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P R A C E K A Z U I S T Y C Z N E
położnictwo

Cyclopia – literature review and a case report

Cyklopia – przegląd literatury i opis przypadku

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Abstract

Cyclopia is a deformation of the facial skeleton with one eye orbit formed in the place where both eyes should be present. As a result of hypoplasia there is absence (hypothesized loss) of central nervous system structures.
Teratogenic factors leading to the occurrence of this anomaly may include irregular cholesterol biosynthesis, viruses, alcohol intake and maternal diabetes. Many authors suggest genetic etiology of this illness.
The following work presents a case of a female patient whose fetus was diagnosed with multiple defects, among others with cyclopia. After pharmacological induction of labor, a male fetus with vital signs was born but died after two hours. As far as cyclopia is concerned, special attention should be paid to proper diagnosis of this pathology at an earliest possible stage of fetal life. Early ultrasound diagnostics of this anomaly must be emphasized most strongly, leading to the conclusion that patients suspected of fetal facial skeleton defects should be referred to medical centers which are qualified in prenatal examinations.

Key words: **pregnancy** / **nervous system malformations** / **holoprosencephaly** / / **fetal mortality** / **prenatal care** /

Streszczenie

Cyklopia to deformacja twarzoczaszki, na którą składa się obecność jednego oczodołu w miejscu, gdzie prawidłowo formują się oczy. W wyniku niedorozwoju dochodzi do utraty struktur ośrodkowego układu nerwowego w linii środkowej.
Czynnikami teratogennymi doprowadzającymi do powstania tej nieprawidłowości mogą być: nieprawidłowa biosynteza cholesterolu, wirusy, alkohol i cukrzyca u matki. Wielu autorów wskazuje także na etiologię genetyczną tego schorzenia.
Opisaliśmy przypadek ciężarnej, której płód cierpiał zespół wad wrodzonych, m.in. cyklopię. Po farmakologicznej indukcji porodu urodził się płód płci męskiej, który zmarł po dwóch godzinach życia. Należy zwrócić szczególną uwagę na odpowiednią diagnostykę tej patologii w możliwie najwcześniejszym etapie życia płodowego. Największy nacisk należy położyć na wczesną diagnostykę ultrasonograficzną tej nieprawidłowości, stąd wniosek o konieczności kierowania pacjentek podejrzanych o wady twarzoczaszki do ośrodków wykwalifikowanych w badaniach prenatalnych.

Słowa kluczowe: **ciąża** / **wady układu nerwowego** / **holoprosencephalia** / / **śmiertelność płodów** / **opieka prenatalna** /

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Fetal developmental defect known as cyclopia has been recognized since ancient times and was first described then. It is a deformation of the facial skeleton with one eye orbit formed in the place where both eyes should be present As a result of hypoplasia there is absence of central nervous system structures in the midline [1]. Teratogenic factors leading to the occurrence of this anomaly may include irregular cholesterol biosynthesis, viruses, alcohol intake and maternal diabetes [2, 3, 4].

The most frequent cause of cyclopia is holoprosencephaly (HPE), a complex cerebral damage resulting from incomplete prosencephalon cleavage and manifesting as hypoplasia of the face and prosencephalon. Clinical expression of this kind of underdevelopment is considerable, from a single cerebral ventricle and cyclopia to a completely clinically mute carrier state of the HPE gene [5, 6]. Holoprosencephaly is a disease present in one in 16.000-20.000 of living births [7]. Authors suggest a genetic etiology of this illness connected with autosomal dominant, family-carried HPE gene [5, 8].

The disease has been proven to be a genetically heterogeneous entity. However an additional environmental factor also plays a significant if not crucial role in its origin. The gene is not homogenic since, as researchers have demonstrated, genetic heterogeneity has a priority influence on the variable clinical picture of the HPE gene defect, which does not always present all the clinical symptoms. That in turn leads to diagnostic difficulties in determination of the proper correlation between the phenotype and the genotype. Multiple research projects were aimed at making distinction into a couple of other mutations responsible for different organ anomalies. These were: SHH, ZIC 2, SIX 3 and the rarest TGIF mutations. The new phenotypes connected with those mutations referred to pathologies of the hypophysis, corpus callosum, malformations resulting in a coloboma of the iris, choanal stenosis and chilognathopalatoschisis [9, 10, 11, 12, 13]. Genetic background of the described anomaly has been thoroughly described, thus opening the door to a more detailed study of the environmental factors influencing the case-specific phenotypic picture.

Cyclopia leads to a number of anatomical anomalies. Connected research describes structural abnormalities revealed with the help of traditional imaging methods, among which MRI appears to be the most crucial one as it enables getting detailed information about malformations localized within the facial skeleton and the internal nervous structures [14, 15].

