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Minor physical anomalies are more common among the first-degree unaffected relatives of schizophrenia patients – Results with the Méhes Scale

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ABSTRACT

Minor physical anomalies are external markers of abnormal brain development,so the more common appearance of these signs among the relatives of schizophrenia patients can confirm minor physical anomalies as intermediate phenotypes. The aim of the present study was to investigate the rate and topological profile of minor physical anomalies in the first-degree unaffected relatives of patients with schizophrenia compared to matched normal control subjects. Using a list of 57 minor physical anomalies (the Méhes Scale), 20 relatives of patients with the diagnosis of schizophrenia and as a comparison 20 matched normal control subjects were examined. Minor physical anomalies were more common in the head and mouth regions among the relatives of schizophrenia patients compared to normal controls. By the differentiation of minor malformations and phenogenetic variants, we have found that only phenogenetic variants were more common in the relatives of schizophrenia patients compared to the control group, however individual analyses showed, that one minor malformation (flat forehead) was more prevalent in the relative group. The results can promote the concept, that minor physical anomalies can be endophenotypic markers of the illness.

1. Introduction

Minor physical anomalies (MPAs) are insignificant errors of morphogenesis which have a prenatal origin and may bear major informational value. The presence of minor physical anomalies is a sensitive physical indicator of embryonic development. Since both the central nervous system and the skin derived from the same ectodermal tissue in utero, minor physical anomalies may be external markers of abnormal brain development. Minor physical anomalies are considered to develop during the first and/or early second trimester of gestation (Pinsky, 1985; Méhes, 1988; Tényi et al., 2004, 2009) and represent potentially valuable indices of disturbances in early neurodevelopment. Once formed they persist into adult life and are readily detected on visual examination of the particular body area. As we (Trixler et al., 1997, 2001; Trixler and Tényi, 2000; Tényi et al., 2009) and others (Akabaliev and Sivkov, 2007) have discussed earlier, differences and contradictions between studies on minor physical anomalies among adults and children with different neuropsychiatric disorders, may be associated, partly, with the problems in the use of the Waldrop-Scale for the detection of these signs. The Waldrop-Scale contains only 18 minor physical anomalies (Waldrop and Goering, 1971) while in recent pediatric literature more than 50 anomalies have been listed (Pinsky, 1985; Méhes, 1988). An other basic problem with the Waldrop-Scale that it makes no distinction between minor malformations, which arise during organogenesis and phenogenetic variants, which appear after organogenesis (Pinsky, 1985; Méhes, 1988; Trixler and Tényi, 2000). A clear distinction between morphogenetic events developing during and after organogenesis is needed. Minor malformations are always abnormal and are qualitive defects of embryogenesis, which arise during organogenesis. All malformations are developmental field defects and usually they are all-or-none anomalies. In contrast phenogenetic variants are quantitative defects of final morphogenesis and arise after organogenesis. Using a list of minor physical anomalies containing 57 minor signs collected by Méhes (1988), previously

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we have studied the prevalence of minor physical anomalies in patients with schizophrenia, bipolar affective disorder, alcohol dependence,Tourette syndrome and major depression (Trixler et al., 1997, 2001; Tényi et al., 2004, 2015; Csábi et al., 2008), and recently the list and detailed definitions has become also acceptable for researchers, who wish to adapt our suggested modifications for the investigation of minor physical anomalies (Trixler et al., 2001).

The endophenotype concept of schizophrenia represents an important approach in the exploration of the neurobiology of the illness. Gottesman and Gould (2003) described an endophenotype as an intermediate phenotype that fills the gap between genes and diseases. Endophenotypes should be: (1) associated with the illness, (2) heritable, (3) state-independent, (4) found in unaffected relatives at a higher rate than in the general population, and (5) shown to co-segregate with the illness within families. As we can see, an important characteristic of an endophenotype, that it can be more commonly found among the healthy, first-degree relatives of patients with schizophrenia. Minor physical anomalies (MPAs) are suggested as endophenotypes on account of the findings that MPAs are more common in schizophrenia patients than in healthy controls (Weinberg et al., 2007; Xu et al., 2011), as trait-markers they can be found also in remission and in a few – but not in all of the – studies, higher prevalences were found in healthy first-degree relatives (Xu et al., 2011). Overviewing the reports on healthy relatives, 14 studies on the prevalence of minor physical anomalies in the relatives of schizophrenia patients can be found with mixed results. The summary of the results of these studies is presented in Tables 1 and 2. Several studies report that relatives have no MPAs elevations and show frequencies similar to those in healthy controls, while other studies report elevated MPAs among the relatives of schizophrenia patients. A consensus can be seen (Xu et al., 2011; Gassab et al., 2013; Tikka et al., 2015; Ambrosio-Gallardo et al., 2015), that further research is needed to clarify minor physical anomaly alternations as endophenotypic markers of schizophrenia.

