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# Minor Physical Anomalies in Children with Hearing Impairment and Normal Controls

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**A B S T R A C T**

*The aim of this research was to assess differences in the frequency of individual minor phyisical anomalies (MPA) between healthy controls and children with hearing impairment (HI) and to find out whether some MPAs are more informative in discriminating between two groups than cumulative Waldrop's scores. The aim was also to investigate the influence of gender on MPA in children with HI and those with normal hearing (NH). The study was carried out on a sample of 424 children (121 children with hearing impairment (82 boys and 39 girls) aged from 5 to 18 and 303 healthy schoolchildren with normal hearing (152 boys and 151 girls) aged from 8 to 16). In HI children, the mean value of MPA was 2.2 times higher than in the controls. Binary Logistic Regression Model is entirely (with all 18 predictors) statistically significant, that is, it recognizes partial deafness The comparisons between the studied groups of boys and girls HI and boys and girls NH showed a higher relative involvement of MPA in boys than in girls. MPA comparison of HI boys versus NH boys and HI girls versus NH girls according to topographic regions revealed that for HI children there were higher mean scores than for the same-sex controls from all regions, but differences are particularly pronounced in the ear and tongue region. However and that the difference is statistically significant for the majority of regions but this difference tended to be more pronounced in girls with relatively better expressed peripheral dysmorphia in the former and craniofacial dysmorphia in the latter. From the obtained results, it can be seen that in HI children, common etiological factors were probably in effect leading to physical anomalies and hearing impairments. Given the present findings of increased MPAs in HI children, further investigations are necessary to determine whether these developmental abnormalities arise from genetic factors or as a consequence of environmental influences.*

***Key words**: abnormalities, epidemiology, gender, developmental disorders, hearing disorders, minor physical anomalies*

## Introduction

It was determined that the occurrence of minor physical anomalies is related to prenatal and perinatal factors. Such small structural deviations or minor anomalies are believed to occur as a result of altered morphogenesis[1]. Minor physical anomalies (MPA) are generally considered to be unusual morphological features of no serious medical or cosmetic consequence for the individual[2]. MPAs are used for identifying alterations in embryonic development[3–5] and predicting major malformations[6], specific genetic syndromes[1,2,6], mental retardation, psychiatric disease[1,7–9], childhood malignancy[6,10], and metabolic disease[11]. In the initial study by Waldrop et al.[12] which originated from an unpublished study by Goldfarb and Botstein (citation by Waldrop, Pederson and Bell[12]), a list of 18 minor physical anomalies of the head, eyes, ears, mouth, hands and feet was made. Most subsequent studies have used Waldrop and Halverson's modified version[13]. Many different terms have been used to describe them: e.g. minor congenital anomalies, minor malformations, minor physical anomalies, informative morphogenetic variants and each of them refers to a mixture of familiar anthropometric variants, minor deformities, dysplasias and malformations[6]. Although, by definition, minor anomalies have an insignificant impact on a per-

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son's well-being, they can be used for diagnostic, prognostic and epidemiological purposes. However, there are signs that a finding of several minor anomalies in the same child increases the likelihood of the existence of a major anomaly[3]. Several epidemiological investigations also established that minor anomalies are found significantly more often in the range of developmental disorders[7–9,14,15]. Opitz (1985) proposed the term *mild malformations* for changes occurring prior to and during organogenesis[16], although this classification does not appear to be of significant clinical importance. The study of MPAs has had a rich history over the past 40 years. MPAs are easy to measure in a non-invasive, inexpensive manner compared to many other risk markers or potential endophenotypes. MPAs as nonspecific markers of generalized maldevelopment can be associated with hearing impairment and could be an indicator of underlying disorder affecting prenatal development causing hearing impairment.

According to research carried out in Europe and the USA, prevalence of children with impaired hearing is between 1.1 and 2.6 *per* 1,000[17–21], whereas in Asia it is between 5.09 and 9.61 *per* 1,000[22,23]. Although, etiologically, there are several different causal factors, it is considered that for a large group of hearing impairment was unknown in 56 percent of children[24]. Research shows that hearing impairment is more common in male children than in female children[24].

Previous studies have shown that the average number of minor anomalies per individual, assessed as a total score, and Waldrop's weighted score of minor anomalies can provide discrimination between healthy controls and children with hearing impairment[25,26]. Some studies indicate that some individual MPAs could be more informative for abnormal development than the cumulative prevalence expressed as total scores (Compton and Walker, 2009)[27]. So Adam and Hudgins (2003)[28] hypothesize that hearing impairment could be associated with some external ear abnormalities, preauricular pits or tags, and facial asymmetry. Because minor anomalies result from prenatal insults and are predominantly genetically determined they could be valuable in stratification of individuals with increased risk for specific maldevelopment.

