

# Minor physical anomalies are more common in children with idiopathic epilepsy

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**Background:** The prevalence of minor physical anomalies (prenatal errors of morphogenesis) was evaluated in patients with idiopathic epilepsy to get indirect data on the possible role of aberrant neurodevelopment in the etiology of the disease. **Aim:** Connecting to current opinions on a possible role of aberrant neurodevelopment in idiopathic epilepsy it seems important to introduce somatic trait marker research focusing on brain maldevelopment. **Methods:** A scale developed by Méhes (1985) was used to detect the presence or absence of 57 minor physical anomalies in 24 patients with idiopathic epilepsy and in 24 matched controls. **Results:** The mean value of all minor physical anomalies was significantly higher in the group of patients compared to controls. In case of 3 minor physical anomalies we could demonstrate statistically significant differences between children with epilepsy and the control sample. Two minor malformations (primitive shape of ears, double posterior hair whorl) and one phenogenetic variant (inner epicanthic folds) had a significantly higher frequency in patients compared to control individuals. **Conclusion:** The overrepresentation of minor physical anomalies in idiopathic epilepsy can strongly support the view that this disorder is related to pathological factors operating early in development.

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**Keywords:** minor physical anomalies, idiopathic epilepsy, neurodevelopment, childhood epilepsy, somatic markers

Idiopathic epilepsy is a syndrome characterised by only epilepsy, with no underlying structural brain lesion or other neurologic signs or symptoms (Engel, 2001). Idiopathic focal epilepsies comprise a group of syndromes characterized by focal-onset seizures where there is no structural brain abnormality and for which there is likely to be a functional mechanism for the epilepsy and electroencephalography abnormalities (Guerrini & Pellacani, 2012). This group includes several syndromes: benign rolandic epilepsy, benign epilepsy with occipital paroxysms, idiopathic photosensitive occipital lobe epilepsy and some less well-defined syndromes. Idiopathic generalized epilepsy (IGE) is a group of epilepsy syndromes with nonfocal mechanism of onset and no identifiable cause other than a genetic predisposition (Panayiotopoulos, 2005). IGE is subdivided into different syndromes based on predominant seizure type and age of onset (Engel, 2001). Childhood absence epilepsy, juvenile absence

epilepsy, juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures are the major subsyndromes of IGE (Nordli, 2005). By definition IGE is not associated with structural abnormalities on conventional magnetic resonance imaging (MRI), however, recent quantitative studies suggest white and grey matter alternations (reviewed by Liu et al., 2011) and ventricular enlargement (reviewed by Jackson et al., 2011) in IGE. A large series of recent studies demonstrated that several developmental factors (congenital brain malformations, altered neuronal signalling during embryonic life, and defects in post-natal maturation of neuronal networks) contribute to epileptogenesis, leading to the concept of epilepsy as a neurodevelopmental disorder (reviewed by Bozzi et al., 2012).

Minor physical anomalies are mild, clinically and cosmetically insignificant errors of morphogenesis which have a prenatal origin and may bear major

informational value for diagnostic, prognostic and epidemiological purposes (Méhes, 1985, 1988). The presence of minor physical anomalies is a sensitive physical indicator of embryonic development. They are of value to the clinical researchers as they serve as indicators of altered morphogenesis that occurred early in gestation. Since both the central nervous system and the skin are derived from the same ectodermal tissue in utero, minor physical anomalies may be external markers of abnormal neurodevelopment. Minor physical anomalies are considered to develop during the first and/or early second trimester of gestation (Méhes, 1985, 1988; Tényi et al., 2009; Trixler et al., 2001) 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. Minor physical anomalies have been found with increased frequency in neurodevelopmental disorders, as autism (Ozgen et al., 2010), attention deficit hyperactivity disorder (Waldrop & Goering, 1971), mental retardation (Méhes, 1988), Tourette syndrome (Csábi et al., 2008), fetal alcohol syndrome (Méhes, 1988), cerebral palsy (Méhes, 1988) schizophrenia (Trixler et al., 2001) and bipolar affective disorder (Trixler et al., 2001). Only a very few reports from the first part of the 20th century suggest that the frequency of minor physical anomalies is increased in patients with epilepsy (Clouston, 1891; Talbot, 1903; Paskind & Brown, 1936), however, no reports are available on the prevalence of minor physical anomalies using scales developed from data on modern dysmorphology.

