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Are reduced head circumference at birth and increased obstetric complications associated only with schizophrenic psychosis? A comparison with schizo-affective and unspecified functional psychoses

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Abstract

Patients with schizophrenia have previously been found to have decreased head circumference (HC) at birth and increased rates of obstetric complications (OCs). To determine whether this is restricted to schizophrenia or also characterizes other rather similar psychoses, 30 patients with schizo-affective disorder or unspecified functional psychosis defined by Research Diagnostic Criteria were compared with 30 demographically matched control cases from the same delivery series on HC and OCs, blindly studied through hospital birth records. As compared with controls, the 30 nonschizophrenic patients had significantly decreased HC but not lower birthweight, shoulder circumference or shorter body length. HC was significantly decreased among female but not male patients. Rates of OCs were not significantly increased in the 30 nonschizophrenic patients versus controls. Neither HC nor OC rates were systematically associated with family history of psychosis or season of birth among patients. The findings indicate that these nonschizophrenic psychoses are similar to schizophrenia in having reduced HC at birth but dissimilar from schizophrenia in not having increased rates of OCs. The findings suggest that the gender focus in schizophrenia's etiology should be broadened to include other rather similar diagnostic categories.

Keywords: Obstetric complications; Schizophrenia; Schizo-affective disorder; Unspecified functional psychosis; Head circumference; Birthweight

1. Introduction

Evidence suggests increasingly that paranatal and perinatal factors are implicated in the etiology of schizophrenia. A vast majority of studies of the obstetric complication (OC) histories of schizophrenic persons show a significant increase in OCs among persons later developing schizophrenia (McNeil, 1995). One of those studies was our investigation of 70 schizophrenic psychosis cases who showed significantly increased rates of total OCs, labor-delivery complications and neonatal complications as compared with demographically similar controls selected from the same hospital delivery series (McNeil et al., 1994). OCs in these schizophrenic persons were most characteristic of cases with a negative family history of psychosis

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and cases born in January–April (Cantor-Graae et al., 1994). Increased rates of OCs were not gender-specific.

Evidence for disturbed prenatal cerebral development in individuals who later develop schizophrenia is found in abnormal cytoarchitectural structure in major subgroups of persons with schizophrenia (Conrad and Sheibel, 1987; Bogerts, 1993) and in significantly reduced head circumference (HC) at birth among persons later developing schizophrenia (McNeil et al., 1993; Kunugi et al., 1995). The etiology of disturbed prenatal cerebral development in schizophrenia is not yet identified. For example, among the 70 preschizophrenic neonates studied by McNeil et al. (1993), reduced HC at birth was not the result of preterm birth, identified pregnancy complications or factors associated with season of birth, but was related to an absence of family history of psychosis. HC reduction at birth characterized females but not males with schizophrenia.

In contrast, the significantly reduced HC recently observed among 67 Japanese schizophrenic patients (Kunugi et al., 1995) was related to a positive family history of psychosis and birth in January–April. In that study, the effects of both gestational age and gender were statistically controlled for rather than investigated.

While increased rates of OCs and disturbance in prenatal cerebral development thus seem to characterize preschizophrenic persons, the question remains as to whether these characteristics are specific only for schizophrenia or also include other psychoses with somewhat similar symptomatology. For example, schizo-affective psychoses are included among the 'schizophrenic' cases in some studies (e.g., DeLisi et al., 1988, 1991; Schwarzkopf et al., 1989), and even other 'schizophrenic-like' psychoses (e.g., unspecified functional psychosis, defined per Research Diagnostic Criteria (RDC, Spitzer et al., 1978) may or may not be included among 'schizophrenic' samples, depending upon the stringency of the diagnostic practice actually employed on location. (Total psychotic samples in some research centers appear to represent only two diagnostic categories, i.e., 'schizophrenia' and 'affective disorder'.)