Since individual minor anomalies may be more relevant for specific type of maldevelopment than cumulative indexes, the aim of this study was to establish whether individual MPAs are more prevalent in children with hearing impairment (HI). Some MPA may be associated with hearing impairment and can serve as relevant discriminant tool for selecting cases with predominant genetic etiology of the underlying developmental disorder.

## Materials and Method

### *Subjects*

The study was carried out on a sample of 424 children from Zagreb (Croatia). The examined group included 121 children with hearing impairment (82 boys, 39 girls) attending special schools for the care and education of children with hearing impairments. Their mean age was 10.98 years (SD=3.06; range, 5 to 18), (boys 11.18 y (SD=2.91; range, 5 to 18), girls 10.54 y (SD= 3.35; range, 5 to 18)). Children with assumed inherited prenatal disorder were excluded from the study.

Impaired hearing was defined as a permanent unaided hearing threshold level for the better ear of ≥31 dB four frequencies 0.5, 1, 2 and 4 kHz[29,30].

Control group consisted of 303 children with normal hearing (NH) (152 boys and 151 girls) with a mean age of 11.52 years (SD=2.24; range, 8 to 16) (boys 11.61 y (SD=2.25; range 8 to 16), girls 11.44 y (SD=2.23; range, 8 to 16)). Children with normal hearing are those in whom partial deafness and deafness were not diagnosed during the obligatory physical examination prior to school enrolment. Children with normal hearing attending the third, fourth and fifth grades were selected randomly from a primary school.

Diagnosis and other data on the child (sex, age and identity number) were taken from the school/institution records. Minor anomalies and evaluation of their severity were determined by a clinical examination of each child.

To avoid possible confusion due to the lack of ethnic and racial references of MPA, both children with hearing impairment and normal controls were of Croatian origin; individuals were excluded if their parental or grandparental ethnic group was other than Croatian.

Procedures were fully explained to all subjects and to their parent or legal guardian. Written informed consent was obtained from subjects or their guardians; the study was performed in accordance with the Declaration of Helsinki.

### *Assessment of MPA*

Subjects were examined using the Waldrop and Halverson (1971) Physical Anomaly Scale[13]. It includes 18 morphological abnormalities from six body regions: head, eyes, ears, mouth, hands, and feet. Abnormalities are scored qualitatively as present (1) or absent (0). The variables such as fine electric hair, head circumference, epicanthus, hypertelorism (intercanthal distance abnormality), low-set ears, adherent ear lobes, high-steeped palate, curved fifth finger and third toe ≥ second are scored in a graded manner, 1 or 2, according to severity; malformed ears, asymmetrical ears, furrowed tongue, single transverse palmar crease, partial syndactyly of two middle toes, big gap between first and second toes was graded by scoring 1; two or more hair whorls, soft and pliable ears and tongue with smooth-rough spots was graded by weight scoring 0. The hypertelorism as well as the head circumference was scored 1 if it differed from the same-sex mean for normal controls by >1.0 ≤1.5 SD and was scored 2 if it differed by more than 1.5 SD.

*Statistics*

Summary scores were calculated for each region of the body, the total for the craniofacial region (MPA-CF), for the peripheral region (MPA-P) and overall total (MPA-T). Anomalies distribution index was determined according to the following formula: (MPA-CF – MPA-P)/ MPA-T. Descriptive statistics was used for data analysis; two-tailed Student's *t* test for independent samples, for comparing of continuous data; two-tailed $\chi^2$-test or Fisher's exact test (in $2 \times 2$ table), for comparing of categorical data; analysis of variance (ANOVA) with Tukey's honestly significant difference, for multiple comparison; and logistic regression to determine which individual MPA and particular topographic region best determine children with normal hearing and children with hearing impairment. The analysis was performed by IBM SPSS Statistics 20; statistical significance was defined as $p< 0.05$.

## Results

The examined and the control groups differed with regard to gender ($\chi^2=10.835$, df=1, p=0.001 – Fisher's exact test) and age (11.52–10.98) ($F=4.133$, $df_1=1$, $df_2=422$, p=0.043). There was no difference in age of boys and girls within the examined group of children with hearing impairment as well as within the group of children with normal hearing.

*Individual MPA*

Children with hearing impairment were more dysmorphic than children with normal hearing in the male and female subgroups (Table 1).

