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Is autism spectrum disorder common in schizophrenia?

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ABSTRACT

A century ago, Kraepelin and Bleuler observed that schizophrenia is often antedated by "premorbid" abnormalities. In this study we explore how the childhood neurodevelopmental problems found in patients with schizophrenia relate to the current concept of autism spectrum disorder (ASD). Forty-six young adult individuals with clinical diagnoses of schizophrenic psychotic disorders were assessed. The Structured Clinical Interview for DSM Disorders (SCID-I) was used in face-to-face psychiatric examination of each individual. In 32 of the 46 cases (70%), collateral information was provided by one or both parents. The Diagnostic Interview for Social and Communication Disorders — eleventh version (DISCO-11) was used when interviewing these relatives. This instrument covers, in considerable depth, childhood development, adaptive functioning, and symptoms of ASD — current and lifetime. There is a strict algorithm for ASD diagnosis. About half of the cases with schizophrenic psychosis had ASD according to the results of the parental interview. The rate of ASD was strikingly high (60%) in the group with a SCID-I diagnosis of schizophrenia paranoid type. The findings underscore the need to revisit the DSM's "either or" stance between ASD and schizophrenia.

1. Introduction

Although the typical symptoms of schizophrenia usually appear in young adulthood, precursors of the disorder may be present during childhood. Children who, in their late teens or adulthood, develop schizophrenia have been described as slightly different from their age peers with regard to motor performance, cognitive development, activity control and social interaction. Even though there have been many of studies of these phenomena, the nature of the neurodevelopmental deviations is still poorly understood.

In the prospective study of the British 1946 birth cohort, differences between children who developed schizophrenia as adults and the general population were found in a range of developmental domains. Speech problems, low educational test scores, solitary play preference, and self-reported anxiety in social situations during childhood were factors associated with schizophrenia in adulthood (Jones et al., 1994). Another extensive cohort-study, the National Child Development Study, found that individuals who later developed schizophrenia differed from schoolmates in several social and emotional domains (Done et al., 1994; Leask et al., 2002). Deviant behaviours at age 4 years and both social and language impairment by age 7 years were found in another prospective cohort study by (Bearden et al., 2000).

Home-videos of patients with schizophrenia as children have been analysed in comparison with siblings in a unique study by Elaine Walker (Walker et al., 1993, 1994). According to this, children who later developed schizophrenia showed more negative emotions and frequently had unusual motoric features compared with their healthy siblings. In 1972 a sample of young Danish children (age 11–13) were videotaped in a standardized condition as part of the Copenhagen High-Risk Study (Schiffman et al., 2004). Adult psychiatric status was later ascertained. The analysis of the videotapes showed that the individuals who developed schizophrenia, as a group, showed deficits in sociability.

Given that genetics are important risk factors for schizophrenia, several high-risk studies have longitudinally followed children who have one or two parents with schizophrenia. Problems in motor and neurological development, deficits in attention and verbal short-term memory, and poor social competence are factors that appear to predict schizophrenia in these studies (Erlenmeyer-Kimling and Cornblatt, 1987; Mednick et al., 1987; Weintraub, 1987; Erlenmeyer-Kimling et al., 2000; Niemi et al., 2003).

Greater awareness about children's circumstances and of the consequences of neurodevelopmental disorders in childhood has led to an increased concern regarding early identification and support of children with such difficulties. Autism Spectrum Disorder (ASD) is considered as a neurodevelopmental disorder with a spectrum of signs and symptoms, the essential features being a triad of impairments of social interaction, communication and imagination. ASD is recognised in children with normal as well as subnormal intelligence. ASD was, until recently, assumed to be a rare condition, but according

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to recent epidemiologic studies using DSM-IV or ICD-10 criteria, the prevalence of ASD is 0.5–1% of the child population (Baird et al., 2006; Fombonne et al., 2009). Symptoms should be present from infancy or early childhood, but they may not become fully manifest until social demands exceed limited capacities (www.dsm5.org). Autism is now diagnosed for the first time in adults and even in elderly people (van Niekerk et al., 2010). This confirms that although autism is present from childhood, it is not always recognized and addressed during the early years.

