

Lack of Gender-Related Differences in Childhood-Onset Schizophrenia

Anna E. Ordóñez, MD, Frances F. Loeb, BA, Xueping Zhou, MHS, Lorie Shora, MS,
Rebecca A. Berman, PhD, Diane D. Broadnax, MSW, Peter Gochman, MA,
Siyuan Liu, PhD, Judith L. Rapoport, MD

Objective: Gender differences, including younger age of onset and greater premorbid deficits in men, have been reported in adult-onset schizophrenia. This study comprehensively evaluated gender differences in childhood-onset schizophrenia (COS), a rare variant of the disorder.

Method: Demographic, premorbid, clinical, familial, and cognitive characteristics, presence of chromosomal abnormalities, and brain magnetic resonance imaging cortical volumes were evaluated in 133 patients with COS. Cortical analyses included age- and gender-matched healthy volunteers ($n = 124$).

Results: Males with COS ($n = 72$) had a slightly but significantly younger age of onset than females with COS (mean age 9.51 ± 2.28 versus 10.29 ± 1.63 years, $t_{131} = 2.21$, $p = .03$), higher verbal IQ scores (83.00 ± 15.97 versus 75.58 ± 15.10 , $t_{89} = 2.24$, $p = .03$), and higher rates of comorbid pervasive developmental disorder (28.17% versus 6.90% , $\chi^2_1 = 9.54$, $p < .01$) and attention-deficit/hyperactivity disorder (43.86% versus 21.43% , $\chi^2_1 = 5.40$, $p = .02$). There were no significant gender differences across other

demographic, IQ, or clinical measurements, frequency of chromosomal abnormalities, family clinical measurements, premorbid functioning, or in gender-by-disorder interactions for magnetic resonance imaging brain measurements.

Conclusion: The present comprehensive examination found few remarkable gender differences in COS. Although less striking than that seen in adult-onset schizophrenia, males with COS had a younger age of onset. Attention-deficit/hyperactivity disorder and pervasive developmental disorder rates were high in COS overall, suggesting greater neurodevelopmental vulnerability in COS. However, the gender ratios of these comorbidities in COS mirror those of the general populations, indicating that these gender differences might be unrelated to COS.

Key words: childhood-onset schizophrenia, gender differences, cortical volumes

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Gender differences in schizophrenia have been reported for several aspects of the disorder.^{1,2} These differences might contribute to the marked heterogeneity of disease presentation, course, and response to treatment.^{3,4} Childhood-onset schizophrenia (COS), a rare, severe, and possibly more homogenous variant of the disorder,^{5,6} has not been comprehensively examined with respect to gender differences.

Variations in the incidence and prevalence of schizophrenia between men and women have been debated, with some reports of increased incidence in men,⁷ whereas epidemiologic studies have reported no difference in prevalence.^{8,9} The significantly younger age of onset in men (roughly 5–6 years earlier^{10,11}) and a second peak of onset in women older than 40 years might contribute to these results.^{3,10,11} Findings on gender differences in symptom presentation and prognosis are less consistent. Several studies have found that women with schizophrenia have less severe negative symptoms and better prognosis than men,^{2,12–14} whereas others have reported minimal to no gender differences.^{15,16} Because an earlier onset of schizophrenia tends to relate to poorer prognosis,¹⁷ the later onset in women might reflect some overall protective effect.

Deficits in premorbid social functioning and cognitive functioning in adult patients with schizophrenia,¹⁸ academic

and occupational adjustment,^{19,20} marriage adjustment,¹⁸ and general premorbid functioning^{13,20} also tend to indicate a mitigating effect for women. However, findings in social functioning^{21–23} and cognitive functioning^{2,3} are less conclusive. Moreover, although psychiatric comorbidities in schizophrenia are common^{24,25} and can affect many of these domains, salient differential effects of gender on frequency of comorbidities in adult-onset schizophrenia appear lacking. In COS, a previous study from this cohort identified greater frequency of pervasive developmental disorder (PDD) diagnoses in males with COS,²⁶ and others have reported greater comorbid attention-deficit/hyperactivity disorder (ADHD) in males with COS.²⁵

Gender differences also have been reported in the brain structure of patients with schizophrenia. Compared with controls, patients with schizophrenia tend to have larger total ventricular volume, smaller absolute whole brain volume, and smaller cerebral gray matter volume.²⁷ Some reports have indicated greater severity of these structural abnormalities in men compared with women, especially with regard to ventricular enlargement.²⁸ However, the findings are highly inconsistent,^{1,2} with some reporting that women show greater decreases in the prefrontal cortex, orbital regions, basal forebrain, anterior cingulate, and posterior supramarginal gyrus, and others reporting greater

relative decreases in fronto-medial and middle frontal cortices, para-cingulate gyrus, and insula.^{29,30} Other studies have found no gender differences with respect to abnormalities in volumes of cortical gray matter, white matter and sulci, lateral and third ventricles, and key subcortical structures.^{31,32} This last point was highlighted in a meta-analysis of 58 magnetic resonance imaging (MRI) studies of patients with schizophrenia, which found that gender was not significantly related to structural differences.²⁷