In boys with hearing impairment, statistically significant differences compared to the controls were found for thirteen MPA: fine electric hair (p=0.006), hair whorls ≥2 (p=0.023), epicanthus (p<0.001), hypertelorism (p= 0.012), low-set ears (p=0.023), malformed ears (p= 0.002), asymmetrical ears (p<0.001), soft and pliable ears (p<0.001), *lingua fissurata* (p<0.001), curved fifth finger (p<0.001), single transverse palmar crease (p= 0.001), partial syndactyly of 2nd and 3rd toes (p<0.001), and big gap between 1st and 2nd toes (p<0.001).

In girls with hearing impairment, statistically significant differences compared to the controls were found for thirteen MPA: fine electric hair (p<0.001), hair whorls ≥2 (p<0.001), head circumference (p=0.008), epicanthus (p=0.002), malformed ears (p=0.041), asymmetrical ears (p<0.001), soft and pliable ears (p<0.001), high-steeped palate (p=0.048), *lingua fissurata* (p<0.001), curved fifth finger (p=0.007), third toe (p=0.019), partial syndactyly of 2nd and 3rd toes (p=0.006) and big gap between 1st and 2nd toes (p<0.001).

Considering the background of higher dysmorphy of children with hearing impairment in both genders, the differences showed some sex-related specifities. For example, the specific anomalies for which statistical significance was found in males were hypertelorism, low-set ears and single transverse palmar crease, while in females these were head circumference, high-steeped palate and third toe. Fine electric hair, hair whorls ≥2, epicanthus, malformed ears, asymmetrical ears, soft and pliable ears, *lingua fissurata*, curved fifth finger, partial syndactyly of 2nd and 3rd toes and a big gap between the 1st and 2nd toes were statistically significantly different in children with hearing impairment compared to the controls of both genders (Table 1).

Table 2 shows that the regions that brought about statistical significance between children with hearing impairment and children with normal hearing also differed in the two genders: eyes and hands in males, mouth in females. Head, ears and feet were the region that accounted for a significant difference in HI children versus controls of both genders.

*MPA by topographic region*

*Intragender comparisons*

HI boys (1) v NH boys (2). Male HI showed higher mean scores than the same-sex controls for all topographic regions (Table 2). The differences were statistically significant (p<0.05) for the head, eyes, ears, hands and feet regions, for the two summary scores, MPA-CF (3.83 v 2.01, 1.91 times increase) and MPA-P (1.98 v 0.83, 2.39 times increase), and for the total MPA score (5.81 v 2.84, 2.04 times increase).

HI girls (3) v NH girls (4). Female HI had higher mean scores than the same-sex controls for all topographic regions (Table 2). The differences reached statistical significance (p<0.05) for the head, ears, mouth and foot regions, for two summary scores, MPA-CF (4.23 *v* 2.02, 2.09 times increase) and MPA-P (2.23 *v* 0.52, 4.29 times increase), and for the total MPA score (6.46 *v* 2.54, 2.54 times increase).

The two intragender comparisons show that HI were significantly more stigmatized with MPA than NH in both sexes, but this difference tended to be more pronounced in girls, largely due to the contribution of the periphery.

*Intergender comparisons*

HI boys (1) v HI girls (3). HI girls appeared to be more dysmorphic than HI boys (Table 2). Girls scored higher than boys for the head, eyes, mouth and the peripheral region of feet, for the two summary scores (MPA-CF (4.23 *v* 3.83, 1.10 times higher) and MPA-P (2.23 *v* 1.98, 1.13 times higher)), and for the total MPA score (6.46 *v* 5.80, 1.11 times higher). Statistical significance, however, was reached only for the ears region (p<0.05).

NH boys (2) v NH girls (4). Table 2 shows that girls have higher mean MPA scores for most of the regions (except head and feet). Summary score MPA-CF was almost equal (2.02 v 2.01). Boys have higher summary score MPA-P (0.83 v 0.52, 1.60 times higher), and the total MPA score (2.84 v 2.54, 1.19 times higher). Statistical significance, however, was reached only for the feet and MPA-P region (p<0.05).

**TABLE 1**
COMPARISON OF MINOR PHYSICAL ANOMALIES (MPA) PREVALENCE RATES BY GENDER BETWEEN CHILDREN WITH HEARING IMPAIRMENT (HI) AND CHILDREN WITH NORMAL HEARING (NH)

