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Summary of Findings

	Grade of Evidence
Epidemiology	C
Age of onset	C
Presentation	C
Course and progression	D
Suspected neuropathology	D
Suspected neurochemical abnormalities	D
Genetic factors	D
Other risk factors	D
Treatment	D

Introduction

Psychosis has carried different meanings since its introduction more than 150 years ago (Beer, 1996). Others have described the social and intellectual contexts that have shaped the concept of psychosis at different times and places (Berrios, 1987; Beer, 1995). Modern classification systems incorporate psychosis in various disorders as a serious disturbance in ''reality testing'' expressed as hallucinations, delusions, thought disturbance, disorganized behavior, or catatonia. Recent advances in neuroscience hold the promise of elucidating the brain mechanisms of psychosis and finding improved antipsychotic treatments. Fujii & Ahmed (2004) have recently proposed conceptualizing psychosis as a neurobiological syndrome with its own pathophysiology and treatment algorithm regardless of etiological factors and underlying diagnoses. This view has heuristic value

for refining current classification systems, focusing research, and tailoring treatments on an individual basis. In this chapter, we report on the characteristics of psychosis superimposed on autism. First, some definitions of autism are presented.

In DSM-IV classification, autism covers the group of the Pervasive Developmental Disorders (PDDs) (American Psychiatric Association, 1994), i.e., Autistic Disorder, Asperger Disorder, Childhood Disintegrative Disorder, Rett's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD NOS). The PDDs are behavioral syndromes with a broad range of severity and characterized by lifelong impaired communication, impaired social interactions, and repetitive interests and behavior (Wing & Attwood, 1987; Rapin, 1997). DSM-IV diagnostic criteria of AD, AsD, and CDD, are shown in Table 12.1. PDD NOS is a residual category that is used to classify cases that do not satisfy full criteria of AD, AsD, or CDD. Rett's Disorder is also listed among the PDDs. However, a causal genetic defect on the X chromosome has been identified

Table 12.1. DSM-IV criteria of selected Pervasive Developmental Disorders (PDDs).

	Autistic Disorder (AD)	Asperger Disorder (AsD)	Childhood Disintegrative Disorder (CDD)
Unique features			
Age of onset	Onset before age 3	-	Onset before age 10
Development	Clinically significant delay in language, cognitive development, self-help skills, adaptive behavior, or curiosity about the environment	No clinically significant delay in language, cognitive development, self-help skills, adaptive behavior, or curiosity about the environment	At least two years of apparently normal development
Regression	Regression in 30%	No regression	Massive regression
Abnormal communication*	+	-	+
Shared features	Qualitative impairment in social interaction (e.g. impairment in nonverbal behaviors, failure to develop peer relationships, impaired expression of pleasure in other people's happiness, lack of social or emotional reciprocity) Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, including motor stereotypies and mannerisms		

*qualitative impairments in communication (e.g. delay or lack of spoken language, inability to initiate or sustain a conversation, stereotyped and repetitive use of language, lack of varied make-believe play)

(Amir *et al.*, 1999). In this report, the PDDs, with the exclusion of Rett's Disorder, are collectively referred to as autism.

The prevalence of autism is 0.1–0.2% (Fombonne, 2003) for narrow diagnosis of autistic disorder and 0.6% for less restrictive diagnoses. Males predominate with approximately a four times higher rate than in females. Prevalence rates have been said to increase, but changes in diagnostic methodology and ascertainment strategy complicate comparisons across time (Fombonne, 2003). The diagnosis of autism is made clinically on the basis of behavioral symptoms that are not apparent until the ages of two to three, at least in classic autism (AD). Although medications can relieve symptoms in some autistic people, there is presently no known cure. The possibility that various metabolic and genetic factors may play a role in the occurrence of autism is a subject of intense research. About one third of autistic people develop some type of epilepsy (Gillberg, 1991b). Increased rates of seizure disorders (Deykin & MacMahon, 1979; Gillberg, 1991b) and worsening of autistic symptoms or overall behavioral deterioration (Gillberg & Schaumann, 1981; Gillberg, 1991a) have been reported around puberty. Cognitive deficits are present in more than half of autistic people (Rutter, 1983).

