pimozide level is

indeed the likely mechanism for cardiac arrhythmia and sudden death. Concern about drug-drug interaction with pimozide and sertraline has recently emerged following a prescribers' alert issued by Pfizer (manufacturer of sertraline). A Medline search in Fall 2003 uncovered one report of fatal interaction between sertraline and pimozide (McIntyre et al, 1997).[1] This case is confounded by the co-administration of moclobemide, which is a selective MAO inhibitor (this drug is known to inhibit CYP450 2C19 (Cho et al, 2002)).[2]

Desta, Soukhova and Flockhart (2002)[3] examined the potential for interaction between sertraline and pimozide. In that investigation, the authors showed that the addition of sertraline has only a modest effect on the serum levels of pimozide. Furthermore, sertraline was not different than several other SSRIs tested. Similarly, azithromycin (in the same family of macrolides as erythromycin and clarithromycin) apparently does not inhibit the metabolism of pimozide. The risk of co-adminstration of sertraline with pimozide may not be greater than co-administration of pimozide with other SSRIs. There are clear differences among macrolide antibiotics. Azithromycin appears safe when used with pimozide; co-administration with erythromycin and clarithromycin should be avoided.

References: 1. McIntyre IM, King CV, Staikos V, et al: A fatality involving moclobemide, sertraline, and pimozide; J Forensic Sciences 1997; 42(5):951-953. 2. Cho JY, Yu KS, Jang IJ, et al: Omeprazole hydroxylation is inhibited by a single dose of moclobemide in homozygotic EM genotype for CYP2C19; British J Clin Pharmacology 2002; 53(4):393-397. 3. Desta Z, Soukhova N, Flockhart DA: In vitro inhibition of pimozide N-dealkylation by selective serotonin reuptake inhibitors and azithromycin; J Clin Psychopharmacology 2002; 22(2):162-168.

Refractory OCD

A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder

McDougle CJ, Epperson CN, Pelton GH, et al: Arch Gen Psychiatry 2000; 57(8):794-801

Abstract: Methods: Seventy adult patients with a primary DSM-IV diagnosis of OCD received 12 weeks of treatment with an SRI. Thirty-six patients were refractory to the SRI and were randomized in a double-blind manner to 6 weeks of risperidone (n = 20) or placebo (n =16) addition. Behavioral ratings, including the Yale-Brown Obsessive Compulsive Scale, were obtained at baseline and throughout the trial. Placebo-treated patients subsequently received an identical open-label trial of risperidone addition. **Results:** For study completers, 9 (50%) of 18 risperidone-treated patients were responders (mean daily dose, 2.2 +/-0.7 mg/d) compared with 0 of 15 in the placebo addition group (P<.005). Seven (50%) of 14 patients who received open-label risperidone addition responded. Risperidone addition was superior to placebo in reducing OCD (P<.001), depressive (P<.001), and anxiety (P =.003) symptoms. There was no difference in response between OCD patients with and without comorbid diagnoses of chronic tic disorder or schizotypal personalty disorder. Other than mild, transient sedation, risperidone was well tolerated. **Conclusions:** These results suggest that OCD patients with and without comorbid chronic tic disorders or schizotypal personality disorder may respond to the addition of low-dose risperidone to ongoing SRI therapy.

Comment: This was the second placebo-controlled study designed to examine the additive benefits of an antipsychotic medication to a selective serotonin-reuptake inhibitor (SSRI) in adults with refractory OCD. The previous study, also carried out by McDougle and colleagues[1], compared the addition of haloperidol or placebo to ongoing treatment with fluvoxamine in 34 adults with refractory OCD. In that study the co-occurrence of tics was associated with a positive response to the addition of haloperidol. This finding did not bear out in the risperidone augmentation trial. The current study does suggest that the addition of low-dose risperidone is an effective strategy in OCD when SSRI monotherapy in not adequate. An open-label study has also been conducted with olanzapine suggesting that it too may be useful in refractory OCD. In this 8-week, open-label study, Koran et al (2000)[2] reported that 3 of 10 subjects showed a positive response to combined treatment. Significant weight gain was observed in 6 of 10 of olanzapine treated patients.

References: 1. McDougle CJ, Goodman WK, Leckman JF, et al: Haloperidol addition in fluvoxamine-refractory obsessive compulsive disorder: A double-blind, placebo-controlled study in patients with and without tics; Arch Gen Psychiatry 1994; 51: 302-308. 2. Koran LM, Ringold AL, Elliott MA: Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder; J Clinical Psychiatry 2000; 61(7):514-517.

Complementary/Alternative Treatments

An open-label trial of St. John's Wort (Hypericum perforatum) in obsessive-compulsive disorder

Taylor LH, Kobak KA: J Clinical Psychiatry 2000; 61(8):575-578

Abstract: Methods: Twelve subjects were evaluated with a primary DSM-IV diagnosis of OCD of at least 12 months' duration. Treatment lasted for 12 weeks, with a fixed dose of 450 mg of 0.3% hypericin (a psychoactive compound in Hypericum) twice daily (extended-release formulation). Weekly evaluations were conducted with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Patient Global Impressions of Improvement Scale, and the Clinical Global Impressions of Improvement scale (CGI) and monthly evaluation with the Hamilton Rating Scale for Depression. **Results:** A significant change from baseline to endpoint was found, with a mean Y-BOCS change of 7.4 points

(p = .001). Significant change occurred at 1 week (p = .020) and continued to increase throughout the trial. At endpoint, 5 (42%) of 12 were rated "much" or "very much improved" on the clinician-rated CGI, 6 (50%) were "minimally improved," and 1 (8%) had "no change." The most common side effects reported were diarrhea (N = 3) and restless sleep (N = 2). **Conclusions:** Significant improvement was found with Hypericum, with a drop-in Y-BOCS score similar to that found in clinical trials. The fact that a significant change was found as early as 1 week into treatment suggests a possible initial placebo response, although improvement grew larger over time. Results warrant a placebo-controlled study of Hypericum in OCD.

