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Obstetrical complications in people at risk for developing schizophrenia

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Abstract

Many factors have been associated with the development of schizophrenia, yet few studies have looked at these same factors in individuals considered at risk for schizophrenia, but who have not yet reached diagnostic threshold. The rate of obstetrical complications was assessed as part of a comprehensive battery in subjects at risk (N=52), or in the first episode of schizophrenia (N=18), and in normal comparison subjects (N=43). The rate of obstetrical complications was increased in the at risk (46%) and first episode (39%) samples compared to the normal comparison (19%) group, however, follow-up analyses were only significant between the at risk and normal comparison subjects. Obstetrical complications may be an important risk factor in identifying vulnerable subjects and ultimately may, along with other risk factors, be part of an algorithm for determining likelihood of developing schizophrenia.

Keywords

Prodromal; Schizophrenia; Obstetrical Complications; Vulnerability Marker

Background

Schizophrenia is a devastating disease that characteristically emerges during late adolescence (Häfner et al 1994). The onset of acute symptoms is typically preceded by a prodromal phase in which patients experience life altering symptoms, such as social dysfunction, mild psychosis, and negative symptoms (Cadenhead 2002; Ventura et al 2004). One goal of research has been to identify specific risk factors to help predict which individuals will develop psychosis from their relatively nonspecific prodromal symptoms (Miller et al 2003). This paper presents the history of obstetrical complications (OC) within a population of subjects considered at risk for schizophrenia or in their first episode of illness.

Previously studied risk factors for schizophrenia include genetic factors (Takahashi et al 2005), paternal age (Brown et al 2002), season of birth (Messias and Kirkpatrick 2001), and intrapartum maternal infections (Brown et al 2004). While these factors have been seen in schizophrenia, they have not been studied in a subsyndromal population.

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Schizophrenia has long been linked to problems with development, leading researchers to question the precise time that the dysfunction begins (Cannon et al 2003). There have been case control (Kendell et al 1996) and cohort (Jones et al 1998) studies that have shown an equivocal relationship between birth trauma and risk for schizophrenia. However, in a case control study from Italy (Preti et al 2000) a two-fold increased relative risk for schizophrenia was seen in people who had obstetrical complications. Additionally, mothers of people with schizophrenia were significantly more likely to have had previous miscarriages or preterm births. In a pooled risk analysis for schizophrenia, an approximately two-fold increased risk for schizophrenia was seen based on all types of birth trauma. Specifically, hypoxic/ischemic events have been shown to be correlated with reductions in frontal and temporal gray matter and cerebrospinal fluid volume in people at genetic risk for schizophrenia (Cannon et al 2002). Other events such as history of prenatal infections, particularly influenza, poor maternal nutrition, and prenatal stress have been consistently shown to have up to a two-fold increase in relative risk in the development of schizophrenia, though causality remains elusive from these correlations (Clarke et al 2006). The number of hypoxic events correlates in a linear fashion with risk for schizophrenia, up to a five-fold increase in risk of subsequent schizophrenia (Cannon et al 2000). To our knowledge, no studies have looked at the frequency of OCs in the population at risk for schizophrenia.

During the prodromal period of schizophrenia, many levels of dysfunction begin to appear, but the patient does not meet DSM-IV criteria for schizophrenia. The term “prodromal” can only truly be used retrospectively, so we refer to this group of subjects as “at risk” for schizophrenia. There is currently controversy about when to initiate treatment with patients at risk for developing schizophrenia-related psychosis (Gorman 2004). Since at least 50% of people with prodromal symptoms never develop schizophrenia, the identification of risk factors that can improve the positive predictive power of the current prodromal criteria is essential (Haroun et al 2006).