Genetic studies have shown numerous direct and indirect links between ASD and schizophrenia (McCarthy et al., 2009; Craddock and Owen, 2010). Specific copy number variants associated with schizophrenia are also linked to a range of neurodevelopmental disorders including ASD, intellectual disability and ADHD (Owen et al., 2011). Neurexin-1, a vulnerability gene for both schizophrenia and ASD, has been proposed to influence brain structure and cognitive function susceptible in both disorders (Voineskos et al., 2011). Family history data support a link between ASD and schizophrenia (Ghaziuddin, 2005).

Neuroimaging studies have shown appreciable brain structural concordances between autism and schizophrenia (Cheung et al., 2010). In a magnetic resonance imaging study by Toal et al. (2009) adults with ASD with or without a history of psychosis and healthy controls were compared. The group with ASD differed from controls in brain regions that are also implicated in schizophrenia. The authors put forward ASD as an alternative 'entry-point' into schizophrenia based on developmental brain abnormalities, suggesting that people with ASD may only require relatively subtle additional abnormalities to develop the positive symptoms of psychosis such as delusions and hallucinations.

Childhood onset schizophrenia, i.e. schizophrenia with onset prior to the age of 13 years, is a rare, very severe condition with poor long-term prognosis. It is antedated by (and "comorbid" with) ASD in 30–50% of the cases (Sporn et al., 2004; Rapoport et al., 2009).

The aim of the present study was to examine the rate of ASD in patients with a clinical diagnosis of schizophrenia, to analyse whether or not ASD is more common in any particular subtype of schizophrenia or if any specific subtype of ASD is more strongly related to schizophrenia, and to evaluate the effect, if any, of gender on any possible association between the two categories.

2. Material and methods

2.1. Subjects

The study group consisted of 46 young adult patients (29 male, 17 female) with a clinical diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder, henceforth referred to as schizophrenic psychoses.

Subjects were first recruited from the only adult psychiatric clinic in the county of Värmland, Sweden. Our original aim was to locate every patient in Värmland with schizophrenic psychosis born between 1972 and 1986, and to invite 30 men and 30 women from this cohort to participate in the study (which is part of a broader study of similarities and differences across schizophrenia and Asperger syndrome). Individuals with diagnosed intellectual disability would not be included.

In Värmland all adult psychiatric services were in the public domain at the time of the study and organized at the county level into one clinic. Staff members at the different psychiatric out-patient departments around the county were informed about the study and asked to screen their service for patients with schizophrenic psychosis. They were asked to inform the patient about the study, to give a standard (oral and written) full description of the study (approved by the Ethics committee, see below). Patients who did not have a current contact were sent a participation inquiry. Individuals with current *severe* psychotic symptoms requiring hospitalisation were approached when symptoms were considered less florid. Patients accepting to participate were included only after written informed consent had been received from each individual. Because of recruitment difficulties, we decided to include three individuals with schizophrenia born in the beginning of 1987.

In due course, a total of 84 patients, 58 men and 26 women, were deemed eligible for the study. Thirty men from Värmland (52% of the whole eligible group) accepted to participate, but two of them withdrew before the first assessment. Seventeen women from Värmland (65% of all eligible women) accepted to participate. Two of them changed their mind before entering the study. One woman was excluded because the diagnosis was not confirmed by a psychiatrist. Thus, 28 men and 14 women with schizophrenic psychosis from Värmland participated in the study. In order to increase the number of participants, we approached an outpatient clinic for patients with psychosis in the city of Gothenburg, from which we unfortunately only managed to recruit one man and three women.