Comment: The conclusions of this study seem overstated given the open-label design and small number of subjects. The 42% rate of subjects classified as "much" or "very much improved" on the Improvement item of the Clinical Global Impression is lower than most studies in OCD.

Cognitive Behavioral Treatment in TS and OCD

Effectiveness of exposure and ritual prevention for obsessive-compulsive disorder: randomized compared with nonrandomized samples

Franklin ME, Abramowitz JS, Kozak MJ, et al: Journal of Consulting & Clinical Psychology 2000; 68(4):594-602

Abstract: The efficacy of exposure and ritual prevention (EX/RP) for reducing symptoms of obsessive-compulsive disorder (OCD) has been demonstrated in several randomized controlled trials (RCTs). However, procedures used in these studies to maximize experimental control may have limited their generalizability to typical clinical practice. Treatment outcome data from 110 clinical patients receiving EX/RP on an outpatient fee-for-service basis were compared with findings from 4 RCTs of EX/RP. Adult patients in the clinical sample were not excluded because of treatment history, concomitant pharmacotherapy, psychiatric comorbidity, age, or OCD severity. Clinical patients achieved substantial and clinically meaningful reductions in their OCD and depressive symptoms following EX/RP, which were comparable with those reported in the RCTs. Findings indicate that EX/RP is a potent treatment for OCD, and its benefits are not limited to select patient samples.

Comment: As with randomized clinical trials with medication, cognitive-behavioral studies often have restrictive inclusion and exclusion entry criteria. These entry criteria are intended to reduce the heterogeneity of the sample and presumably the variability in response. Controlling variability in the development and testing of a treatment is important, but ultimately, treatments must be applied to the real world. Therefore, this study is of interest because it shows that the application of exposure and response prevention is effective for OCD in an outpatient clinic with more liberal entry criteria.

Habit reversal versus supportive psychotherapy for Tourette's disorder: a randomized controlled trial

Wilhelm S, Deckersbach T, Coffey BJ, et al: Amer J Psychiatry 2003; 160(6):1175-1177

Abstract: Methods: Thirty-two patients with Tourette's disorder were randomly assigned to 14 sessions of either habit reversal or supportive psychotherapy. Habit reversal consisted of awareness training, self-monitoring, relaxation training, competing response training, and contingency management. Changes in severity of Tourette's disorder and psychosocial impairment were investigated over the course of the 14-session treatment for the 29 patients who completed at least eight treatment sessions. **Results:** In contrast to the 13 patients in the supportive psychotherapy group, the 16 patients in the habit reversal group improved significantly. The habit reversal patients remained significantly improved over pretreatment at 10-month follow-up. **Conclusions:** Habit reversal may be an effective behavioral treatment for Tourette's disorder.

Behavioral treatments for Tourette syndrome and tic disorders: State of the art

Piacentini J, Chang S: Advances in Neurology 2001; 85:319-331

Treatment of vocal tics in children with Tourette syndrome: Investigating the efficacy of habit reversal

Woods DW, Twohig MP, Flessner C, Roloff T: J Applied Behavior Analysis 2003; 36:109-112

Comment: Habit Reversal was developed in the 1970s by Azrin and Nunn (1974)[1] and refined in the 1980s by Azrin and Peterson (1990).[2] Since then, others have adapted and developed the technique further (Woods et al, 1996).[3] Habit reversal is a behavioral intervention designed to enhance the patient's awareness of tics (e.g., the premonitory urges that often precede tics) and then teach the patient to replace the tic with a competing response. The competing responses typically involve opposing muscle groups from those that are used to perform the targeted tic. To date, most studies have involved single case studies or small case series. These recent studies in adults (Wilhelm et al, 2003) and children (Piacentini and Chang, 2001; Woods et al, 2003) provide more rigorous preliminary data suggesting that habit reversal may be effective in some TS patients. Despite these promising results, this

treatment has yet to be evaluated in a large-scale randomized clinical trial. A consortium empanelled by the Tourette Syndrome Association is pursuing multisite randomized control trials in children and adults with TS.

References: 1. Azrin NH, Nunn RG: Habit reversal: A method of eliminating nervous habits and tics; Behaviour Research and Therapy 1973; 11:619-628. 2. Azrin NH, Peterson AL: Treatment of Tourette syndrome by habit reversal: A waiting-list control group comparison; Behavior Therapy 1990; 21:305-318. 3. Woods DW, Miltenberger RG, Lumley VA: Sequential application of major habit reversal components to treat motor tics in children; J Applied Behavior Analysis 1996; 29:483-493.