This report examines the rate of OCs in people identified as at risk for schizophrenia. While we will not be able to make prospective predictions regarding conversion to psychosis based on these data, the intent of this study is to determine if those who are identified as at risk for schizophrenia based on clinical presentation are more likely to have suffered an obstetrical complication compared to normal comparison subjects. Understanding the relationship between associated findings and potential causal entities in the development of schizophrenia will allow further work in determining risk factors and better means for earlier diagnosis and preventive treatments.

Methods

The Cognitive Assessment and Risk Evaluation (CARE) Program (Seeber and Cadenhead 2005) is a referral clinic that provides longitudinal assessment and treatment of individuals aged 12 to 30 who are considered at risk for schizophrenia or are experiencing their first episode of the illness. Study participants included subjects that are considered to be “at risk” for developing schizophrenia, “first episode” patients who first met diagnostic criteria for schizophrenia within the last year, and “normal comparison” subjects from the community. Normal comparison subjects did not have an Axis I or II diagnosis or a family history of psychosis. At risk and first episode subjects were recruited from local referrals and admissions to local adolescent and adult acute psychiatric units. Inclusion criteria for at risk subjects included a recent deterioration in functioning associated with subsyndromal psychotic symptoms and/or a family history of schizophrenia in a sibling or parent. Additional referral criteria for at risk subjects included behavioral (social withdrawal/isolation, change in behavior, declining academic functioning), or psychotic symptoms that did not meet criteria for schizophrenia or other Axis I disorder (i.e. hearing one’s name being called). Normal

comparison subjects were recruited through fliers at local college campuses and through newspaper advertisements. Exclusion criteria for all groups included history of serious head injury, neurological disorder, substance dependence or drug abuse in the last month. Exclusion criteria were obtained by patient and/or parental report during screening after the referral had been made.

Fifty-two (29M:23F) at risk subjects, 18 (12M:6F) first episode patients, and 43 (22M:21F) normal comparison subjects were recruited for the study. All subjects provided written informed consent after the procedures were fully explained (UCSD IRB #050650). For subjects under the age of 18, parents/guardians provided the consent, while the subject provided an assent to participation in the study. At baseline, all subjects and/or their parents filled out a brief general information form that included demographic information and questions about pregnancy and delivery, maternal drug and alcohol use and developmental milestones. All participants also received a comprehensive clinical, neurocognitive, and psychophysiologic battery that includes an Axis I diagnostic interview (Structured Clinical Interview for DSM-IV Axis I Disorders [SCID] (First et al 1995) or Kiddie Schedule for Affective Disorders and Schizophrenia [KSADS] (Kaufman et al 1996)), Structured Interview for Prodromal Syndromes (SIPS) (Miller et al 1999), assessment of family history information using Family History – Research Diagnostic Criteria (FHRDC) (Andreasen et al 1977), and Structured Interview for DSM-IV Personality (SIDP) (Pfohl et al 1995). First episode patients were not administered a SIPS or SIDP (Seeber and Cadenhead 2005). During the clinical interview, subjects were also queried about their developmental history. At risk subjects and first episode patients are followed in the CARE program on a monthly basis for at least two years while normal comparison subjects are followed biannually.

Subjects were rated using items from the Murray-Lewis Obstetric Complications Scale (MLOCS) (Lewis and Murray 1987) for any of 15 possible OCs, including antepartum, intrapartum, and postpartum events (see Table 2 for rated events). Also compiled were maternal and paternal age at birth, and maternal substance use during pregnancy, though there is no score given for these data. The MLOCS codes complications as definite, equivocal or no complication. For this report,, definite and equivocal complications were grouped together as “complications” and compared with “no complications.” Data were obtained primarily from parent or subject report, and while a systematic effort was made to ascertain official birth records for comparison, these were largely unavailable.

Statistics were compiled using SPSS version 10.0. A χ^2 analysis was performed comparing the at risk, first episode, and control groups using the “complications” or “no complications” groupings for OCs.

Results

There were no statistically significant differences between the groups with respect to age, sex or parental age (Table 1).

