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Original Article / Оригинални рад

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Craniofacial measures and minor physical anomalies in patients with schizophrenia in a cohort of Serbian population

Краниофацијалне мере и мање физичке аномалије код пацијената са схизофренијом у кохорти српске популације

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SUMMARY

Introduction/Objective Craniofacial dysmorphology has been shown as the most prominent among physical anomalies in schizophrenia patients. The aim of the present study was to investigate the frequency of craniofacial anomalies in Serbian schizophrenia patients.

Methods A list of 27 minor physical anomalies (modified Waldrop scale) and 9 ratios of craniofacial measures was used to detect the presence of craniofacial dysmorphology in 126 schizophrenia patients and 124 healthy controls.

Results Comparing to the healthy subjects schizophrenia patients had significantly higher rates of following minor physical anomalies: fine hair, two or more hair whorls, fused eyebrows, wide nose basis, low-seated ears, high steepled and high flat palate, and furrowed tongue (most prevalent were vertical fissures and diffusely distributed fissures) with significance of $p \leq 0.001$. The best predicting parameters for distinguishing between schizophrenics and controls were the inner canthus distance (ICD), the outer canthus distance (OCD), hair whorls (all at level $p = 0.000$), and high steepled palate ($p \leq 0.001$).

Conclusion The results of the present study confirm the neurodevelopmental concept of schizophrenia, being potentially useful for further psychiatric-antropological research. Clinical significance is reflected in the possibility of monitoring in the childhood the potential ectodermal markers of potential mental illness, as well as their comparison with the psychological profile in early adolescence.

Keywords: minor malformations; phenogenetic variants; facial morphometry; schizophrenia phenotype; facial disproportion

САЖЕТАК

Увод/Циљ Дисморфологија краниофацијалних структура показала се као најистакнутија међу физичким аномалијама код схизофрених пацијената. Циљ наше студије је да истражимо учесталост краниофацијалних аномалија код схизофрених пацијената у Србији.

Методе Испитивану групу чинило је 126 схизофрених пацијената, а контролну 124 здрава испитаника. Анализирано је 27 минор физичких аномалија (модификованих по Валдроповој скали) и 9 вредности међусобних односа мерених варијабли.

Резултати У односу на здраве испитанике схизофрени пацијенти су имали значајно већу стопу следећих минор физичких аномалија: танка длака косе, два или више вртлога у власишту косе, спојене обрве, широка база носа, ниско постављене ушне шкољке, високо уско непце, као и избразданост језика (најучесталије су биле уздужне и дифузно постављене бразде) са статистичком значајношћу од $p \leq 0.001$. Статистички посматрано, најбољи предиктивни значај за разликовање схизофрене и контролне групе имале су варијабле: раздаљина између унутрашњих углова очију, раздаљина између спољашњих углова очију, вртлози у власишту косе (сва три параметра на нивоу значајности од $p = 0.000$) и високо непце ($p \leq 0.001$).

Закључак Резултати наше студије подржавају неуроразвојни концепт настанка схизофреније, уз могућност примене у даљим психијатријско-антрополошким истраживањима. Клинички значај се огледа у могућности праћења у детињству потенцијалних ектодермалних маркера могућих душевних болести, те њиховим поређењем са психолошким профилом у раној адолесценцији.

Кључне речи: минор малформације; феногенетске варијанте; морфометрија лица, схизофрени фенотип; диспропорција лица

INTRODUCTION

In the era of technologically advanced and highly precise diagnostic methods, schizophrenia remains a disease whose etiology and pathophysiology remains poorly understood. There are several theories about schizophrenia origin, among which the neurodevelopmental theory being the widely accepted one [1, 2, 3]. During the first trimester of fetal development, the ectoderm and its derivatives

develop intensively – the epidermis, hair, nails, sweat glands, tooth enamel, brain, lining of the mouth, anus and nostrils. Due to the common embryonic origin of the face and the brain, the minor physical anomalies (MPAs) could be considered as potential indices of brain abnormalities linked to schizophrenia [2, 3]. Minor physical anomalies (MPAs) have been defined for the first time by Marden et al. as anomalies which are neither of medical nor cosmetic consequence to the patient, occurring in diverse body regions, such as craniofacial region, mouth, eye, ear, hand and feet region [4]. Minor physical anomalies in behavioral disorders at first were studied in children as associated anomalies with behavioral disturbances [5], and after they have been recognized as indicative in schizophrenia disorders [1, 6, 7, 8].

