Congenital Malformations and Structural Developmental Anomalies in Groups at High Risk for Psychosis

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Objective: *Early somatic developmental anomalies may be one expression of a genetic influence toward psychosis. The purpose of this study was to investigate whether higher rates of early developmental anomalies are associated with heightened genetic risk for psychosis.* *Method:* *Rates of congenital malformations and minor structural developmental anomalies were prospectively investigated in 84 high-risk offspring of women with histories of psychosis of nonorganic origin (schizophrenic, schizoaffective, affective, and other psychoses) and in 100 offspring of demographically similar control women with no history of psychosis. Data were collected by means of multiple physical examinations through the first 3–4 years of the offspring's lives.* *Results:* *The rates of total congenital malformations were high, but the great majority of these malformations in both the index group and the control group represented minor physical aberrations. Rates of congenital malformations in the offspring of the index women (or any specific diagnostic subgroup of these women) were not different from those in the offspring of the control women.* *Conclusions:* *The inferred genetic risk for psychosis does not appear to be associated with greater rates of early somatic developmental anomalies, suggesting that early developmental anomalies do not represent an expression of genetic influence toward psychosis.*

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Evidence suggests increasingly that somatic trauma to the fetus and/or maldevelopment of the offspring during pregnancy or the perinatal period are in some manner associated with the development of psychosis in the same offspring in adulthood (1–6). The relation between early trauma/maldevelopment and later psychosis appears to involve primarily schizophrenia, but some data also suggest an association with schizoaffective (6) and bipolar affective (2) disorders. The specific role of maternal obstetric complications in the development of schizophrenia and other psychoses in the offspring, as well as the relation between obstetric complications and genetic factors, remains to be determined. Perhaps the most likely interpretation of the greater rates of maternal obstetric complications or early developmental anomalies among prepsychotic offspring is that these phenomena represent early fetal trauma, with neurobiological consequences which contribute to the later development of psychosis. An alternative interpretation is that the obstetric complications or developmental anomalies are merely an expression of genetic influence (7–10) or a secondary correlate of other parental environmental influences (4). If the latter were true, obstetric complications would be an epiphenomenon (i.e., a consequence or correlate of psychosis) rather than a primary "somatic trauma" factor contributing to the development of psychosis.

One strategy available at present for investigating the hypothesis that early trauma/developmental anomalies are a direct or indirect expression of genetic influence toward psychosis is to study the rate of early trauma and developmental anomalies in groups of individuals at greater genetic (and perhaps environmental) risk for the psychiatric disorders of interest (11). Numerous such studies have been done regarding maternal obstetric complications, and the extensive evidence obtained to date indicates clearly that pregnancy and birth complications of the type typically registered by prenatal and obstetric services do *not* occur unusually frequently among offspring who are at greater genetic risk for psychoses (4–6, 12). This suggests that neither genetic factors nor the many other possible environmental factors directly associated with parental psychosis influence the occurrence of obstetric complications of the type related to risk for schizophrenia in offspring. Thus, obstetric complications do not appear to represent an epiphenomenon.

In contrast, there appears to be little empirical evi-

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dence concerning whether congenital malformations, including minor structural developmental anomalies, occur unusually frequently among individuals at heightened genetic (and environmental) risk for psychosis. To our knowledge, only three studies have systematically investigated the rates of congenital malformations in the offspring of parents with psychosis. Sobel (13) used psychiatric records to investigate rates of malformations occurring in 222 offspring of schizophrenic women who were in New York state mental hospitals at the time of delivery in 1950–1958. He reported a higher rate of malformations in these offspring (3.2%) than in two separate samples from the general population (about 1%). Similarly, Rieder et al. (14) found that there were significantly more deaths associated with neurological malformations among offspring of parents with various psychiatric illnesses (1.9%) than among offspring of control parents (0%). In contrast, Paffenbarger (15) found no difference in rates of congenital defects between the offspring of 126 women with postpartum psychosis and the offspring of control women (no specific rates of congenital malformations were given for either group). Reports from two other studies (16, 17) included mention of several specific congenital malformations found among the offspring of schizophrenic parents, but no group rates of congenital malformation per se were cited for the samples. The greater frequencies of congenital malformations in high-risk offspring reported in the studies by Sobel and Rieder et al. were thus associated with rather severe conditions (childbirth in mental hospitals, congenital malformations associated with death of the offspring) and represented rather minimal increases in the rates of these malformations (2%–3%) as compared with low control group rates (0%–1%).

