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

Judith Rapoport, M.D., **Alex Chavez, B.S.**, **Deanna Greenstein, Ph.D.**, **Anjene Addington, Ph.D.**, and **Nitin Gogtay, M.D.**
Child Pychiatry Branch, National Institute of Mental Heath (NIMH), Bethesda, MD

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 NIMH (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 Pervasive Developmental Disorder in 30%-50% of cases. Epidemiologic 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 (micro-deletions or duplications) are shared by schizophrenia and autism.

Conclusion—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.

Keywords

Schizophrenia; Childhood; Autism

Introduction

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, 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 utility 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.

Correspondence: Nitin Gogtay, M.D. Child Psychiatry Branch, Building 10, Rm 3N202, 10 Center Drive, MSC 1600, Bethesda, MD 20892, Tel: (301) 435 4494, Fax: (301) 402 7160, Email: gogtayn@mail.nih.gov.

Phenomenology of COS in relation to Autism/PDD

COS is defined as onset of psychosis before age 13 and is a rare and severe form of schizophrenia. Onset is usually after age 7, 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 three years of life. The broader category, Pervasive Developmental Disorder (subsuming Autism, Rett Syndrome, Asperger's Syndrome and Childhood Disintegrative Disorder) has a residual category, PDD-NOS (not otherwise specified), 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 hopefully 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) [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. in a groundbreaking study of 33 British children, of whom 12 had onset before age 13.[16] In addition, the researchers stressed the severity and frequency of prepsychotic developmental disorders in COS.

The observations of Kolvin and colleagues 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 report from the UCLA 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 report, the UCLA group has examined an additional 52 COS probands using the K-SADS-E structured diagnostic interview [16]. Of these, 28 (55%) had histories meeting DSM III-R criteria for autism or PDD (Dr. Robert Asarnow personal communication May 2008). The largest study to date of COS now includes 101 children and adolescents with onset of DSM IV defined schizophrenia before age 13. Of these, one (1%) met criteria for comorbid autism, 2 (2%) for Asperger's Syndrome and 25 (25%) for PDD-NOS, making for a total of 28% with comorbid autism or autism spectrum disorder (ASD) (unpublished data, Nitin Gogtay M.D.). These diagnoses were made by both screening questionnaire and agreement by two board certified child psychiatrists in recognition of the pitfalls of diagnosis by screening instrument alone [19]. PDD-NOS was a persisting and stable diagnosis in these cases, with onset in the first five years of life, while the onset of psychotic symptoms occurred typically 3-5 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 22-24]. 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. 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 NIMH COS cohort, and 39 patients (39%) exhibited one or more of these non-PDD developmental disturbances.

These data are shown in Table I.

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, as they are primarily male ($p = 0.04$) and non-African American ($p = 0.02$) All had failure to develop reciprocal social behaviors as their defining common characteristic, which was temporally and clinically distinct from their later development of psychotic symptoms.

In the ongoing NIMH study to date, 263 family members have been evaluated with structured interviews and parents were administered the Autism Screening Questionnaire (ASQ) for siblings. The average ASQ score was higher among unaffected siblings of children with comorbid PDD/COS than among unaffected siblings of COS patients without PDD, as consistent with previous reports [26]. This finding implies that PDD symptoms are heritable and may serve as trait markers even in unaffected individuals.