The question of whether these early developmental abnormalities and trauma are specific for schizophrenia has two implications: Firstly, if these other 'nonschizophrenic' psychoses are associated with the same HC and OC characteristics as schizophrenia, then inclusion of the other psychoses among the schizophrenic samples will have little effect on study results. However, if the other nonschizophrenic psychoses are dissimilar to schizophrenia, then inclusion of the former cases could substantially change the results for the schizophrenic group which in many studies hover around the level of statistical significance. Secondly, the answer to the question may possibly shed light on the etiological processes involved both in schizophrenia and in other psychoses with similar symptomatology.

The opportunity to investigate the question of specificity-for-schizophrenia was found within a larger patient sample from which the McNeil et al. (1993, 1994) schizophrenic sample was obtained. The larger sample originally compiled by the authors included, in addition to 70 schizophrenic cases, 30 cases with other psychoses. These 30 nonschizophrenic psychoses represented 17 cases with schizo-affective disorder and 13 with unspecified functional psychosis, as defined by RDC. These latter 13 psychoses represent, by definition, a 'remainder' diagnostic group which is not further definable, but which nevertheless belongs to the general category of 'nonschizophrenic psychoses'. While this sample of 30 nonschizophrenic psychoses is small, it has the advantage of having been compiled and assessed together with the schizophrenic patients in an entirely comparable manner. Comparisons of HC and OC results across the schizophrenic and nonschizophrenic psychosis groups should thus be most illustrative concerning specificity for schizophrenia.

Based on previous results for preschizophrenic cases (McNeil et al., 1993; Cantor-Graae et al., 1994; Kunugi et al., 1995), we would predict that the nonschizophrenic psychosis cases will have a significantly smaller HC at birth than their matched controls, and that small HC will be most characteristic of female patients. Negative or conflicting results permit no specific prediction regarding the relationship between HC and the potential background factors of pregnancy complications,

family history of psychosis and season of birth. On the other hand, the nonschizophrenic psychosis cases are predicted to have significantly increased rates of OCs, and OCs should be most prominent among cases with a negative family history of psychosis and among cases born in January–April.

2. Materials and methods

2.1. Subjects

The base sample of 100 psychosis cases was selected from among several hundred randomly selected patients who were born in 1944–1955, who had been admitted by 1976 to the comprehensive psychiatric in-patient facilities in southwest Sweden, and who had a hospital diagnosis of psychosis which was not suggestive of affective or organic psychosis. Patients born after 1943 were chosen for medical record considerations, and the sample thus consisted of patients whose illness had begun by 32 years of age. The base sample consisted of the first 100 of these patients who were born at the comprehensive delivery facility for the City of Malmö (Sweden's third largest city). These patients were re-diagnosed per their psychiatric records by the third author (LGN) using RDC criteria. The 70 cases with schizophrenia have been studied on both HC (McNeil et al., 1993) and OCs (McNeil et al., 1994). The 30 cases with schizo-affective disorder ($n=17$) or unspecified functional psychosis ($n=13$) constituted the current nonschizophrenic patient sample. Nineteen of the 30 cases were female.

For each psychiatric patient, one control case was chosen from the same hospital delivery series, alternating some time before and after the birth of the psychiatric patient. The control was individually matched with the patient on offspring sex and maternal age, parity, social class (defined by occupation) and marital status at time of delivery. All control offspring were alive at the time of discharge from the hospital. All patients and controls were singletons. Mean gestational age (weeks) was similar in patients (39.23 ± 2.08) and controls (39.77 ± 1.57).

2.2. Investigation of head circumference, body size and OCs

The methods used in this study were similar to those in our previous studies of HC and OCs in the 70 schizophrenic patients (McNeil et al., 1993, McNeil et al., 1994). Medical records for pregnancy, birth and the early neonatal period were obtained from Malmö General Hospital and provided information on pregnancy, labor-delivery and neonatal complications, as well as the offspring's birth weight (g), head circumference (cm), body length (cm), shoulder circumference (cm), and gestational age (weeks). This information was recorded prospectively by the attending midwife, and was thus free from bias concerning the long-term outcome for the offspring. The medical records for the total 100 psychosis and 100 matched control cases were examined in random order by the first author, who was blind to the patient-control status of each subject.