Epidemiology

Reviewing psychosis in autism may appear a daunting task at first sight, or an easy one, depending on one's perspective, because of the following issues. Leo Kanner separated autism from early-onset psychosis or childhood schizophrenia in 1943 by stating that the condition he described "differed markedly and uniquely from anything reported so far (Kanner, 1943)." Subsequent studies on childhood psychoses have highlighted differences in cardinal symptoms (e.g. absence of hallucinations in autistic children), course of illness, intellectual functioning, sex distribution, social class, brain abnormalities, age of onset, and family history of schizophrenia (Rutter, 1972). Studies support that autism and schizophrenia cannot often be diagnosed in the same patient (Volkmar & Cohen, 1991). Overall, the evidence seems overwhelming that psychosis does not occur often in people with autism justifying the separate classification of autism since DSM-III. However, there continues to be a provision in DSM-IV (American Psychiatric Association, 1994) that schizophrenia can be diagnosed in individuals with autism who develop characteristic features of schizophrenia with prominent delusions or hallucinations for one month. In the next paragraphs, those few studies that have assessed psychotic symptoms in autism will be reviewed.

Modern criteria of psychosis and schizophrenia have been applied in a few reports of people with autism, especially of the high-functioning type, who

develop chronic psychotic disorders similar to schizophrenia (Petty *et al.*, 1984; Clarke *et al.*, 1989; Kurita, 1999). Petty *et al.* (1984) described the development, by school age or early adolescence, of psychotic symptoms including hallucinations, delusions, and thought disorder satisfying formal criteria of schizophrenia in three children who had been diagnosed with autism during the first years of life. All three cases developed communicative speech and had borderline or normal IQ. The authors note that most autistic children do not develop communicative speech and have IQs in the mentally retarded range, precluding the assessment of hallucinatory experiences, paranoia, and thought disorder, and thus a formal diagnosis of schizophrenia or other psychotic disorder.

Clarke *et al.* (1989) reported two adult cases with Asperger Disorder, one case with atypical autism (PDD NOS) and one case with classic autism, all developing superimposed affective and non-affective psychotic conditions. A fifth case was previously diagnosed with schizophrenia based on enduring obsessional behavior and withdrawal but was rather thought to have Asperger Disorder given the absence of hallucinations or delusions. The authors warn that PDDs may be complicated by psychotic illnesses presenting in adulthood. Conversely, PDDs may be mistaken for psychosis.

Volkmar & Cohen (1991) conducted a chart review on 163 adolescents and adults with well documented histories of autism. About half of the patients were largely or entirely mute. DSM-III-R criteria for a lifetime diagnosis of schizophrenia were applied. Only one patient satisfied unequivocal criteria for schizophrenia, according to their assessments. Around 15 years of age, this male patient started complaining of auditory and occasional visual hallucinations. His speech became difficult to follow and he exhibited catatonia on at least one occasion. The patient had a strong family history of schizophrenia. Other patients had fluctuating bizarre interests and preoccupations that were considered part of autism. No other patients presented with hallucinatory experiences. The authors admit that hallucinations and delusions could not be assessed in the non-verbal patients. It was concluded that within the limitations of a chart review and inadequacy of DSM-III-R criteria of schizophrenia in nonverbal autistic populations, schizophrenia was not more common in autism than in the general population.

There is also evidence that catatonia may be common in adolescents and young adults with autism (Dhossche *et al.*, 2006b). Only two systematic studies of catatonia in autism have been reported (Wing & Shah, 2000; Billstedt, Gilberg & Gilberg, 2005). They suggest that catatonia-like features are present in about one of seven (12–17%) adolescents and young adults with autism and constitute an important source of impairment in this population. In a recent study, 17% of a large referred sample of adolescents and young adults with autism satisfied

modern criteria for catatonia (Wing & Shah, 2000). Thirty persons with autism aged 15 or older met criteria for catatonia. Classic autistic disorder was diagnosed in 11 (37%), atypical autism in 5 (17%), and Asperger disorder in 14 (47%). None of those under the age of 15 had the full catatonic syndrome, although isolated catatonic symptoms were often observed. In the majority of cases, catatonic symptoms started between the ages of 10 and 19. Five individuals had brief episodes of slowness and freezing during childhood, before age 10. Schizophrenia was not diagnosed in any of these patients.

