Pervasive Developmental Disorder and Childhood-Onset Schizophrenia: Comorbid Disorder or a Phenotypic Variant of a Very Early Onset Illness?

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Background: *Childhood-onset schizophrenia (COS) is a severe form of the adult-onset disorder with a high rate of premorbid developmental abnormalities. Early symptoms of pervasive developmental disorder (PDD) have been reported in five independent studies of COS. In this study, we compared evidence for premorbid PDD as a nonspecific manifestation of impaired neurodevelopment seen in schizophrenia, or as an independent risk factor for COS.*

Methods: *Diagnosis of past or current autism or PDD was made according to the DSM-IV criteria. COS patients with and without PDD were compared with respect to neuropsychological, clinical, and neurobiological measures. Several candidate genes for autism were examined in the entire COS sample and the subgroup with PDD using the Transmission Disequilibrium Test (TDT) and Quantitative TDT (QTDT).*

Results: *Nineteen (25%) of COS probands had a lifetime diagnosis of PDD: one met criteria for autism, two for Asperger's disorder, and 16 for PDD not otherwise specified. Premorbid social impairment was most common feature for COS-PDD subjects. The PDD group did not differ from the rest of the COS sample with respect to age of onset, IQ, response to medications, and rate of familial schizotypy. Unexpectedly, two siblings of COS-PDD probands met criteria for nuclear autism. There was no difference between PDD and non-PDD groups with respect to initial brain magnetic resonance imaging (MRI) measures. However, rate of gray matter loss was greater for PDD* ($n = 12$) *than for the non-PDD* ($n = 27$) *subgroup* (-19.5 ± 11.3 *mL/year vs.* -9.6 ± 15.3 *mL/year;* $p = .05$). *None of eight candidate genes for autism were associated with COS or COS-PDD.*

Conclusions: *Premorbid PDD in COS is more likely to be a nonspecific marker of severe early abnormal neurodevelopment. However, the occurrence of two siblings of COS-PDD probands (17%) with nuclear autism remains to be understood.*

Key Words: Autism, child-onset schizophrenia, pervasive developmental disorder

Childhood-onset schizophrenia (COS) appears to be clinically and neurobiologically continuous with the adult disorder (Asarnow and Asarnow 1994; Nicolson and Rapoport 1999) and may represent a more severe and more homogeneous population. Although limited by its rarity, increasing interest in COS over the past 15 years has led to general agreement about its clinical phenomenology.

Since early works of Kolvin and Rutter (Kolvin 1971; Rutter 1972), autism was reliably separated from early-onset schizophrenia, becoming one of the best-validated distinctions in child psychiatry; however, a striking feature of the COS samples relative to adult-onset schizophrenia is the higher rate of early language, social, and motor developmental abnormalities. As shown in Table 1, premorbid social impairment was the most common feature, present in 50%–87% of COS cases across five independent research centers. High rates of language and motor developmental impairment were also noted in each of the five independent COS samples.

For the National Institute of Mental Health (NIMH) COS sample, to date the largest COS sample to be studied, this high rate of developmental abnormalities remains a prominent feature (Alaghband-Rad et al 1995). Frequently the diagnosis of autism or pervasive developmental disorder (PDD) has been raised early in the development in our cases. Although some have claimed that autism per se might be a risk factor for later psychosis (Cantor et al 1982; Clarke et al 1989; Petty et al 1984), the only large study (163 adolescents and adults) with autism found only one patient who had developed true psychosis (Volkmar and Cohen 1991), a rate expected in the general population. A second prospective 22-year follow-up study of 38 patients with autism found no patient to have schizophrenia (Mouridsen et al 1999).

There are two possible interpretations of high level of autism and PDD in COS samples. First, autisticlike behavior may be a nonspecific response to a variety of early developmental insults, and thus premorbid PDD features in early-onset schizophrenia may be an exaggeration of neurodevelopmental abnormalities seen in adult-onset schizophrenia. If this is true, the subgroup of COS patients with PDD would not be expected to differ from the rest of the COS group with respect to clinical and neurobiological measures or genetic risk factors associated with autism. Alternatively, autism may reflect a separate additive risk factor for schizophrenia with very early onset. In this case, the subgroup of COS patients with PDD might be expected to have unique clinical, neurobiological, or genetic features suggesting increased susceptibility for autism.