Birthweight was measured on a balance scale. Body length was measured by placing the child's head against a vertical stop on the bathing table and stretching the child's body down a solid tape measure attached to the table. Head and shoulder circumferences were measured with a nonstretchable, standard oil-cloth tape measure at the maximal horizontal (occipitofrontal) circumference of the head (above the ears and eyebrows) and shoulders (at triceps level), respectively. Birth weight was rounded off to the nearest 10 g and the other three size parameters to the nearest whole cm (still the praxis today). Body length was selected as the most appropriate control variable for general body size in newborns, comparable to that in other research on both newborns (Walker and Emory, 1983) and adults (Andreasen et al., 1987; DeLisi and Goldin, 1987).

As in the previous study, OCs were scored by the first two authors per the McNeil-Sjöström Scale for OCs (McNeil and Sjöström, 1995). This scale yields separate summary scores (representing the number of specific OCs) for pregnancy (PCs), labor-delivery (LDCs), the neonatal period (NCs), and the reproduction in total (Total OCs, representing the sum of PCs, LDCs and NCs). Each OC is rated on a 6-point severity scale, and the

OCs included in the above summary scores were those with a severity level of 4–6 for LDCs, NCs and total OCs, and those with a severity level of 3–6 for PCs. A slightly wider range of severity levels was chosen for PCs due to their basically lower frequency/severity in the combined patient-control sample.

Family history of mental disorder among first- and second-degree biological relatives was assessed independently by the fourth author (TR) on the basis of psychiatric records for the patients. Family history of 'psychosis' was classified as present (i.e., schizophrenia, non-schizophrenic psychoses, psychoses without further specification and, in a first-degree relative of one patient, a markedly schizoid personality) or absent (no history or only non-psychotic mental difficulties). A positive family history was found for 14 (47%) of the 30 psychosis cases. Season of birth was categorized as Winter–Spring (January–April) versus Other (May–December); 37% of the 30 psychosis cases were born in January–April.

The pregnancy complications (PCs) observed among the 30 psychosis and 30 control cases represented instances of hypertension, kidney disorders, pre-eclampsia, eclampsia, bleeding and hyperemesis. For analysis in relation to HC, PCs were scored as present vs. absent, and were present among 43% of the 30 psychosis cases.

Paired *t*-tests were used to compare body size data within the matched patient-control pairs. OC summary scores were tested within matched patient-control pairs using the Wilcoxon matched-pair signed-ranks test (due to the nature of the OC score distributions). Unpaired *t*-tests were used to analyze mean HC associated with the different classes of background factors (season of birth, family history, PCs). Cut-off level for statistical significance was set at <0.05, 2-tailed.

3. Results

3.1. Patient-control differences on body size at birth

As shown in Table 1, the total nonschizophrenic patient group had a significantly smaller HC at birth than did their matched controls. As shown in Fig. 1, there was a general shift toward smaller HC in the patients, as compared with the controls. No significant difference was found between total patients vs. controls on birthweight, body length, shoulder circumference or the ratio between HC and body length.

3.2. Gender as a modifier of patient-control differences on HC and body size

As shown in Table 1, nonschizophrenic female patients were significantly smaller than their sex-matched controls on HC only. In contrast, male patients were not significantly smaller than their sex-matched controls on any of the body size parameters.

3.3. OCs in patients vs. controls

The nonschizophrenic psychosis patients did not differ significantly from control cases on rates of PCs (matched-pairs signed-ranks, $z=0.16$), LDCs ($z=0.20$), NCs ($z=0.04$) or total OCs ($z=0.20$).

3.4. Background factors in relation to HC subgroup and OCs

Among the 30 patients, no significant difference in HC was observed between cases with positive vs. negative family history of psychosis, between cases born in January–April vs. May–December, or between cases with vs. without pregnancy complications (Table 2). Furthermore, total OC rates did not differ significantly (per Wilcoxon matched-pairs signed ranks test) between controls vs. nonschizophrenic patients in the family history-positive or family history-negative subgroups, or between controls vs. nonschizophrenic patients born in January–April or patients born in May–December.