| MPA | Boys (n=234) | | | | Statistical Significance* | | Girls (n=190) | | | | Statistical Significance* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HI (n=82) | | NH (n=152) | | | | HI (n=39) | | NH (n=151) | | | |
| | No. | % | No. | % | $\chi^2$ | p | No. | % | No. | % | $\chi^2$ | p |
| Head | | | | | | | | | | | | |
| Fine electric hair | | | | | 10.20 | 0.006 | | | | | 35.48 | <0.001 |
| 1. Fine hair that is soon awry after combing | 5 | 6.1 | 1 | 0.7 | | | 9 | 23.1 | 2 | 1.3 | | |
| 2. Very fine hair that will not comb down | 2 | 2.4 | 0 | 0.0 | | | 2 | 5.1 | 0 | 0.0 | | |
| Hair whorls ≥2 | 39 | 47.6 | 48 | 31.6 | 5.83 | 0.023 | 17 | 43.6 | 18 | 11.9 | 20.69 | <0.001 |
| Head circumference | | | | | 4.16 | 0.125 | | | | | 9.54 | 0.008 |
| 1. >1.0 ≤1.5 SD | 8 | 9.8 | 22 | 14.5 | | | 6 | 15.4 | 23 | 15.2 | | |
| 2. > 1.5 SD | 13 | 15.9 | 12 | 7.9 | | | 9 | 23.1 | 10 | 6.6 | | |
| Eyes | | | | | | | | | | | | |
| Epicanthus | | | | | 15.49 | <0.001 | | | | | 12.38 | 0.002 |
| 1. Partly covered | 15 | 18.3 | 6 | 3.9 | | | 6 | 15.4 | 5 | 3.3 | | |
| 2. Deeply covered | 1 | 1.2 | 0 | 0.0 | | | 1 | 2.6 | 0 | 0.0 | | |
| Hypertelorism | | | | | 8.86 | 0.012 | | | | | 5.58 | 0.062 |
| 1. >1.0 ≤1.5 SD | 14 | 17.1 | 33 | 21.7 | | | 10 | 25.6 | 21 | 13.9 | | |
| 2. >1.5 SD | 14 | 17.1 | 8 | 5.3 | | | 7 | 17.9 | 16 | 10.6 | | |
| Ears | | | | | | | | | | | | |
| Low-set ears† | | | | | 7.54 | 0.023 | | | | | 0.31 | 0.500 |
| 1. Lower by ≤0.5 cm | 1 | 1.2 | 2 | 1.3 | | | 1 | 2.6 | 2 | 1.3 | | |
| 2. Lower by >0.5 cm | 4 | 4.9 | 0 | 0.0 | | | 0 | 0.0 | 0 | 0.0 | | |
| Adherent ear lobes: | | | | | 3.05 | 0.218 | | | | | 1.64 | 0.441 |
| 1. Straight back toward rear of neck | 16 | 19.5 | 17 | 11.2 | | | 7 | 17.9 | 21 | 13.9 | | |
| 2. Upward and back toward crown of head | 2 | 2.4 | 4 | 2.6 | | | 0 | 0.0 | 5 | 3.3 | | |
| Malformed ears | 6 | 7.3 | 0 | 0.0 | 11.42 | 0.002 | 2 | 5.1 | 0 | 0.0 | 7.83 | 0.041 |
| Asymmetrical ears | 18 | 22.0 | 1 | 0.7 | 32.37 | <0.001 | 4 | 10.3 | 0 | 0.0 | 15.82 | <0.001 |
| Soft and pliable ears | 29 | 35.4 | 2 | 1.3 | 53.74 | <0.001 | 10 | 25.6 | 1 | 0.7 | 35.46 | <0.001 |
| Mouth | | | | | | | | | | | | |
| High-steeped palate | | | | | 3.60 | 0.165 | | | | | 6.06 | 0.048 |
| 1. Flat and narrow at the top | 29 | 35.4 | 66 | 43.4 | | | 19 | 48.7 | 63 | 41.7 | | |
| 2. Definitely steepled | 14 | 17.1 | 14 | 9.2 | | | 9 | 23.1 | 17 | 11.3 | | |
| *Lingua fissurata* | 13 | 15.9 | 3 | 2.0 | 16.11 | <0.001 | 7 | 17.9 | 5 | 3.3 | 11.22 | <0.001 |
| Tongue with smooth-rough spots | 21 | 25.6 | 28 | 18.4 | 1.66 | 0.239 | 11 | 28.2 | 48 | 31.8 | 0.186 | 0.703 |
| Hands | | | | | | | | | | | | |
| Curved fifth finger | | | | | 25.64 | <0.001 | | | | | 9.82 | 0.007 |
| 1. Slightly curved inward toward other fingers | 17 | 20.7 | 4 | 2.6 | | | 4 | 10.3 | 7 | 4.6 | | |
| 2. Markedly curved inward toward other fingers | 2 | 2.4 | 0 | 0.0 | | | 2 | 5.1 | 0 | 0.0 | | |
| Single transverse palmar crease | 13 | 15.9 | 5 | 3.3 | 11.84 | 0.001 | 1 | 2.6 | 3 | 2.0 | 0.05 | 1.000 |
| Feet | | | | | | | | | | | | |
| Third toe | | | | | 4.02 | 0.134 | | | | | 7.94 | 0.019 |
| 1. Equal to 2nd | 0 | 0.0 | 4 | 2.6 | | | 2 | 5.1 | 1 | 0.7 | | |
| 2. Longer than 2nd | 1 | 1.2 | 0 | 0.0 | | | 1 | 2.6 | 0 | 0.0 | | |
| Partial syndactyly of 2nd and 3rd toes | 9 | 11.0 | 0 | 0.0 | 17.35 | <0.001 | 6 | 15.4 | 4 | 2.6 | 10.08 | 0.006 |
| Big gap between 1st and 2nd toes | 44 | 53.7 | 18 | 11.8 | 47.82 | <0.001 | 20 | 51.3 | 4 | 2.6 | 66.40 | <0.001 |