In a report based on a population study (Billstedt *et al.*, 2005), 13 (11%) of 120 autistic individuals between the ages of 17 and 40 (mean age 25.5 years) had clinically diagnosed catatonia with severe motor initiation problems. Another 4 had several catatonic symptoms but not the full syndrome. Autistic disorder was diagnosed in 8 of the 13 people with catatonia; atypical autism was diagnosed in the remaining 5. The proportion of those with autistic disorder in whom catatonia was diagnosed was 11% (8/73); 14% of those with atypical autism (5/35) had catatonia.

An increasing number of case reports and case series of catatonia in autism that satisfy *DSM* criteria for catatonia have been published over the last 15 years (Realmuto & August, 1991; Dhossche, 1998; Ghaziuddin, Quinlan & Ghaziuddin, 2005; Dhossche *et al.*, 2006b).There is considerable overlap of psychomotor symptoms between the two disorders, e.g. muteness, echolalia, stereotypical movements, and other psychomotor peculiarities (Stoppelbein, Greening & Kakooza, 2006). The progression of autistic symptoms into full-blown catatonia has been described in adolescent cases (Dhossche, 1998).

Age of onset

Hallucinations, delusions, and catatonia have only been described in post-pubertal patients with autism (Petty *et al.*, 1984; Clarke *et al.*, 1989; Realmuto & August, 1991; Dhossche, 1998; Kurita, 1999; Ghaziuddin *et al.*, 2005). In the catatonia study of Wing & Shah (2000), all of those with catatonia were aged 15 or older. None of those under age 15 had the full syndrome although isolated catatonic symptoms were often observed. In the majority of cases, catatonic symptoms started between 10 and 19 years of age. Five individuals had brief episodes of slowness and freezing during childhood, before age 10.

Presentation

Autistic people can develop typical symptoms of psychosis, including hallucinations, delusions, thought disorder, and catatonia. Reliance on self-report is

problematic given the cognitive and verbal deficits in this population. A comprehensive clinical psychiatric evaluation should be conducted to diagnose any type of psychosis in people with developmental disorder. There are no widely accepted standardized diagnostic interviews for psychotic disorders in autism or mental retardation, to our knowledge. It is unknown if current catatonia rating scales are applicable in people with autism. Modified criteria for catatonia in autism allowing for baseline levels of stereotypies, echolalia, and other catatonic symptoms have recently been published (Dhossche, Shah & Wing, 2006a), but these need further testing.

High rates of atypical symptoms of psychosis or negative symptoms in autistic people have been reported, but their significance is often unclear. It is unknown if such individuals are prone to develop psychosis or if those symptoms are more related to autism or the frequently associated cognitive deficits. Next, we will review three studies that have directly compared individuals with autism and schizophrenia. Future studies are warranted to show the significance of these findings.

Rumsey, Andreasen, & Rapoport (1986) examined 14 adults with DSM-III diagnoses of autism (mostly high-functioning) and used comparison groups diagnosed with schizophrenia and mania. Autistic individuals had a high incidence and severity of poverty of speech, poverty of speech content, perseveration, and affective flattening. They showed significantly less derailment, illogicality, and ''positive thought disorder'' than schizophrenic or manic patients did. Deficit symptoms, such as negative thought disorder and affective flattening, were similar between autistic and schizophrenic patients.

In another study (Dykens, Volkmar & Glick, 1991), thought disorder was assessed in 11 high-functioning autistic young adults utilizing objective ratings and projective tests. Autistic adults showed more poverty of speech than schizophrenic individuals did. No illogicality was manifest in any of the autistic subjects. On the Rorschach's Schizophrenia Index, no differences were found between autistic and schizophrenic groups suggesting a high incidence of poor reality testing, compromised perceptual accuracy, perceptual distortions, and cognitive slippage in both groups, at least during tests of free-association to stimuli. The authors interpret their findings as evidence of shared features of thought disorder between autism and schizophrenia, but confirm that the presence of similar features does not imply continuity of the disorders.

Finally, symptoms of 14 males with DSM-III-R autism and 14 males with DSM-III-R paranoid schizophrenia were compared in a recent study (Konstantareas & Hewitt, 2001). Instruments for diagnosis and assessment included a structured clinical interview, a schedule for positive symptoms, and a schedule for

negative symptoms. None of the men with paranoid schizophrenia met criteria for autism. Seven of those with autism met criteria for schizophrenia, disorganized type, with mainly negative symptoms (affect flattening, alogia, attentional difficulties). Although many subjects with autism made statements that could be interpreted as delusional (''people pick on me'') or grandiose (''I am the smartest guy around''), these were not seen as psychotic since they could be explained reasonably by living environment and/or cognitive/emotional immaturity.

