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The association between obstetric complications and childhood-onset schizophrenia: a replication study

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ABSTRACT

Background. Many previous studies have shown that individuals who develop schizophrenia in adult life are more likely than normal controls to have a history of obstetric complications (OCs) at birth. However, little attention has been paid to the involvement of OCs in the risk of developing childhood-onset schizophrenia (COS). In our earlier report, we found an association between OCs and the development of COS. In this study, we determined whether the association could be replicated in another, independent set of patients with COS.

Methods. OCs, birth weight and gestational age were retrospectively assessed in 35 children, aged between 14 and 15 years old (average 15·4 years), who met the DSM-III-R criteria for schizophrenia, and in age- and gender-matched controls (children with anxiety disorders).

Results. The COS patients showed significantly greater scores in all of the three measures of OCs according to the Parnas *et al.* scale compared to controls. Moreover, individuals exposed to OCs were about 3·2 times (odds ratio = 3·22; 95% confidence interval, 1·1–9·8) more likely to develop schizophrenia than those without a history of OCs. The mean birth weight was significantly lower in schizophrenics than in controls ($P < 0·05$). The frequency of prematurity signs with weight < 2500 g was significantly higher in schizophrenics than in controls ($P < 0·05$).

Conclusion. Repeatedly reported association between OCs and adult-onset schizophrenia have also been demonstrated in patients with COS. This suggests that there may be a continuity between childhood- and adult-onset schizophrenia.

INTRODUCTION

The contemporary hypothesis on the pathogenesis of schizophrenia proposes the operation of early insults to the brain. This neurodevelopmental hypothesis (Murray & Lewis, 1987; Weinberger, 1987; Takei & Murray, 1998) is, in part, supported by a line of evidence showing that there is an excess rate of obstetric complications (OCs) at birth among individuals who develop schizophrenia in adult life (Lewis, 1989; McNeil, 1995; Kendell *et al.* 1996; Dalman *et al.* 1999). In particular, a recent meta-analysis of 16 case–control studies and two historical cohort studies have found a two-fold increased risk (pooled odds ratio (OR) = 2·0) for the development of schizophrenia in adult life associated with exposure to OCs (Geddes & Lawrie, 1995). In a separate meta-analysis, Verdoux *et al.* (1997), who obtained individual patient data from 11 different studies, have also shown that schizophrenic patients with a history of OCs have an earlier age of onset compared with those without such a history. Similarly, Rosso *et al.* (2000) have reported an association between OCs and an increased risk for early-onset schizophrenia in a Finnish birth cohort study. Despite accumulating evidence that OCs, including low birth weight (Lane & Albee, 1966; Foerster *et al.* 1991; Rifkin *et al.* 1993; Jones *et al.* 1998; Hultman *et al.* 1999), are associated with the development of adult-onset schizophrenia (AOS), little attention has to date been

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paid to childhood-onset schizophrenia (COS) in this regard. Therefore, two questions remain to be answered. First, does COS show a similar pattern of association with OCs that has been described in AOS and secondly, if there is an association, is it stronger in COS than in AOS?

In a preliminary report, we found an association between OCs and the risk of developing schizophrenia in childhood (Matsumoto *et al.* 1999). In contrast, Nicolson *et al.* (1999) found no significant differences in the rate of OCs between individuals with COS and their siblings. However, since the sample sizes used in these studies were small and in the light of the apparent lack of replication, further studies are clearly needed.

In our earlier study, we restricted our sample of cases to those who were first admitted at the age of 13 years or less, but schizophrenia rarely occurs before the age of 16 years. Indeed, the distribution of age-of-onset in this disorder reported by epidemiological studies shows that schizophrenic patients with an onset age before 16 years are rarely seen, and that the rate steeply increases towards the early 20s and then steadily declines (Riecher *et al.* 1989; Castle *et al.* 1993). Therefore, we investigated whether the association between OCs and COS we found in our previous study (Matsumoto *et al.* 1999) would be replicated in an independent set of individuals who were admitted and diagnosed as having schizophrenia between 14 and 15 years of age.