† Point where ear joins the head not in line with corner of eye and nose bride
* $\chi^2$-test (in 2 × 2 table with Yates' correction for continuity) or Fisher's exact test: two-tailed

**TABLE 2**
COMPARISON OF MINOR PHYSICAL ANOMALIES (MPA) BY TOPOGRAPHIC REGIONS BETWEEN CHILDREN WITH HEARING IMPAIRMENT (HI) AND CHILDREN WITH NORMAL HEARING (NH) BY GENDER

| Topographic region | Boys (n=234) | | | | Girls (n=190) | | | | Statistical Significance* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HI (n=82) (1) | | NH (n=152) (2) | | HI (n=39) (3) | | NH (n=151) (4) | | | | | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | (1)(2) | (3)(4) | (1)(3) | (2)(4) |
| Head | 1.00 | 0.92 | 0.63 | 0.75 | 1.38 | 1.29 | 0.42 | 0.67 | <0.05 | <0.05 | >0.05 | >0.05 |
| Eyes | 0.72 | 0.95 | 0.36 | 0.58 | 0.82 | 1.05 | 0.38 | 0.69 | <0.05 | >0.05 | >0.05 | >0.05 |
| Ears | 1.00 | 1.14 | 0.20 | 0.46 | 0.62 | 1.07 | 0.23 | 0.49 | <0.05 | <0.05 | <0.05 | >0.05 |
| Mouth | 1.11 | 0.96 | 0.82 | 0.78 | 1.41 | 1.04 | 0.99 | 0.88 | >0.05 | <0.05 | >0.05 | >0.05 |
| MPA-CF | 3.83 | 1.90 | 2.01 | 1.37 | 4.23 | 2.50 | 2.02 | 1.51 | <0.05 | <0.05 | >0.05 | >0.05 |
| Hands | 0.41 | 0.65 | 0.06 | 0.26 | 0.23 | 0.54 | 0.07 | 0.25 | <0.05 | >0.05 | >0.05 | >0.05 |
| Feet | 1.56 | 1.03 | 0.77 | 0.86 | 2.00 | 1.57 | 0.45 | 0.69 | <0.05 | <0.05 | >0.05 | <0.05 |
| MPA-P | 1.98 | 1.19 | 0.83 | 0.92 | 2.23 | 1.63 | 0.52 | 0.76 | <0.05 | <0.05 | >0.05 | <0.05 |
| MPA-T | 5.80 | 2.66 | 2.84 | 1.97 | 6.46 | 3.79 | 2.54 | 2.02 | <0.05 | <0.05 | >0.05 | >0.05 |
| Index of distribution | 0.32 | 0.36 | 0.42 | 0.48 | 0.32 | 0.38 | 0.57 | 0.42 | >0.05 | <0.05 | >0.05 | <0.05 |

* ANOVA with Tukey's honestly significant difference for multiple comparison

**TABLE 3**
ASSESSMENT OF PROBABILITY OF PARTIAL DEAFNESS ACCORDING TO VARIABLES OF MINOR PHYSICAL ANOMALIES (MPA) – (BINARY LOGISTIC REGRESSION MODEL)