Course and progression

Longitudinal studies of psychosis or catatonia in autism providing information on clinical risk factors and prodromal signs are not available in the literature. In the case reports that were discussed earlier, the psychotic disorder seemed stable and chronic. Larger studies are needed to confirm this.

In the study of Wing & Shah (2000), obsessive-compulsive and aggressive behavior preceded catatonia in some. Visual hallucinations or paranoid ideas were occasionally reported, but no diagnosis of schizophrenia could be made. Referred patients with catatonia were significantly more likely than patients without catatonia to have had impaired language and passivity in social interaction before the onset of catatonia.

Suspected neuropathology

The biological basis of autism and psychosis remains unknown. There are no published accounts of neuropathological findings of psychosis in autism. Developmental processes have been recognized as key to understanding autism (Belmonte *et al.*, 2004). Involvement of different brain areas is widespread and includes the cerebellum, brain stem, frontal lobes, parietal lobes, hippocampus, and amygdale (Palmen *et al.*, 2004).

There have been a few attempts to describe a coherent anatomical or pathophysiological theory of autism. There is some variability between those hypotheses depending on whether the authors considered social, cognitive, or affective abnormalities as the primary deficit in autism. For example, Maurer and Damasio (1982) using anatomical and etiological inferences based on a wide range of autistic symptoms concluded that dysfunction of phylogenetically older parts of the frontal and temporal lobes best accounted for the clinical manifestations of autism. Gualtieri (1991) on the other hand noted similarities between autism and the Klüver-Bucy syndrome, a syndrome described in rhesus monkeys after bilateral temporal lobectomies. This suggested to him that deep temporal and frontal lobes may be involved.

Of some interest is the role of the cerebellum in autism and psychosis. One of the most consistent findings in autism is the selective vulnerability of the cerebellar Purkinje cell (Ritvo *et al.*, 1986; Kemper & Bauman, 1993). Nine brains from patients with well documented autism (six children and three young adult males) have been studied systematically (Bauman, Filipek & Kemper, 1997). All brains showed a marked reduction of Purkinje cells and a variable decrease in granular cells throughout the cerebellar hemispheres. There was no significant gliosis and no retrograde of inferior olivary neurons, suggesting that the abnormalities were acquired early in development at or before the 30th week of gestation. The cerebellum remains an understudied yet important area in both disorders. Evidence for cerebellar involvement in psychosis is limited to imaging studies given the limited number of neuro-anatomical studies. Reductions in cerebellar volume have been reported in chronic schizophrenia (Okugawa, Sedvall & Agartz, 2003), catatonic schizophrenia (Joseph, Anderson & O' Leary, 1985; Wilcox, 1991), and autism (Courchesne *et al.*, 1988).

Suspected neurochemical abnormalities

Neurochemical studies have not been done in people with comorbid autism and psychosis (or catatonia). It is possible that some abnormalities in metabolism of serotonin, dopamine, GABA, and other transmitter molecules are shared between autism and psychosis (and catatonia). However, further speculations are futile at this stage.

Genetic factors

Although a medical or neurological disorder is found in a small proportion of cases with autism, most cases are idiopathic. In those cases, a strong genetic component is likely but the pattern of inheritance is complex. Twin studies show a 60–91% concordance rate in monozygotic twins, depending on whether a narrow or broad phenotype is considered. There are no observations of concordance in dizygotic twins under narrow phenotypic definition and a low concordance (10%) under broader phenotypic definition (Bailey *et al.*, 1995). Sibling recurrence rate has been estimated to be 4.5%. This pattern of sharply increasing risk for first-degree relatives and monozygotic twins relative to the population prevalence does not fit a simple dominant or recessive model, but indicates the involvement of multiple genes interacting with one another to lead to disease susceptibility. No definite susceptibility genes for autism have been discovered, despite the encouraging possibility of candidate regions on chromosomes. Molecular genetic

studies have narrowed down certain candidate regions, with two regions being identified in several (but not all) studies. These are 15q11-13, near the $GABA_A\beta_3$ receptor subunit gene ($GABRB_3$) and a second one on 17q11.2, near the serotonin transporter gene (SLC6A4) (Veenstra-Vanderweele, Christian & Cook, 2004).

