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MEANING AND CLINICAL INTEREST OF MINOR MALFORMATIONS AND NORMAL VARIANTS IN NEONATOLOGY

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ABSTRACT

Congenital malformations can be found in all organ systems of a newborn. Almost two-thirds of congenital malformations have an unknown cause. There are minor (mM) and major (MM) congenital malformations. Searching for minor malformations has its vital place in everyday neonatology practice. Minor malformations are defined as physical variants that have no medical consequences and are mostly located on the face and distal parts of the extremities and are easily noticed. Minor malformations occur in approximately 15% of newborns. Minor congenital malformations are of great importance because they can be an indicator of the existence of major congenital malformations and syndromes. In a one-year retrospective study that analyzed the occurrence of 38 minor malformations through the year 2023 at the University Clinical Hospital of Mostar, there was an incidence of 10.59% of minor malformations. The most frequently recorded minor malformation was deep a sacral dimple at 44.72%, then poorly modeled ears at 15.08%, and moderate rectal diastasis at 14.58%. Three or more minor congenital malformations indicate one or more major congenital malformations. Major congenital malformations are severe structural defects of tissues and organs that endanger life, create serious functional disturbances and hinder the development of the child. In our country, there is currently a recorded incidence of 8.04%. The search for minor malformations in the newborn period is of great importance to children and the whole family, and the search must not be neglected.

Key words: minor malformations, major malformations, newborn, search

INTRODUCTION

Malformations are macroscopically visible defects in the shape (morphology) of a certain part of the body, an organ or its part that occurs during organogenesis, i.e. from the second to the twelfth gestational week, and which are visible at birth (1). Deformations are tissue and organ changes that occurred because of intrauterine damage - usually of a mechanical nature. Disruptions are morphological defects caused by the destruction of tissues that were originally developed normally. A syndrome implies a group of malformations that are the result of a specific cause (2). Congenital malformations are structural changes that occurred prenatally and are visible in the newborn at birth. Structurally, malformations can be divided into minor and major malformations. Minor malformations occur in approximately 15% of newborns (3). They do not impair health but should be seen as a possible indicator of the existence of major malformations. Major congenital malformations are severe structural defects of tissues and organs that endanger life, create serious functional disturbances, and hinder the development of the child (4). Most studies have shown that minor malformations occur more often in children with low birth weight and less gestational age than in term newborns (5). Congenital malformations occur as a result of genetic diseases, but also as a result of the interaction of numerous environmental factors with genes (6). There are many environmental factors such as teratogenic drugs and chemicals, alcohol, maternal infections, ionizing radiation, but also maternal diseases such as unregulated diabetes, epilepsy, phenylketonuria. Each of these exogenous factors will then

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cause a disruption (7, 8). Major malformations are those that have an unfavorable effect on the function of a certain organ, organ system or the social acceptance of the child, and later on the person as an adult. These malfunctions are often recognized immediately at birth, and sometimes intrauterine. On the other hand, minor malformations usually have no major physiological or cosmetic significance, and examples include preauricular appendages, syndactyly and others (7). Minor malformations are often present in the normal population and are physical variants that, based on the frequency of occurrence in the general population, can be divided into minor malformations and normal variants (9). The normal variant is present in more than 4%, and minor malformations appear in less than 4% of the normal population. They are most often found in the facial area and the distal parts of the extremities (3). Minor malformations have no major clinical significance (apart from aesthetic ones), but according to Mehes' scheme of minor malformations, three or more minor malformations require additional diagnostic treatment (table 1) (10).

In previous studies, the incidence of minor malformations is higher in prematurity, and the aim of this study at the Clinic for Children's Disease is to show the frequency of minor malformations and normal variants in term newborns.

