

Cerebrospinal Fluid Biogenic Amines in Obsessive Compulsive Disorder, Tourette's Syndrome, and Healthy Controls

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To examine the role of noradrenergic, dopaminergic, and serotonergic mechanisms in the pathobiology of obsessive compulsive disorder (OCD) and Tourette's syndrome (TS), concentrations of tyrosine (TYR), norepinephrine (NE), 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), homovanillic acid (HVA), tryptophan (TRP), and 5-hydroxyindoleacetic acid (5-HIAA) were measured in the lumbar cerebrospinal fluid (CSF) of 39 medication-free OCD patients, 33 medication-free TS patients, and 44 healthy volunteers. CSF TYR concentrations were reduced ($p < .05$) in the OCD patients compared to the healthy subjects. CSF NE in TS patients was 55%

higher than in healthy controls ($p < .001$) and 35% higher than in OCD patients ($p < .001$). After covarying for height, CSF HVA levels were reduced ($p < .05$) in the OCD group compared to TS patients but not compared to the normal volunteers. No mean differences in CSF MHPG, TRP, and 5-HIAA were observed in this study across the three groups. The CSF NE data support the hypothesis that noradrenergic mechanisms are involved in the pathobiology of TS. Alterations in the balance of noradrenergic, dopaminergic, and serotonergic systems are likely involved in the pathobiology of OCD. [*Neuropsychopharmacology* 12:73-86, 1995]

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Obsessive compulsive disorder (OCD) is a chronic neuropsychiatric condition characterized by recurrent and disturbing thoughts (obsessions) and/or repetitive, relatively stereotyped, behaviors that an individual feels driven to perform (compulsions). In a subset of early-onset OCD patients, the course of illness is complicated by a chronic tic disorder (Pitman et al. 1987; Leonard et al. 1993). Tourette's syndrome (TS) is a chronic neuropsychiatric disorder of childhood onset that is characterized by tics that wax and wane in severity and by an array of associated behavioral problems, including attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) (Robertson 1989; Leckman et al. 1992). Family-genetic studies further suggest OCD may be etiologically heterogeneous with some forms related to TS (Pauls and Leckman 1986; Pauls et al. 1991).

Although a number of neurotransmitter and neu-

romodulatory systems are likely to be involved in the pathobiology of OCD, the strongest evidence concerns the role of serotonergic projections that modulate the activity of the basal ganglia and functionally related cortical and thalamic structures (Insel 1992). The effectiveness of potent or selective serotonin reuptake inhibitors (SSRIs) such as clomipramine (Clomipramine Study Group 1991), fluvoxamine (Goodman et al. 1989a, 1990a), fluoxetine (Pigott et al. 1990), and sertraline (Chouinard et al. 1990) in producing clinical improvement in 40% to 60% of OCD patients is noteworthy in this regard. However, a substantial number of OCD patients do not respond to these agents or experience only modest benefit. One factor that may influence the effectiveness of SSRIs in OCD is whether the patient has a personal history of TS or another chronic tic disorder. For example, McDougle et al. (1993) reported that OCD patients with a comorbid chronic tic disorder showed only a 21% response rate to fluvoxamine compared to a 52% response rate in OCD patients without chronic tics.

Although dopaminergic mechanisms have been implicated in the pathobiology of TS (see Leckman et al. in press-a and Singer, 1993 for reviews), the role of brain dopaminergic systems in OCD has not been carefully studied despite preclinical and clinical data implicating these systems (see Goodman et al. 1990b for a review). Several studies have suggested that tic-related OCD can be distinguished from non-tic-related OCD on the basis of treatment response. For example, McDougle et al. (1990, 1994) found that haloperidol in addition to ongoing SSRI treatment in fluvoxamine-refractory OCD patients was preferentially effective in OCD patients with comorbid tics compared with tic-free OCD patients. Hanna et al. (1991) reached a similar conclusion after finding higher levels of plasma prolactin in OCD patients with a either a positive personal or family history of chronic tics compared to non-tic-related OCD patients. This increase was observed under both basal conditions (50% higher) and post 8 weeks of clomipramine (40% higher). Taken together, these psychopharmacological and neuroendocrine data are consistent with an altered balance of serotonergic and dopaminergic tone in OCD patients with comorbid tics compared to tic-free OCD patients.

Evidence of noradrenergic involvement in the pathophysiology of TS is based in part on the reported beneficial effects of the α_2 adrenergic agonist clonidine (Cohen et al. 1979). Although the effectiveness of clonidine remains controversial (Goetz et al. 1987), several clinical trials provide evidence of a beneficial effect of this agent on motor tics and some of the symptoms of ADHD (McKeith et al. 1981; Borison et al. 1983; Leckman et al. 1991a). Additional support has been based on the rebound exacerbations of tics in patients abruptly withdrawn from clonidine (Leckman et al. 1986), and

on the finding of a blunted growth hormone response to clonidine challenge in children and adults (Leckman et al. 1984; Müller et al. 1994) with TS. Most recently, a series of adult TS patients was found to have high levels of urinary NE excretion in response to the stress of lumbar puncture (LP) (Chappell et al. 1994). Studies of central and peripheral levels of 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), a major metabolite of NE, have been inconclusive (Cohen et al. 1978; Butler et al. 1979; Ang et al. 1982; Singer et al. 1982; Leckman et al. 1988; Bornstein and Baker 1992). In addition, no differences in platelet α_2 adrenoreceptors (Silverstein et al. 1985) or in plasma NE (Lake et al. 1977) have been found.

In open-labeled studies, clonidine has also been reported to improve obsessive compulsive (OC) symptoms (Knesevich 1982; Hollander et al. 1988, 1991), but this effect may be transient (Hollander et al. 1988). No improvement in OC symptoms was observed in a large-scale clinical trial of clonidine in a group of TS patients (Leckman et al. 1991a). In blind comparisons with serotonin reuptake blocking agents, NE reuptake blockers have not been shown to be effective in the treatment of OCD (Zohar and Insel 1987; Leonard et al. 1989; Goodman et al. 1990a). Other studies have attempted to evaluate the role of noradrenergic systems in OCD with the use of challenge paradigms that either seek to stimulate or block α_2 NE receptors, but the results have been inconclusive (Siever et al. 1983; Rasmussen et al. 1987; Hollander et al. 1988; Lee et al. 1990).