PHENOMENOLOGY

The behavioral spectrum of tic disorders: A community-based study

Kurlan R, Como PG, Miller B, et al: Neurology 2002; 59:414-420

Abstract: Methods: In order to overcome the potential confounding by ascertainment bias, the authors conducted a community-based study of school children using direct interviews to determine the prevalence of tic disorders and any comorbid psychopathology. A standard psychiatric interview and standardized rating scales were utilized to diagnose childhood behavioral disorders. **Results:** Of the 1,596 children interviewed, 339 were identified as having tics. The following psychopathologies were found more commonly ($p < 0.05$) in the children with tics: OCD, ADHD, separation anxiety, overanxious disorder, simple phobia, social phobia, agoraphobia, mania, major depression, and oppositional defiant behavior. **Conclusions:** The behavioral spectrum of tic disorders includes OCD, other anxiety disorders, a mood disorder, and attention-deficit and disruptive behavior disorders.

Comment: As described in the reports by Sukhodolsky et al (2003)[1] and Spencer et al (2001)[2], OCD, Attention Deficit Hyperactivity Disorder, and Oppositional Defiant Disorder (ODD) are common co-occurring features in clinical samples of children with TS. Other reports have documented the high frequency of anxiety disorders in clinic cases as well (Coffey et al, 2000).[3] Whether these apparent associations observed in clinic samples are valid or an artifact of the clinical ascertainment is unclear. The results from the community-based study by Kurlan et al (2002) suggest that ADHD, ODD, OCD and other anxiety disorders are more common in children with tic than the group of children without tics. As noted above, despite the careful design of the study, the participation rate in this study was low (see Kurlan et al, 2001 in the Epidemiology section on page 3). It seems likely that families that agreed to participate in the study had children with unexpectedly high rates of psychiatric disorders. Indeed, when the results of this study are compared to other contemporary community-based studies in a similar age group (e.g., Costello et al, 1996),[4] the prevalence of several psychiatric disorders was higher in both groups (those with tics and those without tics). For example, Costello et al (1996)[4] reported a rate of 3.5% for separation anxiety compared to 7.4% in the children without tics. The prevalence of ADHD reported in the Kurlan et al (2002) report was 19.5% for the non tic group—which is substantially higher than the 5% to 10% often cited for school age children (Scahill & Schwab-Stone, 2000).[5] Nonetheless, the relative risk of other psychiatric disorders—especially ADHD, OCD and other anxiety disorders—appears to be higher in children with tics than in children without tics. Furthermore, the presence of ADHD in children with TS predicts greater disability (Sukhodolsky et al, 2003).[1]

References: 1. Sukhodolsky D, Scahill L, Zhang H, et al: Disruptive behavior in children with Tourette's syndrome: Association of ADHD comorbidity, tic severity, and functional impairment; J Am Acad Child Adolesc Psychiatry 2003; 42:98-105. 2. Spencer T, Biederman J, Coffey BJ, et al: Tourette disorder and ADHD; Advances in Neurology 2001; 85;57-78. 3. Coffey BJ, Geller D, Biederman J, et al: Anxiety disorders and tic severity in juveniles with Tourette's disorder; J Amer Acad Child Adolesc Psychiatry 2000; 39:562-568. 4. Costello EJ, Angold A, Burns BJ, et al: The Great Smoky Mountains study of youth: Goals, design, methods, and the prevalence of DSM-III-R disorders; Arch Gen Psychiatry 1996, 53:1129-1136. 5. Scahill L, Schwab-Stone M: Epidemiology of Attention Deficit Hyperactivity Disorder in school-age children; Child Adoles Psych Clinics N Amer 2000; 9(3):541-555.

WAXING AND WANING OF TICS

Assessment of symptom exacerbations in a longitudinal study of children with Tourette syndrome or obsessive-compulsive disorder

Lin H, Yeh CB, Peterson BS, et al: J Amer Acad Child Adolesc Psychiatry 2002; 41:1070-1077

Abstract: Methods: Monthly consecutive Yale Global Tic Severity Scale and Children's Yale-Brown Obsessive Compulsive Scale scores were prospectively obtained in 64 children diagnosed with Tourette's syndrome and/or OCD for periods ranging from 3 to 39 months. Exacerbation thresholds were estimated by using state-of-the-art bootstrap methods. These thresholds were then independently evaluated by asking two expert clinicians to identify, retrospectively, clinically significant exacerbations based on a review of all available clinical and research records. **Results:** The severity of tic and OC symptoms displayed a high degree of intrasubject variability. Exacerbation thresholds, which incorporated the change score from the previous month and the current symptom score, provided the best agreement with those of expert clinicians. When both tic and OC symptoms were present, they showed a significant degree of covariation. **Conclusions:** Evidence-based treatments are coming of age. The use of valid, clinician-rated severity scales will likely become a standard part of clinical practice. Bootstrapping methods may provide a quantitative and convenient way to obtain clinically valid thresholds to assess tic and OC symptom exacerbations. This method has the potential to be applied to other symptom domains where exacerbation thresholds are needed.