METHOD

Cases

The study was conducted in the psychiatric units of two hospitals, the Hamamatsu University Hospital and Tenryu General Hospital. These hospitals are situated in the western part of Shizuoka prefecture, which is located roughly in the centre of mainland Japan. The two hospitals play an essential role in providing mental health care for both juvenile and adult populations, serving a population of approximately 700000 residents.

We started identifying individuals with COS in the Hamamatsu municipal area in 1986. In this study, we focused on individuals who were first admitted to the above hospitals with a diagnosis of schizophrenia before 16 years of age, but those admitted before age 14 years were excluded in this study as they were reported in our earlier study (Matsumoto *et al.* 1999). The study period was for 10 years from 1 April 1986 to 31 March 1996. A consensus diagnosis was made by two experienced child psychiatrists; each conducted an independent semi-structured and face-to-face interview. Those individuals for whom no agreement on the diagnosis was reached were not enrolled in the study. During the period from 1 April 1986 to 31 December 1987, four individuals (three males and one female) were found to fulfil the criteria for schizophrenia according to DSM-III (American Psychiatric Association, 1980). However, since the DSM-III-R (American Psychiatric Association, 1987) diagnostic system was introduced and made available in 1988, these patients were re-diagnosed applying this new system. All met the criteria for DSM-III-R schizophrenia. As a result, DSM-III-R was used throughout the study period. Eventually, we identified 35 COS patients (14 males and 21 females), who were all between 14 and 15 years of age at the time of study enrolment (average 15·4 years, S.D. 0·63). These individuals were followed-up by one of the authors to ensure the consistency of the diagnosis, with a mean follow-up period of 4·7 years (range 1·1 to 10·9 years, S.D. 3·2). However, no diagnostic changes were required.

Psychiatric controls

As a comparison group, we sought out individuals who were first admitted to the same two hospitals at age 14 or 15 years with a diagnosis of anxiety disorder during the period, 1986 to 1996. We identified 43 patients (22 males and 21 females) with an average age of 14·6 years (S.D. 0·51) who met a DSM-III-R diagnosis of a social phobia, generalized anxiety disorder, or overanxious disorder. It is likely that some patients, particularly in childhood, first manifest neurotic features, but subsequently develop a clear picture of schizophrenia. To avoid any diagnostic misclassification, we examined the subsequent course of the illness in these patients. None of these control patients subsequently developed any signs or symptoms of schizophrenia.

Assessment of obstetric complications (OCs)

Obstetric histories in each patient were obtained, during admission, from a face-to-face interview with his or her biological mother using the scale

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Table 1. *Demographic variables between childhood-onset schizophrenics and controls*

	Schizophrenics	Controls*	*P*
N	35	43	
Male : Female, *N* (%)	14 (40) : 21 (60)	22 (51·2) : 21 (48·8)	NS†
Mean age (S.D.)	15·4 (0·63)	14·6 (0·51)	< 0·001‡
SES, *N* (%)			
I, II	10 (28·6)	14 (32·5)	
III	21 (60·0)	22 (51·2)	
IV, V	4 (11·4)	7 (16·3)	NS†

S.D., standard deviation; NS, non-significant; mean age, mean age on the first admission; SES, socio-economic status, corresponding to the Registrar General's classification (UK).

* Controls (psychiatric controls) comprised patients with anxiety disorders (i.e. social phobia, generalized anxiety disorder, or overanxious disorder).

† Chi-square test; ‡ *t* test.

of Parnas *et al*. (1982), which has been frequently used for assessing obstetric data in previous studies and was locally available at initiation of the study. This scale, a 25-item checklist, allocates a weighted score ranging from 1 to 4 for each specific OC (a five-point scale with zero for absence) and provides three types of summary scores for each individual: a frequency score (the number of distinct OCs observed), a severity score (the highest weighted score), and a total score (the sum of the weighted scores). The raters of OCs remained blind to the hypotheses being tested and, during the interview with mothers, to the case–control status of their children.