Several models have been proposed to account for psychiatric comorbidity[27]. As Krueger and Markon have reviewed, comorbidity may reflect causality between the conditions, alternate forms of the same disorder, unique subgroups that share both attributes, or different manifestations of a single or correlated underlying liability. The only one of these models with some research-based links to schizophrenia comes from a subgroup of PDD–NOS defined as Multiple Complex Developmental Disorder (MCDD). MCDD is observed in children ages 12-18 years and is characterized by impaired sensitivity to social stimuli, as well as thought disorder, bizarre and disorganized thinking, inappropriate affect and mood lability [12, 14]. Although less disturbed than children with autism with respect to social interaction, communication and stereotyped and rigid behaviors, children with MCDD were more disturbed with respect to flagrant thought disorder, anxieties and aggression[14, 28]. The diagnosis of very early onset schizophrenia was considered by the initiators of the MCDD construct, but the relative frequency of the MCDD group suggested it was a broader group from which schizophrenia might emerge. Moreover, follow up studies of MCDD indicate that by adolescence and young adulthood, 22% and 64% respectively, convert to (some form of) psychosis[29] or resembled subjects in psychosis high-risk groups [13]. The MCDD constellation remains relatively ignored by clinicians in the United States as almost all work on this has been carried out in the Netherlands.

I. Brain Imaging

The growing literature on brain imaging abnormalities in COS will not be reviewed here. In autism, the best agreed upon finding is increased head size/total brain volume seen in the first three years of age based on cross sectional studies [30, 31]. This brain overgrowth that precedes or coincides with the appearance of signs and symptoms of autism suggests that it may be a fundamental aspect of the pathologic process[32]. There remains controversy, however, as to whether the brain anatomic developmental curves for autistic and control groups remain parallel or converge in later years [31, 33] because at later ages the findings are inconsistent[34] The diffuse network of brain regions affected has shifted attention to more widespread mechanisms at the neuronal level.

There is little overlap between the reported anatomic brain abnormalities in autism and COS. COS studies show a striking loss of cortical gray matter (GM) in early ages that progresses through adolescent years, which appears to be an exaggeration of the normal pattern of cortical brain development [35, 36]. This global GM loss in COS also declines with age, eventually circumscribed only to prefrontal and superior temporal cortices resembling the typical adult schizophrenia pattern seen by age 24 [37]. The reason for what on first glance looks to be "normalization" of COS brain scans with age, is that the healthy controls "catch up" with the patients with respect to late adolescent cortical thinning.

Although limited by lack of prospective and fetal studies, at this point it appears that in autism there is an acceleration or excess of early postnatal brain development (1-3 years), whereas in COS there is exaggeration of the brain maturation processes of childhood and early adolescence (10-16 yrs). Both could be seen as "increased gain" of general developmental processes, albeit at different stages; both patterns could also be seen as an abnormal "shift to the left" with respect to age compared to normal brain development, with autism showing initial overgrowth and COS showing greater "pruning down" of the cortex in early and middle parts of the trajectory; both accelerations normalizing with age.

Genetics

There are numerous direct and indirect genetic data linking autism and schizophrenia[38-41]. Specifically, various candidate gene and linkage studies and expression studies utilizing postmortem brain samples, as well as studies of copy number variants (CNVs) in schizophrenia, have yielded a handful of genetic associations that have also been reported for autism [42, 43]. Large alterations in chromosme region or number are increased in COS[44]. Genomic microduplications and deletions or CNVs underlie many serious illnesses and neurodevelopmental syndromes[45]. Selected results representing these emerging overlapping genetic findings are summarized in Table II, and given that a comprehensive review of this rapidly growing literature is beyond the scope of this paper, we highlight some of the most compelling findings below.

The VCFS (chromosome 22q11) deletion shows high rates of childhood autism spectrum disorders (30 of 60: 50%) and psychotic symptoms (16 of 60: 26.7%) [42]. Although screening of 103 autistic subjects showed no cases of 22q.11 deletion [46], given that the rate of 22q11 deletion in the general population (1/4000) and in schizophrenia (0.4%) is low, this negative finding is not surprising. Hemizygous deletion in the 22q11 region is a highly nonspecific risk factor for a number of neurodevelopmental disorders (speech and language particularly) as well as other disorders such as OCD. Nonetheless, the 22q11 deletion is the third largest genetic predictor of schizophrenia (25 times the population risk), behind having an affected monozygotic twin or two affected parents. The rate of 4% observed in the NIMH COS cohort is significantly higher than the 0.4% observed in unselected adult onset samples[47].