Comment: This paper confirms what families and clinicians have noted for many years. Tics and OCD symptoms fluctuate over time. Using the Total Tic score of the Yale Global Tic Symptom Severity Scale (YGTSS) and the Total Score of the Children's Yale–Brown Obsessive Compulsive Scale (CYBOCS), the study showed that a 9-point increase on the YGTSS and a 7-point increase on the CYBOCS constituted a clinically and statistically significant exacerbation. The duration of an exacerbation was 9 weeks for tics and 13 weeks for OCD symptoms. It is interesting to note that the clinical trials by Sallee et al (2000) and Scahill et al (2003) (see treatment section, page 9) each showed a reduction of 9 to 10 points on the Total Tic score of the YGTSS. Recent studies of SSRIs in children show improvement of 6 to 9 points on the CYBOCS (Geller et al, 2001; March et al, 1998; Riddle et al, 2001).[1-2-3] Taken together, these data suggest that these measures (Total Tic score of the YGTSS and the Total score of the CYBOCS) are sensitive to change. Furthermore, these benchmarks (9 points on the YGTSS and 7 points on the CYBOCS) are relevant for tracking improvement following initiation of treatment and stability of gains once expected change has been achieved. Another implication of this study is that clinicians may advise waiting before increasing medication if the exacerbation is below these benchmarks.

References: 1. Geller DA, Hoog SL, Heiligenstein JH, et al: Fluoxetine Pediatric OCD Study Team: Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial; J Amer Acad Child Adolesc Psychiatry 2001; 40(7):773-779. 2. March JS, Biederman J, Wolkow R, et al: Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial; JAMA 1998; 280(20):1752-1756. 3. Riddle MA, Reeve EA, Yaryura-Tobias JA, et al: Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial; J Amer Acad Child Adolesc Psychiatry 2001; 40(2):222-229.

STRUCTURAL NEUROIMAGING IN TS

Subcortical volumes in girls with Tourette syndrome: support for a gender effect

Zimmerman AM, Abrams MT, Giuliano JD, et al: Neurology 2000; 54(12):2224-2229

Abstract: Methods: MRI-based subcortical assessment was completed on 19 girls with TS age 7 to 15 years, 11 with TS only, and 8 with TS plus attention deficit hyperactivity disorder (TS + ADHD), and on 21 age- and sex-matched controls. The structures measured were the caudate, putamen, globus pallidus, and lateral ventricle volumes. Whole-brain-corrected volumes and asymmetry indices were compared using two- and three-group designs (i.e., TS versus control; TS-only versus TS + ADHD versus control). **Results:** Two-group comparisons demonstrated no robust significant differences between girls with TS and gender-matched controls. Three-group comparisons demonstrated that TS-only subjects had significantly small lateral ventricles compared with TS + ADHD and control subjects. Because the two-group comparisons of the current study differed from previous reports of putamen asymmetry index as a marker for TS, retrospective comparisons with data from boys were performed. These additional comparisons showed that girls with TS had putamen asymmetry indices similar to those of boys with TS; however, control girls also showed those same patterns. **Conclusions:** Basal ganglia volume and asymmetry differences do not distinguish the girls with TS from matched controls. Gender differences confound the association between putamen asymmetry and TS. Although the numbers are small and the clinical significance is unclear, this study further indicates that girls with TS-only have smaller lateral ventricular volumes than control subjects and those with TS + ADHD.

Regional brain and ventricular volumes in Tourette syndrome

Peterson BS, Staib L, Scahill L, et al: Archives of General Psychiatry 2001; 58(5):427-440

Abstract: Methods: High-resolution anatomical magnetic resonance images were acquired in 155 TS and 131 healthy children and adults. The cerebrums and ventricles were isolated and then parcellated into subregions using standard anatomical landmarks. **Results:** For analyses that included both children and adults, TS subjects were found to have larger volumes in dorsal prefrontal regions, larger volumes in parieto-occipital regions, and smaller inferior occipital volumes. Significant inverse associations of cerebral volumes with age were seen in TS subjects that were not seen in healthy controls. Sex differences in the parieto-occipital regions of healthy subjects were diminished in the TS group. The age-related findings were most prominent in TS children, whereas the diminished sex differences were most prominent in TS adults. Group differences in regional ventricular volumes were less prominent than in the cerebrum. Regional cerebral volumes were significantly associated with the severity of tic symptoms in orbitofrontal, midtemporal, and parieto-occipital regions. **Conclusions:** Broadly distributed cortical systems are involved in the pathophysiology of TS. Developmental processes, sexual dimorphisms, and compensatory responses in these cortical regions may help to modulate the course and severity of tic symptoms.

Basal ganglia volumes in patients with Gilles de la Tourette syndrome

Peterson BS, Thomas P, Kane MJ, et al: Arch Gen Psychiatry 2003; 60:415-424

Abstract: Methods: Basal ganglia volumes were measured on high-resolution magnetic resonance images acquired for 154 children and adults with TS and 130 healthy control subjects. Repeated-measures analyses tested hypotheses concerning regional specificity, age effects, and abnormal asymmetries in the basal ganglia of subjects with TS. Subjects with prior neuroleptic exposure had larger basal ganglia volumes and were excluded from further statistical analyses. **Results:** Caudate nucleus volumes were significantly (P =.008) smaller in children and adults with TS. Lenticular nucleus volumes also were smaller in adults with TS and in children with TS who were diagnosed

as having comorbid obsessive-compulsive disorder. Regional anatomical asymmetries did not differ across groups. Regional volumes did not correlate significantly with the severity of tic, obsessive-compulsive disorder, or attention-deficit/hyperactivity disorder symptoms. **Conclusions:** Reduced caudate nucleus volumes may be a good candidate marker for a trait abnormality in the structure of the basal ganglia in persons with TS. Smaller lenticular nucleus volumes may be an additional marker for the presence of comorbid obsessive-compulsive disorder and for the persistence of tic symptoms into adulthood. Brain regions other than the basal ganglia may have greater clinical relevance in determining the severity of tic symptoms.