Statistical analysis

The frequency, severity, and total scores for OCs were compared between schizophrenic patients and control patients using the Mann–Whitney *U* test. Birth weight and gestational age, which were found to be normally distributed, were compared between the two groups using the *t* test. The birth weight was further compared between the two groups after adjustment for gestational age using analysis of covariance (ANCOVA), in which gestational age was set to a covariate. When one or more items of OCs based on the scale of Parnas *et al*. (1982) were rated as present, such an individual was designated as 'OC-positive'. The rate of OC-positive was compared between schizophrenics and psychiatric controls. The chi-squared test was used to examine the level of significance, and the odds ratio (OR) was calculated to assess the strength of the association. In order to compare the frequency of each OC between schizophrenic and control groups, Fisher's exact test was used, and OR computed. All statistical analyses were carried out with the Statistical Package for the Social Sciences, version 7.5 (SPSS, 1997).

RESULTS

Demographic characteristics

There were no significant differences between schizophrenics and psychiatric controls in their distribution of sex or socio-economic status (see Table 1). The mean age of first admission was significantly higher in schizophrenics than in controls ($t = -5{\cdot}73$, $P < 0{\cdot}001$).

Comparison of obstetric complications (OCs) between schizophrenics and controls

Table 2 shows the means of three types of OCs summary scores for schizophrenics and psychiatric controls. COS patients showed a significantly greater score in all three measures compared with the controls. When the same analyses were repeated separately for sex, significant differences were found in males, with male schizophrenics showing a higher score in all three measures compared with the corresponding controls. A similar pattern could also be seen in females; that is, females with COS tended to have higher scores in all three measures compared with control females. However, these differences did not achieve statistical significance.

The OC-positive rate was significantly higher in schizophrenics than in psychiatric controls ($\chi^2 = 4{\cdot}49$, df = 1, $P < 0{\cdot}05$); with the OR for the risk of developing schizophrenia associated with OCs being 3·2 (95% confidence interval, CI,

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Table 2. *Comparison of obstetric complications between childhood-onset schizophrenics and controls*

		Frequency score		Severity score		Total score	
	N	Mean (S.D.)	Significance	Mean (S.D.)	Significance	Mean (S.D.)	Significance
Total							
Schizophrenics	35	0·54 (0·89)	$U = 590$ $Z = -2·23$	0·80 (1·28)	$U = 574$ $Z = -2·43$	1·17 (2·05)	$U = 573$ $Z = -2·45$
Controls*	43	0·16 (0·43)	$P < 0·05$	0·16 (0·43)	$P < 0·05$	0·19 (0·55)	$P < 0·05$
Male							
Schizophrenics	14	0·64 (1·08)	$U = 101$ $Z = -2·39$	0·64 (0·93)	$U = 100$ $Z = -2·44$	1·07 (1·82)	$U = 100$ $Z = -2·44$
Controls*	21	0·05 (0·22)	$P < 0·05$	0·05 (0·22)	$P < 0·05$	0·05 (0·22)	$P < 0·05$
Female							
Schizophrenics	21	0·48 (0·75)	$U = 203$ $Z = -0·88$	0·90 (1·48)	$U = 194$ $Z = -1·15$	1·24 (2·23)	$U = 193$ $Z = -1·17$
Controls*	22	0·27 (0·55)	NS	0·27 (0·55)	NS	0·32 (0·72)	NS

The measurement of each score was based on the scale of Parnas *et al.* (1982).
S.D., Standard deviation.
* Controls (psychiatric controls) comprised patients with anxiety disorders (i.e. social phobia, generalized anxiety disorder, or overanxious disorder).