A greater percentage of OCs were present in both the at risk and first episode groups compared to the normal comparison subjects (Table 2), but the differences were only significant between the at risk and normal comparison groups. There was no statistically significant increase in the frequency of OCs seen in the at risk group when compared to the first episode group. Overall, the most commonly reported complications among the groups were Cesarean section, incubator/blue/resuscitation, nuchal cord and abnormal gestational age.

When looking at risk factors for prenatal complications, maternal alcohol use showed a trend level increased rate in the at risk and first episode group compared to the control group while there were no statistically significant differences in the rate of maternal smoking or maternal

drug use between the groups. Regarding parental age, our sample had very few fathers (25%) or mothers (6.5%) over the age of 35 at the time of birth. There was no difference in the occurrence of OCs within the at risk subjects with mothers over 35 years of age while there was a trend for children of older fathers to have an increased rate of OCs (Fisher Exact p=0.07).

Due to the diagnostic heterogeneity of the at risk sample, we assessed whether there were specific clinical features in at risk subjects who had a history of OCs versus those who did not (Table 3). There were no differences in the occurrence of OCs when Axis I diagnosis, schizotypal personality disorder or family history of psychosis were assessed.

Discussion

Individuals identified as at risk for schizophrenia or in their first episode of illness were more likely to have a history of OCs as compared to normal comparison subjects. Previous investigations regarding OCs in schizophrenia have shown mixed results (Cannon et al 2002). This paper focuses on a population considered at risk for development of schizophrenia, in the hopes of identifying additional vulnerability markers that may ultimately be linked with future outcome.

While this data does not provide evidence of a causal link between obstetrical complications and the development of psychosis, the increased rate of OCs in our at risk sample does provide an additional factor that may be taken into consideration when a person presents with putatively prodromal characteristics. In this manner, our results are consistent with the findings by Yun, et al in their high risk sample from the PACE program in Australia (Yun et al 2005). Identifying possible risk factors for psychosis in this subsyndromal sample is important because these individuals have already begun to experience social and occupational dysfunction and may require early treatment to prevent progression towards psychosis (McGlashan et al 2006).

One limitation to this study is the small sample size. Our study was unable to generate the statistical power needed to look at specific OCs, although OCs that seem to best differentiate the experimental groups from the normal comparison subjects are those that may represent evidence of fetal distress (prematurity, incubator time, nuchal cord). A greater sample size would allow for differentiation of specific intrapartum and postpartum events that may contribute different degrees of risk from each other. Prospective, collaborative studies should be done with a larger sample to help clarify this issue. Prior research on OCs and schizophrenia has suggested that large samples are necessary to avoid confounds and to more accurately delineate the types of traumas that may confer greater risk (Zornberg et al 2000).

In addition, many of our subjects did not know their birth history in detail. This leads to the possibility of recall bias as parents and/or subjects may not accurately remember precise terminology necessary for determining exactly what type of complications, if any, occurred. For example, some listed as a complication that they were born via Cesarean delivery. However, the indication for such a procedure was not necessarily specified as routine or due to significant maternal or fetal distress.

There is an additional problem with potential attribution bias as parents or subjects considered at risk for schizophrenia may be more likely to try and search for a reason, such as an otherwise trivial obstetrical event, that might explain the current situation that they are faced with clinically.

As the search for vulnerability markers for schizophrenia continues, we plan to develop further prospective studies and group collaborations to look at the role of OCs and their relationship to schizophrenia. Ultimately, the goal of such research would be to create a tool — perhaps similar to the cardiovascular risk factor calculators for predicting risk of impending

cardiovascular disease (Wierzbicki et al 2000) — for calculating risk for schizophrenia more precisely. This may entail combining the endophenotype, clinical, and genetic risk factor data in a more complete model. As we are able to identify additional potential factors to include in this algorithm, more precise questions can be addressed in further prospective studies.