There are also a few studies that suggest that there are shared genetic risk factors between autism and certain types of psychosis. First, DeLong (1994) found increased rates of affective disorder, particularly bipolar disorder, in family members of autistic probands. In a sample of 40 autistic children and adolescents, without neurological disease, from 37 families, he reported a family history for bipolar disorder in 29 (78%) families. In another family study (Piven *et al.*, 1991), the rate of major depressive disorders was higher in parents of autistic probands than in parents of non-autistic probands.

Second, parental schizophrenia-like psychosis and affective disorder were significant risk factors for autism in offspring in a nationwide Danish case-control study of 698 children diagnosed with autism between 1972–1999 (Larsson *et al.*, 2005). Relative risks were 3.44, 95% CI 1.48–7.95 and 2.91, 95% CI 1.65–5.14, for parental schizophrenia-like disorder and affective disorder respectively. Other significant variables were breech presentation (RR = 1.63), low Apgar score at 5 minutes (RR = 1.89), and gestational age at birth less than 35 weeks (RR = 2.45). Weight for gestational age, parity, number of antenatal visits, parental age, or socioeconomic status were not significant risk factors. These findings support that perinatal factors and parental psychopathology are associated with risk of autism. It remains an open question whether perinatal adversity was due to environmental factors, factors associated with autism in the fetus, or a combination of these and possibly other (unmeasured) variables.

Finally, it has also been noted that about 40% of children with onset of schizophrenia before age 10 had symptoms of autism during infancy and early childhood (Watkins, Asarnow & Tanguay, 1988). In a sample of children with childhood-onset schizophrenia (COS) (before their 13^{th} birthday), 19 of 75 (25%) of children with COS had a lifetime diagnosis of PDD (Sporn *et al.*, 2004). Two siblings of children with COS were diagnosed with classic autism (AD). This suggests a familial link between certain types of autism and childhood-onset schizophrenia.

Future family psychiatric studies assessing psychotic disorders, including catatonic subtypes, as risk factors for autism are warranted. Previous studies have typically not separated out catatonic subtypes of schizophrenia, affective disorder, or other psychotic disorders. The only genome scan reporting on catatonic schizophrenia gave a linkage signal in the region 15q11.2-q21.1

(Stöber *et al.*, 2000). This region has also been linked with autism (Cook *et al.*, 1998; Menold *et al.*, 2001; Nurmi *et al.*, 2003) and bipolar disorder (Papadimitriou *et al.*, 1998; Otani *et al.*, 2005). Finding shared genes for autism, catatonia, and bipolar disorder would support the hypothesis of common biological pathways between these disorders. GABA receptor subunit genes located on 15q11-13 warrant special attention as candidate shared genes (Dhossche, 2004).

Other risk factors

It is conceivable that other risk factors such as adverse life events or medical/neurological illnesses may precipitate psychosis in some individuals with autism as in individuals without autism or any other developmental disorder. However, there are no systematic studies in this area. The clinician evaluating a possible psychotic episode should inquire about sudden psychosocial changes or adverse events, and rule out medical/neurological illnesses associated with psychosis.

Treatment

There are no controlled trials of psychosis or catatonia in autism in the literature. However, it is reasonable to treat the autistic patient with current antipsychotic treatment once a diagnosis of psychosis is made. This reflects the practice of using the primary treatments for hyperactivity, aggression, anxiety, and obsessive features in people with autism and other developmental disorders. Atypical antipsychotics, especially risperidone (Hardan *et al.*, 1996; Shea *et al.*, 2004), also seem useful in decreasing the overall level of behavioral and emotional disturbance in autism. There are a handful of case reports of autistic patients diagnosed with a catatonia with a positive response to benzodiazepines (Dhossche & Bouman, 1997; Dhossche, 1998) and ECT (Zaw *et al.*, 1999; Ghaziuddin *et al.*, 2005; Fink, Taylor & Ghaziuddin, 2006). These treatments have shown efficacy in catatonic patients without autism (Fink & Taylor, 2003). Firm conclusions about the efficacy of these treatments in autistic patients with catatonia must await future controlled trials (Dhossche *et al.*, 2006a).

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