With one exception (Swedo et al. 1992), previously reported CSF studies of biogenic amines have not addressed the potential differences between OCD patients with versus without a personal or family history of a tic disorder (Thorén et al. 1980; Insel et al. 1985; Lydiard et al. 1990). In addition, none of the available CSF reports include sizable numbers of both OCD and TS patients in the same study. None of the prior CSF studies of OCD reported concentrations of the amino acid precursors tyrosine (TYR) and tryptophan (TRP), nor did they measure CSF levels of norepinephrine (NE). Prior CSF studies of biogenic amines in TS have yielded inconclusive results and have been limited by small sample sizes (Cohen et al. 1978; Butler et al. 1979; Leckman et al. 1988) and a failure to examine the effects of comorbid OCD (Cohen et al. 1978; Butler et al. 1979).

As part of a comprehensive study of monoamines, precursors, and metabolites, we measured the lumbar CSF concentrations of TYR; NE; MHPG; homovanillic acid (HVA), a major CNS metabolite of dopamine and a minor metabolite of NE; tryptophan (TRP); and 5-hydroxyindoleacetic acid (5-HIAA), the major central metabolic of serotonin, in TS and OCD patients and in a group of healthy controls. We hypothesized that OCD patients with comorbid tic disorders would more closely resemble (in terms of their neurochemical

profile) TS patients with concomitant OC symptoms than OCD patients without a personal or family history of chronic tics. We further hypothesized that TS patients, but not OCD patients, would have elevated indices of central noradrenergic function and that these elevations would be more closely associated with the current severity of motor tics than of phonic tics.

SUBJECTS AND PROCEDURES

Subjects

CSF was obtained in a standardized fashion from a total of 116 subjects (39 patients with OCD, 33 patients with TS, and 44 normal controls). Most of the OCD and normal control subjects were recruited locally within the State of Connecticut. Patients were recruited from a wider geographic area with the help of the national Tourette Syndrome Association (TSA) and local TSA chapters in Connecticut, New York, Massachusetts, Rhode Island, New Jersey, and Pennsylvania. Members of the state TSA organizations were contacted by letter and invited to participate in a range of ongoing studies. Each medication-free member who expressed an interest in participating in a research study was contacted. Preliminary reports concerning this data set have appeared elsewhere (Leckman et al. 1988, 1990b).

Patients were initially diagnosed clinically using DSM-III-R criteria. Patients and controls, their first-degree relatives (parents, siblings), and spouses, if available, also completed a semi-structured diagnostic interview based on the Diagnostic Interview Schedule, as previously described (Pauls and Hurst 1987). Final diagnoses were made independently and blindly (with respect to their ascertainment) by two diagnosticians (JFL and DLP) using all available information (Leckman et al. 1982). Prior estimates of the agreement between these two rates using Cohen's κ coefficient have all been above .90 (indicating excellent agreement) for the diagnoses of TS, OCD, ADHD, and major depression. When diagnostic disagreements arose, a joint review of all materials was performed and a "best estimate" consensus diagnosis was made. In comorbid cases in which an individual received both a diagnosis of OCD and a tic disorder, a "principal diagnosis" was assigned based on the individual's clinical presentation and level of disability associated with each set of symptoms. Based on these diagnostic estimates, five patients were dropped from the study because they were not judged to have a principal diagnosis of either OCD or TS. Seven normal control subjects were found to have a positive family history of either OCD or a tic disorder and were excluded from this sample. In the four- and five-group diagnostic comparisons, the remaining OCD patients

were further subdivided into two groups: those with a personal or family history of TS or a chronic tic disorder ($n = 11$) and those without such a history ($n = 28$). In the five-group diagnostic comparisons, the TS cases were subdivided into those with OCD (TS + OCD, $n = 18$) and those without OCD (TS alone, $n = 12$).

In the final data set of 104 subjects, there was insufficient lumbar CSF to permit determination of NE in seven subjects; HVA, TRP, and 5-HIAA in three subjects; TYR in one subject; and MHPG in one subject.

Procedures

Subjects gave informed consent before participating in the study. Subjects were medication-free for a minimum of 4 weeks (two months in the case of neuroleptics and fluoxetine) prior to the lumbar puncture (LP). All subjects were in good health and received a physical examination, standard hematologic and clinical chemistry studies, urinalysis, and electrocardiogram to screen for medical disorders. Height and weight were recorded at the time of admission. Percent ideal body weight (for height and sex) was transcribed from actuarial tables (Society of Actuaries 1959).

Subjects were asked to adhere to a low monoamine diet for one day prior to the LP. After a carbohydrate breakfast, subjects were placed at bed rest between 7:00 and 8:00 A.M. for 4 to 5 hours prior to the procedure. Vital signs were taken at regular intervals using standard techniques. The last set of vital signs prior to the LP was at 12:00 noon and included supine systolic and diastolic blood pressures plus supine heart rate. At 12:30 P.M., the LP was performed in the lateral decubitus position using the L4-L5 interspace. A total of 11 to 21 ml of CSF was collected. The first ml was used for clinical studies. The next five ml (2 to 6 ml) were initially collected in a separate tube, mixed, aliquoted, and used to measure the concentrations of the monoamines, their precursors, and metabolites. Aliquots were frozen at -70° to -80° C until they were assayed.

Clinical Ratings

Patients and controls received an extensive psychiatric evaluation at the time of the LP, including clinician ratings of severity of OC and tic symptoms using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al. 1989b, 1989c) and the Yale Global Tic Severity Scale (YGTSS) (Leckman et al. 1989), respectively.

