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Discrimination Effect of the Biomarkers Minor Physical Anomalies Between Schizophrenic Patients and Mentally Healthy Subjects

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The aim of the study is to analyze the predictive value of minor physical anomalies in the binominal model schizophrenic patients-mentally healthy subjects as an index of neurodevelopmental etiology of schizophrenia.

128 schizophrenic patients (66 men, 62 women) and 103 normal controls (49 men, 54 women) are examined with modified Waldrop Physical Anomaly Scale. Predictive value of minor physical anomalies is analyzed with discriminant analysis.

The two-group discriminant analysis distinguishes well between schizophrenic patients and control subjects with 8 independent predictor variables. The variables that contribute to prediction of schizophrenic patient-control subject include high/steepled palate, fine electric hair, third toe [3] second, big gap between I and II toes, epicanthus, abnormal head circumference, hypertelorism, abnormal hair whorls, malformed ears have significant independent contribution to prediction of patient-control status. The model classifies correctly the two groups in 79.57% of the cases and slightly better the controls than the schizophrenics (85.4% vs. 74.8%).

The data of the study show discernible prevalence of morphological anomalies in large cohort of schizophrenic patients in comparison with control subjects. The studies of minor physical anomalies in schizophrenic patients allude to a disturbed neurodevelopment and increased predisposition to development of schizophrenia that could be used for stratification of the risk in future prevention attempts.

Key words: schizophrenia, neurodevelopmental hypothesis, minor physical anomalies, Waldrop scale.

Introduction

Validity of psychiatric disorders as a whole and schizophrenia in particular is determined to some extent by detection of discernible biomarkers. Biomarkers are measurable indicators of underlying disease process (Buchsbaum, M.S., R.J. Haier, 1983), which appear predominantly in psychotic individuals, show greater incidence in their family members and predict development of psychotic disorders in children with high

genetic risk. Biomarkers should be irreversible and allow non-invasive and reliable measurement (Garver, D.L., 1987). Plausible biomarkers at advanced stage of validation in schizophrenia include neurocognitive deficits, characteristic alterations in some evoked potentials, disorders in the smooth eye tracking, increased frequency in smooth (non-localizing) neurological signs and neuroimaging findings of brain structural abnomalies (Szymanski S, J.M. Kane, J.A. Lieberman, 1991; Ivleva, E.I. et al., 2009).

The presence of the biomarkers mentioned at the disease onset or even earlier appears a major argument in favour of the neurodevelopmental hypothesis put forward in the schizophrenia etiology (Weinberger, D.R., 1987; Murray, R.,1994). In its contemporary formulation the neurodevelopmental hypothesis share three assumptions: 1) the primary pathogenetic defect is an early derangement of the central nervous system development that occurs in the early prenatal period; 2) the period of action is relatively short, i.e., it is essentially static; and 3) the consequences of this static process remain relatively latent until long after the primary effect (Woods, B., 1998). Symptoms, typical of the disease, might occur some decades later, perhaps after functional maturation of the nervous system, i.e., in the process of neuronal pruning in adolescence that might occur excessively or improperly (Feinberg, I.,1982/1983; McGlashan, T.H., R.E. Hoffman, 2000).

The concept that early brain disruptions predispose to schizophrenia development is supported by the findings that some schizophrenic patients present morphological evidence of slight developmental abnormalities with probably prenatal origins (Petronius, A., 2004). Minor physical anomalies (MPAs) are slight dysmorphic features mainly in the craniofacial region and limbs that normally have no functional or cosmetic significance (Buckley, P.F.,1998; Weinberg, S.M., E.A. Jenkins, M.L. Marazita, B.S. Maher, 2007), but deserve interest as markers of prenatal maldevelopment. The anomalies appear of particular importance when they are found in ectodermal derivatives or in structures on which aberrant brain morphology can be projected. Regarding the ectodermal origin of the brain, presence of excess of such anomalies may be related to CNS maldevelopment (Waldrop, M.F., F.A. Pedersen, R.Q. Bell, 1968; Steg, J.P., J.L. Papoport, 1975). As the anomalies indicate adverse events during critical periods of the prenatal development, usually the first or early second trimester, MPAs may contribute to understanding the nature and time of occurrence of certain disruptions (Persaud, T., 1979).

The aim of the present study is to analyze the predictive value of MPAs in the binominal model schizophrenic patients-menthally healthy subjects as an index of neurodevelopmental etiology of schizophrenia.