| MPA | B | S.E. | Wald | df | p | Exp(B) | 95% C.I. for Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Fine electric hair (yes) | 2.803 | 0.929 | 9.101 | 1 | 0.003 | 16.492 | 2.669 | 101.887 |
| Hair whorls ≥2 (yes) | 1.205 | 0.393 | 9.382 | 1 | 0.002 | 3.336 | 1.543 | 7.210 |
| mult1Head circumference (cm) | –0.393 | 0.101 | 15.209 | 1 | <0.001 | 0.675 | 0.554 | 0.823 |
| Epicanthus (yes) | 1.929 | 0.656 | 8.645 | 1 | 0.003 | 6.884 | 1.903 | 24.906 |
| Asymmetrical ears (yes) | 4.967 | 1.222 | 16.513 | 1 | <0.001 | 143.545 | 13.080 | 1575.269 |
| Soft and pliable ears (yes) | 3.594 | 0.829 | 18.781 | 1 | <0.001 | 36.364 | 7.159 | 184.716 |
| *Lingua fissurata* (yes) | 3.007 | 0.622 | 23.344 | 1 | <0.001 | 20.228 | 5.973 | 68.505 |
| Tongue with smooth-rough spots (yes) | –1.178 | 0.491 | 5.756 | 1 | 0.016 | 0.308 | 0.118 | 0.806 |
| Curved fifth finger (yes) | 1.473 | 0.625 | 5.548 | 1 | 0.018 | 4.363 | 1.281 | 14.861 |
| Third toe (yes) | 3.153 | 0.976 | 10.429 | 1 | 0.001 | 23.414 | 3.454 | 158.720 |
| Big gap between 1st and 2nd toes (yes) | 3.391 | 0.478 | 50.377 | 1 | <0.001 | 29.686 | 11.639 | 75.715 |
| Constant | 13.958 | 5.204 | 7.195 | 1 | 0.007 | 1153621.173 | | |

In HI children, genders showed a reversed anomaly pattern compared with genders in controls. HI girls exhibited a greater increase in MPA than HI boys compared to the same sex controls in the regions of head, eyes, mouth and feet, while the opposite trend was seen in the other two regions – ears, and hands.

The eighteen variables which are commonly used for cumulative Waldrop's scores were used for the assessment of possible discrimination between HI children and controls using Binary Logistic regression Model (Table 3). Due to low frequency of more severe forms of MPA, in this model the variables were included in the binary form, that is, in categories present/absent. Since boys and girls statistically significantly differ in only several MPAs (Table 2), they were examined together in this model. The entire model (all 18 predictors) is statistically significant, $\chi^2$ (18, N=424)=297.7, p<0.001, which proves that the model recognizes partial deafness. The model entirely explains between 50.5% (Cox & Snell $R^2$) and 72.3% (Nagelkerke $R^2$) of dependent variable variance. Validity of the model is confirmed by the results of the Hosmer & Lemeshow test ($\chi^2$=3.35, df=8, p=0.910). Out of 18 predictors, that is components of MPA, only those which statistically significantly contribute to the model are included in Table 3. The strongest predictors are asymmetrical ears, with a 143.545 ratio of probability, which shows that when the anomaly of asymmetrical ears is present, the chance of the subject belonging to HI children group is that much greater. The predictors with

**TABLE 4**
ASSESSMENT OF PROBABILITY OF PARTIAL DEAFNESS ACCORDING TO TOPOGRAPHIC REGIONS – (BINARY LOGISTIC REGRESSION MODEL)

| Topographic Region | B | S.E. | Wald | df | p | Exp(B) | 95% C.I. for Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Head | –1.592 | 0.353 | 20.349 | 1 | <0.001 | 0.204 | 0.102 | 0.406 |
| Eyes | 0.543 | 0.174 | 9.691 | 1 | 0.002 | 1.721 | 1.223 | 2.422 |
| Ears | 1.073 | 0.205 | 27.272 | 1 | <0.001 | 2.924 | 1.955 | 4.373 |
| Mouth | 0.387 | 0.162 | 5.673 | 1 | 0.017 | 1.472 | 1.071 | 2.024 |
| Hands | 1.297 | 0.328 | 15.596 | 1 | <0.001 | 3.658 | 1.922 | 6.963 |
| Feet | 2.214 | 0.312 | 50.188 | 1 | <0.001 | 9.150 | 4.960 | 16.882 |
| Constant | –3.451 | 0.344 | 100.379 | 1 | <0.001 | 0.032 | | |

falling values are as follows: soft and pliable ears (probability ratio 36.364), a big gap between 1st and 2nd toes (probability ratio 29.686), third toe (probability ratio 23.414), *lingua fissurata* (probability ratio 20.228), fine electric hair (probability ratio 16.492), epicanthus (probability ratio 6.884), curved fifth finger (probability ratio 4.363) and hair whorls ≥2 (probability ratio 4.363). Predictors such as head circumference with a probability ratio 0.6884 and *lingua fissurata* with a probability ratio 0.308 show that the chance of the subject belonging to the HI children group is that much smaller. Model sensitivity, that is, recognizing the actual positive (partially deaf) cases amounts to 79.3%, and specificity, that is, recognizing the actual negative (healthy) cases amounts to 95.7%. The model accurately classifies 91% of all subjects.