Comment: The pathophysiology of TS is presumed to involve dysregulation of cortico-striato-thalamo-cortical (CSTC) circuitry. These MRI volumetric studies as well as other recent functional imaging studies support this view (Adler et al, 2000; Muller-Vahl et al, 2000).[1-2] Zimmerman et al (2000) report on 19 girls with TS compared with 21 controls. The two papers by Peterson et al (2001; 2003) are separate analyses conducted on the same sample, which included both children and adults with TS and age-matched controls. Both the Zimmerman et al and Peterson et al, studies observed lower caudate volumes in TS compared to controls. The difference was not statistically significant in the study by Zimmerman et al (2000), but this may have been due to the small sample size. Peterson et al, (2003) observed significantly reduced caudate volumes in both children and adults with TS compared to age-matched controls. Zimmerman et al noted smaller putamen volumes in their pediatric sample, which was only seen in the adults with TS in the study by Peterson and colleagues. Another difference was observed in ventricular volumes. Zimmerman et al reported smaller lateral ventricular volumes in their sample of girls with TS only. By contrast, Peterson et al (2001) noted that TS plus ADHD trended toward smaller ventricular volumes. Furthermore, males with TS had significantly larger ventricles in the occipital horns.

These findings also point to potentially complicated age and gender brain volume differences in TS. For example, in their examination of basal ganglia volumes, Peterson et al (2003) found that caudate volumes were reduced in both child and adult TS patients, but the reduced volumes in the globus pallidus and putamen were only observed in the adult sample. In addition, the gender differences by age (children vs adults) were more prominent in controls than in the TS samples. The meaning of these apparent age and gender effects could be informed by longitudinal studies.

References: 1. Adler CM, McDonough-Ryan P, Sax KW, et al: fMRI of neuronal activation with symptom provocation in unmedicated patient with obsessive compulsive disorder; J Psychiatric Research 2000; 34(4-5):317-24. 2. Muller-Vahl KR, Berding G, Brucke T, et al: Dopamine transporter binding in Gilles de la Tourette syndrome; J Neurology 2000; 247(7):514-520.

Other Imaging Studies of Interest

Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention disorders

Peterson BS, Leckman JF, Tucker D, et al: Archives of General Psychiatry 2000; 57(4):364-372

Abstract: Methods: Antistreptococcal antibody titers were measured in 105 people diagnosed as having CTD, OCD, or attention-deficit/hyperactivity disorder (ADHD) and in 37 community controls without a disorder. Subjects were unselected with regard to their history of streptococcal exposure. Basal ganglia volumes were measured in 113 of these subjects (79 patients and 34 controls). **Results:** A DSM-IV diagnosis of ADHD was associated significantly with titers of 2 distinct antistreptococcal antibodies, antistreptolysin O and anti-deoxyribonuclease B. These associations remained significant after controlling for the effects of CTD and OCD comorbidity. No significant association was seen between antibody titers and a diagnosis of either CTD or OCD. When basal ganglia volumes were included in these analyses, the relationships between antibody titers and basal ganglia volumes were significantly different in OCD and ADHD subjects compared with other diagnostic groups. Higher antibody titers in these subjects were associated with larger volumes of the putamen and globus pallidus nuclei. **Conclusions:** These findings suggest that the prior reports of an association between antistreptococcal antibodies and either CTD or OCD may have been confounded by the presence of ADHD. They also support the hypothesis that in susceptible persons who have ADHD or OCD, chronic or recurrent streptococcal infections are associated with structural alterations in basal ganglia nuclei.

Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET

Singer HS, Szymanski S, Giuliano J, et al: Amer J Psychiatry 2002; 159(8):1329-1336

Abstract: Methods: Seven adults with Tourette's syndrome and five age-matched comparison subjects each received two positron emission tomography (PET) scans with high specific activity [11C]raclopride. The first scan followed an intravenous injection of saline; the second followed an intravenous injection of amphetamine. The relative dopamine release was estimated as the percentage difference in binding potential between the postsaline and postamphetamine scans. **Results:** Binding potential determined after the initial [11C]raclopride scan did not significantly differ between Tourette's syndrome and comparison subjects. After amphetamine challenge, the mean value of intrasynaptic dopamine in the putamen (as determined by true equilibrium bolus estimation) increased by 21% in the subjects with Tourette's syndrome and did not change in the comparison subjects; the mean values increased by 16.9% and decreased by 1.8%, respectively, when measured by the constrained method. Dopamine release in the caudate region was not significantly different in the Tourette's syndrome and comparison subjects.

Conclusions: Greater putamen dopamine release was seen in adults with Tourette's syndrome than in comparison subjects after a pharmacologic challenge with amphetamine. These results suggest that the underlying pathobiology in Tourette's syndrome is a phasic dysfunction of dopamine transmission.