Material and Methods

Subjects

The subjects for this study were 128 schizophrenic inpatients (66 men, 62 women) consecutively admitted in the Clinic of psychiatry in Plovdiv. Their mean age was 32.09 (SD=9.73) years, mean duration of illness 8.02 (SD =7.33), mean number of hospitalizations 4.98 (SD= 5.36). The patients satisfied DSM-IV criteria for a diagnosis of schizophrenia (American Psychiatric Association, 1994) on the basis of case records review, semistructured interview (by V.A. the study psychiatrist) based on a checklist of items from DSM-IV and information obtained from relatives in order to enhance the validity of the diagnosis. Potential subjects were excluded if they had a history of drug or alcohol abuse, identifiable neurological disorder (seizure disorder, head injury, multiple sclerosis etc.), any signs of mental retardation or somatic disorder with neurological components.

The normal comparison group comprised 103 mentally healthy subjects (49 men, 54 women) with a mean age 39.65 (SD=10.68) years and socio-economic background comparable to that of the patients. Normality was defined as the absence of a major axis I or axis II disorder according to DSM-IV (American Psychiatric Association, 1994). They satisfied exclusion criteria similar to those applied to the patients. In addition, to better separate the control from the schizophrenic group, potential normal controls were excluded if they had a first-degree relative with a history of a psychotic disorder, major affective disorder or suicide.

To avoid eventual confound due to the lack of ethnic and racial references of MPA both the patients and normal controls were of Bulgarian origin; individuals with parental or grandparental ethnicity other than Bulgarian were also excluded.

The study was approved by the local Ethics Committee and all subjects gave written informed consent to participate.

Assessment of Minor Physical Anomalies

The subjects were examined with a slightly modified Waldrop Physical Anomaly Scale (Waldrop et al., 1968). It includes 19 morphological abnormalities (Table 2) from six body regions: head, eyes, ears, mouth, hands, and feet. Most of the abnormalities are scored qualitatively as present (1) or absent (0). The variables fine electric hair, head circumference, epicanthus, intercanthal distance, low seated ears, high/steepled palate and third toe ^{3} second are scored in a graded manner – 1 or 2, according to severity.

All examinations were performed by the same examiner (S.S., the study anatomist). Reliability studies were conducted using a second assessor (Z.L.), who was not otherwise involved in the study. Cohen's *k* for concordance between categorical/ordinal scores were all >0.75 and intra-class correlation coefficients for continuous measures – > 0.78. Acceptable level of reliability was not reached for curved 5th finger ($k < 0.60$).

Statistical Analysis

To assess the predictive value of MPA in schizophrenia a two-group discriminant analysis was performed. The analysis allows discrimination between groups on the base of several predictor variables. The correlations between the variables are controlled and the variables analyzed in group. In our model the predictor variables are the 19 MPAs from the Waldrop Scale.

The data were analyzed with SPSS 14.0. Statistical significance was defined as $p<.05$, two-tailed.

Results

The two-group discriminant analysis distinguishes well between schizophrenic patients and control subjects with 8 independent (predictor) biomarkers, classifying correctly 79.57% of the cases (Fig. 1).

Among the biomarkers entered into the equation (Fig. 1), high/steepled palate, fine electric hair, third toe ^{3} second, big gap between I and II toes, epicanthus, abnormal head circumference, hypertelorism, abnormal hair whorls, malformed ears have significant independent contribution to prediction of patient-control status.

The model classifies correctly the two groups and slightly better the controls than the schizophrenics (85.4% vs. 74.8 (Fig. 2).

Predictor biomarkers	Wilks' lambda		% Correctly classified by step
	F	p	
Entering the model			
1. High/steepled palate	56.1515	.000	**68.40%**
2. Fine hair	38.0653	.000	**72.73%**
3. Gap between I and II toe	30.0457	.000	**76.62%**
4. Epicanthus	25.4624	.000	**78.35%**
5. Head circumference	22.1005	.000	**76.96%**
6. Hyper(hypo)telorism	20.2454	.000	**77.39%**
7. Hair whorls ≥ 2	18.8440	.000	**76.52%**
8. Malformed ears	17.6057	.000	**79.57%**

Fig. 1. Two-group discriminant analysis between schizophrenic patients and control subjects with independent variables – biomarkers MPAs

Actual group	Cases	Predicted group affiliation	
		Controls	Schizophrenia
Controls	103	88 85.4%	15 14.6%
Schizophrenia	127	32 25.2%	95 74.8%
Totally		79.57%	

Fig. 2. Classification results

Discussion

The data of the study show discernible prevalence of morphological anomalies in large cohort of schizophrenic patients in comparison with control subjects. The results comply with the data published in a number of other publications (Petronis, A., 2004; Buckley, P.F.,1998; Weinberg, S.M., E.A. Jenkins, M.L. Marazita, B.S. Maher, 2007). In the present study an attempt to deal with the methodological shortcomings of previous studies is made. Main advantages appear the precise clinical evaluation using clear morphological characteristics, reliable statistical methods and adequate power compared with previous studies.