Ratings of depression and anxiety were also evaluated using the clinician-rated Hamilton Depression and Anxiety Scales (HAM-D and HAM-A, respectively) (Hamilton 1959, 1967). The 21-item version of

the HAM-D scale was modified by omitting the last item on OC symptoms so that scores could range from 0 to 61. The 14-item HAM-A scale was used, with scores potentially ranging from 0 to 56. Comorbid psychiatric diagnoses were established using the same best estimate procedures described above for TS and OCD.

Assays for CSF Biogenic Amines

The concentrations of TYR, HVA, TRP, and 5-HIAA in the CSF were determined by using a previously described sensitive and specific high performance liquid chromatography (HPLC) assay with interassay coefficients of variation of 5% to 9% (Anderson et al. 1979; Leckman et al. 1988).

Levels of NE were determined by HPLC following alumina extraction of 0.5 to 2.0 ml of CSF (Anderson et al. 1988). An interassay coefficient of variation for the CSF NE assay of 7.5% ($n = 15$) was observed for replicate samples, with a detectability limit of less than 25 pg/ml (0.15 pmol/ml). The concentration of MHPG in the CSF was determined by HPLC (Anderson et al. 1981) with an interassay coefficient of variation of 6.7% ($n = 12$) and a limit of detectability of less than 1 ng/ml (5.43 pmol/ml). All assays were performed blindly to the diagnostic and clinical status of the subjects.

Statistical Analysis

Taken as a whole, CSF measures of TYR, NE, HVA, and 5-HIAA were not normally distributed. Log transformation of these values resulted in normal distributions for CSF TYR, NE, and HVA. A square root transformation of the CSF 5-HIAA levels yielded a normal distribution. Results are reported as mean \pm one standard deviation. Chi-square, Student's unpaired t test (two-tailed), and general linear models procedures (followed by the Duncan's Multiple Range Tests to account for multiple comparisons) were performed to compare CSF measures across groups. The principal models used to evaluate diagnostic status (an independent class variable) were a three-group model (normals versus OCD versus TS), a four-group model (normal versus non-tic-related OCD versus tic-related OCD versus TS), and a five-group model (normal versus non-tic-related OCD versus tic-related OCD versus TS + OCD versus TS alone). Efforts were made to evaluate the effects of comorbid depression and anxiety by using the comorbid diagnoses (current, past, never) as class variables and by using the current ratings of depression and anxiety as continuous variables in the multivariate analyses. Spearman and Pearson correlation coefficients were calculated, as appropriate, to test for possible associations among variables. In the exploratory analyses, corrections for mul-

tiples tests of association (e.g., Bonferroni or Scheffé adjustments) were not employed.

RESULTS

Sample Characteristics

Demographic and clinical data on the 104 subjects (60 males and 44 females, aged 13 to 63) included in this report are presented in Table 1. As noted, no significant differences with regard to sex, current age, height, weight, or percent of ideal body weight were found comparing the three diagnostic groups.

As expected, ratings of OC symptom severity ($F[2,99] = 107, p < .0001$) and tic severity ($F[2,99] = 155, p < .0001$) clearly distinguished the three primary diagnostic groups (Table 1). Based on the HAM-D and HAM-A, the overall comparisons across the three diagnostic groups were highly significant for both symptoms of depression ($F[2,99] = 38.2, p < .0001$) and anxiety ($F[2,78] = 47.9, p < .0001$). Post hoc testing revealed that the OCD patients were significantly more depressed and anxious than the TS patients ($p < .001$) and that the TS patients in turn were significantly more depressed and anxious ($p < .001$) than the normal controls (Table 1).

Table 2 presents the frequency of lifetime comorbid psychiatric diagnoses in the two patient groups. High rates of comorbidity for major depression and anxiety disorders were observed in both the TS and the OCD groups. A lifetime diagnosis of ADHD was present in 39% of the TS patients and 12% of the OCD patients.

Based on the vital signs collected just prior to the LP, the overall comparisons across the three diagnostic groups was found to be significant for supine heart rate ($F[2,79] = 4.09, p = .02$) but not for supine systolic or diastolic blood pressures. Post hoc testing revealed that the OCD patients on average had a significantly ($p < .05$) higher heart rate (78 ± 14 bpm) than the normal controls (68 ± 9 bpm) with the TS patients falling in between (71 ± 14 bpm).

Univariate Analyses

In an effort to identify potentially confounding demographic, physiological, and psychological variables a series of univariate analyses was performed with the entire data set in which current age, height, weight, percent ideal body weight, supine systolic and diastolic blood pressures (obtained just prior to the LP), heart rate, and the clinician ratings of depression and anxiety were correlated with each of the CSF measures. Given the number of analyses, correlations with p values of $< .001$ are needed to be significant using a Bon-

Table 1. Demographical and Clinical Characteristics

	Normal Controls (<i>n</i> = 35)	Tourette's Syndrome (<i>n</i> = 30)	Obsessive Compulsive Disorder (<i>n</i> = 39)
Sex (M/F)	22/13	21/9	17/22
Current age (yrs)	32.9 ± 10.6 (19.1 to 58.2)	29.4 ± 8.2 (13.1 to 43.6)	35.6 ± 14.1 (18.5 to 63.1)
Height (cm)	172 ± 10 (142 to 189)	175 ± 10 (157 to 196)	169 ± 11 (131 to 188)
Percent ideal body weight (%) ^a	102 ± 12 ¹ (82 to 137)	104 ± 19 (81 to 162)	100 ± 13 ² (79 to 129)
OC symptom onset (yrs)		10.8 ± 6.9 ³ (2.0 to 26.0)	20.0 ± 11.1 (2.0 to 58.0)
OC severity (YBOCS - Total) ^b		12.0 ± 10.9 (0.0 to 34.0)	25.3 ± 7.1 ⁴ (12.0 to 36.0)
Tic symptom onset (yrs)		7.0 ± 3.1 (3.0 to 19.0)	5.0 ± 3.6 ⁵ (2.0 to 9.0)
Tic severity (YGTSS) ^c		49.9 ± 18.9 ⁷ (8.0 to 84.0)	9.8 ± 13.5 (0.0 to 34.0)
Severity of anxiety (HAM-A) ^d	0.7 ± 1.5 ⁸ (0.0 to 8.0)	8.6 ± 6.1 ⁹ (0.0 to 21.0)	14.2 ± 7.0 ⁸ (1.0 to 29.0)
Severity of depression (HAM-D) ^e	0.9 ± 1.8 (0.0 to 8.0)	10.3 ± 9.5 ¹⁰ (0.0 to 34.0)	16.2 ± 9.0 ⁴ (0.0 to 38.0)

^a Ideal body weight based on age, sex, and height; ^b Yale-Brown Obsessive Compulsive Scale; ^c Yale Global Tic Severity Scale; ^d Hamilton Depression Scale (21 item version modified to exclude the last item on OC symptoms); ^e Hamilton Anxiety Scale (14 item).