The approximately 500kb microdeletion and microduplication event on 16p11.2 now reported in approximately 1% of cases of autism[43, 48, 49], some *de novo* and some inherited, was observed also in 2 of the NIMH COS patients. It was also reported in a family with siblings with mild mental retardation [50]. Like the region on 22q11, CNVs in the 16p11.2 region may prove to be a similarly nonspecific risk factor for various neurodevelopmental disturbances. CNVs in both the 22q11 and 16p11 regions will likely be among the more commonly observed risk factors in that the genomic architecture in these regions are flanked by areas of segmental duplications which are more prone to genomic rearrangements during meiosis.

Deletions, disruptions and missense mutations in Neurexin 1 (NRXN1) have been reported recently in several cases with autism[48, 51-54], and two cases with schizophrenia [43, 55, 56].

Altogether, these findings provide evidence that rare (and common) variants at the NRXN1 locus likely predispose individuals to autism, schizophrenia, or both.

Finally, several recent publications have reported increased rates of rare CNVs in different samples of schizophrenia and autism[48, 57, 58]. Interestingly, within our COS sample, the presence of a large chromosomal abnormality and/or rare CNV that disrupts a gene was much more common among the COS patients with prior history of any developmental disturbance: 28 of 63 (44%) as compared to 4 out of 29 (14%) with a "clean" history of premorbid development (p=0.005). Taken together, rare structural variants may account for a large proportion of the variance in disease etiology and are likely to uncover many new candidate regions and genes.[42, 59, 60]

While there are intriguing genetic links between schizophrenia and autism spectrum disorders, these do not support any model in themselves, except to suggest the probability that many individually rare genetic abnormalities affect common pathways containing hundreds of genes that effect neuronal development and regulation. The commonality of several genes for different syndromes, however, presents a chance to link the disorders at a molecular level. Several fundamental questions of mechanism remain to be explored. For example, genetic pleiotropy (multiple phenotypic effects from a single gene) is well established in neurodevelopmental disorders [61], leaving open the question whether different mutations in the same genes, modifying genes, environmental influences, or perhaps stochastic events, determine which disorder is manifest.

Discussion

The subtle developmental delays that are seen in large prospective cohort studies of adult onset schizophrenia are seen in exaggerated form in childhood onset cases[10, 62]. Early onset schizophrenia has also shown strong comorbidity with pervasive developmental disorders in two of the three large studies in which this was measured systematically, although until now this has received less attention. Comorbidity is the most straightforward way to describe such findings, but as noted above, this association does not imply any one model, and both causal or independent associations are possible.

While associations between these conditions are not striking to the treating clinician, there are new data to indicate that in fact autism and schizophrenia are more likely to be seen in the same patients [63] and families. A link between the two disorders has been suggested in a handful of studies in adult populations [13, 64-66], and epidemiologic and larger patient-population data show familal schizophrenia-like psychosis to be a risk factor for (narrowly defined) autism [67]. That these findings are not seen in clinical practice may be explained by the heterogeneity of these populations, which dilutes the effects in smaller samples. Alternately, under the current diagnostic hierarchy (in which autism and schizophrenia are mutually exclusive) if a person develops autism as a young child, they may be unlikely to receive a diagnosis of schizophrenia later on, even if new symptoms emerge.

Various explanations for a schizophrenia-autism association are possible. Developmental disorders per se may be risk factors for schizophrenia[68], and indicators of early fetal disturbance such as minor physical anomalies have been found increased in both autism and schizophrenia[69]. It is of interest that the rare chromosomal abnormalities and/or copy number variants found in the NIMH COS population[58] are most common in patients with either the "delay" type or the PDD premorbid disturbances than in those with "clean" prior histories and may be related more to the early developmental disturbance than to schizophrenia per se. This is being tested in a current study.