Few studies have examined gender differences in brain development in early-onset schizophrenia (EOS) or COS. A small longitudinal study (N = 21) found that men with EOS had more frontal gray matter loss compared with controls than women with EOS, although that study was underpowered to detect change in women owing to the small sample size (23.81% women, n = 5).³³ Previous studies from this cohort found no gender differences in cortical thickness and subcortical volume development^{34,35} or development of total cortical gray matter³⁶ in patients with COS. Nevertheless, although changes in cortical brain volume are among the most consistently reported abnormalities in adult-onset schizophrenia and COS, a thorough and systematic evaluation of potential gender differences remains lacking.^{37,38}

The present study explored gender differences more comprehensively in a larger sample of patients with COS. Specifically, demographics, clinical presentation, premorbid functioning, cognitive ability, presence of chromosomal abnormalities, brain MRI cortical volumes, and family clinical data were examined. Because COS is in several respects continuous with later-onset schizophrenia,^{39,40} the authors expected that the more consistently reported gender

differences, such as poorer premorbid functioning and younger age of onset in men, might be more prominent for patients with COS.

METHOD

Participants

Patients were recruited as part of an ongoing longitudinal study of COS at the National Institute of Mental Health (NIMH).⁴¹ Criteria for selection and inclusion have been described previously.^{41,42} Briefly, children and adolescents 6 to 18 years old who met *DSM-III-R/DSM-IV* criteria for schizophrenia with onset before 13 years of age and with a prepsychotic IQ above 70 were nationally recruited. In total, 133 patients with COS (72 males and 61 females) participated in the study. In addition, 124 age- and gender-matched healthy volunteers formed the control group for analyses of brain structure.

Clinical and Neuropsychological Measurements

A research team that included 2 psychiatrists collected the clinical data of patients with COS, including a structured interview with the patient and their parents at screening or admission.⁴³ Interviews included the Scale for the Assessment of Positive Symptoms,⁴⁴ the Scale for the Assessment of Negative Symptoms,⁴⁵ the Brief Psychiatric Rating Scale,⁴⁶ the Simpson-Angus Extrapyramidal Side Effect Scale,⁴⁷ and the Abnormal Involuntary Movement Scale.⁴⁸ Rates of comorbid ADHD were determined using the Schedule for Affective Disorders and Schizophrenia (K-SADS).⁴³ Because the K-SADS does not include the PDD diagnosis, all children were screened with the Autism Screening Questionnaire⁴⁹ and further assessed by clinical interview. Comorbid PDD was given when the history and thorough review of clinical records showed clear PDD/autistic spectrum symptoms before the onset of psychosis with

TABLE 1 Demographic Data for Male and Female Patients With Childhood-Onset Schizophrenia

Variables	Males (54.14%)		Females (45.86%)		Test Statistic (df)	p Value
	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n		
Age at onset (y)	9.51 ± 2.28	72	10.29 ± 1.63	61	$t_{131} = 2.21$	.03
Race		72		60		
Caucasian	41 (56.94)		33 (55.00)		$\chi^2_3 = 1.17$	.76
African American	19 (26.39)		20 (33.33)			
Asian	4 (5.56)		2 (3.33)			
Other	8 (11.11)		5 (8.33)			
Ethnicity		71		60		
Hispanic	7 (9.86)		9 (15.00)		$\chi^2_1 = 0.80$	.37
Non-Hispanic	64 (90.14)		51 (85.00)			
Parental SES		71		60		
1	13 (18.31)		9 (15.00)		Fisher's exact test = 4	.13
2	24 (33.00)		17 (28.33)			
3	18 (25.35)		23 (38.33)			
4	16 (22.54)		8 (13.33)			
5	0 (0.00)		3 (5.00)			
IQ		53		38		
Full IQ	79.02 ± 16.20		74.66 ± 16.33		$t_{89} = 1.26$	.21
Verbal IQ	83.00 ± 15.97		75.58 ± 15.10		$t_{89} = 2.24$	.03
Performance IQ	77.57 ± 16.74		77.05 ± 18.30		$t_{89} = 0.14$	.89

Note: Boldface type indicates statistical significance. Socioeconomic status (SES) was based on a 2-factor index of social position by Hollingshead⁶⁵: 1 = highest SES, 5 = lowest SES. SD = standard deviation.

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