As we (Trixler et al., 1997; Trixler & Tényi, 2000) and others (Akabaliev & 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 & Goering, 1971) while in recent pediatric literature more than 50 anomalies have been listed (Méhes, 1988; Pinsky, 1985; Opitz, 2000). Another 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 (Méhes, 1988; Trixler & Tényi, 2000; Pinsky, 1985; Opitz, 2000). Based on the report of the International Working Group (Spranger et al., 1982) in 1985, both Opitz (2000) and Méhes (1988) urged a clear dis-

inction between morphogenetic events developing during and after organogenesis. Minor malformations are always abnormal and are qualitative 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. Morphologically phenogenetic variants are the exact equivalents of normal antropometric variants. Using a list of minor physical anomalies containing 57 minor signs collected by Méhes (1985, 1988) we have previously studied the prevalence of minor physical anomalies in patients with schizophrenia (Trixler et al., 1997, 2001), alcohol dependence (Trixler et al., 1997), bipolar affective disorder (Tényi et al., 2009), major depression (Tényi et al., 2004, 2009), Tourette syndrome (Csábi et al., 2008) and autism (Tényi, 2013) and the list and detailed definitions have become also acceptable for researchers who wish to adapt our suggested modifications for the investigation of minor physical anomalies (Trixler, 2001).

The aim of the present study was to investigate the rate and topological profile of minor physical anomalies in a group of patients with idiopathic epilepsy. The following hypotheses have been tested: (1) Minor physical anomalies are more common in patients with idiopathic epilepsy than in normal subjects, (2) a higher rate of minor physical anomalies is found predominantly in the head and facial regions in patients compared to normal controls. We consider that this kind of clinical morphological marker study can give indirect data concerning the neurodevelopmental component of the etiology of idiopathic epilepsy.

## MATERIAL AND METHODS

### *Participants*

Using a list of minor physical anomalies 57 minor signs collected by Méhes (1985, 1988) 24 consecutively admitted patients for an outpatient evaluation or consultation because of idiopathic epilepsy (13 patients with generalized and 11 children with focal) were evaluated, among the patients' parents there was no subject with the diagnosis of epilepsy, the investigated patients were without intrauterine antiepileptic drug exposure. As controls 24 sex-, age- and ethnic origin-matched children were evaluated. Patients were recruited from the outpatient clinic of the Department of Pediatrics, University of Pécs.

Inclusion criteria were: (1) seizure semiology and electroencephalographic features of generalized or focal epilepsy; (2) no evidence of developmental disabilities or neurologic disorders; (3) normal neurologic examinations; (4) neither abnormal nor unusual findings on conventional MRI by experienced neuro-radiologists. The distribution of the gender of patients has showed 14 boys and 10 girls, the mean age of the patients was  $12.8 \pm 4.9$ . All patients lived with their families and attended regular schools. Children with comorbid diagnoses (mental retardation and with any other neuropsychiatric diagnoses) were excluded from this study. The comparison group of children were from another ward from our Department, with the diagnosis of viral upper respiratory tract infection. Both parents and children gave consent, no compensation was given for participation in the study.