4. Discussion

To determine whether reduced head circumference at birth and increased rates of OCs are specific for schizophrenic psychoses vs. other similar psychoses, 30 neonates later developing schizo-affec-

Table 1
Body size at birth in nonschizophrenic patients and matched controls

Body size variable	Patient group		Control group		Paired *t*-test			95% CI for patient-control difference
	Mean	(s.d.)	Mean	(s.d.)	*t*	*df*	*p*	
All patients ($n=30$ patient-control pairs)								
Head circumference	33.83	(1.74)	34.67	(1.35)	2.59	29	0.016	−4.28 to +2.62
Birthweight	3334.8	(542.8)	3427.0	(485.4)	0.82	29	n.s.	−1297.2 to +1112.5
Body length	50.07	(2.36)	50.67	(2.29)	1.22	29	n.s.	−5.87 to +4.67
Shoulder circumference	35.93	(2.56)	36.77	(2.03)	1.74	29	n.s.	−5.98 to +4.32
Ratio: head circumf.: body length	0.676	(0.021)	0.685	(0.034)	1.19	29	n.s.	−0.093 to +0.075
All male patients ($n=11$ patient-control pairs)								
Head circumference	34.91	(1.22)	35.27	(1.42)	0.84	10	n.s.	−3.16 to +2.44
Birthweight	3625.9	(387.5)	3586.4	(461.5)	0.26	10	n.s.	−965.2 to +1044.3
Body length	51.27	(1.74)	51.00	(2.24)	0.40	10	n.s.	−4.12 to +4.66
Shoulder circumference	37.45	(1.64)	37.55	(2.16)	0.15	10	n.s.	−4.15 to +3.97
Ratio: head circumf.: body length	0.681	(0.025)	0.692	(0.030)	0.87	10	n.s.	−0.093 to +0.071
All female patients ($n=19$ patient-control pairs)								
Head circumference	33.21	(1.72)	34.31	(1.20)	2.52	18	0.022	−4.86 to +2.64
Birthweight	3166.3	(556.3)	3334.7	(486.5)	1.10	18	n.s.	−1477.1 to +1140.3
Body length	49.37	(2.43)	50.47	(2.37)	1.69	18	n.s.	−6.70 to +4.48
Shoulder circumference	35.05	(2.61)	36.32	(1.86)	1.92	18	n.s.	−6.86 to +4.34
Ratio: head circumf.: body length	0.673	(0.018)	0.681	(0.037)	0.81	18	n.s.	−0.017 to +0.001

tive or unspecified functional psychoses were compared with demographically similar control neonates on head circumference and general body size at birth as well as rates of OCs. As had previously been found for 70 schizophrenic cases sampled in the same general patient series, the 30 nonschizophrenic psychosis cases had significantly reduced HC as compared with matched controls. HC was the only physical size parameter to show a significant reduction at birth in these 30 patients with nonschizophrenic psychoses (Table 1). As had also been the case for schizophrenic patients, reduced HC at birth was characteristic of females but not males with nonschizophrenic psychoses. Given the current sample size, perhaps it is all the more impressive that the significantly reduced HC in the nonschizophrenic female patients so closely parallels that for the larger schizophrenic group.

In contrast, these 30 patients with nonschizophrenic psychoses did not show the schizophrenic patients' disproportionately smaller HC in relation to body length. Furthermore, no relationship was found among the 30 nonschizophrenic cases between reduced HC and negative family history of psychosis, which had been the case among the 70 schizophrenic patients. This lack of relationship was apparently not due to low rates of family history of psychosis, fully 47% of the 30 nonschizophrenic patients having such a history, and absolutely no relationship being found between HC and family history (Table 2). The results in the current study should clearly be re-tested on larger samples.