Volume reduction in the caudate nucleus following stereotactic placement of lesions in the anterior cingulate cortex in humans: a morphometric magnetic resonance imaging study

Rauch SL, Kim H, Makris N, et al: J Neurosurgery 2000; 93(6):1019-1025

Abstract: **Methods:** Morphometric magnetic resonance (MR) imaging methods were used to assess volume reductions in subcortical regions following anterior cingulate lesioning in nine patients. Magnetic resonance imaging data obtained before and 9 +/- 6 months following anterior cingulotomy were subjected to segmentation and subcortical parcellation. Significant volume reductions were predicted and found bilaterally within the caudate nucleus, but not in the amygdala, thalamus, lenticular nuclei, or hippocampus. Subcortical parcellation revealed that the volume reduction in the caudate nucleus was principally referrable to the body, rather than the head. Furthermore, the magnitude of volume reduction in the caudate body was significantly correlated with total lesion volume. **Conclusions:** Taken together, these findings implicate significant connectivity between a region of anterior cingulate cortex (ACC) lesioned during cingulotomy and the caudate body. This unique data set complements published findings in nonhuman primates, and advances our knowledge regarding patterns of cortical-subcortical connectivity involving the ACC in humans. Moreover, these findings indicate changes distant from the site of anterior cingulotomy lesions that may play a role in the clinical response to this neurosurgical procedure.

Comment: The study by Peterson et al, (2000) suggests a stronger association between ADHD and streptococcal infection than tic disorders or OCD. Another interesting finding was the observation that higher antibody levels were associated with larger basal ganglia volumes. This finding is particularly interesting because using identical imaging and analytic techniques in a larger sample, Peterson et al (2003) reported smaller basal ganglia volumes in TS. Finally, in a study comparing patients with rheumatic fever and Sydenham's chorea, Mecadante et al, (2000)[1] reported high rates of tic disorders, OCD and ADHD in the Sydenham's chorea group. Also pre-existing ADHD increased the risk of developing chorea. The amphetamine challenge study by Singer et al, (2002) and the structural study by Rauch et al, (2000) provide confirmatory information to support the central role of frontal-basal ganglia circuits in the pathophysiology of TS and OCD.

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AUTOIMMUNITY AND TS

Anti-striatal antibodies in Tourette syndrome cause neuronal dysfunction

Hallett JJ, Harling-Berg CJ, Knopf PM, et al: J Neuroimmunology 2000; 111(1-2):195-202

Abstract: Serologic studies of children with Tourette syndrome (TS) have detected anti-neuronal antibodies but their role in TS has not been explored. Stereotypies and episodic utterances, analogous to involuntary movements seen in TS, were induced in rats by intrastriatal microinfusion of TS sera or gamma immunoglobulins (IgG) under noninflammatory conditions, as found in TS. Immunohistochemical analysis confirmed the presence of IgG selectively bound to striatal neurons. These data support the hypothesis that binding of an anti-neuronal antibody from some children with TS induced striatal dysfunction and suggest a possible cause for the basal ganglia alterations observed in children with TS.

Antibodies against neural, nuclear, cytoskeletal, and streptococcal epitopes in children and adults with Tourette's syndrome, Sydenham's chorea, and autoimmune disorders

Morshed SA, Parveen S, Leckman JF, et al: Biological Psychiatry 2001; 50(8):566-577

Abstract: **Methods:** We looked for the presence ot total and IgG antibodies against neural, nuclear, cytoskeletal and streptococcal epitopes using indirect immunofluorescent assays and Western blot techniques in three patient groups: TS (n = 81), SC (n = 27), and a group of autoimmune disorders (n = 52) and in normal controls (n = 67). Subjects were ranked after titrations of autoantibodies from 0 to 227 according to their level of immunoreactivity. **Results:** TS patients had a significantly higher mean rank for total antineural and antinuclear antibodies, as well as antistreptolysin O titers. However, among children and adolescents, only the total antinuclear antibodies were increased in TS patients compared to age matched controls. Compared to SC patients, TS patients had a significantly lower mean rank for total and IgG class antineural antibodies, significantly lower IgG class anticytoskeletal antibodies, and a significantly higher rank for total antinuclear antibodies. Compared to a mixed group of autoimmune disorders, the TS patients had a significantly lower mean rank for total and IgG class antineural antibodies, total and IgG class antinuclear antibodies, IgG class anticytoskeletal antibodies, and a significantly higher rank for antistreptococcal antibodies. **Conclusions:** TS patients had significantly higher levels of total antineural and antinuclear antibodies than did controls. Their relation to IgG class antineural and antinuclear antibodies, markers for prior streptococcal infection, and other clinical characteristics, especially chronological age, was equivocal.

Antistreptococcal, neuronal, and nuclear antibodies in Tourette syndrome

Loiselle CR, Wendlandt JT, Rohde CA, Singer HS: Pediatric Neurology 2003; 28(2):119-125

Abstract: Previous studies have suggested associations between Tourette syndrome and attention-deficit-hyperactivity disorder and antistreptococcal antibodies and between Tourette syndrome and antinuclear antibodies. In this study, antistreptolysin O, antideoxyribonuclease B, antinuclear, and antineuronal antibodies were measured in 41 children with Tourette syndrome and 38 controls, selected without regard to history of streptococcal infection. Results revealed that mean antistreptococcal titers did not differ between diagnostic groups. In addition, multiple regression analysis was unable to predict antistreptococcal antibody titers according to age and diagnosis. The frequency of elevated antistreptolysin O titers, based on a cutoff of 1:240, was significantly higher (P = 0.04) in patients with attention-deficit-hyperactivity disorder (64%) than in the group without attention-deficit-hyperactivity disorder (34%) but not when dichotomized according to age-matched normal values. No analysis of antideoxyribonuclease B titers identified any differences between groups. Antinuclear antibody titers were at least 1:160 in three of 33 Tourette syndrome patients; only one subject manifested a homogeneous staining pattern. Multiple regression analyses were unable to predict antinuclear, antineuronal, or anti-HTB-10 antibody titers according to the combination of age, diagnosis, and antistreptococcal titer. We suggest that longitudinal rather than single-point-in-time laboratory measurements be evaluated before definitive conclusions are drawn on associations between the diagnosis of Tourette syndrome, attention-deficit-hyperactivity disorder, or obsessive-compulsive disorders and antistreptococcal or antinuclear antibody titers.