Minor physical anomalies are thought to have a prenatal origin, being the consequences of ectodermal malformation, either caused by different noxae, or are genetically conditioned. Until today, many authors reported the excess of MPAs occurrence in people with autism, attention deficit hyperactivity disorder, epilepsy, fetal alcoholic syndrome, schizophrenia, and even pedophilia [9–15]. Minor physical anomalies were found being positively associated with reduced prefrontal volume and enlarged basal ganglia volumes [16]. According to the vascular-inflammatory theory of schizophrenia origin, genetically modulated inflammatory response damages the microvascular system of the brain in reaction to environmental agents (infections, hypoxia and physical trauma), leading to the abnormalities of central nervous system metabolism [17]. However, this theory cannot explain the higher prevalence of MPAs in schizophrenia patients, nor in their first-degree relatives [18].

The use of the Waldrop scale brought some issues, among them the absence of distinction between minor malformations, which arise during organogenesis, and phenogetic variants, which appear after organogenesis. Some authors emphasized the need to make this distinction in order to indicate the time and nature of brain adverse events [10, 19]. The minor malformations are qualitative defects of embryogenesis being always abnormal, while the phenogenetic variants are quantitative defects of final morphogenesis. The organogenesis involves thresholds, i.e. all-or-none traits, while the phenogenesis (the final morphogenesis) represents the process of developmental “fine-tuning” [19].

Several studies indicated that among patients with schizophrenia the craniofacial region had the MPAs more commonly than the other regions [2, 3, 6]. Gourion et al. found the facial asymmetry, cleft palate and multiple hair whorls as the most discriminating among other MPAs [6]. In the study of Lane et al. the most prevalent MPAs were the high palate, palate ridge, supraorbital ridge and epicanthus [3]. Trixler et al. found that specific anomalies of the mouth and head as furrowed tongue, flat occiput and primitive shape of ears might have more relevance to the hypothetical neurodevelopmental failure than did the cumulative prevalence of MPAs [20].

This study has an aim to determine the craniofacial MPAs prevalence in schizophrenia patients in this region of Europe. We sought to compare the occurrence of the MPAs between schizophrenia patients and healthy controls, and to determine predictors of schizophrenia among MPAs.

METHODS

Subjects

Study group consisted of 126 schizophrenic inpatients (68 males and 58 females, mean age 35.02 ± 10.31y) who had been hospitalized at the Clinical Center of Vojvodina in Novi Sad, Department of Psychiatry, in the period January 2012 - December 2015. All the patients satisfied the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a diagnosis of schizophrenia (APA 2013) on the basis of case records review (Diagnostic and Statistical Manual of Mental Disorders, DSM-5, 2013). Potential subjects were excluded if they had a history of drug or alcohol abuse, a neurological disorder (seizure disorder, head trauma, multiple sclerosis, etc.), or any signs of mental retardation or somatic disorder with neurological components. The mean age of first neuroleptic treatment was 30.23 years (SD = 8.91, range = 16–53), the mean length of illness since first psychotic episode was 11.77 years (SD = 9.87, range = 0–36), and mean age at time of study was 42.70 years (SD = 12.70, range = 19–64). The family history of mental disorder was present in 43 (33.96%) patients, and 24 (18.86%) of them had at least one suicide attempt. All patients with schizophrenia included 75 subjects with undifferentiated sub-type, 24 with paranoid sub-type, 24 with schizoaffective disorder and 3 with disorganized sub-type.

The control group was comprised of 124 healthy subjects (61 males and 63 females, mean age 32.00 ± 13.38y). All subjects were interviewed by trained psychiatrist using Structured Clinical Interview for DSM-5 Non-patient Version to ensure the absence of major mental disorders.

All subjects were of Caucasian race. Migrants from other regions or states were excluded to avoid a geographical bias. Written informed consents were obtained from all participants. The study was approved by the institutional Ethics Committee of the Clinical Center of Vojvodina and is in compliance with the Helsinki Declaration.