We posit a pathophysiologic link with disturbance in brain developmental timing for both disorders at ages approximating the onset of these disorders. The abundant genetic links do not support a model in which one disorder causes the other. Since each disorder exists primarily in separate form, i.e. most cases of autism\PDD or schizophrenia are not comorbid, these findings are most likely to help sort out the almost certain heterogeneity for both disorders that has been problematic for genetic research. The nonspecificity of the identified variants also provides an opportunity for understanding the disorders at a molecular level. If the same genes, for example, cause both disorders, this could be because of various genetic or environmental modifying factors producing a different timing or mode of action that in turn leads to a particular phenotype. Alternatively, if different genes are implicated in the same phenotype then there would be great interest in seeing what underlying neurobiological pathways might in common be affected by these genes. These strategies will be of crucial importance for future clinical neuroscience research.

In summary, two disorders that have been distinguished since DSM-III, are again linked using newer research methods. It is likely that genetic studies in childhood disorders will increasingly implicate patterns of brain developmental disturbance leading us to group disorders in novel ways. This is being tested in a current study of non schizophrenic children with similar developmental delays. It is anticipated that this group too will be enriched with CNVs and it may be that these developmental delays are in themselves a risk for psychosis at any age. Epidemiologic studies of schizophrenia need to more carefully screen relatives for PDD/ASD and a follow up of larger samples of patients with autism participating in genetic studies would be particularly informative in terms of the likelihood of psychosis onset, and predictors of this outcome.

There are no immediate clinical implications for these findings. Shortcomings of DSM IV include frequent use of NOS diagnoses and high rates of comorbidity. The data presented for PDD-NOS and COS in this review show how clinical phenotypes do not relate simply to genetic risk factors. The linking of autism and schizophrenia in family studies does not fit with typical clinical experience. An immediate practical implication of this report is that training of adult psychiatrists needs to include the diagnosis of adults with autism and autism spectrum/PDD to better discriminate milder forms of autism spectrum and schizophrenia spectrum disorders for future family studies. Finally, sorting out what exactly we mean by genetic and syndromal heterogeneity will be a cornerstone of future clinical neuroscience.

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Table I

Table I (a). ASD and Non-ASD developmental disorders in 97 patients with COS in the NIMH cohort*

Developmental Disorder	Count
ASD Diagnosis	28
PDD-NOS	24
Asperger	1
Autism	3
No-ASD diagnosis, but with a prior Developmental Disorder	39
Language Development Problems	29
Rhythm	0
Articulation	12
Comprehension	11
Production	14
Mutism	2
Speech Delay	19
Motor Developmental Problems	24
Tics	1
Repetition	8
Clumsiness	10
Motor Delay	15
Failure to develop age-appropriate social behaviors	13
No ASD or developmental language, motor or social disorder (ASD type)	30

Table I (b). Characteristics of PDD-NOS in patients with COS in the NIMH cohort (n=101)

Impaired Social Interaction	
Impaired ability to initiate or sustain social conversation	58%
Social withdrawal/poor social skills	58%
No age-appropriate friendships	42%
Impaired cooperative play	47%
Problems with imaginary play	21%
CHILDREN WITH ONE OR MORE SOCIAL IMPAIRMENT	100%

Table I (a). ASD and Non-ASD developmental disorders in 97 patients with COS in the NIMH cohort*

Developmental Disorder	Count
CHILDREN WITH TWO OR MORE SOCIAL IMPAIREMENTS	74%
Verbal/nonverbal Communication	
Incorrect pronoun use	16%
Language delay	37%
Lack of facial expressions	53%
Poor nonverbal communication	16%
Idiosyncratic language	47%
CHILDREN WITH ONE OR MORE COMMUNICATION IMPAIRMENT	84%
CHILDREN WITH TWO OR MORE COMMUNICATION IMPAIRMENTS	53%
Restricted, Repetitive and Stereotyped Behavior Patterns	
Inflexible adherence to routines and rituals	42%
Repetitive movement	37%
Encompassing preoccupation / Restricted interests	47%
CHILDREN WITH ONE OR MORE BEHAVIOR IMPAIRMENT	74%
CHILDREN WITH TWO OR MORE BEHAVIOR IMPAIRMENTS	37%
Echolalia	53%
CHILDREN IMPAIRED IN ALL THREE CATEGORIES	58%
CHILDREN IMPAIRED IN TWO OR MORE CATEGORIES	100%
SOCIAL & COMMUNICATION IMPAIRMENT	84%
COMMUNICATION & BEHAVIOR IMPAIRMENT	58%