References

Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria: reliability and validity. Archives of General Psychiatry 1977;34:1229–1235. [PubMed: 911222]

Brown AS, Begg MD, Gravenstein S, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 2004;61:774–780. [PubMed: 15289276]

Brown AS, Schaefer CA, Wyatt RJ, et al. Paternal age and risk of schizophrenia in adult offspring. Am J Psychiatry 2002;159:1528–1533. [PubMed: 12202273]

Cadenhead KS. Vulnerability markers in the schizophrenia spectrum: implications for phenomenology, genetics, and the identification of the schizophrenia prodrome. Psychiatr Clin North Am 2002;25:837–853. [PubMed: 12462863]

Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry 2002;159:1080–1092. [PubMed: 12091183]

Cannon TD, Rosso IM, Hollister JM, Bearden CE, Sanchez LE, Hadley T. A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. Schizophrenia bulletin 2000;26:351. [PubMed: 10885636]

Cannon TD, van Erp TG, Bearden CE, et al. Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions. Schizophr Bull 2003;29:653–669. [PubMed: 14989405]

Clarke MC, Harley M, Cannon M. The role of obstetric events in schizophrenia. Schizophrenia bulletin 2006;32:3. [PubMed: 16306181]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P, Version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute; 1995.

Gorman JM. Beating psychosis to the punch: the treatment options debate. CNS Spectr 2004;9:572. [PubMed: 15273647]

Häfner H, Maurer K, Löffler W, et al. The epidemiology of early schizophrenia. Influence of age and gender on onset and early course. British Journal of Psychiatry. Supplement 1994;76:29–38.

Haroun N, Dunn L, Haroun A, Cadenhead KS. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. Schizophrenia bulletin 2006;32:166. [PubMed: 16207892]

Jones PB, Rantakallio P, Hartikainen AL, Isohanni M, Sipila P. Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 north Finland general population birth cohort. Am J Psychiatry 1998;155:355–364. [PubMed: 9501745]

Kaufman, J.; Birmaher, B.; Brent, D.; Rao, U.; Ryan, N. Kiddie-SADS-Present and Lifetime Version (K-SADS-PL, Version 1.0). Pittsburgh: University of Pittsburgh, School of Medicine; 1996.

Kendell RE, Juszczak E, Cole SK. Obstetric complications and schizophrenia: a case control study based on standardised obstetric records. Br J Psychiatry 1996;168:556–561. [PubMed: 8733793]

Lewis SW, Murray RM. Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. J Psychiatr Res 1987;21:413–421. [PubMed: 3326936]

McGlashan TH, Zipursky RB, Perkins D, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. The American journal of psychiatry 2006;163:790. [PubMed: 16648318]

Messias E, Kirkpatrick B. Summer birth and deficit schizophrenia in the epidemiological catchment area study. J Nerv Ment Dis 2001;189:608–612. [PubMed: 11580004]

Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull 2003;29:703–715. [PubMed: 14989408]

Miller TJ, McGlashan TH, Woods SW, et al. Symptom assessment in schizophrenic prodromal states. Psychiatr. Q 1999;70:273–287. [PubMed: 10587984]

Pfohl, B.; Blum, N.; Zimmerman, M. The Structured Interview for DSM-IV Personality (SIDP-IV). Iowa City, Iowa: Department of Psychiatry, University of Iowa; 1995.

Preti A, Cardascia L, Zen T, Marchetti M, Favaretto G, Miotto P. Risk for obstetric complications and schizophrenia. Psychiatry research 2000;96:127. [PubMed: 11063785]

Seeber K, Cadenhead. How does studying schizotypal personality disorder inform us about the prodrome of schizophrenia? Current Psychiatry Reports 2005;7:41–50. [PubMed: 15717986]

Takahashi S, Faraone SV, Lasky-Su J, Tsuang MT. Genome-wide scan of homogeneous subtypes of NIMH genetics initiative schizophrenia families. Psychiatry Res 2005;133:111–122. [PubMed: 15740987]