The aim of the present study was to investigate the rate and topological profile of minor physical anomalies-using the Méhes Scale to differentiate minor malformations and phenogenetic variants-in the relatives of patients with schizophrenia comparing them to normal control subjects. The following hypotheses have been tested: (1) minor physical are more common in the relatives of schizophrenia patients compared to normal controls, which promotes the hypothesis, that MPAs can be endophenotypic markers of schizophrenia, (2) a higher rate of minor physical anomalies is found predominantly in the head and facial regions among the relatives of schizophrenia patients,pointing at aberrant early (first and second trimester) brain development.

2. Material and methods

2.1. Study subjects

Using a list of 57 minor physical anomalies collected by Méhes (1988), 20 first-degree unaffected relatives of patients with the diagnosis of schizophrenia were examined. 11 parents and 9 siblings were included in the study, the mean age of the relatives was 58.6 ± 6.2 years. Only four relatives were at the at-risk age for schizophrenia (2 relatives at the age of 36 and 2 relatives at the age of 41), all the other relatives age was 53 years or more. As a comparison 20 normal control subjects matched for sex, age and ethnic origin were also observed for minor physical anomalies. Controls were excluded if they endorsed any personal or family history (in the first- or second-degree relatives) of psychotic disorders, mood disorders and schizotypal personality disorder. First-degree relatives of schizophrenia patients were excluded if they endorsed a personal history of psychotic disorders, mood disorders or schizotypal personality disorder. For all participants, psychotic disorders, mood disorders and schizotypal personality disorder were ruled out independently by two experienced psychiatrists according to the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 2000). All available clinical information and data were obtained from structured clinical interviews.

2.2. Examination of minor physical anomalies

We have used the Méhes Scale for evaluation of minor physical anomalies, which includes 57 minor signs (Trixler et al., 1997, 2001; Tényi et al., 2009). Minor physical anomalies are connected to body regions for comparison and analysis of data. A clear differentiation between minor malformations and phenogenetic variants were introduced, the scale and detailed definitions were published earlier

Table 1
The prevalence of minor physical anomalies in the relatives of schizophrenia patients – review of studies.

Authors	I. Group: relatives	II. Group: healthy controls	MPA scales	Results
Ismail et al. (1998)	21	75	Modified Waldrop-Scale	Significantly higher prevalence in the I Group
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Gourion et al. (2004b)	76	44	Gourion-Scale	Significantly higher prevalence in the I Group
Gourion et al. (2004a)	45	42	Gourion-Scale	Significantly higher prevalence in the I Group
Ambrosio-Gallardo et al. (2013)	284	249	Gourion-Scale	Significantly higher prevalence in the I Group
Gassab et al. (2013)	59	71	Gourion-Scale	Significantly higher prevalence in the I Group
Lawrie et al. (2001)	152	35	Waldrop-Scale	Significantly higher prevalence in the I Group
Green et al. (1994)	33	40	Modified Waldrop-Scale	No significant difference
Gourion et al. (2003)	36	42	Gourion-Scale	No significant difference
Compton et al. (2007)	44	54	Lane-Scale, Waldrop-Scale	No significant difference
Gabalda and Compton (2010)	36	47	Lane-Scale, Waldrop-Scale	No significant difference
Aksoy-Poyraz et al. (2011)	66	52	Yoshitsugu-Scale	Significantly higher prevalence in the I Group
Tikka et al. (2015)	30	30	Extended Waldrop-Scale	Significantly higher prevalence in the I Group
Ambrosio-Gallardo et al. (2015)	218	249	Gourion-Scale	Significantly higher prevalence in the I Group