Autism Spectrum Disorders and Childhood-Onset Schizophrenia: Clinical and Biological Contributions to a Relation Revisited

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ABSTRACT

Objective: To highlight emerging evidence for clinical and biological links between autism/pervasive developmental disorder (PDD) and schizophrenia, with particular attention to childhood-onset schizophrenia (COS). **Method:** Clinical, demographic, and brain developmental data from the National Institute of Mental Health (and other) COS studies and selected family, imaging, and genetic data from studies of autism, PDD, and schizophrenia were reviewed. **Results:** In the two large studies that have examined this systematically, COS is preceded by and comorbid with PDD in 30% to 50% of cases. Epidemiological and family studies find association between the disorders. Both disorders have evidence of accelerated trajectories of anatomic brain development at ages near disorder onset. A growing number of risk genes and/or rare small chromosomal variants (microdeletions or duplications) are shared by schizophrenia and autism. **Conclusions:** Biological risk does not closely follow *DSM* phenotypes, and core neurobiological processes are likely common for subsets of these two heterogeneous clinical groups. Long-term prospective follow-up of autistic populations and greater diagnostic distinction between schizophrenia spectrum and autism spectrum disorders in adult relatives are needed. *J. Am. Acad. Child Adolesc. Psychiatry,* 2009;48(1):10–18. **Key Words:** schizophrenia, childhood, autism, genetics, brain development.

The separation of autism from childhood-onset psychoses, particularly schizophrenia, was an important advance for the study of childhood psychopathology. The lack of this distinction in *DSM-II*[1] evolved to a delineation of autism/pervasive developmental disorder (PDD) as a separate category from early-onset schizophrenia in *DSM-III*[2] based on clinical, familial, and follow-up studies. *DSM-III-R*, *DSM-IV*, and *DSM-IV-TR* further elaborated the PDD category.[3,4] This distinction enabled decades of research validating different patterns with respect to familial, brain imaging, and genetic risk.[5–8] Clinically, this has been a basic and self-evident distinction as age of onset, differential diagnosis, and treatment of the two conditions differed.[9] This review supports the clinical use of the distinction, but systematic studies of childhood-onset schizophrenia (COS) show high comorbidity between COS and PDD, and the emergence of some common family, genetic, and imaging findings warrants further review and comment.

PHENOMENOLOGY OF COS IN RELATION TO AUTISM/PDD

Childhood-onset schizophrenia is defined as onset of psychosis before age 13 years and is a rare and severe form of schizophrenia. Onset is usually after age 7 years, positive and negative symptoms are prominent, and prognosis is poor.[10] In contrast, *autism* is defined by abnormal behavior in the spheres of communication, social relatedness, and stereotyped behaviors within the first 3 years of life. The broader category, PDD

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(subsuming autism, Rett syndrome, Asperger syndrome, and childhood disintegrative disorder) has a residual category, PDD not otherwise specified (NOS), which is based on the social relatedness symptoms for autism but allows for different age of onset and fewer other spheres. Thus, *DSM-IV-TR* PDD-NOS requires failure to develop appropriate reciprocal social behaviors as a necessary defining feature.[11] Inevitably, there will be further subdivisions, and it is hoped that brain imaging and genetic studies will provide clues about how to do this. One particular category, multiple complex developmental disorder (MCDD), discussed below, is a possible bridge with schizophrenia.[12–14]

When advances in psychiatry permitted the field to conceptualize psychotic disorders and developmental disorders as distinct, the phenomena of PDD and COS as comorbid disorders could be explored. In the *DSM-II*, autism was referred to as schizophrenia, childhood type, and was characterized by "atypical and withdrawn behavior," "failure to develop identity separate from the mother's," and "general unevenness, gross immaturity, and inadequacy in development." However, important post–*DSM-II* work conducted by Kolvin and others focused on the contrast between very-early-onset schizophrenia (with typical onset after age 7 years)[15] and earlier onset autism. This research was influential in making the distinction between childhood-onset schizophrenia and autism in the *DSM-III*. The phenomenology of childhood-onset schizophrenia was described by Kolvin et al.[16] in a groundbreaking study of 33 British children, of whom 12 had onset before age 13 years. In addition, the researchers stressed the severity and frequency of prepsychotic developmental disorders in COS.

The observations of Kolvin and coworkers have been replicated in virtually every study of early-onset schizophrenia with findings of developmental abnormalities primarily for communication, motor abnormalities, and/or social relatedness.[10,17] For example, an early article from the University of California, Los Angeles COS study found that 39% of a sample of 33 patients had symptoms of autism years before onset of schizophrenia.[18] Since the initial 1988 article, the University of California, Los Angeles group has examined an additional 52 COS probands using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic version structured diagnostic interview.[15] Of these, 28 (55%) had histories meeting *DSM-III-R* criteria for autism or PDD (R. Asarnow, personal communication, May 2008). The largest study to date of COS includes 101 children and adolescents with onset of *DSM-IV*–defined schizophrenia before age 13 years. Of these, one (1%) met criteria for comorbid autism, 2 (2%) for Asperger syndrome, and 25 (25%) for PDD-NOS, for a total of 28% with comorbid autism or autism spectrum disorder (ASD; N.G., unpublished data, 2003). These diagnoses were made by both screening questionnaire and agreement by two board certified child and adolescent psychiatrists in recognition of the pitfalls of diagnosis by screening instrument alone.[19] Pervasive developmental disorder-NOS was a persisting and stable diagnosis in these cases, with onset in the first 5 years of life, whereas the onset of psychotic symptoms occurred typically 3 to 5 years later.

Premorbid developmental disturbance in schizophrenia is hardly a new concept, and schizophrenia itself is widely regarded as a neurodevelopmental disorder.[20] Large cohort studies of the antecedents of schizophrenia have documented subtle developmental delays long predating the onset of psychosis.[21–24] A prospective pediatric population study found a relatively specific pattern of childhood developmental disturbance consisting of impairments in neuromotor, receptive language, and cognitive development that were seen only among children later diagnosed as having schizophreniform disorder.[25] Developmental impairments also predicted self-reported psychotic symptoms at age 11 years. These impairments were termed *pan developmental dysmaturation*, more consistent with the findings of the (adult-onset) schizophrenia cohort studies consisting primarily of developmental lags. These too are common in the National Institute of Mental Health (NIMH) COS cohort, and 39 patients (39%) exhibited one or more of these non-PDD developmental disturbances. These data are shown in Tables 1, 2, and 3.

Thus, two sets of somewhat different early developmental disturbances are seen. One set includes members of the COS sample who met criteria for a *DSM-IV-TR* PDD-NOS (n = 28) and another set (n = 39) who had language, motor, or social impairments stemming from impulsivity or anxiety. Of note, the PDD + COS subjects' demographic patterns follow those reported in the literature for PDD generally because they are primarily male (p = .04) and non–African American (p = .02). All had failure to develop reciprocal social behaviors as