Informative Morphogenetic Variants in Patients With Schizophrenia and Alcohol-Dependent Patients: Beyond the Waldrop Scale

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Objective: The authors evaluated the presence or absence of informative morphogenetic variants in patients with schizophrenia compared with alcohol-dependent patients. Method: Taking into consideration the criticisms of the Waldrop Scale, which was widely used until recently to define the presence of informative morphogenetic variants, the authors evaluated the presence or absence of 56 informative morphogenetic variants in 50 consecutively admitted patients with schizophrenia and 50 consecutively admitted alcohol-dependent patients. They made a distinction between minor malformations (those developing during organogenesis) and phenogenetic variants (those developing after organogenesis). A kappa index above 75% was considered reliable. Results: Thirty-four of the 56 informative morphogenetic variants met the authors' reliability criterion. Patients with schizophrenia had significantly higher rates of three minor malformations (furrowed tongue, multiple buccal frenula, and hemangioma) and two phenogenetic variants (protruding auricle and large tongue). Conclusions: The results suggest that using finer distinctions in the evaluation of informative morphogenetic variants in schizophrenia may open new perspectives in the research of the neurodevelopmental background of schizophrenia.

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Informative morphogenetic variants are mild, clinically and cosmetically insignificant errors of morphogenesis that have a prenatal origin and may have major informational value for diagnostic, prognostic, and epidemiologic purposes (1). Several studies comparing informative morphogenetic variants in patients with schizophrenia and control subjects have shown an excess of informative morphogenetic variants in patients with schizophrenia (2–5). Positive correlations between informative morphogenetic variants and congenital cognitive and behavioral deviations have been shown in numerous studies (6, 7).

A major methodological problem is that these studies—following the pioneering work of Mary Waldrop and her colleagues (7)—used the Waldrop Scale to determine the rate of informative morphogenetic variants. Problems with this scale have received extensive evaluation (6, 8). The Waldrop Scale makes no distinction between minor malformations, which arise during organogenesis, and phenogenetic variants, which appear after organogenesis. Most of the criticisms of the scale emphasized Opitz' point (8) that a clear distinction between morphogenetic events occurring during and after organogenesis is needed (6). In other words, minor malformations are always abnormal and can point to problems during organogenesis, but phenogenetic variants are developmentally identical to "normal variants."

Although studies using the Waldrop Scale resulted in important insights into the possible neurodevelopmental background of schizophrenia, recent research interest in the neurodevelopmental etiology of schizophrenia clearly requires a distinction between minor malformations and phenogenetic variants because they might indicate the time and nature of the supposed insult (viral infection or obstetrical complications, for example). In addition, the Waldrop Scale contains only 18 informative morphogenetic variants, but more than 50 informative morphogenetic variants have been listed in the pediatric literature (6, 8).

Using a scale including 56 informative morphogenetic variants, we undertook the present study to evaluate patients with schizophrenia, using alcohol-dependent patients as reasonably acceptable comparison subjects (4).

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METHOD

Using a list of informative morphogenetic variants containing 56 minor signs established by pediatric researchers (6), we evaluated 50

consecutively admitted patients with schizophrenia and 50 consecutively admitted alcohol-dependent patients. Details of the list are given elsewhere by Méhes (6); the signs are listed in appendix 1. All items of the Waldrop Scale except head circumference and longer third toe were included in this list. Three examiners investigated the patients; two of them were aware and one was not aware of the psychiatric diagnoses. Calculations of interobserver reliability were integrated. The kappa index was calculated for each informative morphogenetic variant. Only informative morphogenetic variants with a kappa coefficient above 75% were further analyzed.

Minor malformations were differentiated from phenogenetic variants. The psychiatric diagnoses were made by using DSM-IV. Written informed consent was obtained after the procedure had been fully explained to the patients, and the procedure was approved according to institutional guidelines. The comparison patients were matched in sex, age, and ethnic origin. The examination of informative morphogenetic variants was done qualitatively (present or absent), and no scores were used, but, where it was possible, measurements were taken with calipers and tape. Techniques and standards of measurements were borrowed from the work of Feingold and Bossert (9) and Méhes (6).

Chi-square cross-table analyses were done by using independent samples; all tests were two-tailed.