Here we present an update on the diagnosis and rate of PDD and autism in our COS sample and a comparison of this subgroup with the larger COS sample without early PDD features. Based on the phenomenology of autism, the hypotheses were that the COS-PDD subgroup would have earlier onset of psychotic illness, lower IQ, greater severity of illness, poorer response to antipsychotic medications, and poorer outcome.

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Table 1. Premorbid Developmental Abnormalities in Childhood-Onset Schizophrenia: Observations from the Research Sites

Study	Subject No.	Age of Onset	Premorbid Developmental Abnormalities
Kolvin et al 1971	33	<15	87%: social abnormalities; 49%: major milestone delay; 46%: speech delay
Asarnow and Ben-Meir 1988 (UCLA)	17	<13	Very poor scores on PAS (4.1 ± 1.0); poor premorbid social functioning
Watkins et al 1988 (UCLA)	18	<12	Premorbid language deficits: 72%; Motor deficits: 72%; Symptoms of infantile autism: 39%; PDD NOS: 17%
Russell et al 1989, 1894 (UCLA)	35	<12	PDD features: 26%; transient premorbid autistic symptoms (hand flapping, echolalia, unusual interests): 40%
Green 1992 (NYU)	38	<12	Poor premorbid intellectual functioning: insidious onset in 79%
Alaghband-Rad et al 1995 (NIMH)	23	<13	Language delay/disorders: 43%; motor impairment: 36%; Social impairment: 50% (PAS = 2.3 ± 1.6); PDD features: 36%; infantile autism or Asperger syndrome: 13%; transient motor PDD features: 30%
Hollis 1995 (UK)	18	7–13	Language impairment: 44%; motor impairment: 28%; social impairment: 50%; more social and language impairment than in adolescent onset

NIMH, National Institute of Mental Health; NOS, not otherwise specified; NYU, New York University; PAS, Cannon-Spoor Premorbid Adjustment Scale; PDD, pervasive developmental disorder; UCLA, University of California at Los Angeles; UK, United Kingdom.

Based on reported brain abnormalities in autism, it was predicted that brain imaging of the COS-PDD subgroup would show larger total brain volume (Courchesne et al 2003; Hardan et al 2001; Piven et al 1995), particularly in the younger patients, as well as reduced thalamic (Tsatsanis et al 2003) and increased cerebellar volume (Piven et al 1997). If the "autism as additional risk" model is correct, we also hypothesized that in this sample, there would be an overtransmission of alleles of one or more of the risk genes for autism.

Methods and Materials

Subjects

Accrual of subjects for the NIMH childhood-onset schizophrenia study has been described elsewhere (Nicolson and Rapoport 1999). Briefly, children ages 6–18 meeting DSM-III-R/DSM-IV criteria for schizophrenia with onset of psychosis before their 13th birthday were recruited nationally. Diagnostic process was extensive and included detailed review of medical and school records and full-day, in-person interviews with children and their parents using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-E and K-SADS-PL; Ambrosini et al 1989; Kaufman et al 1997). Prepsychotic IQ of less than 70 or significant medical or neurologic conditions were exclusionary. Diagnosis was confirmed by an inpatient observation during a 1- to 3-week medication-free period. Severity of clinical symptoms was assessed using the Brief Psychiatric Rating Scale (Overall and Gorham 1962), Scale for the Assessment of Positive Symptoms (Andreasen 1984), Scale for the Assessment of Negative Symptoms (Andreasen 1983), and Clinical Global Impression Scale (Guy 1976).

Diagnosis of Autism or PDD

Diagnosis of past or current autism or pervasive developmental disorder (PDD) in probands was made according to DSM-IV criteria (American Psychiatric Association 1994) based on chart review of all available clinical, neuropsychological, and school records; clinical interview of a patient and parents performed by a team of three psychiatrists with a high rate of agreement on diagnosis (McKenna et al 1994); and the Autism Screening Questionnaire (ASQ; Berument et al 1999), administered to the parent(s) of the proband. The interrater reliability for the ASQ was high (interclass correlation coefficient = .77).