We compared the number of eligible patients from Värmland in our study with results from another study, a nation-wide Swedish study using register data, performed by Hultman and colleagues as part of the International Schizophrenia Consortium study (ISC, 2008). In that study cases were identified via the Swedish Hospital Discharge Register, which contains a register of all individuals hospitalized in Sweden since 1973. Each record contains the main discharge diagnosis, and secondary diagnoses. Patients with discharge diagnoses of schizophrenia who had at least two admissions were included. From the county of Värmland a total of 80 individuals (50 men and 30 women) born in our target years 1972–1986 met these criteria. In contrast to our study, subnormal intelligence was not an exclusion criterion. Numbers are not widely discrepant from those that we found, providing some support for the notion that our eligible group of participants is as close to a representative sample of individuals with a clinical diagnosis of schizophrenic psychosis as would be possible to identify and contact in a general population setting. According to these numbers, the prevalence of schizophrenic psychosis in Värmland for persons born in 1972 to 1986 was 0.2%.

2.2. Parents

Once included and contacted, the participants were asked for permission for us to contact their parents for an interview. Five participants did not give such permission. The other parents were contacted by mail with a separate participation inquiry. Parents of 21 men and 11 women accepted to participate and were interviewed.

2.3. Instruments used

2.3.1. SCID

All participants included had a definite or (in a few cases) preliminary clinical diagnosis of schizophrenic psychosis. In order to confirm these diagnoses, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First and Gibbon, 2004) was used in face – to face interview with the participants (by the second author).

2.3.2. WAIS-III

Global intellectual ability was measured using the full-scale Swedish version of the Wechsler Adult Intelligence Scale – III (Wechsler, 1997). Ten participants were not able to participate in this testing due to practical reasons (for example: difficulties coming to the clinic at a set time, being overwhelmed by the thought of being tested). A full WAIS-III protocol was included for 21 men and 15 women.

2.3.3. DISCO-11

Since patients with schizophrenia often have marked difficulties in social interaction and communication along with flat affect due to negative symptoms, we decided not to assess the probands directly for ASD. There would be a marked risk that difficulties that are secondary to schizophrenia would be rated as primary deficits in social interaction and communication. Instead we focused on examining any presence of ASD during childhood and adolescence. Parents were interviewed with the Diagnostic Interview for Social and Communication Disorders (DISCO-11) (Wing et al., 2002). The DISCO is a semi-structured interview and covers a wide range of developmental domains. An algorithm is included for different diagnostic categories: ICD-10 criteria for Autism, Asperger syndrome, Atypical autism with atypical onset age and/or atypical symptoms (World Health Organization, 2004), Kanner and Eisenberg criteria for Autism (Eisenberg and Kanner, 1956), Gillberg criteria for Asperger syndrome (Ehlers and Gillberg, 1993), and Wing and Gould criteria for Autistic spectrum disorder (Wing and Gould, 1979). The DISCO schedule is investigator based; the interviewer is to elicit enough information from the informant to make a judgement as to the most appropriate rating for each item. The interviewer is to encourage the informant to describe examples of behaviour or to relate illustrative anecdotes. Since recall of the timing of events is much less reliable than the memory of their occurrence, the age when a specific behaviour occurred is not coded, apart from a few items concerning developmental skills. The interviewer is to code behaviour that the informant remembers easily and clearly. If informants have to search their memory and remain uncertain, the item is coded as absent or not known. The interview is structured to collect information about the current situation ("current") as well as information about development and previous ("ever") behaviour. In the present study, one primary aim was to explore the behaviour during childhood development. Hence, in scoring the DISCO-11, the score "ever" was consistently used *only for earlier behaviour*, meaning that if behaviour was currently present but was not present during childhood it would be scored only as "current".

Another adaptation of the DISCO-11 was to leave out the questions about schizophrenia. Schizophrenia is an exclusion criterion for autism in the algorithm which would preclude examination of whether or not the two conditions might co-exist.

The psychometric properties, including inter-rater reliability, of both the original and the Swedish version of the DISCO are excellent according to methodological studies (Leekam et al., 2002; Nygren et al., 2009). The criterion validity is excellent when compared with clinical diagnosis as well as compared to another frequently used diagnostic interview, the Autism Diagnostic Interview, ADI (Lord et al., 1994; Nygren et al., 2009). One advantage of the DISCO in comparison with the ADI is that it includes