¹ *n* = 34, ² *n* = 26, ³ *n* = 16, ⁴ *n* = 38, ⁵ *n* = 4, ⁶ *n* = 6, ⁷ *n* = 27, ⁸ *n* = 30, ⁹ *n* = 21, ¹⁰ *n* = 29.

ferroni adjustment. Using this threshold, none of these correlations were significant. Using a $p < .05$ threshold, log transformed CSF TYR was correlated with current age ($r = .23$, $p < .02$) and inversely correlated with the HAM-A ratings of anxiety ($r = -.30$, $p < .01$); log transformed CSF NE was correlated with supine and diastolic ($r = .23$, $p = .05$) blood pressures measured prior to the LP; CSF MHPG was correlated with percent ideal body weight ($r = .28$, $p = .007$); and both log transformed CSF HVA ($r = -.23$, $p < .02$) and square-root transformed CSF 5-HIAA ($r = -.27$, $p < .01$) were inversely correlated with height. No significant correlations were observed with either weight or

heart rate at the time of the LP for any of the CSF measures.

A second group of analyses was performed to examine the potentially confounding effects of sex and comorbidity with either major depression (current, past, never) or generalized anxiety disorder (GAD) (current, past, never). No sex differences were observed for any of the CSF measures. None of the CSF measures differed based on the subjects' history of major depression. Only CSF TRP was found to differ depending on the subjects' status concerning GAD ($F(2,85) = 5.28$, $p < .007$) with the 12 subjects with a current diagnosis of GAD having 21% higher levels ($p < .05$) of CSF TRP

Table 2. Current and Lifetime Comorbid DMS-III-R Psychiatric Diagnoses for TS and OCD Groups

Comorbid Diagnosis	Primary Diagnosis	
	Tourette's Syndrome (<i>n</i> = 30) <i>n</i> (%)	Obsessive Compulsive Disorder (<i>n</i> = 39) <i>n</i> (%)
Obsessive compulsive disorder	18 (60)	NA
Tourette's syndrome	NA	1 (3)
Chronic motor tic disorder	NA	6 (15)
Major depression		
Current	5 (18) ²	14 (40) ¹
Lifetime	18 (64)	30 (86)
Generalized anxiety disorder		
Current	1 (7) ³	11 (31) ¹
Lifetime	14 (52)	26 (74)
Panic disorder, lifetime	8 (33) ⁵	12 (35) ⁴
Any other anxiety disorder, lifetime	4 (17) ⁵	14 (41) ⁴
Attention-deficit hyperactivity disorder	11 (39) ²	4 (12) ⁴

¹ *n* = 35, ² *n* = 28, ³ *n* = 27, ⁴ *n* = 34, ⁵ *n* = 24, NA = not applicable.

than either the subjects with a past history of generalized anxiety disorder or those that had no past history of GAD.

Comparisons of CSF Measures across Diagnostic Groups

As an initial test, a multivariate analysis of variance was performed that included all of the CSF measures as dependent variables and subject diagnosis as the independent variable (using both three-, four-, and five-group diagnostic models described above). All three models found a significant effect of diagnosis (three-group model: $F[12,172] = 4.13$, $p = .0001$; four-group model: $F[18,241] = 3.55$, $p = .0001$; and five-group model: $F[24,294] = 2.81$, $p = .0001$).

CSF TYR. The overall comparison of log transformed CSF TYR levels across the three groups revealed significant group differences ($F[2,100] = 5.61$, $p = .005$). Post hoc testing indicated that the OCD group had significantly lower ($p < .05$) levels of CSF TYR than the normal controls (Figure 1A). A similar result was obtained in the four- and five-group comparisons (four-group: $F[3,99] = 4.33$, $p = .007$; and five-group:

$F[4,98] = 3.24$, $p = .02$). In both the four- and five-group models, the post hoc testing indicated that the OCD patients without tics had significantly lower CSF TYR levels than the normal control subjects ($p < .05$). Inclusion of current age as a continuous covariate increased the amount of the variance associated with the diagnostic groups for each of the models evaluated. In these analyses, current age was found to be independently associated with CSF TYR. The inclusion of sex in these models did not alter the results of the comparisons across the diagnostic groups. In all of the models, the OCD patients without tics continued to have significantly ($p < .05$) lower levels of CSF TYR compared to the normal control subjects.