The ultrasound examination based on the most up-to-date techniques available can also give a lot of information [16]. In case of cyclopia these examinations can easily visualize the following structures: olfactory organ situated just above the single fissure constituting the orbit, the encephalon visible as a homogenic doughy formation which reminded the researchers of a "pancake" of a lobeless prosencephalon type, a state of undifferentiated telencephalon partially surrounding one ventricle. What is particularly interesting is lack of encephalon structures such as the cerebral falx or the corpus callosum, as well as lack of the ethmoid bone components. These are the typical features of hypoplasia in the cerebral midline [17].

Diagnosis of abnormal ultrasound images of the orbits and individual fetal bone structures usually does not present difficulties in obstetrics and gynecology. These pathologies are most frequently correctly diagnosed in the first and second trimester by the doctors managing pregnant women referred to the centers of the higher order. Diagnosis of these anomalies in the first trimester in the vast majority of cases correlates with hypothetical diagnosis of the cyclopic embryopathy which suggests the formation of these structures in the third week of the embryonal development [18, 19].

After the origin and closure of the nervous tube, its frontal part widens. Resulting from two narrowings, there are three primary cerebral vesicles in this part: prosencephalon, mesencephalon and rhombencephalon. In the fifth month of development, the prosencephalon should be further divided into two secondary vesicles. As a result of the anomalies there may be a single-vesicle prosencephalon. This pathology may be clinically manifested as cyclopia. It is characterized by the lack of visual ducts and the septum pellucidum. Moreover, the characteristic rhino-frontal process and the changed cranial vault are present. The remaining facial structures, apart from various deformations, may resemble normal structures in the imaging examinations [20]. In rare cases single-ventricle prosencephalon may take the form of cyclopia in which the lack of regular facial tissues results in the formation of a single orbit with one organ. Several researchers tried to observe and explain the causes of morphogenetic defects with the help of MRI, but up-to-now no comprehensive and clear answer has been found [20, 21].

One center documented a case of pregnancy with cyclopia using MRI in prenatal diagnosis. In case of this pregnant patient no prenatal action of widely used and well-known teratogens such as stimulants, drugs or diabetes predisposing to the formation of this defect was found. A stillborn was delivered in whom the examination revealed the rhinal duct to be 2,5cm long and 1,2cm wide. The crown-rump length of the fetus was 38,1cm. The external structure of the ribs, chest and abdomen showed no pathologies. Polydactyly in the right foot and the left hand was found. The ears were thickset. The MRI examination performed with application of appropriate scanning options revealed absence of cerebral division into hemispheres. In the place of prosencephalon there was a single-ventricle doughy structure.

Moreover, it was observed that the ventricle was continuously going into a relatively big space resembling a cyst. In detailed MRI imaging the following structures were missing: longitudinal fissure of the brain, cerebral falx, corpus callosum, septum pellucidum, bulb and the olfactory tract. There could also be observed a thick mass of undivided nuclei of the thalamus and resulting from that the lack of third ventricle's formation. The MRI revealed the existence of the eye buds, contacting with the two optical nerves which where then changing into one wider nerve going to the diencephalon on the thalamic level. Significant osseous changes within the facial skeleton were observed, among others in the osseous elements of the orbit and the superior nasal concha.

However, the inferior nasal concha and the maxilla were structurally regular. The ocular surface of the upper jaw was dislocated in relation to the normal location, while the interior conchae were shifted downwards and had no contact with the nasal area. The shape of the olfactory organ was described as tubular, rooted above the fissure in which the single eye was located. Successively taken MRI cross-sections revealed the final point of the olfactory organ as an incisure of the ethmoid bone which in turn was present in a residual form with remaining parts of the

orbit above the two eye buds. The nose bud resembling a tubular structure was rooted above the single eye. Detailed examinations pictured the point of the bud in the residual ethmoid bone. The root of the bud formed a kind of "roof" of the single orbit. The upper and middle conchae were forming the superior and side wall and the frontal bone was the base of the middle part of the orbit. The great and the small wing of the sphenoid bone were forming the interior curvature of the single orbit. The inferior nasal conchae and the upper jaw were normally developed. Also, the palate was regular. The upper jaw, the inferior conchae became disintegrated parts of the orbital complex, which are usually elevated by the upper jaw, and were replaced by the irregular formation of the great and small wings of the sphenoid bone and the indirectly connected zygomatic process. Although the orbital part of the upper jaw was different from its regular anatomical location, the inferior conchae were directed downwards and they had no contact with the nasal region. Also, the pre-maxillary component was characteristic as it was supposed to reflect the regular dental alveolus containing the upper incisor but failed to do so [15].