Assessment of MPAs

The presence of MPAs was assessed in craniofacial region using a modified Waldrop scale [5], incorporating 13 elements from the original Waldrop scale, elements listed in other author's scale and

new elements that we added in this modified scale (tables 1 and 2). The assessment of MPAs was done qualitatively (present or absent) without scores being used. Craniofacial measures were obtained using sliding caliper, spreading caliper and nonstretchable measuring tape (Holtain Ltd, Croswell, UK) to the nearest 0.1 cm, as distances between standard anthropological landmarks (Figure 1). Body height was measured using GPM anthropometer to the nearest 0.1 cm (Sieber&Hegner, Zürich, Switzerland) with the subject standing straight up without shoes. Head circumference was measured using Holtain flexible but non-stretchable tape (Holtain Ltd, Croswell, UK), to the nearest 0.1 cm; it was measured from just above the glabella to the most posterior prominent point of the occipital bone.

Inner canthus distance (ICD) and outer canthus distance were put into the ratio because of the statistical reasons.

In order to determine which type of the tongue fissures was the most prominent several items were added to the modified Waldrop scale: continuous longitudinal fissure, discontinuous longitudinal fissure, one central and two shorter longitudinal fissures, only transverse fissures, transverse fissures in the posterior third of the tongue with a longitudinal fissure apically, vertical fissure running along the midline and few fissures diffusely distributed across the dorsal tongue surface, fissures diffusely distributed across the dorsal tongue surface, without any fissures, with rough spots.

Low-seated ears were determined using a slightly modified definition – the lowest point of the earlobe positioned in line between nose and mouth, or in line with mouth or lower.

Assessment reliability

Before the statistical analysis the interrater reliability was tested and the kappa coefficient was >0.75 for categorical measures, and the intraclass correlation coefficient for the continuous variables was between 0.5 and 0.9 (moderate/good reliability).

Statistical analysis

Two-tailed Fisher's exact probability or Pearson Chi-Square tests for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables were used to compare variables between two groups. We used the binary logistic regression to determine the best predictors of schizophrenia among those MPAs.

The multiple univariate logistic regression was used to determine predictors of schizophrenia among MPAs. Also, all the variables with odds ratio of 1.5 or higher with $p \leq 0.05$ were put in a model for diagnosing schizophrenia based on MPAs. The model was tested using the Hosmer-Lemeshow goodness of fit statistics. Post-hoc Bonferroni corrections have been done for all statistical tests used in this study to avoid error due to multiple comparisons. The IBM SPSS Statistics for Windows, version 19.0 was used for all analyses (IBM Corp., Armonk, NY, USA). We used a Two-way MANOVA (Group × Gender) to compare some of the measured continuous variables in participants within the research and control groups.

RESULTS

In the present study, 4 continuous variables were measured (Table 1) and 27 categorical variables were assessed (Table 2), and divided into the hair, eyes, nose, ear, palate and tongue items. Schizophrenia patients had significantly lesser head circumference and body height, and higher values of SSTD, ICD and OCD. Significantly higher rate of the following MPAs was found in schizophrenia patients: fine hair, two or more hair whorls, fused eyebrows, wide nose basis, low-seated ears (the lowest point of the earlobe in line with mouth or lower), high-steepled palate and furrowed tongue - vertical fissure running along the midline.

A Two-way MANOVA (Group × Gender) was used to compare the measured variables in participants between the research and control groups (Table 3). The dependent variables were reduced to three variables, due to high correlation among the continuous variables. The MANOVA yielded a significant group effect ($\Lambda = 0.648$, $F(1,126) = 14.567$, $p < 0.0001$), gender effect ($\Lambda = 0.403$, $F(1,126) = 39.767$, $p < 0.0001$) and interaction effect ($\Lambda = 0.926$, $F(1.126) = 2.150$, $p < 0.05$).