CSF NE. The overall comparison of log transformed CSF NE levels across the three diagnostic groups revealed significant group differences ($F[2,94] = 8.28$, $p = .0005$). As predicted, post hoc testing revealed that the TS group had significantly higher ($p < .001$) levels of CSF NE than either the normal controls or the OCD patients (Figure 1B). On average, the TS patients had levels of CSF NE that were 55% higher than the normal controls and 35% higher than the OCD patients. The overall four- and five-group comparisons were also

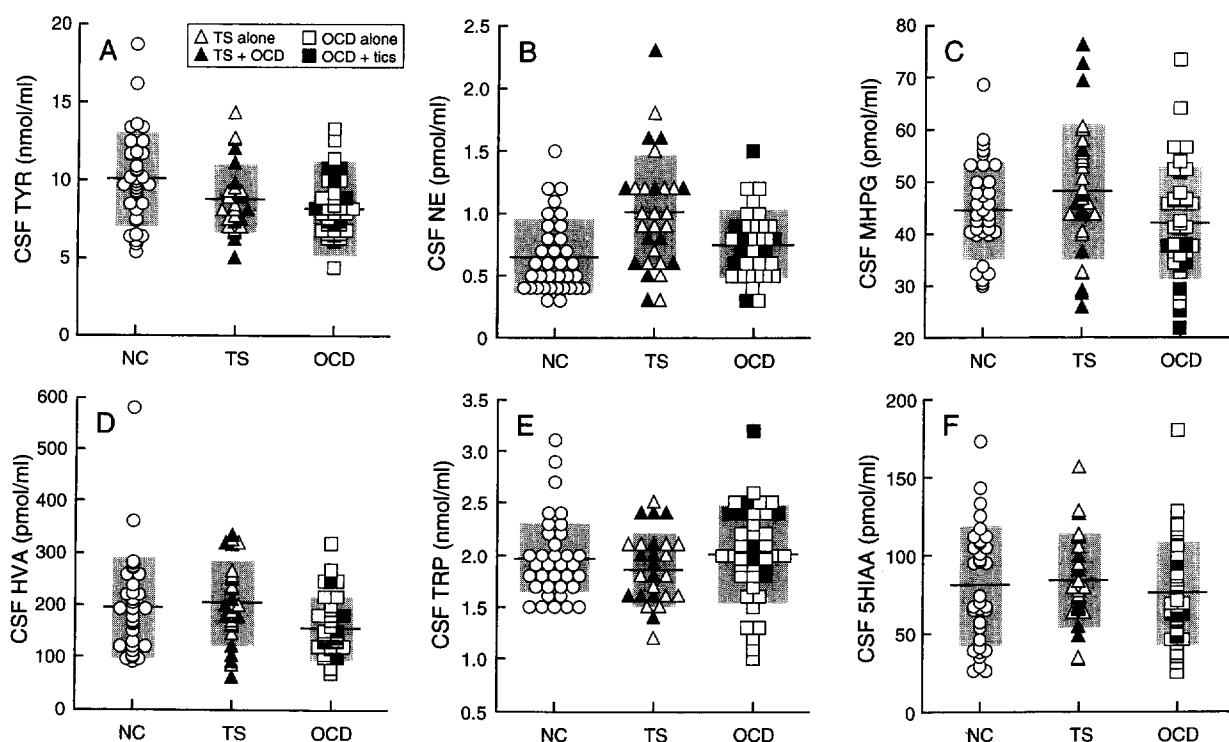


Figure 1. CSF tyrosine (TYR), Norepinephrine (NE), 3-methoxy, 4-hydroxyphenylethylene glycol (MHPG), homovanillic acid (HVA), tryptophan (TRP), and 5-hydroxyindoleacetic acid (5-HIAA) in TS, OCD, and Normal Control Subjects. The OCD and TS groups had significantly lower levels of CSF TYR ($p < .05$) than the normal controls (A). The TS group had significantly higher levels of CSF NE ($p < .001$) than either the normal controls or the OCD patients (B). The OCD group had significantly lower levels of CSF HVA ($p < .05$) than the TS patients, but not the normal controls (D). No mean differences in CSF MHPG, TRP, or 5-HIAA levels were found among the three major diagnostic groups (C, E, and F, see text).

significant (four-group: $F[3,93] = 5.48, p = .0002$; five-group: $F[4,92] = 4.57, p = .002$). In post hoc testing, we found that individuals with full-blown TS, either as a whole or considered separately (TS alone and TS + OCD), had significantly higher ($p < .05$) levels of CSF NE compared to the normal controls. Individuals with tic-related OCD (0.78 ± 0.31 pmol/ml) did not differ significantly from the remaining OCD cases (0.74 ± 0.26 pmol/ml). Inclusion of either systolic or diastolic blood pressure as a continuous covariate in the diagnostic group comparisons did not alter the significance of the overall comparisons based on diagnosis. In these analyses, however, diastolic blood pressure ($p = .02$) was found to be independently related to CSF NE levels. The inclusion of sex in these models did not alter the results of the comparisons across the diagnostic groups.

CSF MHPG. The overall comparison of CSF MHPG levels across the three diagnostic groups approached significance ($F[2,100] = 2.49, p = .09$) (Figure 1C). The mean CSF MHPG values of the TS patients were higher than those of the other two diagnostic groups. The overall four-group comparison (normals versus TS versus tic-related OCD versus other OCD) was significant ($F[3,99] = 2.72, p < .05$), with individuals with tic-related OCD having on average lower CSF MHPG than any of the other groups. The overall five-group comparison (normals versus TS alone versus TS + OCD versus tic-related OCD versus other OCD) was not significant ($F[4,98] = 2.02, p < .10$). Inclusion of percent ideal body weight as a continuous covariate also strengthened the overall three- ($p = .02$) and four-group ($p = .04$) comparisons but did not alter the five-group comparison. The inclusion of sex as a class variable in these models did not alter the results of the comparisons across the diagnostic groups.

CSF HVA. The overall comparison of log transformed CSF HVA levels across the three diagnostic groups revealed significant group differences ($F[2,98] = 3.11, p = .05$). Post hoc testing indicated that the OCD group had significantly lower ($p < .05$) levels of CSF HVA than the TS patients but not the normal control subjects (Figure 1D). A similar trend was obtained in the four-group comparison ($F[3,97] = 2.14, p = .10$) and the five-group comparison ($F[4,96] = 1.89, p = .12$). Inclusion of height as a continuous covariate increased the amount of the variance associated with the diagnostic groups for both the three-group ($F[3,97] = 5.61, p = .001$), four-group comparisons ($F[4,96] = 4.20, p = .004$), and five-group comparisons ($F[5,95] = 4.11, p = .002$). In these analyses, height was found to be independently associated with CSF HVA. In addition, the mean CSF HVA level for the tic-related OCD group was intermediate between the TS and tic-free OCD groups. The inclusion of sex

as a class variable in these models did not alter the results of the comparisons across the diagnostic groups.