Table 3. *OC (obstetric complication)-positive rate in childhood-onset schizophrenics and controls*

	N	OC+ (%)	χ^2	OR	95% CI
Total					
Schizophrenics	35	12 (34·3)	4·49	3·22	1·06, 9·76
Controls	43	6 (14·0)	< 0·05		
Male					
Schizophrenics	14	5 (35·7)	5·67	11·11	1·13, 109·35
Controls	21	1 (0·05)	< 0·05†		
Female					
Schizophrenics	21	7 (33·3)	0·60	1·7	0·44, 6·55
Controls	22	5 (22·7)	NS		

OC+, Number of OC-positive subjects; OR, odds ratio; CI, confidence interval.
† Fisher's exact test.

1·1–9·8) (see Table 3). When the same analysis was repeated for sex separately, the best estimates or OR for both sexes were found to be in the same direction (i.e. an increased rate of OCs in schizophrenic patients). However, there was a much greater risk for male schizophrenics (OR = 11·1) compared with female schizophrenics (OR = 1·7), and males alone achieved statistical significance ($P < 0·05$).

Table 4 shows the frequency of each individual OCs in patients with COS and in controls. The rate of 'signs of prematurity with weight < 2500 g' was significantly higher in COS patients than in controls (Fisher's exact test, $P = 0·04$). Although the rate of 'premature rupture of membrane' was higher in patients with COS than in controls, the difference did not reach a significant level. 'Caesarean section' occurred less frequently in COS patients compared with controls, and the difference approached the marginally significant level (Fisher's exact test, $P = 0·06$).

Comparison of birth weight and gestational age in schizophrenics and controls

COS patients weighted significantly less at birth compared to controls ($t = 2·4$, $P < 0·05$) (see Table 5). When the same analysis was repeated for sex separately, no significant difference emerged in males or females. There was no significant difference in the gestational age between COS patients and controls (Table 5).

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Table 4. *Comparison of specific obstetric complication between childhood-onset schizophrenics and controls*

Type of obstetric complication	Schizophrenics $N = 35$ *N* (%)	Controls $N = 43$ *N* (%)	*P* value†	OR	95% CI
Pregnancy					
Toxaemia	0 (0)	1 (2·3)	1·00	—	—
Hypertension	1 (2·9)	0 (0)	0·45	—	—
Delivery					
Bad foetal position	6 (17·1)	2 (4·7)	0·13	4·24	0·8, 22·51
Premature rupture of membrane	3 (8·6)	0 (0)	0·09	—	—
Caesarean section	0 (0)	5 (11·6)	0·06	—	—
Forceps delivery	1 (2·9)	0 (0)	0·45	—	—
Asphyxia	2 (5·7)	0 (0)	0·2	—	—
Twins	2 (5·7)	0 (0)	0·2	—	—
Signs of prematurity, weight < 2500 g	4 (11·4)	0 (0)	0·04	—	—
Labour time > 24 h	0 (0)	1 (2·3)	1·00	—	—

OR, Odds ratio; CI, confidence interval.
† Fisher's exact test.

Table 5. *Comparison of birth weight and gestational age between childhood-onset schizophrenics and controls*

		Birth weight (g)				Gestational age (weeks)			
	N	Mean (S.D.)	Mean difference	95% CI of difference	*t* *P*	Mean (S.D.)	Mean difference	95% CI of difference	*t* *P*
Total									
Schizophrenics	35	2813 (520)	295	44, 546	2·41	39·8 (1·77)	0·02	−0·95, 1·00	0·47
Controls	43	3108 (292)			<0·05	39·8 (1·15)			NS
Male									
Schizophrenics	14	2834 (655)	337	−272, 945	1·32	39·6 (0·55)	0·4	−1·37, 0·51	−0·98
Controls	21	3171 (278)			NS	39·2 (1·27)			NS
Female									
Schizophrenics	21	2803 (467)	246	−48, 539	1·75	39·8 (2·08)	0·5	−0·75, 1·83	0·89
Controls	22	3049 (299)			NS	40·4 (0·65)			NS

S.D., Standard deviation; CI, confidence interval; NS, non-significant.