Ventura J, Nuechterlein KH, Green MF, Horan WP, Subotnik KL, Mintz J. The timing of negative symptom exacerbations in relationship to positive symptom exacerbations in the early course of schizophrenia. Schizophr Res 2004;69:333–342. [PubMed: 15469205]

Wierzbicki AS, Reynolds TM, Gill K, Alg S, Crook MA. A comparison of algorithms for initiation of lipid lowering therapy in primary prevention of coronary heart disease. J Cardiovasc Risk 2000;7:63–71. [PubMed: 10785876]

Yun Y, Phillips LJ, Cotton S, et al. Obstetric complications and transition to psychosis in an "ultra" high risk sample. Australian and New Zealand journal of psychiatry 2005;39:460. [PubMed: 15943647]

Zornberg GL, Buka SL, Tsuang MT. The problem of obstetrical complications and schizophrenia. Schizophr Bull 2000;26:249–256. [PubMed: 10885627]

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Table 1

Demographics

Group	Sex (M/F)	Age (range)	Maternal Age at Birth (Range)*	Paternal Age at Birth (Range)**
At Risk (N=52)	29/23	18.4 (12–30)	27.8 (17–45)	30.7 (17–53)
First Episode (N=18)	12/6	20.2 (13–33)	29.6 (20–36)	31.6 (20–41)
Normal Comparison (N=43)	22/21	20.2 (12–29)	27.7 (17–34)	30.6 (20–41)

There were no differences between groups in sex ratio, age or parental age.

* Data available for 38 AR, 7 FE, and 33 NC subjects.

** Data available for 35 AR, 7 FE, and 30 NC subjects.

Table 2

Percent obstetrical complications by group

	At Risk (N=52)	First Episode (N=18)	Normal Comparison (N=43)	All Subjects (N=113)
No complications	53.8%	61.1%	81.4%	65.5%
Complications	46.2%*	38.9%**	18.6%	34.5%
Cesarean delivery	15.4%	16.7%	18.6%	16.8%
Incubator/"blue"/resuscitation	13.5%	—	—	6.2%
Nuchal cord	11.5%	—	—	5.3%
Abnormal gestational age	7.7%	—	—	3.6%
Breech position	—	—	4.7%	1.8%
Low birth weight	1.9%	—	—	0.9%
Use of high forceps	3.8%	—	—	1.8%
Preeclampsia	3.8%	—	—	1.8%
Premature rupture of membranes	1.9%	—	—	0.9%
Twin birth	1.9%	—	—	0.9%
Abnormal labor duration	3.8%	—	—	1.8%
Other	5.8%	22.2%	—	6.2%
Maternal Alcohol Use†	10.2%	12.5%	0%	
Maternal Smoking††	6.1%	6.3%	2.4%	
Maternal Drug Use††	2.0%	6.3%	0%	

*At Risk vs. Normal Comparison, χ^2=8.0, df=1, p=0.005

**First Episode vs. Normal Comparison, χ^2=2.8, df=1, p=0.112

†AR vs. NC, χ^2=4.5, df=1, p=0.059, FE vs. NC, χ^2=5.4, df=1, p=0.073

††NS

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Table 3

The relationship of comorbid conditions and parental age to obstetrical complications in at risk subjects

Comorbid Condition	All at risk subjects (N=52)	No complications (N=27)	Complications (N=27)
Depression	30.8%)	25.9%	36.0%
Anxiety disorders	42.3%	51.9%	32.0%
Schizotypal personality disorder	44.2%	44.4%	44.0%
1st degree family history of psychosis	23.1%	22.2%	24.0%
Maternal age >35 at time of birth*	10.5%	9.5%	11.8%
Paternal age >35 at time of birth**	25.7%	11.8%	38.9%

* Data available for 38 AR subjects (N=21 with no OCs, N=17 with OCs).

** Data available for 35 AR subjects (N=17 with no OCs, N=18 with OCs