CSF TRP. The overall comparison of CSF TRP levels across the three groups showed no significant group differences ($F[2,98] = .99, NS$) (Figure 1E). In contrast, the results of the four- and five-group comparisons were significant (four-group: $F[3,97] = 3.05, p = .03$; five-group: $F[4,96] = 3.09, p = .02$). In both the four- and five-group comparisons, the post hoc testing indicated that the OCD patients with tics had significantly higher CSF TRP levels than did any of the remaining groups ($p < .05$). Inclusion of the subjects' sex or status concerning GAD did not alter these findings (data not shown). However, in these analyses the effect of a current diagnosis of GAD continued to be significant ($p < .05$).

CSF 5-HIAA. The overall comparison of square root transformed CSF 5-HIAA levels across the diagnostic groups revealed no significant differences (Figure 1F). Inclusion of sex as a class variable or height as a continuous covariate did not alter the findings of the original comparisons across the diagnostic groups.

Ratios of CSF Measures. In an exploratory set of analyses, we also examined the potential value of ratios of various CSF measures to discriminate major diagnostic groups. With the exception of the TYR/TRP ratio, none of the other ratios of CSF measures incrementally increased the amount of the variance associated with the competing diagnostic models. The overall comparison of the log transformed CSF TYR/TRP ratio across the three groups revealed significant group differences ($F[2,98] = 8.68, p = .0003$). Post hoc testing indicated that the OCD group had a significantly lower TYR/TRP ratio ($p < .01$) than the normal controls or the TS group (Figure 1E). A similar result was obtained in the four- and five-group comparisons (four-group: $F[3,97] = 6.17, p = .0007$; five-group: $F[4,96] = 5.20, p = .0008$). In univariate analyses across the entire data set, log transformed CSF TYR/TRP ratio was found to be associated with current age ($r = .22, p < .03$). Inclusion of age as a continuous covariate increased the amount of the variance associated with the diagnostic groups for both the three- ($F[3,97] = 9.17, p = .0001$), four- ($F[4,96] = 7.10, p = .0001$), and five-group comparisons ($F[5,95] = 4.11, p = .002$). In these analyses, current age was found to be independently associated with the CSF TYR/TRP ratio. Inclusion of sex as a class variable in these models did not alter the results of the comparisons across the diagnostic groups. CSF TRY/TRP was inversely correlated with scores on the HAM-D ($r = -.35, p < .0003$) and HAM-A ($r = -.42, p < .0001$). However, inclusion of these variables in ANCOVA comparisons across diagnostic groups did not alter the initial findings reported above (data not shown). This ratio

was also found to be associated with a comorbid diagnosis of GAD ($F[2,85] = 5.94, p = .004$). The inclusion of the patients' status regarding GAD as a class variable did not alter the outcome of the three-, four-, or five-group diagnostic comparisons.

Relationship of CSF Measures to Current Ratings of Tic and Obsessive-Compulsive Symptom Severity

Analyses were performed to examine the potential relationship between CSF measures of the biogenic amines and clinical ratings of OC and tic symptom severity. If the CSF measure was not normally distributed, Spearman correlations were performed. The only predicted relationship was a positive association of CSF NE and current motor tic severity. A total of 51 correlations were performed for the OC symptom severity ratings with the various CSF measures within either the entire sample or within subgroups of OCD patients (using a Bonferroni adjustment, a p value of less than .001 would be required for significance). For the tic severity ratings, a total of 30 correlations were performed with the various CSF measures within either the entire sample or within the tic disorder patient groups (using a Bonferroni adjustment, a p value of less than .002 would be required for significance).

OC Symptom Severity. TYR was found to be inversely associated with current OC symptom severity in the entire sample (Y-BOCS: obsessions, $r = -.26, p = .01$; compulsions, $r = -.20, p = .04$; total score, $r = -.25, p = .01$). However, this association was not confirmed when either the tic-related OCD or the tic-free OCD samples were considered separately. Indeed, within the tic-free OCD group an association with an opposite sign was found for current compulsions, as measured on the Y-BOCS ($r = .60, p = .002$).

Across the entire sample, CSF HVA was inversely correlated with ratings of current OC symptom severity (Y-BOCS: obsessions, $r = -.23, p = .03$; compulsions, $r = -.16, p = .11$; total score, $r = -.20, p = .05$). However, these associations were only observed in the tic-related OCD group (Y-BOCS: obsessions, $r = -.34, p = .04$; compulsions, $r = -.31, p = .06$; total score, $r = -.33, p < .05$).

CSF TRP was found to be marginally associated with current OC symptom severity in the entire sample (Y-BOCS: obsessions, $r = .14$, NS; compulsions, $r = .18, p = .08$; total score, $r = .16, p = .10$). This association was much stronger in the tic-related OCD group (Y-BOCS: obsessions, $r = .40, p = .01$; compulsions, $r = .39, p = .02$; total score, $r = .42, p = .01$) compared to the tic-free OCD group, where none of these correlations were significant.

No correlations were observed between CSF NE, MHPG, or 5-HIAA and clinician severity ratings of ob-

sessions or compulsions on the Y-BOCS. We were particularly interested in the possible association between CSF 5-HIAA and obsessions of violence based on our earlier case reports of two individuals in this sample (one with TS and OCD and the other with non-tic-related OCD) who had very low levels of CSF 5-HIAA (Leckman et al. 1990b). Dichotomizing the sample on the basis of the presence or absence of violent obsessions, however, did not yield a significant result.

CSF TYR/TRP was also found to be inversely associated with current OC symptom severity in the entire sample (Y-BOCS: obsessions, $r = -.43, p = .0001$; compulsions, $r = -.39, p = .0001$; total score, $r = -.42, p = .0001$). This association, however, was found only in the tic-related OCD group (Y-BOCS: obsessions, $r = -.45, p = .005$; compulsions, $r = -.37, p = .02$; total score, $r = -.44, p = .006$) and not in the tic-free OCD group.