MATERIALS AND METHODS

A one-year retrospective study was conducted. The research was carried out at the Clinic for Gynecology and Obstetrics of UCH Mostar's "Department for Newborns". Data was collected from children's records and the mother's medical history, and at the Clinic for Pediatrics, Department for Neonatology and Intensive Care from discharge letters and transfer lists of newborns. All newborns were involved in the study, including term newborn who were born at a gestational age from $37^{+0/7}$ to $41^{+6/7}$ weeks and newborns born with lower birth weight and chromosomal abnormalities. The study included all newborns who met the above criteria as of January 1, 2023 until January 1, 2024. The parameters considered the newborn child's gender, gestational age, Apgar score, birth weight, birth length, and minor anomalies - malformations such as: preauricular appendages, low-laid ears, high-arched palate, small chin, simian line, antimongoloid shaped eye slits, partial syndactyly of 2 and 3 fingers, accessory wart, umbilical hernia, moderate rectus diastasis and other minor malformations. Also, the parameters considered the mother's age, number of pregnancies, births, abortions, method of conception, course of pregnancy, pathological conditions during pregnancy (hypertension, diabetes, infections prior to delivery, hypothyroidism), method of delivery, medications during pregnancy, and other available data from medical records. For the neonatological examination, the most practical was that of Mehes' scheme, with 38 mM items (Table 1). We adhered to this scheme (10). All term newborns were examined during the first 24 hours of life, and if minor malformations were noticed, they were recorded in the clinical status of the newborn's temperature chart. Major malformations were registered according to EUROCAT recommendations (11). The newborn's birth weight is determined with a digital scale manufactured by Momert, model MM6475, immediately after birth, and the progress of the neonate was monitored by daily weighing with the aforementioned scale. The gestational age of the newborn is calculated based on the date of birth and the date of birth of the pregnant woman.

Statistical analysis

R Studio (RStudio Team 2021) was used for statistical analysis and graphical display of data: Integrated Development Environment for R. (RStudio, PBC, Boston, MA URL http://www.rstudio.com/) and Microsoft Excel for Microsoft 365 MSO (Version 2111. Microsoft Corporation, Redmond, WA, USA). For the nominal variables in the research, the frequencies of occurrence were stated, and the differences between the frequencies were tested with the Chi-squared test.

RESULTS

In the period from January 1, 2023 until January 1, 2024, a total of 1,880 children were born (1,872 live births, 8 stillbirths), and some minor malformations were observed

Table 1. Mehes' scheme of minor malformations (10)

Head and neck: Small mandible, Prominent forehead, Flat occiput, Prominent occiput, Extra posterior cervical skin	**Foot:** Partial syndactyly 2nd and 3rd toes, Wide distance between 1st and 2nd toes, Broad hallux, Hallux dorsiflexion, Prominent heal
Eye: Epicanthic folds, Mongoloid slant, Antimongoloid slant, Short palpebral fissures, Hypertelorism, Ptosis	**Thorax:** Short sternum, Accessory nipples, Wide set nipples
Ears: Small ears, Asymmetrical size, Poorly modeled ears, Low-set ears, Preauricular tags, Preauricular fistula	**Abdomen:** Umbilical hernia, Inguinal hernia, Moderrate rectal diastasis
Mouth: Small oral opening, Large tongue, High-arched palate, Bifid uvula	**Skin:** Raised and large hemangioma(s) Large pigmented nevi, Deep sacral dimple
Hand: Simian crease, Clinodactyly, Single crease on 5th fingers	