In conclusion, the present results based on small samples of patients with schizo-affective or unspecified functional psychosis might suggest that reduced HC at birth is characteristic of both female schizophrenic patients and female patients with nonschizophrenic psychoses. In contrast, the patients with nonschizophrenic psychoses do not show the differentially increased history of OCs which typically characterizes schizophrenic patients (McNeil, 1995). The implications of these findings are: (a) that the same factor(s) that disturb prenatal cerebral development in preschizophrenic neonates may possibly also be active in neonates destined to develop other similar psychoses; but (b) that the role of OCs as contributors to these nonschizophrenic psychoses is highly unclear. The inclusion of schizo-affective and/or unspecified

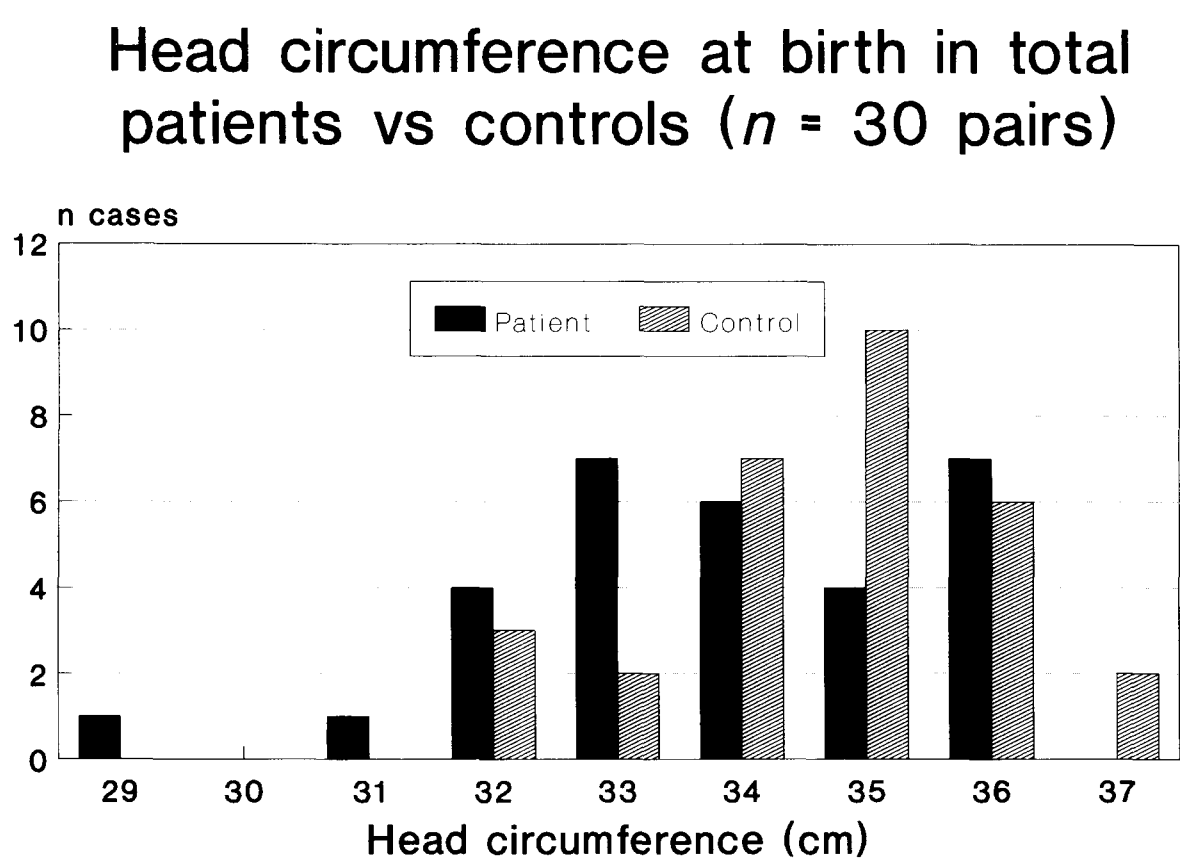

Fig. 1. Head circumference at birth in patients and controls.