Table I (a). ASD and Non-ASD developmental disorders in 97 patients with COS in the NIMH cohort*

Developmental Disorder	Count
SOCIAL & BEHAVIOR IMPAIRMENT	74%

Table I (c). Childhood Onset Schizophrenia [70]: PDD vs. Non-PDD

Clinical and Demographic Characteristics

	PDD (n=28) Mean (SD)	Non-PDD (n=73) Mean (SD)	t (df=94-68)	p
ASQ Score	18.67 (7.85)	4.12 (4.35)	11.08	<0.001
SES	54.73 (29.51)	63.88 (29.76)	1.34	0.18
Age of Psychosis Onset	9.76 (2.18)	10.35 (1.94)	1.27	0.21
IQ	79.33 (15.50)	74.10 (18.84)	1.06	0.29
GAS	32.84 (12.18)	33.29 (10.84)	0.17	0.86
Sex - % male	71%	52%	$X^2_{(df=1)} = 3.11$	0.08
Race - % AfrAmer:Oth:Cauc	14%:21%:64%	33%:26%:41%	$X^2_{(df=2)} = 4.99$	0.083

*97 out of 101 with complete data

ASD-Autism Spectrum Disorder, PDD-NOS- Pervasive Developmental Disorder Not Otherwise Specified.

SD- Standard Deviation, dF- Degrees of Freedom, X^2 – chi squared, ASQ-Autism Screening Questionnaire, SES- Socio-Economic Status, GAS – Global Assessment of Severity, AfrAmer-African American, Oth- Other, Cauc-Caucasian

Table II

Genomic regions and genes associated with both autism and schizophrenia

Chromosome	Gene(s)	Schizophrenia data	Autism data	Comment
22q11.2 (3 Mb hemizygous deletion)	> 50	Many studies + 4 cases COS, COS>AOS	30%PDD[71]	Nonspecific risk but both increased; [71]
16p11.2	24	500kb duplication in 2% of NIMH COS cohort[58]	1% of 5 autism populations have microdeletion or duplication[43, 48, 49]	COS CNVs both inherited; one case has comorbid PDD[58]
2p16.3	NRXN1	MZ twins concordant for COS with deletion; affected sib pair with inherited deletion[56, 58]	Deletions, disruptions, and mutations identified in several cases[48, 51, 52, 54, 72]	Growing evidence for both autism and COS; different regions of gene affected
Xq28	MECP2	1 case reported with mutation[73]	Rett's gene; autism Increased	Strong data for autism
1q42	DISC1	Disrupted gene identified in single large multiplex pedigree; numerous association studies[74]	Single association study with same haplotypes reported for schizophrenia[60]	Strong evidence for schizophrenia
7q35-q36.1	CNTNAP 2	Deletions in 2 unrelated patients[75]	Linkage, association, and gene expression in autism [76, 77]	Growing evidence in both schizophrenia and autism
7q22.1	RELN	Decreased mRNA in postmortem brain linkage[70] & association with working memory[78, 79]	Many linkage, association, and functional studies [40, 80]	
2q31.1	GAD1 (encodes GAD67)	10 studies show decreased GAD67 in schizophrenia postmortem brain[81]; 2 studies show association[82, 83]	Protein reduced in postmortem brain[84, 85]; multiple studies report linkage in region	

COS- Childhood Onset Schizophrenia, AOS – Adult Onset Schizophrenia, CNV – Copy Number Variation, MZ – Monozygous, mRNA – messenger RNA