Because K-SADS does not address the diagnosis of PDD, clinical diagnosis of autism or PDD was made in cases when history indicated clear symptoms of autistic/PDD spectrum was present before the onset of psychosis that were still observable at the time of the NIMH evaluation. Special attention was paid to differentiating autistic symptoms from negative symptoms of schizophrenia, that is, lack of motivation of schizophrenia from abnormal or unusual interests of autism, blunted affect of schizophrenia from social impairment typical for autistic children (initial failure to develop nonverbal communicative behavior, age-appropriate friendships, lack of reciprocity, etc.). Such symptoms as echolalia, verbal or motor stereotypies, and poor language comprehension were viewed as primarily belonging to the autistic spectrum. Age of onset of PDD/autistic symptoms was recorded because in some cases of PDD the symptoms emerge after the first 3 years of life.

Evaluation of Premorbid Functioning

Premorbid (1 year before the onset of psychosis) characteristics were assessed using the Cannon–Spoor Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al 1982) and an adaptation of the premorbid development rating scale used by Hollis (Hollis 1995). On this scale, presence or absence of premorbid abnormalities in the four general areas of functioning (social interactions, speech and language, motor behavior, and school adjust-

ment, a total of 15 subcategories) was recorded after detailed review of the medical and school records. The sum of these scores comprised a total score of premorbid developmental dysfunction. Interrater reliability for two raters on this measure was high ($\kappa = .9$).

Other Neurobiological Measures

All probands were invited for a 2-year follow-up interview during a 2- to 6-year period in which the stability of clinical diagnoses and clinical severity were reassessed using the same diagnostic instruments. Long-term response to and tolerance of antipsychotic medications (especially clozapine) was evaluated based on the clinical rating scales. At baseline and at each follow-up visit, subjects were administered the Wechsler Intelligence Scale for Children—Revised (Wechsler 1974), Wechsler Intelligence Scale for Children—Third Edition (Wechsler 1991), or the Wechsler Adult Intelligence Scale—Revised (Wechsler 1981).

Structured anatomic brain magnetic resonance imaging (MRI) scans were obtained for all probands and repeated every 2 years. Scans were obtained on the same GE 1.5-Tesla Signa scanner using the same imaging protocol (axial slice thickness = 1.5 mm, echo time = 5 msec, repetition time = 24 msec, flip angle = 45°, acquisition matrix = 192 × 256, number of excitations = 1, and field of view = 24 cm). Total and regional gray and white matter volumes were generated by an automated system, which classifies tissue according to voxel intensity using a probabilistic atlas and provides lobar (frontal, parietal, temporal, and occipital) parcellation of cortical brain volumes (Giedd et al 1999). For subjects with two or more scans, we calculated the rate of total gray matter reduction, defined as follow-up scan value minus first scan value divided by time elapsed between scans and expressed as milliliter per year (a negative value representing volume reduction).

Family Evaluation

Parents and siblings 18 or older of COS subjects were evaluated using clinical and structured diagnostic interviews, including the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (versions III, III-R, and IV; Endicott and Spitzer 1978) and the Structured Interview for DSM-IV Personality (Pfohl et al 1995). Siblings under 18 were evaluated using K-SADS-E and K-SADS-PL and Diagnostic Interview for Children and Adolescents (Reich 2000). Schizophrenia spectrum disorder was defined as presence of schizophrenia, schizoaffective disorder, or schizotypal personality disorder. Siblings were also evaluated with the ASQ (Berument et al 1999) and clinically for presence or absence of symptoms of PDD or autism.

Statistical Analysis

Analyses were performed using NCSS software (Hintze 2001). Demographic, clinical, and neurobiological variables were compared for COS-PDD and non-PDD subgroups using *t* tests or chi-square. Cross-sectional brain MRI measures were compared between COS subjects with and without PDD using a general linear analysis of variance model. Although the COS-PDD and non-PDD groups were close in age at the time of initial evaluation, the PDD group had more male subjects, and thus analyses were adjusted for gender. Because of the numerous comparisons, we used a significance level of $p = .01$. Rate of total gray matter change for COS subjects with two or more scans was compared between COS-PDD and non-PDD subgroups using a *t* test.