Logistic regression analysis

Whole model of multiple univariate logistic regression including all 12 predictors was statistically significant, $X^2 = 170.67$ $p \leq 0.001$ ($df = 13$, $n = 250$) (Table 4). Values of tolerance in collinearity diagnostics showed no significant multicollinearity between investigated predictors. This model described between 52.4% (R Square of Cox and Snell) and 69.9% (R Square of Nagelkerke) of variance in schizophrenia status. The Hosmer-Lemeshow test as an index of model fitness indicated a good predictive ability of this model ($p = 0.791$). As it was presented in Table 3, 4 from 13 investigated items made significant ($p \leq 0.0038$) independent contribution to prediction of patient-control group status. According to this logistic regression model significant predictors of

schizophrenia were: ICD, OCD, two or more hair whorls and high-steepled palate. This model correctly classified 85.2% of patients and 91% of the comparison subjects, with overall classification of 88.3%.

DISCUSSION

To the best of our knowledge, this is the study with the highest number of subjects in cohort of Serbian population on the prevalence of MPAs in schizophrenic patients. Four following MPAs were indicative as predictors of schizophrenia and confirmed by logistic regression model: ICD, OCD, two or more hair whorls, low-seated ears (the lowest point of the earlobe in line with mouth or lower) and high-steepled palate. The mouth region have been shown as highly susceptible to MPAs in schizophrenic patients [3, 6, 7], with the highest prevalence of the palate and tongue anomalies [21]. Our results are consistent with findings confirming significantly higher rates of the high-steepled palate among schizophrenic patients (57.1% *vs.* 25.0%). Facial-cerebral morphogenesis has been postulated as a primarily midline process, and dysmorphology in schizophrenia patients' face affects principally the midfacial region including the development of the palate [2]. The midfacial region is populated with the cells of the cranial neural crest during the embryogenesis, which could explain coincidence of midfacial minor anomalies and schizophrenic disorder. The maxilla and mandible are derived from the cranial neural crest cells from the diencephalon and anterior part of the mesencephalon, while the nasal processes are derived from the diencephalon and anterior part of the mesencephalon [22].The latter could be brought into relation with the wider nasal base reported by Gourion et al. [6, 23].

Four of the six minor malformations were significantly more common in the group of schizophrenia patients than in the control group: fine hair, two or more hair whorls, high palate, furrowed tongue ($p<0.01$). Most studies showed furrowed tongue to be significant marker of schizophrenia without respect to the type of furrows; Scutt et al. reported higher rate of large tongue [24], while other studies scored randomly furrowed tongue, transversely furrowed tongue or tongue with smooth-rough spots [25]. Our study revealed significantly higher prevalence of only one tongue features type in schizophrenic patients: vertical fissure running along the midline and few fissures diffusely distributed cross the dorsal tongue surface (15.9 *vs.* 2.4%).

Some epidemiological studies suggest that height and schizophrenia are inversely correlated [26, 27]. Our study showed that both men and women were significantly shorter in research group with large effect size. Bacanu et al. explained that the height and schizophrenia disorder are likely to have mostly overlapping genetic causes of discordant effect [28]. Body height was used to relativize

the value of head circumference, and this ratio was significantly higher in study of Mishra et al. [29], which is also in line with results of Huang et al. [8]. Our study confirmed these findings only in male population – circumference relative to body height has been revealed as significantly greater ratio in male schizophrenia patients, but without any statistically significant difference in total sample.

Association between brain anomalies and hair variations could be justified by their common developmental origin. Our results showed that 65.1% of schizophrenic patients have two or more hair whorls, which is in consonance with the results of Gourion et al. [6]. The fine electrical hair was observed more often in the schizophrenic patients regardless the gender, but showed weak predictive power. Gourion et al. also showed significantly higher rate of fine electrical hair in schizophrenic patients [6].

There were no significant differences between the groups regarding the eye features except of the fused eyebrows that were found in more than 30% of schizophrenic patients. Gourion et al. reported fused eyebrows as a statistically insignificant item [6]. Concerning the measurements in eye region, Elizarraras-Rivas et al. found significantly greater ICD and OCD in schizophrenia patients of Mexican population [30], as well as we did in our population – the ICD and OCD were statistically greater. The position of the ears in our study was defined differently than in the most of previous studies considering the level of the lowest point of the earlobe instead [6, 31]. The majority of schizophrenic patients (58.7%) had the lowest point of the earlobe in line with mouth or lower with high statistical significance ($p = 0.000$). The statistically significant presence of low-seated ears in schizophrenia patients was previously found by Gourion et al. [6]. However, this item was recognized as insignificant in studies of Chinese [20] and Bulgarian population [31]. Other ear items in our study did not differ significantly between the groups.