### Methods

We have used the Méhes Scale for evaluation of minor physical anomalies, which includes 57 minor signs (Trixler et al., 2001). The evaluated minor physical anomalies are shown in Table 1. All items in the Waldrop-scale except for head circumference and longer third toe were included in our list of minor physical anomalies. A clear differentiation between minor malformations and phenogenetic variants were introduced, the scale and detailed definitions were published earlier (Trixler et al., 2001). The scale is appropriate for use with both adult and pediatric patients. In all cases patients and their parents gave informed consent, the study was performed in accordance with the Declaration of Helsinki and was evaluated following institutional guidelines. Two examiners investigated all patients and controls separately. The raters were trained by Professor Károly Méhes, and they participated earlier in many minor anomaly studies, and they have a long clinical experience in dysmorphology. The diagnoses of the patients were evaluated according to the modified diagnostic criteria published by the International League Against Epilepsy (ILEA) Task Force on Classification and Terminology (Engel, 2001). The examination of minor physical anomalies was done qualitatively (present or absent) without scores being used, but where it was possible, measurements were taken with callipers and tape to improve the objectivity of examination. Techniques and standards of measurement were borrowed from the works of Feingold and Bossert (1974) and Méhes (1988).

### Statistics

Before the statistical analyses interrater reliability was tested and the kappa coefficient was 0.75 for all items. Statistical analyses were carried out by applying the Fisher's Exact Test for the analyses of all markers, Odds Ratios and 95% confidence intervals were calculated. For the analysis of the frequency of each individual minor physical anomalies two-sided Fisher's exact probability test was used.

### RESULTS

We should consider as a robust finding that in the idiopathic epilepsy sample two patients had more than 6 minor physical anomalies, one patient had 5, seven individuals had 3 or 4, six patients had 2 anomalies and five patients had 1 anomaly. In the control group no subject had more than 2 minor physical anomalies, two subjects had 2 anomalies, ten subjects had 1 anomaly and twelve were without any minor physical anomalies.

The observed frequency of minor physical anomalies for the patient and control groups were tested by Fisher's Exact test, the mean value of all signs was significantly higher among the patients group compared to controls ( $p=0.011$ , OR:7.000, CI (1.641; 29.854)). In the case of three minor physical anomalies we could demonstrate statistically significant differences between the children with epilepsy and the control sample. As it can be seen in Figure 1., in the case of 2 minor malformations (primitive shape of ears, double posterior hair whorl) and of 1 phenogenetic variant (inner epicanthic folds) a significantly higher frequency was observed compared with control individuals.

### DISCUSSION

Since the available evidence indicates that minor physical anomalies arise through processes which act during the early stages of embryonic and fetal life, the overrepresentation of these anomalies in patients with idiopathic epilepsy can support the view that this disorder is related to factors operating early in development. In our study, we have found a significantly higher number of anomalies in the case of two minor malformations which arise during the organogenesis, and in the case of one phenogenetic variant, which arises after organogenesis. It seems important to mention that from the three minor anomalies which were significantly more common among the patients with

**Table 1.** The Méhes Scale

Minor malformations	Phenogenetic variants
Preauricular tag	Small mandible
Preauricular pits	Confluent eyebrows
Lip pit	Short palpebral fissures
Bifid uvula	Mongoloid slant
Supernumerary nipples	Antimongoloid slant
Partial syndactyly toes 2-3	Inner epicanthic folds
Pigmented naevi	Hypertelorism
Cafe-au-lait spots	Asymmetrical size of ears
Haemangioma	Protruding auricle
Sacral haemangioma	Low set of ears
Prominent occiput	Soft and pliable ears
Prominent forehead	Abnormal philtrum
Flat forehead	Large and small oral opening
Flat occiput	High arched palate
Primitive shape of ears	Large tongue
Cup ears	Short sternum
Earlobe crease	Wide-set nipples
Simian crease	Acromial dimples
Sydney line	Deep sacral dimple
Single flexion crease on the 5th finger	Unusual length of fingers
Soke crease	Clinodactyly
Prominent heel	Hallucal abnormality
Double posterior hair whorl	Wide distance between 1 and 2 toes
Multiple buccal frenula	Nail hypoplasia
Furrowed tongue	Dimple on the tuberositas tibiae
Brushfield spots	Dimple on the elbow
Fine electric hair	
Tongue with smooth and rough spots	
Frontal upwap	
Lack of earlobe	
Double antihelix	