Genetic Analysis

As part of a candidate gene study in COS, we studied single nucleotide polymorphisms (SNPs) in the genes that have previously been reported to be associated with autism (*GABRB3*, Menold et al 2001; *SLC6A4,* Kim et al 2002; Klauck et al 1997; *ADA,* Lucarelli et al 2002; *GRIK2/GLU6,* Jamain et al 2002; *GRM 8*, Serajee et al 2003; *RELN* Persico et al 2001; *WNT2,* Wassink et al 2001) to see whether there is an additional risk for COS. The SNPs in and around candidate loci were selected from Celera and dbSNP databases. Number of SNPs per candidate gene varied between three and nine depending on the gene sizes. Transmission disequilibrium test (TDT) by individual SNP locus and 3-SNP haplotypes was performed using algorithms in the TDTPHASE and TRANSMIT programs. All *p* values were computed empirically with 100,000 bootstrap replicates. The TDTs were examined for the entire COS sample and for the COS-PDD subgroup separately. In addition, we performed the quantitative transmission disequilibrium test (QTDT), which allowed testing for association and transmission disequilibrium (Hintze 2001) with ASQ score as a quantitative trait.

Results

Of 75 COS probands, 19 had a lifetime diagnosis of PDD (25%), of whom 1 met criteria for autism (past and current), 2 for Asperger's disorder (past and current), and 16 for PDD not otherwise specified. Demographic and clinical data for COS patients with and without PDD are presented in Table 2.

In 12 of 19 cases (63%), the diagnosis of PDD was made before patients entered the NIMH study. In most cases (15 of 19; 79%), PDD symptoms had been present before age 3 years; however, four patients had had relatively normal early development, and PDD symptoms appeared between ages 4 and 6 years.

As expected, there were more male subjects in the COS-PDD group; however, the COS-PDD subgroup did not differ from the non-PDD subgroup with regard to ethnicity, age of onset of psychotic illness, or cognitive performance. There were no differences in any of the measures between subjects with earlier versus later (after age 3) onset of PDD.

Predictably, subjects with PDD had higher scores on the ASQ, Hollis Premorbid Development Scale, and PAS (see Table 2). According to PAS and Hollis scales, premorbid abnormalities most common for subjects with PDD were problems with sociability, peer relationship, poor school adaptation, and abnormal interests (see Table 3). Abnormal motor behaviors characteristic for this subgroup included rocking, twirling, head banging, and hand flapping. Analysis of the ASQ led to similar conclusions: poor social skills were most characteristic of this group. According to the analysis of the ASQ, more than 65% of PDD-COS patients did not have a best friend, were not able to play cooperatively with other children or play imaginative games, were not interested in other children of the same age, and did not have reciprocal ("to and fro") conversation. Motor abnormalities characteristic for autism (flapping, spinning, etc.) were present in 12 of 19 (63%) COS-PDD patients.

The COS-PDD and non-PDD groups did not differ with respect to baseline or 2- to 6-year outcome clinical measures: Clinical Global Impression Scale (3.9 ± .7 vs. 4.6 ± 1.2; $t = 1.92$, $p = .06$), Scale for the Assessment of Positive Symptoms (18.1 ± 11.3 vs. 19.8 ± 14.0; $t = .39$, $p = .69$), Scale for the Assessment of Negative Symptoms (35.7 ± 25.3 vs. 47.4 ± 27.2; $t = 1.40$, $p = .16$), and Brief Psychiatric Rating Scale (46.9 ± 7.5 vs. 52.4 ± 12.9; $t = 1.48$, $p = .14$). There was also no difference in