The same model is created with MPA by topographic regions as predictors (Table 4). That model is entirely (with all six predictors) statistically significant $\chi^2$ (6, N=424)=191.9, p<0.001 which shows good predictive ability of this model as well. The model entirely explains between 36.4% (Cox & Snell $R^2$) and 52.2% (Nagelkerke $R^2$) of dependent variable variance; Hosmer & Lemeshow test ($\chi^2$=5.94, df=8, p=0,654). In Table 4, all six predictors are stated because each of them statistically significantly contributes to the model. The strongest predictors were the feet (9.150 times increase), followed by hands (3.658 times increase), ears (2.924 times increase), eyes (1.721 times increase) and mouth (1.472 times increase). The head as a predictor with a probability ratio of 0.204 shows the chance of the subject belonging to the HI group is that much smaller. Model sensitivity amounts to 62%, while specificity amounts to 92.1%. The model accurately classifies 83.5% of cases.

### *Index of anomaly distribution*

In the HI children, the total MPA score is higher in females than in males. The two genders also showed similar topographic predilections in anomaly increase compared to same-sex controls but on different levels (Table 2).

HI girls showed a proportionately higher increase in MPA-P (2.23 *v* 0.52, 4.29 times) than in MPA-CF (4.23 *v* 2.02, 2.09 times), while in HI boys the increase in MPA-P (1.98 *v* 0.83, 2.39 times) was higher than in the craniofacial complex (3.83 *v* 2.01, 1.91 times).

The above-mentioned tendencies reflect in the index of anomaly distribution of the groups (Table 2). Male HI had a lower index of anomaly distribution than the same-sex controls (0.32 *v* 0.42, p>0.05), which reflects a tendency towards a relatively greater increase of the peripheral compared to the craniofacial stigmatization. Female HI had a statistically significant lower index of anomaly distribution than the same-sex controls (0.32 *v* 0.57, p<0.05).

### *Group × gender interaction*

The group × gender interaction for MPA-CF in HI and NH children was examined by an ANOVA model with main effects (combined) group status and gender and two-way group × gender interactions. Mean MPA CF in HI group amounted to 3.96 (3.83 boys, 4.23 girls), and in the NH group it was 2.01 (2.01 boys, 2.02 girls). The difference was significant only in groups (HI-NH children).

The same model was developed for MPA-P and MPA T in HI and NH children.

Mean MPA P in the HI group amounted to 2.06 (1.98 boys, 2.23 girls), and in the NH group it amounted to 0.67 (0.83 boys, 0.52 girls). The difference was also significant both in groups and according to gender.

Mean MPA T in the HI group amounted to 6.02 (5.80 boys, 6.46 girls), and in the NH group it amounted to 2.69 (2.84 boys, 2.54 girls). The difference was significant only in groups (HI-NH children).

## Discussion and Conclusion

From previous research, it is a known fact that minor physical anomalies may provide powerful tool in clarification of the etiology of the underlying developmental disorder. Furthermore, MPAs have been studied u various medical and dental fields[1,5–9,11,15,25]. It has been determined that MPAs are consistently at a higher frequency in children with impaired development than in healthy individuals, which has been confirmed by the results of

this study[7–9,14,26]. In this paper, the examined and the control groups differed regarding gender, which is to be expected since hearing impairments are more common in male children than in female children[24]. The most striking differences were observed for the minor anomalies affecting ears and tongue. It is expected to find more developmental disturbances affecting ears and head in subjects with HI[26]. According to Adam and Hudgins[28] it is expected to find hearing impairment associated with some external ear abnormalities and facial asymmetry.

The comparison between the studied groups of boys and girls HI and boys and girls NH showed a higher relative occurrence of MPA in boys than in girls. However, the difference was slightly more expanded in the HI group.

Head, eyes, ears, mouth, hands and feet are parts of the body on which different deviations from a normal morphogenesis can be more easily detected. However, those who do not have a clear concept of žnormal' and žabnormal' for these structures are unable to clearly describe the existing changes which they encounter when examining a person with a dysmorphia of any etiology. Therefore, MPAs are not usually assessed for clinical purposes, though some minor anomalies may be observed incidentally during routine clinical interactions and physical examination. MPAs are typically recorded for research purposes.

Along with a higher prevalence of certain MPAs in boys and in the HI as well as in the control group and likewise in the two intergender comparisons by topographic regions, in the HI boys group, a statistically significant difference in the mean value of MPA of the ear region (ear derives from six rudiments) was determined. It seems that girls have higher mean MPA scores for most of the regions. Also, summary scores of MPA for craniofacial and peripheral region as well as the total score is higher in girls from the HI group ($p>0.05$). These increased scores suggest the either presence of severe impairments or are the consequence of environmental influences.