DISCUSSION

In our previous study (Matsumoto *et al.* 1999), we reported that a history of OCs (obstetric complications) was associated with the development of COS (childhood-onset schizophrenia). We previously focused on those who were diagnosed as having schizophrenia before 14 years of age. Therefore, in order to render the current study independent, we restricted our patients to those who were diagnosed with the disorder at ages 14 to 15 years. As mentioned earlier, COS is a rare condition and an onset before the age of 16 years is rarely seen in schizophrenia. We therefore designated those individuals who developed the condition before 16 years of age as a single group. To assemble sufficient numbers with such rare conditions, the present study was carried out over a 10-year period and involved an area with large catchment.

In this study, we found that COS patients had significantly greater scores than psychiatric controls (i.e. patients with anxiety disorders) for all three types of OC measurements according to the scale of Parnas *et al.* (1982). In addition, the OR (odds ratio) for the development of the disorder was 3·2, which was almost identical to

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that demonstrated in our previous study (OR = 3·5) (Matsumoto *et al.* 1999). Therefore, the data from these two independent studies strongly support an association between OCs and COS.

Geddes & Lawrie (1995) have demonstrated a two-fold increased risk (OR = 2·0) for the development of schizophrenia associated with exposure to OCs in their meta-analysis of a sample of patients with AOS (adult-onset schizophrenia). However, the scales of OCs used in the present study differs from that (the scale of Lewis *et al.* 1989) used in the study of Geddes & Lawrie, and thus there is a limitation on any direct comparisons. Nevertheless, it is noteworthy that the best estimate of OR at 3·2 for the development of COS in our sample associated with a history of OCs was higher than that (OR = 2·0) in the study of Geddes *et al.* (1999). However, since the 95% confidence interval of OR in the present study is wide (1·1–9·8) and the lower limit (i.e. 1·1) was below 2·0, we cannot conclude that the strength of the association is definitely higher in COS than in AOS. It can be emphasized, however, that our two independent studies have shown an almost identical OR, and hence it is possible that if the sample size were augmented, the confidence limits would become narrower and then the lower limit would ultimately exceed 2·0. Moreover, our results are in line with those of the recent studies by Verdoux *et al.* (1997) and Rosso *et al.* (2000) who examined a sample of patients with AOS, showing that the earlier the age of onset, the greater the occurrence of OCs.

There were gender differences in the occurrence of OCs in patients with COS. The sample size of male schizophrenics ($N = 14$) was relatively small compared to that of females ($N = 21$); however, significantly increased OCs were found in the male but not the female schizophrenics compared with their respective controls. Similarly, the strength of the association between OCs and COS was greater in the male than the female schizophrenics. The risk of developing schizophrenia among males with a history of OCs was about 11 times (OR = 11·1) greater than among those without OCs, whereas the corresponding risk for females was < 2 (OR = 1·7). However, the 95% confidence interval of OR in male schizophrenics was very wide (1·1–109·4), indicating that the estimated OR in male schizophrenics is not reliable. Furthermore, a visual inspection of Table 3 shows that the positive-OC rate (36%) for male schizophrenics was almost identical to that for female schizophrenics (i.e. 33%), whereas the rate was variable for controls (nearly 0% for male controls *versus* as high as 23% for female controls). Therefore, it appears that the gender differences ostensibly seen in our sample are attributable to the compositional differences between sexes in the control group rather than patient group. Clarifying the issue of gender difference awaits further exploration with larger studies to minimize the random variation.

Although there was no significant difference in gestational age between schizophrenics and controls, the mean birth weight was significantly lower in schizophrenics than in controls ($P < 0·02$). This is consistent with the findings in AOS, as it has frequently been reported that individuals with AOS are of lower birth weight than the comparison control group (Lane & Albee 1966); Foerester *et al.* 1991; Rifkin *et al.* 1994; Jones *et al.* 1998; Hultman *et al.* 1999). In addition, there was a tendency for both male and female schizophrenics in our sample to weigh less at birth compared with their respective controls, but these differences did not reach statistical significance.