**Figure 1.**

Minor malformations	Patients with epilepsy	Control subjects	Statistical significance (Fisher's Exact Test, two-sided)
Primitive shape of ears	8	1	p= 0.023
Double posterior hair whorl	11	0	p<0.001
Phenogenetic variants	Patients with epilepsy	Control subjects	Statistical significance (Fisher's Exact Test, two-sided)
Inner epicanthic folds	5	0	p=0.050

epilepsy, all the three involved the regions of the head, suggesting a stronger relationship with abnormal neurodevelopmental processes. Previous minor physical anomaly studies (Trixler et al., 1997, 2001) indicated that increased frequency of specific anomalies of the mouth and the head has a huge relevance to the hypothetical neurodevelopmental failure. Increased frequency of minor physical anomalies has been observed in persons with epilepsy (Paskind & Brown, 1936). In a classical report inner epicanthic folds were found in 43% of intellectually normal adults with epilepsy (Paskind & Brown, 1936), while in another study a clear evidence of inheritance was obtained for epicanthus, studying minor anomalies in offsprings of epileptic mothers (Gally et al., 1988). We also emphasize the essential informative importance of the significantly increased rate of double posterior hair whorl in our sample, as abnormal hair patterings may call attention to impaired early development of the central nervous system (Méhes, 1985; Smith & Gong, 1974; Frias & Carey, 1996).

Our results on the significantly higher prevalence of minor physical anomalies in idiopathic epilepsy support the importance of data on structural abnormalities of the brain reported in idiopathic epilepsy. In 1917, Thom was first to note ventricle enlargement in patients with epilepsy, he reported lateral ventricle dilation following postmortem examinations of patients with idiopathic epilepsy (Thom, 1917). Studies with single voxel magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopic imaging (MRSI) have provided evidence of both cortical and deep grey matter abnormalities, particularly in frontal lobe and thalamus, in IGE patients (Savic et al., 2004; Doelken et al., 2010). Liu et al (2011) reported on distinct white matter abnormalities in different idiopathic generalized epilepsy syndromes. Children with new-onset IGE had significantly larger lateral and third ventricle volumes relative to the control group, and these abnormalities did not progress over a 2-year interval (Jackson et al., 2011).

To see as a limitation of the study, we should be cautious not to speculate from this minor physical anomaly study on the timing of possible genetic and/or epigenetic insults influencing brain development as further studies on different population cohorts are needed to clarify minor physical anomaly profile of patients with idiopathic epilepsy.

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## A minor fizikális anomáliák gyakoribbak gyermekkori idiopátiás epilepsziában

**Háttér:** A minor fizikális anomáliák (amelyek a prenatális agyfejlődés zavarainak markerei) gyakoriságát tanulmányoztuk idiopátiás epilepsziában szenvedő gyermekek körében, hogy indirekt adatokat nyerjünk a kórkép idegfejlődési hátteréről. **Módszerek:** A vizsgálatban egy Méhes (1985) által kidolgozott skálát használtunk, amellyel 57 minor fizikális anomália gyakoriságát vizsgáltuk 24 idiopátiás epilepsziában szenvedő és 24 illesztett kontroll gyermek esetében. **Eredmények:** A minor fizikális anomáliák szignifikánsan gyakoribban voltak észlelhetőek a betegek csoportjában a kontrollokkal összehasonlítva. Három anomália individuális elemzése során találtunk statisztikailag szignifikáns különbséget a két csoport között. Két minor malformáció (primitív fül, dupla hátsó hajforgó) és egy fenogenetikai variáns (epicanthus) volt gyakoribb az idiopátiás epilepszia miatt kezelt betegek csoportjában. **Következtetés:** A minor fizikális anomáliák gyakoribb megjelenése idiopátiás epilepsziában valószínűsíti, hogy a prenatális agyfejlődés szakaszában szerepet játszó patológiás faktorok szerepet játszanak a kórkép kialakulásában.

**Kulcsszavak:** minor fizikális anomáliák, idiopátiás epilepszia, idegfejlődés, gyermekkori epilepszia, szomatikus markerek