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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

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

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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 nine ratios of craniofacial measures was used to detect the presence of craniofacial dysmorphology in 126 schizophrenia patients and 124 healthy controls.

Results Compared to the healthy subjects, schizophrenia patients had significantly higher rates of the 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, the outer canthus distance, 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-anthropological research. Clinical significance is reflected in the possibility of monitoring the potential mental illness in childhood through potential ectodermal markers, as well as the possibility of their comparison with the psychological profile in early adolescence.

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

INTRODUCTION

In the era of technologically advanced and highly precise diagnostic methods, schizophrenia remains a disease whose etiology and pathophysiology remain poorly understood. There are several theories about schizophrenia origin, among which the neurodevelopmental theory is 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, minor physical anomalies (MPAs) could be considered as potential indices of brain abnormalities linked to schizophrenia [2, 3]. MPAs were defined for the first time by Marden [4] 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. MPAs in behavioral disorders were initially studied in children as associated anomalies with behavioral disturbances; later, they were recognized as indicative in schizophrenia disorders [1, 5–8].

MPAs are thought to have prenatal origin, being the consequences of ectodermal malformation, either caused by different noxae, or genetically conditioned. To date, many authors reported an excess of MPAs' occurrence in people with autism, attention deficit hyperactivity disorder, epilepsy, fetal alcoholic syndrome, schizophrenia, and even pedophilia [9–15]. MPAs were found to be 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 the central nervous system's 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 along some issues, among them the absence of distinction between minor malformations, which arise during organogenesis, and phenogenetic variants, which appear after organogenesis. Some authors emphasized the

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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. Organogenesis involves thresholds, i.e. all-or-none traits, while 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. [6] found the facial asymmetry, cleft palate and multiple hair whorls as the most discriminating among other MPAs. In the study by Lane et al. [3], the most prevalent MPAs were the high palate, palate ridge, supraorbital ridge and epicanthus. Trixler et al. [20] found that specific anomalies of the mouth and head, such as furrowed tongue, flat occiput, and primitive shape of the ears, might have more relevance to the hypothetical neurodevelopmental failure than the cumulative prevalence of MPAs did.

The objective of this study is to determine the prevalence of craniofacial MPAs in schizophrenia patients in this region of Europe. We sought to compare the occurrence of MPAs between schizophrenia patients and healthy controls, and to determine predictors of schizophrenia among MPAs.

METHODS

Subjects

The study group consisted of 126 schizophrenic inpatients (68 males and 58 females, mean age 35.02 ± 10.31 years) 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 the first neuroleptic treatment was 30.23 years (SD = 8.91, range = 16–53), the mean length of illness since the first psychotic episode was 11.77 years (SD = 9.87, range = 0–36), and the mean age at time of study was 42.70 years (SD = 12.70, range = 19–64). Family history of mental disorders was present in 43 (33.96%) patients, and 24 (18.86%) of them had at least one suicide attempt. The group of patients with schizophrenia included 75 subjects with undifferentiated sub-type, 24 with paranoid sub-type, 24 with schizoaffective disorder, and three with disorganized sub-type.

The control group comprised 124 healthy subjects (61 males and 63 females, the mean age being 32 ± 13.38 years). All the subjects were interviewed by a trained psychiatrist using Structured Clinical Interview for DSM-5 Non-patient Version to ensure the absence of major mental disorders.

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

Assessment of minor physical anomalies

The presence of MPAs in the craniofacial region was assessed using a modified Waldrop scale, 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) [5]. The assessment of MPAs was done qualitatively (present or absent) without scores being used. Craniofacial measures were obtained using a sliding caliper, a spreading caliper, and nonstretchable measuring tape (Holtain Ltd., Croswell, UK) to the nearest 0.1 cm, as distances between standard anthropological landmarks. 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 a flexible but non-stretchable tape (Holtain Ltd.), to the nearest 0.1 cm; it was measured from just above the glabella to the most posterior prominent point of the occipital bone.

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

In order to determine which type of tongue fissures was the most prominent one, several items were added to the modified Waldrop scale: continuous longitudinal fissure, discontinuous longitudinal fissure, one central and

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

Variables	Patients (n = 123)	Control (n = 108)	p	95% CI
	X ± SD (cm)			
Head circumference[1]	54.98 ± 2.8	56 ± 2.22	0.002*	0.769–0.944
Inner canthus distance[1]	3.38 ± 0.49	2.79 ± 0.45	0.000**	6.191–23.067
Outer canthus distance[2]	9.71 ± 1.24	8.78 ± 1.46	0.000**	1.292–1.885
Body height	170.55 ± 10.76	176.38 ± 10.29	0.000**	3.209–8.455

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

Table 2. Comparison of categorical variables between patients with schizophrenia and controls, the results of the Pearson's χ^2 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%)	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	2.559–8.03
	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	0.526–1.67
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	0.413–5.45
	Soft and pliable ears[1]	64 (50.8%)	55 (44.4%)	0.308	1.295	0.787–2.13
	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 fissure[4]	38 (30.2%)	40 (32.3%)	0.752	0.917	0.537–1.567
	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	0.686–6.24
	Vertical fissure running along the midline and a 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	1.656–15.38
	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

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

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 a 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 the nose and the mouth, or in line with the 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 0.5–0.9 (moderate/good reliability).