Tic Severity. CSF NE was correlated with motor ($r = .44, p = .0002$) and phonic tics ($r = .38, p = .001$) in the overall data set. As predicted within the group of individuals with a personal history of tic disorder, there was a trend towards a significant correlation between CSF NE and current severity of motor tics ($r = .31, p < .10$) but not phonic tics.

CSF TRP was inversely associated with indices of tic severity in the entire sample (YGTSS: motor tics, $r = -.22, p = .09$; phonic tics, $r = -.37, p = .002$; total score, $r = -.27, p = .03$). Within the tic disorder group (TS + tic-related OCD), these associations were even stronger, particularly for the phonic tics (YGTSS: motor tics, $r = -.24$, NS; phonic tics, $r = -.74, p = .0001$; total score, $r = -.44, p = .02$). No associations were found between current indices of tic severity and CSF TYR, MHPG, HVA, 5-HIAA or the ratio of CSF TYR/TRP.

DISCUSSION

This study emphasizes the close interrelationship between TS and OCD. Phenomenologically this is reflected in the high rates of comorbidity. In this study, 60% of the TS subjects were diagnosed with OCD, and 18% of the OCD patients were diagnosed with either TS or a chronic tic disorder (Table 2). This is a well-documented observation, with most case series reporting rates of OCD among adult TS cases in the range of 40% to 80% (see Leckman 1993 for a review). A recent population-based study found that 42% of the individuals diagnosed with TS also had OCD (Apter et al. 1993). Less data are available concerning the rates of tic disorders among OCD patients, but the reported rates range from 7% to 59% (Rasmussen and Tsuang 1986; Pitman et al. 1987; Leonard et al. 1993; Holzer et al. 1994).

The high rates of depression and other disorders in OCD and TS are also well-recognized phenomena (Rasmussen and Tsuang 1986; Robertson et al. 1993) that have the potential to confound neurobiological studies. We have addressed this issue by identifying those individuals with current and past comorbid psychiatric diagnoses, by rating the current level of anxiety and depression using well-established clinical rating instruments, and by incorporating this information into the analyses of the CSF data. However, such approaches are necessarily imperfect and caution is warranted in interpreting our results. Comorbid ADHD may well be another important source of variability, particularly in the TS group. However, given the age of our sample, the small number of subjects with a diagnosis of ADHD ($n = 15$, Table 2), and their uneven distribution across the diagnostic groups, we have not been able to examine this question in detail.

With these caveats and limitations in mind, let us consider the CSF data in light of the two hypotheses that motivated this study.

Is Tic-related OCD a Distinct Subgroup of OCD?

Our CSF data are inconclusive with regard to the question of whether tic-related OCD is a neurobiologically distinct form of OCD. In most instances, the mean CSF levels of the biogenic amines in the tic-related OCD group were either intermediate between the TS and the tic-free OCD groups (CSF TYR and HVA) or closer to the tic-free OCD group (CSF NE, TYR/TRP ratio). The correlational data, however, are more suggestive of the tic-related group being distinct. For example, CSF HVA levels were inversely associated with current ratings of OCD in the tic-related group (partialing out the effects of height, the observed correlation between the Y-BOCS total score and CSF HVA was $-.40$ ($p = .01$), whereas this association was not seen in the tic-free OCD group. Similarly, the ratio of CSF TYR/TRP was inversely associated with current ratings of OCD in the tic-related group (partialing out the effects of age, the observed correlation between the Y-BOCS total score and CSF TYR/TRP ratio was $-.40$ ($p = .01$)), but this relationship was not found in the tic-free OCD group. Given the number of correlations performed and their potential instability, however, it is difficult to put much weight on these results.

These data join a growing body of clinical and natural history data (Pitman et al. 1987; George et al. 1993; Holzer et al. 1994; Leckman et al., in press-b), neuroendocrinological data (Hanna et al. 1991; Leckman et al. 1994), and pharmacological data (McDougle et al. 1990, 1993, 1994) that do support the distinction between tic-related OCD and non-tic-related or tic-free OCD. Further study is required to resolve these differences, es-

pecially because treatment response to SSRIs may be influenced by the relative balance of dopaminergic and serotonergic activity (McDougle et al. 1990, 1993, 1994).

The finding of reduced levels of CSF TYR in OCD compared to normals is intriguing and may relate to the absence of any exacerbation in SSRI-remitted OCD patients following acute TRP depletion (Barr et al. 1944). Given the common transport system for large neutral amino acids including TRP and TYR (Fernstrom et al. 1973; Perez-Cruet et al. 1974), TRP depletion would be expected to increase brain TYR and shift the CSF TYR/TRP ratio in the direction of the normal range.

Heuristically, the observation that dopaminergic neurons become TYR sensitive when they become physiologically active may also be relevant (During et al. 1989). Tyrosine loading or depletion before and after pharmacological trials that alter the intrinsic activity of dopaminergic neurons may prove to be a useful approach to characterize further these putative OCD subtypes (Lehnert and Wurtman 1993).

Our findings are also reasonably consistent with prior CSF studies in OCD in which CSF 5-HIAA was reported to be unchanged (Thorén et al. 1980; Lydiard et al. 1990) or elevated (Insel et al. 1985) compared to normal controls. Although some OCD patients in this sample have both very low CSF 5-HIAA and severe obsessions of violence (Leckman et al. 1990b), we were not able to extend this finding across the entire group of OCD patients with violent obsessions. Future studies that address this issue may want to include prospectively a separate dimensional rating of the severity of violent obsessions as this would permit a more definitive evaluation of the possible association of very low CSF 5-HIAA and obsessions of violence.

CSF studies of TS patients have variously reported CSF HVA to be unchanged (Leckman et al. 1988), reduced (Butler et al. 1979), or elevated (Takano and Ishiguro 1993) compared to normal controls. It may be important to reanalyze these data sets taking into account the presence of OC symptoms in the participating TS patients, given our finding that CSF HVA was found to vary inversely with the severity of OC symptoms.