Despite the general tendency to craniofacial localization of MPA, the analysis does not support the hypothesis of craniofacial model of MPA regional distribution. Discriminant analysis determines a set of biomarkers that distinguish sufficiently enough the schizophrenic patients from the control subjects. The independent variables with significant contribution to prediction of the status schizophrenic patient-control subject are high/steepled palate, fine electric hair, third toe – second, big gap between I and II toes, epicanthus, abnormal head circumference, hypertelorism, abnormal hair whorls,

malformed ears. As the discriminant analysis creates one possible biomarker profile, it could be accepted that as a whole the results of the study suggest more frequent but not unique localization of the biomarkers MPAs in the head and face region.

The pattern of changes in the morphological characteristics in our study is not unidirectional. So, the changes in the intercanthal distance can present with both increased and decreased values. That suggests that the changes can be a casual outcome of general neurodevelopmental defect or define different neurodevelopmental defects, which in turn allow better characterisation of the subgroups of schizophrenic patients.

The studies of MPA biomarkers in schizophrenic patients allude to a disturbed neurodevelopment and increased predisposition to development of schizophrenia. They offer a suitable way to throw a bridge across the time (to the pre- and perinatal period), in search of the effect of presumptive disontogenic events. The potential diagnostic value of each of these biomarkers for evaluation of diathesis-stress conditions is limited in terms of time and character of the neurodevelopmental processes as wells as degree of disease susceptibility when applied alone. These should be used in combination to create a diagnostic profile, which defines specific psychiatric syndromes with greater accuracy on the diagnosis than just the clinical standards.

Although MPAs are not specific for schizophrenia, they suggest a risk of development of that disease in presence of neurodevelopmental abnormalities. Some anomalies, nasal volumes, palate anomalies or craniofacial dismorphology in particular, could be informative in further evaluation of the specific pathogenesis of schizophrenia. Depending on the possibilities of high-tech microarray technologies and recent data of investigations on spontaneous mutations, MPAs could prove to be useful in idendification of etiological subtypes or loci of genetic anomalies in schizophrenia. It has to be elucidated whether MPAs, being fixed markers throughout childhood and adolescence, far preceding the prodromes and psychosis onset, could be used for stratification of risk in future prevention attempts.

References

1. Buchsbaum, M. S., R. J. Haier, 1983. Psychopathology: Biological approaches. – Annual Review of Physiology, **34**,401-430.
2. Buckley, P. F.,1998. The clinical stigmata of aberrant neurodevelopment in schizophrenia. – J. NervMentDis., **186**, 79-86.
3. Feinberg, I.,1982/1983. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? – J. Psychiatr. Res., **17**, 319-334.
4. Garver, D. L., 1987. Methodological issues facing the interpretation of high-risk studies: Biological heterogeneity. – Schizophrenia Bulletin, **13**, 525-529.
5. Ivleva, E. I. et al., 2009. Genetics and intermediate phenotypes on the schizophrenia-bipolar disorder boundary. – Neurosci. Biobehav. Rev. (2009), doi 10.1016/ j.neubiorev., **11**.022.
6. McGlashan, T. H., R. E. Hoffman, 2000. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. – Arch. Gen. Psychiatry, **57**, 637-48.
7. Murray, R.,1994. Neurodevelopmental schizophrenia: The rediscovery of dementia praecox. – British Journal of Psychiatry, (165Suppl. 25) 6-12.
8. Persaud, T., 1979. Teratogenesis: Experimental Aspects and Clinical Implications. VEB Gustav Verlag; Jena, Germany.
9. Petronis, A., 2004. Schizophrenia, neurodevelopment, and epigenetics. – In: M.S. Keshavan, J.L. Kennedy, R.M. Murray (Eds.) Neurodevelopment and Schizophrenia. Cambridge University Press, Cambridge, 174-190.
10. Steg, J. P., J. L. Papoport, 1975. Minor physical anomalies in normal, neurotic, learning disabled, and severely disturbed children. – J. Autism Childhood Schizophr., **5**, 299-307.
11. Szymanski, S, J. M. Kane, J. A. Lieberman. A Selective review of biological markers in schizophrenia. – Schizophrenia Bull. **17**(1), 1991, p. 99.

12. Waldrop, M.F., F.A. Pedersen, R.Q. Bell, 1968. Minor physical anomalies and behavior in preschool children. – Child Dev., **39**, 391-400.
13. Weinberg, S. M., E. A. Jenkins, M.L. Marazita, B. S. Maher, 2007. Minor physical anomalies in schizophrenia: a meta-analysis. – Schizophr. Res., **89**, 72-85.
14. Weinberger, D.R., 1987. Implications of normal brain development for pathogenesis of schizophrenia. – Arch. Gen. Psychiatry, **44**,660-669.
15. Woods, B., 1998. Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. – American Journal of Psychiatry, **155**, 1661-1670.