To facilitate an understanding of the mechanisms involved in OCs as a risk factor, we also examined the frequencies of individual OCs in association with COS. We found that the presence of 'signs of prematurity with weight < 2500 g' was higher in COS patients than in controls ($P < 0·05$). However, since our study with a small number of subjects was certainly not appropriate for examining each individual OC, more large scale studies are clearly required.

As our study relied upon OCs data obtained from maternal recall, the accuracy of the information could be called into question. However, O'Callaghan *et al.* (1990), who compared maternal reports on obstetric histories with information from actual maternity hospital records documenting the relevant pregnancy and delivery events, have concluded that maternal recall can be a strikingly reliable source of obstetric information in relation to research into schizophrenia. Another recent study of Gureje *et al.* (1994) also demonstrated the credibility and accuracy of maternal recall on OCs. In addition, our patients with COS were, by

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definition, younger at the time of study enrolment than those with AOS for whom most prior OCs studies (i.e. retrospective case–control studies) have been conducted. The amount of time lapsed between the exposure and the recall was an important indicator of the accuracy of recall (Rothman & Greenland, 1998). Therefore, it is reasonable to assume that the mothers in our study could, with relative ease, recall the obstetric events that had occurred 14–15 years before compared with mothers in previous studies, who were prompted to recall events that occurred two or more decades previously (i.e. mothers of patients with AOS). Moreover, we obtained the Maternal and Child Health Handbook (MCHH) (this is a special notebook that is given to each pregnant woman in Japan in which detailed pregnancy and delivery histories are recorded) from a subsample ($N = 12$) of our patients with COS. We found that there was no disparity in the events of OCs, gestational age, and birth weight between the maternal reports and the data recorded in MCHH, providing further evidence that maternal reports were fairly reliable. It should also be stressed that mothers as well as the interviewers in this study were unaware of the study hypotheses throughout the study period (1986–1996) and also of the recent reports showing the association between OCs and the development of the disorder (Geddes *et al*. 1999). Nevertheless, we acknowledge that the current study is limited by reliance upon maternal recall rather than desirable contemporaneous obstetric records (some records were available but for the patient group alone as mentioned above) that are exempt from recall bias.

Another limitation to the study lies in the fact that control patients have not passed the risk age for the development of schizophrenia, and may yet develop the condition later in life. However, we attempted to follow-up the control group over as long a period as possible, and found that none of the controls had developed schizophrenia over the subsequent follow-up period. However, even if a fraction of the controls were misclassified and go on to develop schizophrenia, any resulting bias arising from this would have reduced rather than exaggerated the association we found.

The excess of females (male : female = 14 : 21) in our schizophrenic sample may need some explanation. Many previous studies have demonstrated a higher prevalence of schizophrenia in males than in females (Castle & Murray, 1991; Iacono & Beiser, 1992; Kendler & Walsh, 1995). However, since schizophrenia rarely occurs before the age of 16 years (Reicher *et al*. 1989; Castle *et al*. 1993), little is known about the gender difference in the prevalence of COS. A recent study of Frazier *et al*. (1996) has shown the predominance of males among patients with COS, while an epidemiologically-based large study from England (Galdos *et al*. 1993) showed that the cumulative risk of first admission was higher among young girls aged 11–14 years than boys of the same age, which is compatible with our data. Nevertheless, in the face of a paucity of data, clarifying any gender difference in the prevalence awaits further studies.

The current study with an independent set of individuals with COS has replicated our previous report (Matsumoto *et al*. 1999), providing further support for the association between OCs and the development of COS. As mentioned above, individuals who develop the disorder before 16 years of age can hardly be anticipated. However, clinicians, albeit very rarely, encounter early manifestation of the condition in some individuals during childhood as in our sample of COS in the present study. One may raise the question of whether there are distinct factors (or disease processes) underlying the two conditions, COS and AOS. As the strong relationship has been suggested between OCs and AOS (Lewis, 1989; McNeil, 1995; Kendell *et al*. 1996) and our studies show a similar pattern of association in patients with COS, these results suggest that there may, at least in part, be a continuity between childhood- and adult-onset schizophrenia.

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