Do TS Patients Have Elevated Measures of Noradrenergic Activity?

To our knowledge, this is the first study to report elevated CSF NE levels in TS patients. As such, this report provides further support for the hypothesis that noradrenergic mechanisms are involved in the pathobiology of TS, as first articulated by Cohen et al. (1979). The observed elevation of CSF NE in TS subjects appears to be independent of cardiovascular status, as well

as of clinical ratings of depression, anxiety, and OC symptoms.

The elevated level of NE in the lumbar CSF reflects the activity of coeruleospinal neurons. In animal studies, these coeruleospinal neurons have been shown to be anteriorly directed collaterals in the midbrain reticular formation (Guyenet 1980). If similar collateral projections are present in humans, increased levels of NE in the lumbar CSF would likely be indicative of increased release of NE in more rostral CNS sites.

The predicted association between CSF NE and motor tic severity was not as robust as expected. This prediction was based on the results from clinical trials in which clonidine was found to be more effective in reducing motor tics than phonic tics (Leckman et al. 1991a). In this population, the four individuals whose CSF NE levels were entirely beyond the normal range all had severe TS. In three of the four cases current motor tic severity was above 18 on the YGTSS (in the severe to extremely severe range). The neuroanatomical basis for the possible relationship between motor tics and central NE activity is unclear. Possible mechanisms include direct effects on the neocortex, which may also play a role in modulating the activity of the corticostriothalamocortical (CSTC) circuits that have been implicated in TS (Leckman et al. 1991b; Peterson et al. 1993; Singer et al. 1993). Alternatively, indirect mechanisms may play some role. For example, ascending noradrenergic projections can influence the activity of the CSTC circuits indirectly through their effect on dopamine-containing neurons in the substantia nigra and ventral tegmental area, which in turn innervate striatal, hypothalamic, and mesolimbic areas, as well as the prefrontal cortex (Tassin et al. 1979; Herve et al. 1982; Grenhoff and Svennson 1993; Grenhoff et al. 1993). A similar argument can be made for indirect effects via NE projections to the serotonin containing cells of the dorsal raphe, which in turn project to sites within the CSTC circuits.

The findings with regard to CSF MHPG levels were less robust with only some of diagnostic group comparisons reaching statistical significance. The mean differences, however, were in the predicted direction and CSF MHPG and NE were significantly intercorrelated with the TS sample ($r = 0.43$, $p = .02$, $n = 28$).

We did not prospectively evaluate the relationship between CSF NE and MHPG levels and response to clonidine treatment. However, based on medical records and patient reports of the TS patients ($n = 15$), we did find a trend ($r = .50$, $p < .07$) between CSF NE levels and an individual's responsiveness to clonidine (after partialing out the association between CSF NE and the diastolic blood pressure at the time of the LP).

Previous reports have shown that clonidine and other central α_2 agonists can dramatically reduce CSF NE levels (Cubeddu et al. 1984; Mefford and Garrick

1989), so that we might expect that those patients with high levels of CSF NE and severe motor tics would benefit the most from clonidine treatment. Further prospective studies of this and related questions are warranted.

The observed correlations between CSF NE and diastolic blood pressures are consistent with previous reports when normotensive and hypertensive patients were taken together (Eide et al. 1979; Cubeddu et al. 1984). However, these relationships appear to be independent of the mechanisms responsible for the elevated CSF NE levels seen among the TS patients in this series.

Although we doubt that alterations in central noradrenergic mechanisms are etiologically responsible for the genetically determined TS vulnerability (Pauls and Leckman 1986; Price et al. 1988), it seems plausible that alterations in the activity of central noradrenergic systems may play an important role in mediating the severity of tic symptomatology over the life span (Leckman et al. 1992). Such alterations may be an important prognostic factor in determining which TS patients go on to have a malignant course in adulthood. Evidence in support of this hypothesis comes from collateral portions of this study, in which we found elevated levels of CSF corticotrophin releasing factor in TS patients compared to normal controls (Chappell et al. in press). We also found that some severely affected TS patients demonstrated a heightened responsiveness to the stress of the LP compared to the normal volunteers (Chappell et al. 1994).

The hypothesis that central noradrenergic systems may play an important role in mediating the severity of tic symptomatology over the life span is also consistent with the near-universal observation that tic symptoms increase during periods of stress (Jagger et al. 1982; Bornstein et al. 1990). The observed increased activity of the NE system may also be related to levels of maternal stress experienced during gestation reported by some mothers of severely affected TS patients (Leckman et al. 1990a; Leckman and Peterson 1993).

Other monoamine systems are likely to be involved in the pathobiology of tic disorders (Leckman et al., in press-a; see Singer 1993 for reviews). The robust negative correlation between CSF TRP and phonic tic symptoms is suggestive in this regard. Indeed, including both CSF NE and TRP in a linear regression, it is possible to account for 22% of the variance (adjusted r -square) in motor tics and 58% of the variance in phonic tics (adjusted r -square).

It is well known that neurochemical measurements from the lumbar CSF provide, at best, an imperfect index of central activity. The rich complexity of monoaminergic projections throughout the neural axis including the spinal cord, their circadian rhythms, the potential for right-left differences, as well as rostral-caudal and in some cases caudal-rostral gradients and

differences in diffusion and transport rates into and out of the CSF from both central and peripheral sources combine to limit severely the interpretability of CSF findings. Indeed, the results of a single tap may not agree well with data from continuous sampling procedures. Despite these limitations, the integrative function of many of the monoaminergic systems in the CNS and ANS may permit some global inferences from CSF measures that may be more precisely explored using ligand-based SPECT and PET studies or measurements based on *in vivo* MR spectroscopy.

Future studies of the role of biogenic amine mechanisms in TS and OCD, based on continuous sampling techniques of lumbar CSF or imaging-based techniques, may provide important information that can be translated into improved treatment regimens. Such studies may also add to our prognostic acumen and our ability to monitor variables relevant to the long-term outcome of OCD, TS, and related disorders.

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