Previous study of Ivkovic et al. on MPAs in a cohort of Serbian population had included lesser subjects and had studied just minor physical anomalies of mouth and palate. They showed that there was no statistically significant difference between schizophrenia patients and control subjects in observed MPAs [32].

Regarding the time and nature of abnormalities, our study indicate they occur during and after organogenesis, since the minor malformations and phenogenetic variants both differ between schizophrenia patients and control subjects. Noted higher frequency of minor malformations and/or phenogenetic variants in research group cannot determine with certainty the exact time of brain adverse event in prenatal period, but could point out the potential prenatal period of higher neurological sensitivity.

CONCLUSION

Results of this study contribute to the existing body of knowledge and support the neurodevelopmental hypothesis of schizophrenia. The inner canthus distances, outer canthus distances, two or more hair whorls and high-steepled palate showed the best discriminative power.

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Table 1. Student's t-test, comparison of continuous variables between patients with schizophrenia and controls

Variables	Patients (N = 123)	Control (N = 108)	p	OR	95% CI
	X ± SD (cm)				
Head circumference[1]	54.98 ± 2.80	56.00 ± 2.22	0.002*	0.852	0.769–0.944
Inner canthus distance[1]	3.38 ± 0.49	2.79 ± 0.45	0.000**	11.950	6.191–23.067
Outer canthus distance[2]	9.71 ± 1.24	8.78 ± 1.46	0.000**	1.560	1.292–1.885
Body height	170.55 ± 10.76	176.38 ± 10.29	0.000**	0.949	3.209–8.455

[1]Waldrop et al. [5]; [2]Huang et al. [8];
OR – odds ratio; CI – confidence interval;
*p ≤ 0.0045(Bonferroni correction);
**p ≤ 0.001

Table 2. Comparison of categorical variables between patients with schizophrenia and controls, the results of Pearson Chi-Square test

Morphological features		Patients (N = 126)	Control group (N = 124)	p	OR	95% CI
		N (%)				
Hair	Fine hair – going up soon after combing[1]	68 (54.0%)	41 (33.1%)	0.001**	2.373	1.422–3.963
	Fine hair – not going down after combing[1]	64 (50.8%)	23 (18.5%)	0.000**	4.533	2.559–8.030
	Two or more hair whorls[1]	82 (65.1%)	15 (12.1%)	0.000**	13.542	7.054–26.001
Eyes	Epicanthus[1]	7 (5.6%)	2 (1.6%)	0.116	3.588	0.731–17.624
	Eyebrows fused[2]	41 (32.5%)	17 (13.7%)	0.001**	3.036	1.612–5.718
	Heterochromia[2]	4 (3.2%)	1 (0.8%)	0.215	4.033	0.444–36.599
Nose	Wide nose basis[3]	65 (51.6%)	21 (16.9%)	0.000**	5.226	2.911–9.382
	Nostrils anteverted[2]	30 (23.8%)	31 (25%)	0.827	0.938	0.526–1.670
Ear	Low-seated ears – the lowest point of the earlobe in line with mouth or lower[4]	74 (58.7%)	20 (16.1%)	0.000**	7.400	4.079–13.425
	Low-seated ears - the lowest point of the earlobe in line with the area between nose and mouth[4]	48 (38.1%)	67 (54%)	0.012	0.524	0.316–0.867
	Adherent earlobes[1]	67 (53.2%)	59 (47.6%)	0.377	1.251	0.761–2.056
	Lower part of earlobes towards back	7 (5.6%)	2 (1.6%)	0.116	3.588	0.731–17.624
	Malformed ears[1]	5 (4%)	0	0.999	-	-
	Asymmetrical ears[1]	6 (4.8%)	4 (3.2%)	0.538	1.500	0.413–5.450
	Soft and pliable ears[1]	64 (50.8%)	55 (44.4%)	0.308	1.295	0.787–2.130
	Preauricular skin tag[3]	0 (0%)	3 (2.4%)	0.999	-	-
Palate	High-steepled palate[1]	72 (57.1%)	31 (25%)	0.000**	4.000	2.335–6.852
	High flat palate[1]	38 (30.2%)	21 (16.9%)	0.015	2.118	1.158–3.875
Tongue	Continuous longitudinal	38 (30.2%)	40 (32.3%)	0.752	0.917	0.537–1.567