Table 2. Demographic and Clinical Data for COS Patients with and without PDD

	COS with PDD ($n = 19$)	COS without PDD ($n = 55$)	Statistics (t test[a] or chi-square[b])
Age of Onset	9.22 ± 2.04	10.09 ± 2.10	$t = 1.53$; $p = .13$
Gender: *n* Male Subjects (%)	15 (79)	28 (51)	$\chi^2 = 4.56$; $p = .03$
Ethnicity, *n* (%)			χ^2 ($df = 4$) = 2.60; $p = .62$
Caucasian	12 (63)	25 (46)	
African American	3 (16)	16 (29)	
Asian	2 (11)	4 (7)	
Hispanic	1 (5)	6 (11)	
Other	1 (5)	4 (7)	
Parental SES	2.26 ± 1.04	2.84 ± 1.21	t ($df = 72$) = 1.83; $p = .07$
Total PAS Score	18.47 ± 4.08	12.53 ± 7.08	$t = 3.08$; $p = .003$
ASQ Score	19.47 ± 8.20	4.32 ± 4.62	$t = 9.28$; $p < .0001$
Hollis Score	7.16 ± 2.33	3.32 ± 2.61	$t = 5.63$; $p < .0001$
Schizotypal Personality Disorder (Symptom Number)			
Fathers ($n = 16$ and $n = 48$)	2.3 ± 2.6	1.3 ± 1.4	$t = 1.87$; $p = .06$
Mothers ($n = 18$ and $n = 54$)	1.0 ± 1.1	1.5 ± 1.8	$t = 1.01$; $p = .3$
Siblings ($n = 5$ and $n = 26$)	.8 ± 1.3	1.1 ± 1.5	$t = .48$; $p = .6$
Total family ($n = 39$ and $n = 128$)	1.5 ± 1.9	1.4 ± 1.6	$t = .50$; $p = .6$
Familial Schizophrenia Spectrum Disorder, *n* (%)	5/18 (28)	13/50 (26)	$\chi^2 = .02$; $p = .88$
ASQ Score in Siblings ($n = 10$ and $n = 23$)	8.5 ± 11.4	.2 ± .4	$t = 2.69$; $p = .01$
Autism (siblings), *n* (%)	2/12 (17)	0/29 (0)	Fisher's Exact Test $p = .02$

ASQ, Autism Screening Questionnaire; COS, child-onset schizophrenia; PDD, pervasive developmental disorder; SES, socioeconomic status; PAS, Cannon-Spoor Premorbid Adjustment Scale.

[a] $df = 72$.

[b] $df = 1$.

COS-PDD patients' tolerance of or response to clozapine (5 of 12 PDD-COS patients met criteria for clinical response on clozapine).

Comparison of COS-PDD and non-PDD subgroups with regard to the initial anatomic brain MRI measures showed that after control for gender, the groups did not differ significantly on total and regional gray and white matter volumes or thalamic and cerebellar volumes (see Table 4); however, in a comparison of the 12 PDD with 27 non-PDD COS patients who had two or more MRI scans, the rate of gray matter reduction was more rapid for the COS-PDD group (19.5 mL/year vs. 9.6 mL/year; $t = 2.1$; $p = .05$).

Risk genes for autism showed no association with the diagnosis of COS (with or without PDD or combined) or to the ASQ score. Familial diagnosis of schizophrenia spectrum disorder or number of symptoms of schizotypal personality disorder did not differ between PDD and non-PDD subgroups; however, siblings of the PDD-COS probands had significantly higher score on the ASQ, and 2 of 12 (17%) siblings of PDD probands had been diagnosed with nuclear autism.

Discussion

Counter to our expectations, a comorbid lifetime diagnosis of PDD or autism did not predict early age of onset, lower cognitive performance, or poor long-term outcome. In addition, COS-PDD subgroup did not differ from the rest of the COS sample on any of the clinical and neuropsychological measures. Thus, our clinical data do not support a prediction that an autistic subgroup has a unique clinical pattern.