in 199 (10.59%) newborns. In total, 16 newborns out of 199 (8.04%) had one of the major malformations. More than 53% of mothers whose child had one of the malformations gave birth between the ages of 30 and 39, while the least represented age group was of mothers under 20. The largest number of mothers gave birth naturally, 138 (69.35%) of them. The highest number of children with some type of malformation was registered in first pregnancies, 93 (46.73%). As many as 197 (98.99%) of women giving birth, had natural insemination, and only 2 (1.01%) had medically assisted insemination. 183 (91.96%) of women who gave birth had no previous abortions, while 12 (6.03%) of them had 1 abortion. In the categories where mothers had at least one abortion, no statistically significant differences were noticed between the frequencies of the observed types of malformation. All pregnant women were monitored for certain pathological conditions during pregnancy. The largest number of women giving birth were without pathological conditions, 153 (74.63%). Among women in labor who had at least one pathological condition, the largest number of them had hypothyroidism 32 (15.61%). The largest number of mothers did not use any medication during pregnancy, 157 (77.34%), and of those who used drugs, the largest number of them used levothyroxine sodium, 31 (15.27%). Malformation of the oral cavity was the most frequent malformation in pregnant mothers who did not use any therapy, 45.72%, and in pregnant mothers who used levothyroxine sodium, 10.55%. In groups where mothers used antidiabetic or antihypertensive drugs, all malformations were equally represented. As stated earlier, a total of 199 children were born, of which 116 (58.29%) were boys and 83 (41.71%) were girls ($\chi2 = 5.47$, df = 1, $p < 0.05$). The largest number of boys and girls had a birth weight between 2500 and 3500 grams, and a length between 53 and 56 centimeters. The largest number of male and female children were born between the 37th and 42nd week. Additionally, the study analyzed how many children have up to three and how many more than 3 stigmata. In total, 168 (84.42%) of the children had less than 3 stigmata, while 31 (15.58%) of them had three or more stigmata ($\chi2 = 94.31$, df = 1, $p < 0.01$). From the above mentioned data, it is clearly visible that those children who had some type of malformation on the eyes ($\chi2 = 5.54$, df = 1, $p < 0.05$), head and neck ($\chi2 = 6.26$, df = 1, $p < 0.05$) mostly had at least 2 additional malformations. All subjects who had one of the malformations on their hand also had at least 2 other malformations. In malformations of the abdomen ($\chi2 = 13.33$, df = 1, $p < 0.01$) and oral cavity ($\chi2 = 40.33$, df = 1, $p < 0.01$), a greater number of children had up to three malformations. Children with skin malformations had no additional malformations. In malformations of the chest, feet, and ears, no statistically significant differences were observed between the frequencies of children who had up to 3 malformations and those children who had more than 3 malformations. Statistically significant differences were noticed between the observed frequencies of different types of malformations ($\chi2 = 182.31$, df = 9, $p < 0.01$). Thus, the most frequent malformation was the deep sacral dimple, where as many as 89 (44.72%) of children had this type of malformation. Of the other malformations, the most common were poorly modeled ears observed in 30 (15.08%), and moderate rectus diastasis observed in 29 (14.57%) (Table2). In total, there were 16 (8.04%) of the children with major malformations. Among 199 children, cytogenetic analysis confirmed Down syndrome in 6 cases (3.02%), and cleft palate was identified in 8 (4.02%). Out of the children who had one of the major malformations, the largest number of them had a malformation of the cardiovascular system, 4.02% ($\chi2 = 9.63$, df = 3, $p < 0.05$). No statistically significant differences were noticed between the observed frequencies of different types of minor malformations in children who had one of the major malformations ($\chi2 = 20.22$, df = 23, $p = 0.63$). In 16 children with one of the major malformations, 8 of them (50.00%) had more than three minor malformations, and the same number of children had up to three malformations (Table 3).

Table 2. Ten most frequent minor malformations

Minor malformations	N	%	χ2	df	p
Deep sacral dimple	89	44,72	182.31	9	<0.01
Poorly modeled ears	30	15,08			
Moderate rectal diastasis	29	14,57			
Hypertelorism	18	9.05			
Wide distance between st and 2nd toes	18	9.05			
High-arched palate	18	9.05			
Small mandible	17	8.54			
Low-set ears	17	8.54			
Preauricular tags	12	6.03			
Extra posterior cervical skin	12	6.03			

Table 3. Frequency of minor malformations in newborns with some type of major malformation

Minor malformations	N	%	χ2	df	p
Wide distance between 1st and 2nd toes	7	43,75	20.22	23	0.63
Extra posterior cervical skin	6	37.5			
High-arched palate	6	37,5			
Hypertelorism	5	31,25			
Small mandible	5	31,25			
Small ears	5	31,25			
Epicanthic folds	4	25			
Prominent heal	4	25			
Clinodactyly	4	25			
Simian crease	4	25			

DISCUSSION

The clinical features of genetic diseases are varied. Various malformations and congenital abnormalities that are already present intrauterine or postpartum can arouse the suspicion that it is a genetic disease. Therefore, clinical features, i.e. the clinical examination of the child, is an extremely important part of diagnostics. Suspicion of a genetic disease can be aroused by various forms of facial dysmorphic disorder: wide face, coarse facial features, protruding lateral parts of the frontal bone, widely spaced eyes, mongoloid or anti-mongoloid shaped eyes, microphthalmia, epicanthus, wide and high nose root, low-laid and malformed ears, microtia, macrotia and anotia, macrostomia and microstomia, cleft lip and cleft palate, as well as high-laid palate. Any morphological change with an incidence greater than 4% in the population is a normal variation in development (12). Some authors state that normal variation is any morphological category with an incidence greater than 6% (13).