Furthermore, the studies to date appear to have included only major congenital malformations. Considerable scientific interest has more recently been directed toward congenital aberrations termed "minor physical anomalies." Minor physical anomalies are minor congenital malformations found primarily in the ectoderm (18, 19); they develop during the first trimester of pregnancy as a result of genetic or other teratogenic factors. Minor physical anomalies may represent signs of early developmental anomaly occurring at approximately the same gestational time as major CNS development. Furthermore, since many minor physical anomalies develop in the same embryonic layer as does the CNS, minor physical anomalies might represent an externally visible sign of parallel developmental deviation in the CNS itself (18, 19). Evidence suggests that minor physical anomalies occur with greater frequency among persons with schizophrenia, autism, mental retardation, hyperactive or inhibited behavior, learning difficulties, and speech and hearing difficulties (3, 18–23), thus supporting a coupling of early developmental anomaly and the subsequent development of a range of different mental disorders.

Further study of the rate of both major congenital malformations and minor developmental anomalies among offspring at high risk for psychosis is therefore indicated. Data collected in our prospective study of the offspring of pregnant women with histories of psychosis and the offspring of pregnant control women with no history of psychosis (24) provided the opportunity to investigate this topic in several maternal psychosis groups and demographically similar control groups. The data on congenital malformations were obtained from examinations conducted on numerous occasions during the offspring's first several years of life, thus providing a long-term assessment of somatic developmental anomalies that reflect pre- or perinatal maldevelopment. The hypothesis tested was that the offspring of women with psychosis more frequently have congenital malformations than do the offspring of normal control women.

METHOD

The index sample consisted of 84 offspring of pregnant women who registered at the comprehensive prenatal clinics in southern Sweden during a 4.5-year sampling period (1973–1977), who had histories of hospitalization for nonorganic psychosis before the current pregnancy, who participated in the longitudinal study (24), and for whose offspring information was available concerning the presence of congenital malformations. Table 1 shows the distribution of the maternal psychiatric diagnoses in the 84 cases according to the Research Diagnostic Criteria (RDC) (25) and the project's own diagnostic criteria (24). Project criteria include schizophrenic, cycloid, affective, and other, "nonendogenous" psychoses. The RDC definitions of schizophrenic disorders and affective disorders (manic, bipolar, and major depressive) are broader than the project criteria for these two types of disorders, and the RDC schizophrenic and affective disorder subjects included all project-criteria schizophrenic and affective disorder subjects, respectively, plus a number of subjects from the project-criteria "other psychoses" group. The use of the two diagnostic systems in parallel provides the opportunity to study the effects of breadth of diagnostic definitions on study results (26, 27).

The control sample consisted of 100 offspring of pregnant women with no history of psychosis who were matched with the women in the index sample with respect to the clinic at which they received prenatal care, maternal parity, age, social class, and marital status during pregnancy; who participated in the longitudinal study (24); and for whose offspring there was information regarding congenital malformations. Each diagnostic group had its own matched control group.

Informed consent was obtained after the procedures had been fully explained. Only one perinatal death (of a control subject) and no postnatal deaths occurred in the samples.

Information concerning congenital malformations in the entire group of 184 offspring was obtained from well-baby clinic records covering repeated physical ex-

TABLE 1. Rates of Congenital Malformations in Offspring of Mothers With Histories of Nonorganic Psychosis and in Matched Control Subjects

		Malformation									
		None		Some		Variant		Minor		Major	
Group	N	N	%	N	%	N	%	N	%	N	%
Total index	84	54	64	30	36	15	18	9	11	6	7
Total control	100	61	61	39	39	23	23	9	9	7	7
Mother's diagnosis according to RDC											
Schizophrenia	33	23	70	10	30	4	12	2	6	4	12
Matched control	39	19	49	20	51	13	33	3	8	4	10
Schizoaffective disorder	15	10	67	5	33	3	20	2	13	0	0
Matched control	16	11	69	5	31	2	13	2	13	1	6
Affective disorder	26	15	58	11	42	6	23	3	12	2	8
Matched control	30	22	73	8	27	5	17	2	7	1	3
Unspecified functional psychosis	10	6	60	4	40	2	20	2	20	0	0
Matched control	15	9	60	6	40	3	20	2	13	1	7
Mother's diagnosis according to project criteria											
Schizophrenia	16	11	69	5	31	3	19	1	6	1	6
Matched control	22	12	55	10	45	5	23	2	9	3	14
Cycloid psychosis	15	10	67	5	33	2	13	2	13	1	7
Matched control	18	11	61	7	39	5	28	1	6	1	6
Affective illness	14	8	57	6	43	3	21	3	21	0	0
Matched control	18	12	67	6	33	3	17	2	11	1	6
Psychogenic psychosis	6	3	50	3	50	1	17	2	33	0	0
Matched control	7	4	57	3	43	2	29	1	14	0	0
Postpartum psychosis	16	10	63	6	38	5	31	0	0	1	6
Matched control	18	10	56	8	44	3	17	3	17	2	11
Other psychoses	17	12	71	5	29	1	6	1	6	3	18
Matched control	17	12	71	5	29	5	29	0	0	0	0