An animal model of Tourette's syndrome

Taylor JR, Morshed SA, Parveen S, et al: Am J Psychiatry 2002; 159(4):657-660

Abstract: **Methods:** Sera from 12 patients with Tourette's syndrome with high levels of antineural or antinuclear antibodies were infused bilaterally into the ventrolateral striatum of rats. Sera from 12 additional Tourette's syndrome patients and 12 normal subjects (both groups with low levels of autoantibodies) were infused for comparison. Rates of oral stereotypies were recorded by observers who were blind to the origin of the infused sera. **Results:** Oral stereotypies significantly increased in the rats infused with sera from the patients with high levels of autoantibodies. **Conclusions:** The results are consistent with an autoimmune etiology in a subset of cases of Tourette's syndrome.

Striatal antibodies in children with Tourette's syndrome: multivariate discriminant analysis of IgG repertoires

Wendlandt JT, Grus FH, Hansen BH, Singer HS: J Neuroimmunology 2001; 119(1):106-113

Abstract: Antineuronal antibodies have been postulated to be the underlying pathophysiology in TS and other neuropsychiatric disorders. Serum antibodies from 20 children with TS, and 21 control subjects against human striatum, globus pallidus, muscle, and HTB-10 cells were assayed by Western blot techniques. A MANOVA differentiated between TS and control blots, and a discriminant analysis demonstrated which variables contributed most to differences between groups. Prominent differences between TS and control blots were identified using striatal epitopes in contrast to similar patterns shown between groups for globus pallidus, muscle and HTB-10 tissue, supporting striatal autoimmune involvement in TS pathophysiology.

On defining Sydenham's chorea: where do we draw the line?

Murphy TK, Goodman WK, Ayoub EM, Voeller KK: Biological Psychiatry 2000; 47(10):851-857

Abstract: Sydenham's chorea (SC) is a major manifestation of rheumatic fever characterized by an array of neuropsychiatric symptoms that vary in severity, timing, and character. Some of the same symptoms are seen in Tourette's syndrome and childhood-onset obsessive-compulsive disorder. Genetic vulnerability appears to play a role in all three conditions. The term PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcus) has been introduced to describe a putative subset of obsessive-compulsive disorder and Tourette's syndrome that bears some resemblance to Sydenham's chorea. This article discusses whether PANDAS should be subsumed under Sydenham's chorea, thus expanding the diagnostic boundaries of Sydenham's chorea to include primarily neuropsychiatric presentations now classified as cases of obsessive-compulsive disorder or Tourette's syndrome. We conclude that PANDAS is a useful construct, but that it would be premature to view it as a subset of Sydenham's chorea—whether defined narrowly or broadly.

Comment: The current status of the autoimmune hypothesis remains obscure. On one hand, as described above, there are a number of studies demonstrating the presence of autoantibodies using different techniques (Singer et al, 1998).[1] In one study, removal of these antibodies through plasma exchange resulted in improvement (Perlmutter et al, 1999),[2] which has also shown promising results in other autoimmune disorders (Levy et al, 1999).[3] Several labs have introduced sera from TS patients with high levels of autoantibodies in an effort to induce tic-like movements or stereotypies in animals with some intriguing results. On the other hand, not all labs have successfully identified high levels of autoantibodies in patients whose clinical picture fits the hypothesis (Singer et al, 1999).[4]

Furthermore, the positive findings in the one study with plasma exchange have not been replicated. Moreover, a treatment study of prophylactic penicillin was not effective at preventing symptom exacerbation (Garvey et al, 1999).[5] Finally, despite the intriguing findings that have been reported when sera of patients with high levels of autoantibodies were injected into laboratory animals, other labs have been unable to replicate these results. To address this last issue, several investigators are now engaged in sharing methods in order to clarify the discrepant findings and move forward on the investigation of the autoimmune hypothesis. In addition, several centers are currently engaged in longitudinal studies to examine the temporal relationship between symptom exacerbation and streptococcal infection.

References: 1. Singer HS, Guiliano JD, Hansen, BH, et al: Antiobodies against human putamen in children with Tourette syndrome; Neurology 1998, 50:1618-1624. 2. Perlmutter SJ, Leitman SF, Garvey MA, et al: Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood; Lancet 1999; 354(9185):1153-1158. 3. Levy LM, Dalakas MC, Floeter MK: The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid; Annals of Internal Medicine 1999; 131(7):522-530. 4. Singer HS, Giuliano JD, Hansen BH, et al: Antibodies against a neuron-like (HTB-10 neuroblastoma) cell in children with Tourette syndrome; Biol Psychiatry 1999; 46(6):775-80. 5. Garvey MA, Perlmutter SJ, Allen AJ, et al: A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections; Biological Psychiatry 1999; 45(12):1564-1571.