We conducted a one-year survey from 2023 until 2024 and compared it with a similar survey from 28 years ago, conducted in the same geographic area and in the same hospital, on almost the same number of births (14, 15). Šumanović D. et al, state in their research through 1995/1996, that the incidence of minor malformations stood at 23.7% (14, 15). This research was carried out at the end of the war in Bosnia and Herzegovina. In our research, after almost 28 years, the incidence of minor malformations was halved to 10.59%. Most studies have shown that minor malformations occur more often in children with low birth weight and less gestational age than in term newborns (4), which is not the case in our study. Most of our newborns with minor malformations were born after the 37th week of gestational age and with proper weight for gestational age. The results may be different for each population because the studies were conducted in relatively distant and different geographical regions. Neonatologists and medical staff are the first to notice minor malformations in newborns. Thus, Sawardekar states the incidence of minor malformations in a regional hospital in Oman was at 12.4% per 1000 births (16). A study from Egypt by El Awady H. et al., reported an incidence of 21.6% (17). A study from Congo reported that 34.8% of newborns had one minor malformation, 11.6% had two, and 4.3% had three (18). The presence of three or more minor malformations was associated with a 4.5 times higher risk of death (19). 25.4% of newborns born to mothers who used prescription opioids during pregnancy were diagnosed with major or minor congenital malformations (20). Some characteristics in one population may be minor malformations, and in another a normal variant of development. Thus, Tsai et al. report the simian line and mongoloid-shaped eye slits as a normal variant for Chinese newborns (21). In other ethnic groups, however, these signs serve as predictive markers for some chromosomal aberrations and specific syndromes (10).

Down syndrome and cleft palate accounted for 56% of oral cavity malformations in our study population of 199 children. Of these, six children had Down syndrome and eight had cleft palate. Common minor oral malformations in these children included high-arched palate, bifid uvula, small oral opening, large tongue. Hod M. et al., investigated the prevalence of minor congenital malformations in newborns of mothers with gestational diabetes, and this prevalence was between 19.4% and 20.5%. In our study, however, it was an almost imperceptible percentage of 3.45% (22). In this study, the most common pathological condition of the mother was hypothyroidism 32/15.61%. According to Kolobarić et al. (23), women with hypothyroidism had significantly higher rates of gestational diabetes (15%) and preeclampsia (3.5%). Gestational diabetes itself carries the prevalence of minor congenital malformations. In our research, the most common minor malformation was a deep sacral dimple in as much as 44.72%, which is also confirmed by research almost three decades ago in the same area of ours (15). This is in favor of the normal variants of our geographical area. Pediatric neurosurgeons concur that imaging studies are not required for newborns and infants presenting with simple sacral dimple (24). Immediately after the birth of the newborn, already in the delivery room, an orientation examination should be done in which we look for malformations. Some of the congenital malformations are immediately noticeable and do not necessarily endanger the child's life. An example of such malformations can be ear deformations, which in our research is the second most frequent malformation: poorly modeled ears at 15.08%. Bader D. et al. (25) report a frequency for malformation of the ears of 43.1% and state that the male gender is more frequently affected by this, coinciding with our research. However, there are malformations that are not immediately visible and can endanger the child's life, such as congenital anomalies of the heart. Almost three decades ago, the aforementioned study from our geographical area (15) stated the incidence of major malformations of 57.5%, and in our study the prevalence of major malformations was 8.04%. We can contribute this big drop to better prenatal care of pregnant women, the improvement of prenatal diagnostics and the improvement of the socio-economic conditions of pregnant women. El Awady H. et al. report a major incidence at 78.4%, and the cardiovascular system was most often affected in 32.4%. This coincides with our research (17). Newborns with congenital heart disease exhibit a broad

spectrum of dysmorphism (26). The great importance of minor malformations is that in 90% of all newborns who have 3 or more minor malformations, a major malformation also exists. Thus, minor malformations indicate the possible presence of major malformations (27). The risk of major malformations increases with the number of minor malformations. Any newborn with 3 or more minor malformations must be clinically treated and major malformations such as cardiac, renal or spinal anomalies must be sought. Newborns who were discharged after 24 hours from the maternity hospital and who had 3 minor malformations were recommended further diagnostic and ultrasound treatment. Newborns who were transferred to the Clinical Department of Neonatology with three or more minor malformations were subjected to diagnostic processing.

CONCLUSION

Awareness of the presentation and frequency of minor malformations in the population is crucial for neonatologists, who must distinguish between abnormal findings and normal variations. Recognizing minor malformations in a newborn, especially when their number exceeds three, should prompt a diagnostic search for the presence of major malformations. Neonatologists, as pediatricians managing the youngest population, have a unique opportunity to be the first to identify abnormalities in children and to make clinical judgments on the health risks they may pose. The results of our study strongly suggest that any newborn with three or more minor malformations should undergo an extended clinical evaluation due to the higher risk of associated major malformations.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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