RESULTS

A kappa coefficient above 75% was found in 34 of the 56 informative morphogenetic variants; the remaining 22 were excluded from statistical analysis. The cumulative rate of informative morphogenetic variants was not significantly higher in the group of patients with schizophrenia. Two of the patients with schizophrenia had more than five informative morphogenetic variants, 19 had one to five, and 29 had no informative morphogenetic variants. None of the alcohol-dependent patients had more than five informative morphogenetic variants, 10 had one to five, and 40 had no informative morphogenetic variants. Five of the informative morphogenetic variants were significantly more common in the group of patients with schizophrenia than in the comparison patients. Three of these were minor malformations: furrowed tongue (kappa=0.76, χ^2=9.46, df=1, p<0.01), multiple buccal frenula (kappa= 0.77, χ^2=8.27, df=1, p<0.01), and hemangioma (kappa= 0.76, χ^2=15.94, df=1, p<0.01). The other two were phenogenetic variants: protruding auricle (kappa=0.78, χ^2= 10.69, df=1, p<0.01) and large tongue (kappa=0.76, χ^2=8.31, df=1, p<0.01). Two of the three minor malformations found significantly more often in patients with schizophrenia were abnormalities of the mouth (furrowed tongue and multiple buccal frenula); the other was an abnormality of the skin (hemangioma). None of the informative morphogenetic variants examined occurred more frequently in the comparison patients.

DISCUSSION

The present investigation was meant to be the first step toward a longer study of the frequency of informative morphogenetic variants in schizophrenia. The results support earlier findings (2–5), and the distinction between minor malformations and phenogenetic variants enabled us to obtain data on whether informative morphogenetic variants developed during or after organogenesis. The findings suggest that abnormalities occur both during (60%) and after (40%) organogenesis: the patients with schizophrenia had an excess of both minor malformations and phenogenetic variants. Two of the three types of variants that developed during organogenesis and three of the five minor malformations and phenogenetic variants were abnormalities of the mouth. A similar distribution was observed in some earlier studies (2, 5).

These data may be used to increase our understanding of the timing of risk during pregnancy. The phase specificity of risk factors is indicated by the particular ontogenetic step with which they interfere.

Epidemiologic data provide evidence that infection with the influenza virus increases the incidence of schizophrenia only when the infection occurs in the second trimester of pregnancy. By contrast, the effect of severe malnutrition, which increases the incidence of schizophrenia in female offspring only, seems to be limited to the first trimester (10). This, combined with the findings of the present study, calls attention to the fact that the effects of both virus infection and severe malnutrition in the development of schizophrenia require further consideration.

The findings suggest the need for further research using a comprehensive list of informative morphogenetic variants and distinguishing minor malformations from phenogenetic variants for a possible construction of a neurodevelopmental subgroup of schizophrenia. This "congenital" subgroup might represent a form of schizophrenia with an aberrant prenatal brain development.

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APPENDIX 1. Informative Morphogenetic Variants

Minor Malformations

- Preauricular tag
- Preauricular pits
- Lip pit
- Bifid uvula
- Supernumerary nipples
- Partial syndactyly toes 2 and 3
- Pigmented nevi
- Cafe-au-lait spots
- Hemangioma
- Sacral hemangioma, pigmented nevi
- Prominent occiput
- Prominent forehead
- Flat forehead
- Flat occiput
- Primitive shape of ears
- Cup ears
- Earlobe crease
- Simian crease
- Sydney line
- Single flexion crease on the fifth finger
- Sole crease
- Prominent heel
- Double whorl
- Multiple buccal frenula
- Furrowed tongue
- Brushfield spots
- Fine electric hair
- Tongue with smooth and rough spots
- Frontal upswap
- Lack of earlobe
- Double antihelix

Phenogenetic Variants

- Small mandible
- Confluent eyebrows
- Short palpebral fissures
- Mongoloid slant
- Antimongoloid slant
- Inner epicanthus folds
- Hypertelorism
- Asymmetrical size of ears
- Protruding auricle
- Low-set ears
- Soft and pliable ears
- Abnormal philtrum
- Large/small oral opening
- High arched palate
- Large tongue
- Short sternum
- Wide-set nipples
- Acromial dimples
- Deep sacral dimples
- Unusual length of the fingers
- Clinodactyly
- Hallucal abnormality
- Wide distance between toes 1 and 2
- Nail hypoplasia
- Dimple on the tuberositas tibiae
- Dimple on the elbow