	fissure[4]					
	Discontinuous longitudinal fissure[4]	**41 (32.5%)**	**40 (32.3%)**	**0.927**	**1.025**	**0.603–1.742**
	One central and two shorter longitudinal fissures[4]	**12 (9.5%)**	**11 (8.9%)**	**0.843**	**1.091**	**0.462–2.575**
	Only transverse fissures[4]	**9 (7.1%)**	**3 (2.4%)**	**0.093**	**3.129**	**0.827–11.847**
	Transverse fissures in the last third of the tongue with a longitudinal fissure apically[4]	**10 (7.9%)**	**5 (4%)**	**0.196**	**2.070**	**0.686–6.240**
	Vertical fissure running along the midline and few fissures diffusely distributed across the dorsal tongue surface[4]	**20 (15.9%)**	**3 (2.4%)**	**0.001****	**7.683**	**2.220–26.583**
	Fissures diffusely distributed across the dorsal tongue surface[4]	**18 (14.3%)**	**4 (3.2%)**	**0.004**	**5.047**	**1.656–15.380**
	Without any fissures[1]	**12 (9.5%)**	**14 (11.3%)**	**0.663**	**0.834**	**0.370–1.884**
	With rough spots[1]	**44 (34.9%)**	**39 (31.5%)**	**0.531**	**1.184**	**0.698–2.007**

[1]Waldrop et al. [5]; [2]Ismail et al. [33] ; [3]Gourion et al. [6]; [4]New/modified items;
OR – odds ratio; CI – confidence interval;
***p ≤ 0.0018 (Bonferroni correction);**
****p ≤ 0.001**

Table 3. Two-way MANOVA (Gender X Group) of selected continuous variables

Variable	Gender	Group	Mean	SD	p	η_p^2
Body height	female**	Research	163.37	6.12	0.000**	0.532
		Control	169.07	6.94		
	male**	Research	179.64	7.14		
		Control	183.59	7.94		
Head circumference	female**	Research	53.60	2.31	0.000**	0.178
		Control	55.33	1.92		
	male	Research	56.60	2.46		
		Control	56.68	2.32		
(Inner canthus distance + outer canthus distance)/2	female**	Research	6.61	0.84	0.002*	0.044
		Control	5.47	0.71		
	male	Research	6.71	0.80		
		Control	6.10	1.00		

SD – standard deviation; η_p^2 – partial eta-squared;
***p ≤ 0.007 (Bonferroni correction);**
****p ≤ 0.001**

Table 4. Multiple univariate logistic regression model for prediction of group status of schizophrenic patients and normal comparison subjects based on minor physical anomalies

Variable	Beta estimate	SE	χ^2 (df = 13)	p
Inner canthus distance	3.906	0.773	25.558	0.000**
Outer canthus distance	-1.156	0.320	13.050	0.000**
Fine hair – not going down after combing	0.853	0.501	2.894	0.089
Fine hair –going up soon after combing	0.098	0.464	0.044	0.833
Two or more hair whorls	2.049	0.521	15.475	0.000**
Eyebrows fused	0.318	0.552	.332	0.565
Wide nose basis	0.545	0.519	1.104	0.293
Low-seated ears – the lowest point of the earlobe in line with mouth or lower	1.257	0.470	7.162	0.007
High-steepled palate	1.698	0.532	10.191	0.001**
High flat palate	1.225	0.593	4.268	0.039
Vertical fissure running along the midline and few fissures diffusely distributed across the dorsal tongue surface	1.425	1.001	2.028	0.154
Fissures diffusely distributed across the dorsal tongue surface	1.847	0.983	3.529	0.060
Constant	-4.882	1.625		

SE – standard error; df – degree of freedom;
***p ≤ 0.0038 (Bonferroni correction);**
****p ≤ 0.001**