Statistical analysis

Two-tailed Fisher's exact probability or Pearson's χ^2 tests for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables were used to compare variables between the two groups. We used the binary logistic regression to determine the best predictors of schizophrenia among the MPAs.

The multiple univariate logistic regression was used to determine schizophrenia predictors 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 were 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

Table 3. Ratios between body height and head circumference, Student's t-test

Variables	Patients (n = 123)	Control (n = 108)	p	95% CI
	X ± SD			
BH/HC	3.10 ± 0.16	3.15 ± 0.18	0.054	0.0005–0.08
BH/HC – males	3.17 ± 0.14	3.23 ± 0.15	0.018*	0.011–0.116
BH/HC – females	3.05 ± 0.15	3.06 ± 0.02	0.722	0.045 ± 0.065

HC – head circumference, BH – body height; CI – confidence interval;
*p ≤ 0.05

Table 4. Two-way MANOVA (Sex X Group) of selected continuous variables

Variable	Sex	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

(group × sex) to compare some of the measured continuous variables in participants within the research and control groups.

RESULTS

In the present study, four 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 subnasion–stomion distance, 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.

The head circumference put into the ratio with body height has shown a significant difference only in male patients, while in female patients and in total sample there was no statistical significance (Table 3).

A two-way MANOVA (group × sex) was used to compare the measured variables in participants between the research and control groups (Table 4). The dependent variables were reduced to three variables, due to high correlation among the continuous variables. The MANOVA yielded a significant group effect ($\Lambda = 0.648$, $F(1,126) = 14.567$, $p < 0.0001$), sex 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

The entire model of multiple univariate logistic regression including all 12 predictors was statistically significant, $\chi^2 = 170.67$, $p \leq 0.001$ ($df = 13$, $n = 250$) (Table 5). Values of tolerance in collinearity diagnostics showed no significant multicollinearity between investigated predictors. This model described between 52.4% (R^2 of Cox and Snell) and 69.9% (R^2 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, four of 13 investigated items made significant ($p \leq 0.0038$) independent contribution to the 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 the overall classification of 88.3%.

DISCUSSION

To the best of our knowledge, this is the study with the highest number of subjects in a cohort of Serbian population on the prevalence of MPAs in schizophrenic patients. The four following MPAs were indicative as predictors of schizophrenia and confirmed by the logistic regression model: ICD, OCD, two or more hair whorls, and high-steepled palate. The mouth region has been shown as highly susceptible to MPAs in schizophrenic patients, with the highest prevalence of the palate and tongue anomalies [3,

Table 5. Multiple univariate logistic regression model for the 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	0.32	13.05	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	0.332	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	0.47	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

6, 7, 21]. Our results are consistent with findings confirming significantly higher rates of the high-steepled palate among schizophrenic patients (57.1% *vs.* 25%). 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 the 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]. Gourion et al. [6] reported that the latter could be brought into relation with the wider nasal base [23].

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 eyebrows fused, wide nose basis ($p < 0.01$). Most studies showed furrowed tongue to be a significant marker of schizophrenia without respect to the type of furrows; Scutt et al. [24] reported higher rate of large tongue, 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 the research group, with large effect size. Bacanu et al. [28] explained that the height and schizophrenia disorder are likely to have mostly overlapping genetic causes of discordant effect. Body height was used to relativize the value of head circumference, and this ratio was significantly higher in a study by 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 a significantly greater ratio in male schizophrenia patients, but without any statistically significant difference in the 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]. Fine electric hair was observed more often in the schizophrenic patients regardless of the sex, but it showed weak predictive power. Gourion et al. [6] also showed significantly higher rate of fine electrical hair in schizophrenic patients.

There were no significant differences between the groups regarding the eye features except of the fused eyebrows, which were found in more than 30% of schizophrenic patients. Gourion et al. [6] reported fused eyebrows as a statistically insignificant item. Concerning the measurements in the eye region, Elizarrarás-Rivas et al. [30] found significantly greater ICD and OCD in schizophrenia patients in the Mexican population, as did we in our population – ICD and OCD were statistically greater. The position of the ears was defined differently in our study than in most of the 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 the studies of the Chinese and the Bulgarian population [20, 31]. Other ear items in our study did not differ significantly between the groups.

A study on MPAs by Ivković et al. [32] in a cohort of the Serbian population included less subjects and studied just the MPAs of the mouth and palate. They showed that there

was no statistically significant difference between schizophrenia patients and control subjects in observed MPAs.

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

CONCLUSION

The 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.

Conflict of interest: None declared.

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Краниофацијалне мере и „минор“ физичке аномалије код болесника са схизофренијом у кохорти српске популације

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САЖЕТАК

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

Метод Испитивану групу чинило је 126 схизофрених болесника, а контролну 124 здрава испитаника. Анализирано је 27 „минор“ физичких аномалија (модификованих по Валдроповој скали) и девет вредности међусобних односа мерених варијабли.

Резултати У односу на здраве испитанике схизофрени болесници 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 следеће 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 могућих ектодермалних маркера душевних болести у детињству, те њиховог поређења са психолошким профилом у раној адолесценцији.

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