aminations during the first 3–4 years of life (28). In addition to these routine pediatric examinations, all but 13 of the infants were also examined by one or more project researchers; the first author examined 154 infants at delivery, and 127 were examined by the second author on the third or fourth day postpartum. In 11 of the 13 cases in which the infant was not seen by a project researcher, information about the child's condition was obtained from clinic personnel at the time of delivery. The current study included systematic evaluation for not only major congenital malformations but also minor congenital malformations and minor physical anomalies such as birthmarks, simian line, sacrococcygeal pits, etc.

All congenital malformations identified through these three sources were classified (by the third author) according to the system of Ekelund et al. (29) as representing variants, minor structural abnormalities, or major congenital malformations; the last were further subdivided into dubious or insignificant type and gross type. In table 1 and in the statistical analyses, if a child had multiple congenital malformations belonging to more than one of these three categories, classification of the child as having major congenital malformations was given priority over classification as having minor congenital malformations or variants, and minor congenital malformations were given priority over variants.

The frequency of offspring having no congenital malformation versus those having some congenital malformation was analyzed statistically for both the total index sample and each diagnostic group and its matched control subjects with the use of chi-square and Fisher's exact probability tests. The hypothesis indicated one-tailed analyses.

RESULTS

Congenital Malformations in the Total Sample of Index Plus Control Offspring

The rates of total congenital malformations and the frequencies of subjects categorized as having no congenital malformations, variants, minor congenital malformations, and major congenital malformations are shown in table 1. The nature and frequencies of the specific congenital malformations observed in the index group and the control group are shown in table 2.

Among the total 184 offspring, 69 (38%) had at least one congenital malformation, and eight (4%) had two. More than half (58%, N=45) of the total congenital malformations (N=77) in these 184 offspring belonged to the variant category, while 25% (N=19) represented minor congenital malformations, and 17% (N=13) were major congenital malformations. A number of the major malformations identified (positive Ortolani's sign, cardiac murmur, pyloric stenosis) belonged to the subgroup termed "dubious or insignificant" by Ekelund et al. (29), and only a few subjects (2%, N=4 of 184) had major congenital malformations of the gross type (table 2). Among the 18 subjects with minor congenital malformations, one had two different minor malformations and four others also had malformations classified as variants. Three of the 38 subjects with only

TABLE 2. Frequencies of Specific Congenital Malformations in Offspring of Mothers With Histories of Nonorganic Psychosis and in Matched Control Subjects

Malformation	Index Group (N=84)	Control Group (N=100)
Variant		
Hemangioma	5	12[a]
Nevus		2[a]
Undescended testes	1	2
Umbilical hernia	3	2
Inguinal hernia	2	1
Hydrocele	1	3
Strabismus	3	3
Simian line	2	2[a]
Epicanthus folds		1[a]
Minor structural abnormality		
Slight ear dysplasia	2	2
Minor malpositions of feet/toes/ fingers; syndactyly	2	5
Sacrococcygeal pits	3	1
Minor genital malformations	1	1
Open fontanel at 2.5 years	1	
Slight facial dysplasia and suspected ocular albinism	1	
Major congenital malformations		
Dubious or insignificant type		
Positive Ortolani's sign (treated)	4	2
Cardiac murmur		2
Pyloric stenosis	1	
Gross type		
Pes calcaneovalgus		2
Pes equinovarus	1	
Hypospadias		1

[a]One subject also had a congenital malformation classified as a minor abnormality and was counted in that group.

variants had two different congenital malformations. All subjects with major congenital malformations had only one malformation each.