Neurobiologically, the data are complex. The predicted profile of brain abnormalities (total brain and cerebellar enlargement) was not seen; however, we found that the PDD-COS group has a trend toward a more rapid gray matter reduction. This fact is interesting in two contexts: progressive gray matter might be associated with either the hypothesized exaggerated neuronal pruning in schizophrenia (Feinberg 1992) or with deceleration of brain growth in autism during the adolescence, following an early acceleration (Courchesne et al 2001). It is possible to hypothesize that these two processes are pathogenetically similar or have an additive effect in COS. The alternative

Table 3. Premorbid Abnormalities in COS patients with and without PDD as Measured by Adapted Hollis Scale

	COS with PDD ($n = 19$) *n* (%)	COS without PDD ($n = 53$) *n* (%)	Chi-Square Test or Fisher's Exact Test
School Delay	15 (79)	29 (55)	Fisher's $p = .09$
Social Problems	19 (100)	35 (66)	Fisher's $p = .003$
Language Delay/Problems	15 (79)	26 (49)	Fisher's $p = .03$
Motor Delay/Problems	15 (79)	17 (32)	Fisher's $p = .0005$
Social + Language + Motor	12 (63)	10 (19)	$\chi^2 = 12.93$; $p = .0003$

COS, child-onset schizophrenia; PDD, pervasive developmental disorder.

Table 4. Brain Magnetic Resonance Imaging Measures for COS with and without PDD and Control Subjects

	PDD-COS ($n = 16$)	Non-PDD-COS ($n = 45$)	2×2 factorial ANOVA[a]
Age	14.7 ± 1.5	14.2 ± 2.6	$t = .74$; $p = .46$
TCV	1112.9 ± 98.2	1051.9 ± 21.3	$F(1,57) = .95$, $p = .33$
Total Gray Matter	711.1 ± 61.5	666.7 ± 85.1	$F(1,57) = .05$, $p = .82$
Total White Matter	401.8 ± 47.4	385.2 ± 52.1	$F(1,57) = .15$, $p = .70$
Cerebellum	136.6 ± 11.0	128.7 ± 13.5	$F(1,57) = .26$, $p = .61$
Frontal GM	215.7 ± 20.3	205.7 ± 8.1	$F(1,57) = .14$, $p = .71$
Parietal GM	115.3 ± 11.4	108.9 ± 5.1	$F(1,57) = .05$, $p = .83$
Temporal GM	185.2 ± 13.7	173.9 ± 1.8	$F(1,57) = .02$, $p = .88$
Thalamus	17.7 ± 1.9	16.6 ± 1.7	$F(1,57) = 2.61$; $p = .11$

ANOVA, analysis of variance; COS, child-onset schizophrenia; GM, gray matter; PDD, pervasive developmental disorder; TCV, thalmic and cerebellar volumes.

[a]PDD and gender as independent variables.

explanation, however, is much more likely: the patterns of brain responding to genetic abnormality or environmental insult are limited, and during brain development, normal pruning may be exaggerated by certain precipitants. Thus, in autism, greater synaptic production early in life (that reflected by greater early brain volume and increased neuronal density) may trigger exaggerated pruning. In schizophrenia, an unknown precipitant may do the same to an initially normal size brain.

In our sample a number of reported risk genes for autism did not appear to be related either to the diagnosis of COS or to the ASQ score. Although our study is underpowered to find such a relationship, the sample sizes from which the initial observations were made ranged from 52 to 172. Alternatively, symptoms of PDD or autism may not be a unique risk factor for early-onset schizophrenia, but a nonspecific sign of an early brain disturbance or insult. Most striking is that of 12 siblings of PDD-COS probands, two (17%) met full criteria for autistic disorder, a total rate (4.9%) similar to that seen for probands with nuclear autism (Jorde et al 1991). This fact implies a familial–genetic connection between COS and autism.

Limitations of our study include small sample with significant ethnic heterogeneity, lack of brain volumetric data from earlier developmental stages (i.e., head circumference at birth), using the ASQ instead of the Autism Diagnostic Interview, probable clinical and etiologic heterogeneity for autism and COS, and possible referral bias (i.e., children with more than one disorder are more likely to participate in the national study). In addition, PDD-NOS is a nonspecific diagnosis in itself, representing a mixed group of conditions from subthreshold autism to nonspecific developmental disorders.

Our primary conclusion is that the early brain developmental disturbance typical of COS leads to an additional feature reminiscent of autism/PDD. Other data support strong genetic effects for this group that are similar to that seen with adult onset schizophrenia (AOS). Prospective studies of large PDD and autism samples will be needed to answer the question of whether premorbid PDD is a risk factor for later-onset psychosis.

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