The comparison of MPA in HI boys *v* NH boys and HI girls *v* NH girls in terms of topographic regions pointed to the fact that in children with hearing impairment there were higher mean scores than the same-sex controls for all topographic regions and that this difference was statistically significant for the majority of topographic regions but this difference tended to be more pronounced in girls with relatively stronger expressed peripheral dysmorphia in the first and craniofacial dysmorphia in the second region. Due to the overlap in the periods of prenatal development, MPAs may arise in areas that are far from the craniofacial complex. Therefore, in the complex process of morphogenesis, a greater number of MPA can be common also in distant regions as a result of the co-occurring prenatal effects.

Previous investigations pointed to the fact that the group of HI children significantly differed from NH children[26]. In this study, the mean MPA T in the HI group was 2.2 times higher than in NH group. Since boys and girls differed statistically in a significant manner only in several MPAs, their MPAs were processed together in the Binary Logistic Regression Model. This model recognizes hearing impairment ($p<0.05$). Out of 18 MPAs, 7 increase the chance that the subject could belong to the HI group. As it is expected, the strongest predictors are asymmetrical ears as well as soft and pliable ears. It is considered that mild external ear maldevelopments in the form of MPAs might be associated with hearing impairment in children[28]. Our results confirm this hypothesis. Two predictors (head circumference and *lingua fissurata*) decrease the chance that the subject could belong to the HI children.

The model based on MPA by topographic regions as predictors in total (with all six predictors) is also statistically significant. The strongest predictors are MPA-P. The head as a predictor shows that the chance that the subject belongs to the HI children group is that much lower.

MPAs occur in healthy population as well but they are more present in individuals with developmental disorders during the morphogenesis[1,6]. Research findings to date suggest that MPAs originate from both prenatal insults and genetic factors but genetic factors might be predominant[28]. Obviously, the epidemiology of hearing impairment still remains a challenge with a lot of unanswered questions concerning the nature and time of dysmorphic events in hearing impairment and the way they might cause development of the disease. Our results show that MPA-s may provide powerful tool for discrimination between HI children and healthy controls. Anomalies affecting external ears, head and tongue seems to be the most informative. Further studies are needed to assess relative contribution of genetic and environmental factors to the underlying developmental disturbance leading to hearing impairment.

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## TJELESNE MINOR ANOMALIJE U DJECE OŠTEĆENA I UREDNA SLUHA

## S A Ž E T A K

Svrha ovog rada je utvrditi: razlike u frekvenciji tjelesnih minor anomalija (MPA) između djece uredna sluha (DUS) i djece s idiopatskim oštećenjem sluha; jesu li pojedine MPA značajnije u diskriminaciji ispitivanih skupina od kumulativnih Waldropovih skorova te istražiti utjecaj spola na MPA u ispitivanim skupinama. Istraživanje je provedeno u uzorku 424 djece (121 dijete s oštećenjem sluha (82 dječaka i 39 djevojčica) u dobi od 5 do 18 godina i 303 DUS (152 dječaka i 152 djevojčice) u dobi od 8 do 16 godina). U djece oštećena sluha (DOS) je prosječna vrijednost MPA 2,2 puta veća od DUS. Binary Logistic regression Model je u cjelini (sa svih 18 prediktora) statistički značajan tj. prepoznaje nagluhost. Usporedba MPA u dječaka i djevojčica u DOS i u DUS je pokazala kako je relativno učešće MPA veće u dječaka. Usporedba MPA u dječaka s oštećenjem sluha nasuprot dječaka uredna sluha i u djevojčica s oštećenjem sluha nasuprot djevojčica uredna sluha prema topografskim regijama je pokazala kako su u djece s oštećenjem sluha veći prosječni skorovi MPA u oba spola i to u svim regijama, ali da je ta razlika osobito izražena u regiji uha i jezika. Razlika je statistički značajna za većinu regija, ali je naglašenija u djevojčica i to primarno u perifernim, a sekundarno u kraniofacijalnim regijama. Prema dobivenim rezultatima u skupini DOS su tijekom ranog razvoja vjerojatno djelovali zajednički etiološki faktori, koji dovode do tjelesnih anomalija i slušnih oštećenja. S obzirom na dobivene rezultate tj. visoku zastupljenosti minor anomalija u DOS u daljnjim istraživanjima će se procijeniti relativni doprinos genetskih i okolišnih čimbenika na temeljne razvojne poremećaje koji dovode do oštećenja sluha.