ISSUE OF THE ISSUE

by **Donald L. Gilbert M.D., M.S.**

Deep Brain Stimulation (DBS) and Tourette Syndrome

A great deal of excitement has been generated by a recent media report on the use of deep brain stimulation (DBS) in a Cleveland-area man diagnosed with Tourette Syndrome (TS). The patient had described "muscle spasms that were so forceful and unpredictable" that he had difficulty walking and had to drink with a sippy cup. The University Hospitals of Cleveland neurosurgical team, led by Robert Maciunas, MD, were "awestruck" at the improvement, which occurred within hours of turning on the surgically placed brain stimulator. After the surgery, the patient appeared on Good Morning America and on The Oprah Winfrey Show. A website, Medical News Today, reported: "Tourette Syndrome completely cured by brain surgery" (April 2004). Despite the dramatic effects in this patient, we know very little about the usefulness of DBS in TS.

DBS surgery involves placing a multi-contact electrode deep into one or both sides of the brain into specific nodal areas within brain circuits responsible for voluntary and involuntary movements (Alexander et al, 1986; Mink, 2001; Redgrave et al, 1999).[1-2-3] These nodes include thalamic subnuclei, globus pallidus internus, and subthalamic nucleus. The electrodes are guided into these locations combining stereotactic imaging methods and intra-operative microelectrode recording. These electrodes are connected to a programmable pulse generator and battery placed in the patient's body. The electrode's electrical signal is believed to counteract the abnormal signal in the brain region where it has been placed. The strength of the electrical signal can be adjusted after the surgery to optimize results.

Neurosurgery for Tourette Syndrome dates back more than 40 years, to the era before there were CT scans or MRI scans (Temel and Visser-Vandewalle 2004).[4] Originally, functional neurosurgery was ablative—meaning that a scar was placed into a brain location believed to be overactive. Scarring the region reduced this overactivity and thereby reduced the disease symptoms. Unfortunately, the results of ablative surgeries cannot be modified post-operatively. Thus, sub-optimal placement or size of the lesion, particularly bilaterally, sometimes led to bad outcomes. Using animal models of human neurological diseases (for example, the primate MPTP model of Parkinson's), researchers improved neurosurgical technology. The use of electrodes rather than permanent scars, and the development of combined neurology/ neurosurgery movement disorder specialty teams have made functional neurosurgery much safer and more effective. The mechanism of DBS, however, is likely more complex, as stimulating electrodes could activate or inactivate nearby neurons and axons (Starr et al 1998).[5] DBS was approved in the US for Parkinson's Disease and Essential Tremor in 1997, and approved for Idiopathic Dystonia in 2003. DBS is not approved for Tourette Syndrome.

For several reasons, although the use of Deep Brain Stimulation for neurological disorders is very exciting news, with regard to Tourette Syndrome, DBS should be considered highly experimental.

First, far less is known about the alterations in brain function that occur in TS than in Parkinson's Disease, so the best placement of the stimulator in the brain is uncertain.

Second, the Cleveland-area patient who received DBS manifested symptoms that are unusual, even in severe TS. The pre-operative videotape shows this man struggling

with a variety of arm movements, interfering with extending his arms. Most patients with TS do not tic or spasm during brief, purposeful movements. This is why severe patients can usually drink from an ordinary cup with no problem. Thus, the apparent "miraculous" benefit in this unusual patient may not occur in other patients with TS.

Third, three adults with Tourette Syndrome had already received DBS surgery in the Netherlands, the first about 5 years ago. These patients obtained considerable, but less miraculous, benefit. They also reported some sexual side effects and fatigue (Visser-Vandewalle et al, 2003).[6] Although medication can cause these side effects as well, it is clear that DBS is not free of adverse effects. Indeed, there may be serious short-term (bleeding in the brain, infection) and long-term (device failure, need for surgery to replace batteries, other unknown outcomes) risks associated with DBS. These risks have to be weighed against possible benefit. Understanding long-term side effects of DBS is a very important area of ongoing research in Parkinson's Disease. Even more pertinent to TS may be the DBS complications experienced by patients with Dystonia. These patients have muscle contractions in the upper torso and neck, causing DBS electrodes to break or erode through the skin at very high rate. We do not yet know whether similar complications will occur in TS patients with head and neck tics.

Fourth, most patients that seek medical attention for TS are children or adolescents. Symptoms of TS often get milder in the late teenage or adult years (Goetz et al,1992; Leckman et al,1998).[7-8] It is not currently possible to identify which children will go on to have severe symptoms in adulthood. Thus, the use of DBS in severely affected children or adolescents is not warranted.

Fifth, this is an expensive procedure that requires long-term expert monitoring. U.S. Insurance companies will be reluctant to cover this on the basis of a single case report.

Finally, since DBS has been reported in only a few TS patients worldwide, conclusions about short and long term benefit of DBS for severe TS are premature. Additional adults with severe TS symptoms should receive this experimental surgery, but it needs to be done by skilled functional neurosurgery teams on appropriately selected, severely affected adults with TS. For the time being, DBS for TS should be considered highly experimental research, not routine patient care.

Further information on DBS and Tourette Syndrome will be forthcoming. The TSA - USA Scientific Advisory Board has announced it will convene an expert panel to review current research on DBS and will report back to the TS community.

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