Congenital Malformations in the Index Versus the Control Offspring

As shown in table 1, the index and control groups were very similar to each other in rates of total congenital malformations, variants, minor congenital malformations, and major congenital malformations. Division of the sample according to the different maternal psychiatric diagnostic subgroups and their demographically matched control groups yielded quite small subgroups with congenital malformations, but the data suggested that the rates of malformations for the specific diagnostic groups were not notably different from those for their respective control groups. Diagnosis of maternal psychosis according to the RDC versus the project criteria led to no notable differences in rates of congenital malformations among the offspring of mothers with schizophrenic, schizoaffective/cycloid, and affective disorders. Furthermore, the specific types of congenital malformations found in the total index group were well distributed across the different psychiatric diagnostic subgroups. No significant difference was found on any of the statistical comparisons, and the hypothesis of greater rates of congenital malformations in index cases was not supported by the results.

DISCUSSION

In this prospective study, offspring of women with histories of nonorganic psychosis were found not to differ from offspring of normal control women in rates of congenital malformations classified in several different ways. This absence of index-control differences was not due to an insufficient frequency of congenital malformations in the samples. More than one-third of the offspring in the combined index and control samples had one or more of the broad range of physical deviations classified as congenital malformations, and 7% had major congenital malformations.

The rates of congenital malformations observed in a sample will be influenced by the intensity of scrutiny and examination during a given period, the length of follow-up, and the breadth of physical deviations subsumed within the concept of congenital malformations and developmental anomalies. The very high rate of total congenital malformations observed in both the index and control samples was likely due to all of these factors. 1) A broad range of aberrations was intentionally selected for inclusion among congenital malformations, and indeed a great majority (83%) of the malformations identified were variants or minor structural abnormalities, while only 17% were major classical congenital malformations, and even fewer (5%) were gross major congenital malformations. 2) Congenital malformations were identified through multiple examinations, including extra neonatal physical examinations done for research purposes and with special attention paid to minor deviations. 3) The data reflected a long observation time for the identification of congenital malformations, that is, the first 3–4 years of life; previous studies indicate that the rate of identified malformations doubles if children are followed up through 5 years of age rather than just examined perinatally (30). Furthermore, the possibility that factors which increase the risk of congenital malformations were found in both samples cannot be excluded. For example, both index and control mothers were unusually old at the time of these births (24).

Whatever the reasons for the high total rates of congenital malformations, the identification procedure was applied in a comparable manner to the index and control groups, and the two groups were found not to differ in these rates. Because the rates in the index and control groups did not differ, further possible analyses to determine any relations between these malformations and other factors such as maternal obstetric complications and maternal medication during pregnancy are not indicated, as might have been the case if the index subjects had had higher rates of congenital malformations.

The similar rates of congenital malformations in the index and control groups could be interpreted in several different ways. There could be a relation between greater genetic risk and the occurrence of congenital

malformations, but this relationship would not be discernible in the present study because too few of these high-risk offspring would have the gene (or genes) for psychosis. Unfortunately, there is no certain knowledge about the true frequency of psychosis-related genes in the offspring of, for example, one schizophrenic parent (31). Although the true rate of expected gene carriers in our offspring samples cannot be estimated prior to identification of the psychosis-related gene (or genes) or the true genetic mode of inheritance, the frequency of gene carriers could, nevertheless, have well exceeded the rate of expected psychotic cases in these offspring groups (10%–25%) (24). For example, relatively low rates of concordance for schizophrenia have been observed in modern studies of monozygotic twins (32), and these pairs by definition have a genetic makeup that is "sufficient" to permit the development of schizophrenia in at least one of the twins.

Whatever the true rate of gene carriers in the index offspring, an existing relationship between psychosis-related genes and congenital malformations should have led to at least a nominally greater rate of congenital malformations in the index group than in the control group, but this was clearly not the case in the current findings. Moreover, the offspring of the schizophrenic mothers tended to show notably lower rates of congenital malformations than did the offspring of their matched control subjects (table 1), and schizophrenia is the disorder for which the most evidence of early trauma and maldevelopment exists (1–6).

In contrast, the findings appear more to suggest that there is no relation between greater genetic risk and the occurrence of congenital malformations. If this interpretation is true, then the congenital malformations that are observed with greater frequency among persons who become schizophrenic are not the result of genetic influence associated with that disorder but, rather, are the result of other teratogenic influences of possible etiological relevance for psychosis.

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