Table 2
Mean head circumference (cm) for patient subgroups with different background factors

Background factor	Head circ.		Statistical analysis		
	Mean	s.d.	*t*-test	*df*	*p*
Family history of psychosis					
Positive history ($n=14$)	34.00	1.30	0.49[a]	25	n.s.
Negative history ($n=16$)	33.69	2.09			
Season of birth					
January–April ($n=11$)	34.00	1.61	0.39	28	n.s.
May–December ($n=19$)	33.74	1.85			
Pregnancy complications					
Some ($n=13$)	33.77	2.17	0.17	28	n.s.
None ($n=17$)	33.88	1.41			

[a]Welch's approximate *t*-test.

functional psychosis cases among 'schizophrenic' samples would thus perhaps have little effect on study results concerning HC at birth, but might tend to diminish differences between schizophrenic and control samples on OCs. Furthermore, the gender results for HC at birth in the nonschizophrenic psychosis group suggest that females and males may have different early biological bases for their disorders and that the gender focus in schizophrenic research should be broadened to include other somewhat similar diagnostic categories.

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References

Andreasen, N.C., Nasrallah, H.A., Coffman, J.A., Olson, S.C., Grove, W.M. and Dunn, V. (1987) Hat size in schizophrenia. Arch. Gen. Psychiatry 44, 674–676.

Bogerts, B. (1993) Recent advances in the neuropathology of schizophrenia. Schizophr. Bull. 19, 431–445.

Cantor-Graae, E., McNeil, T.F., Sjöström, K., Nordström, L.G. and Rosenlund, T. (1994) Obstetric complications and their relationship to other etiological risk factors in schizophrenia. A case-control study. J. Nerv. Ment. Dis. 182, 645–650.

Conrad, A.J. and Sheibel, A.B. (1987) Schizophrenia and the hippocampus: the embryological hypothesis extended. Schizophr. Bull. 13, 577–587.

DeLisi, L.E., Boccio, A.M., Riordan, H., Hoff, A.L., Dorfman, A., McClelland, J., Kushner, M., VanEyl, O. and Oden, N. (1991) Familial thyroid disease and delayed language development in first admission patients with schizophrenia. Psychiatry Res. 38, 39–50.

DeLisi, L.E., Dauphinais, I.D., Goldin, L.R. and Gershon, E.S. (1988) In: D.L. Dunner, E.S. Gershon and J.E. Barrett (Eds.), Relatives at Risk for Mental Disorder. Raven, New York, NY, pp. 267–277.

DeLisi, L.E. and Goldin, L.R. (1987) Hat size in schizophrenia. Arch. Gen. Psychiatry 44, 672–673.

Kunugi, H., Nanko, S., Takei, N., Saito, K., Murray, R.M. and Kazamatsuri, H. (1995) Small head circumference at birth in schizophrenia. Schizophr. Res. 15, 192–193.

McNeil, T.F. (1995) Perinatal risk factors and schizophrenia: selective review and methodological concerns. Epidemiol. Rev. 17, 107–112.

McNeil, T.F., Cantor-Graae, E., Nordström, L.G. and Rosenlund, T. (1993) Head circumference in 'preschizophrenic' and control neonates. Br. J. Psychiatry 162, 517–523.

McNeil, T.F., Cantor-Graae, E. and Sjöström, K. (1994) Obstetric complications as antecedents of schizophrenia: empirical effects of using different obstetric complication scales. J. Psychiatr. Res. 28, 519–530.

McNeil, T.F. and Sjöström, K. (1995) McNeil-Sjöström Scale for Obstetric Complications. Department of Psychiatry, Lund University, Malmö.

Schwarzkopf, S.B., Nasrallah, H.A., Olson, S.C., Coffman, J.A. and McLaughlin, J.A. (1989) Perinatal complications and genetic loading in schizophrenia: preliminary findings. Psychiatry Res. 27, 233–239.

Spitzer, R., Endicott, J. and Robins, E. (1978) Research Diagnostic Criteria rationale and reliability. Arch. Gen. Psychiatry 35, 773–782.

Walker, E. and Emory, E. (1983) Infants at risk for psychopathology: offspring of schizophrenic parents. Child Dev. 54, 1269–1285.