In case of cyclopia, there is histological evidence that the nasal bud resembling a tube consists of epithelium and a muscular layer characteristic for this organ. The tube may be the antero-superior part of the nasal cavity which developed in the absence of the middle components such as the cribrum, pecten and the septal cartilage. The formation of proper residual nasal capsule and the sphenoid bones have been found out to depend on the mesodermal integrity at the beginning of fetal life. Olfactory plates forming near the end of the fourth week of a regular development deepen, creating the nasal cavity which normally widens towards the cranial cavity. The tissue surrounding this area later becomes the nasal capsule bud. Absence of the ossification center of the presphenoid bone between the small wings, which later would create the sphenoid body, will lead to failure in the intentional deviation of the cavity widening towards the rhino-pharyngeal cavity. Instead, the higher part of the nasal capsule will develop a spheroid concha-like element which would fill up the later part of the ethmoid bone. In the end, resulting from lack of the nasal septum where the nasal components of the upper jaw should be fixed, a single tube is formed, usually placed above the eyes. Absence of the nasal cartilage will be the basis for the skeleton formation disorder and the later abnormal partial osseous connection of the facial bones [15].

Cyclopia was also examined with the help of reconstructional CT. Estimation of the facial skeleton morphology revealed that the integrity of trigeminal nerves is necessary for proper formation of its structures and any disturbance in their differentiation is conductive to deformations and irregular shaping of the facial skeleton structures [15].

Deformations of the facial skeleton are present in about 80% of holoprosencephaly cases, what reflects the developmental disorder of the central nervous system. Research has shown a wide variety of the anomaly forms, from minimal facial skeletal deformation to microcephaly usually occurring together with a single upper incisor. Researchers, pointing to the multiplicity of changes which had already begun in embryogenesis and which were responsible for the developmental pathologies, wished to draw attention to the etiological background of this disease inevitably connected with genetic defects strictly influenced by environmental factors. Taking into account the latter, the relatively frequent occurrence of holoprosencephaly in diabetic women should be highlighted and prenatal diagnosis in those patients ought to be emphasized [22].

Around 50% of single-cell prosencephaly cases are connected with cytogenetic disorders and, most frequently, with chromosome 13 trisomy or with monogenetic syndrome [7, 23]. Observations of these cytogenetic disorders led to the discovery that there are at least twelve loci which probably contain the genes implying HPE pathogenesis.

Presently, in holoprosencephaly the following genes known in humans are known: SHH on 7q36, ZIC2 on 13q32, SIX3 on 2p21 and TGIF on 18p11.3 [12, 24, 25]. In their attempt to explain genetic etiology of holoprosencephaly, researchers described a case of a patient with partial 18p deletion formed as a result of the mother's unexplained t translocation (1:18) and an additional SHH mutation. That patient presented with microcephaly, a developmental disorder defined as a formation of too small cerebral cranium towards the facial skeleton and a single incisor phenotypically connected with it and with a submicroscopic 7q deletion [7].

The new not yet fully-known etiological aspects of the described disease are also worth mentioning. Transplacental viral infection, especially with cytomegalovirus, is a significant factor influencing abnormal fetal eye development. Only introductory studies are available which do not explain CMV infection and eye development in detail. Further discoveries have suggested that the virus also takes part in abnormal central nervous system formation and may influence the occurrence of holoprosencephaly [2]. Looking for other factors causing fetal cyclopia, salicylates were confirmed to be a reason for cyclopia and anomalies in the development of prosencephalon. Since there had been many doubts concerning the influence of salicylates on the fetal nervous system development, it was finally conclusively proven that they indeed have a harmful impact on the fetus, leading to underdevelopment of the prosencephalon and cyclopia in fetuses whose mothers were taking 4 grams of a compound containing salicylates daily [26]. Another significant factor able to cause the described developmental disorder is alcohol intake during pregnancy. The worst complication of fetal alcoholic syndrome (FAS) is cyclopia. During research on animals [4] it occurred that alcohol, apart from causing cyclopia, also damages the retina and the eye-lid. As mentioned already, metabolic disorders also have an effect on the structure formation of the central nervous system. Attention should be paid to cholesterol biochemical transformation disorders. It turned out that the anomalies arising during its biosynthesis may be a significant cause of teratogenity and holoprosencephaly. Cholesterol is a critical element for regular embryonal development. Its lack causes prosencephalon formation abnormalities and may lead to a single eye and the nasal structure being located just above it. In the majority of investigated cases absence of hypophysis was also noted [9, 27].

The improper cholesterol metabolism may be the result of hereditary defect manifesting itself as the lack of 7 dehydrocholesterol reductase synthesis. In the most advanced form, it leads to cyclopia, monorhinia and to lack of the division of cerebral hemispheres. Cholesterol and its proper metabolism has the function of inductor of proper development of the regular nervous tube, including among others eye buds formation and cerebral division into hemispheres.

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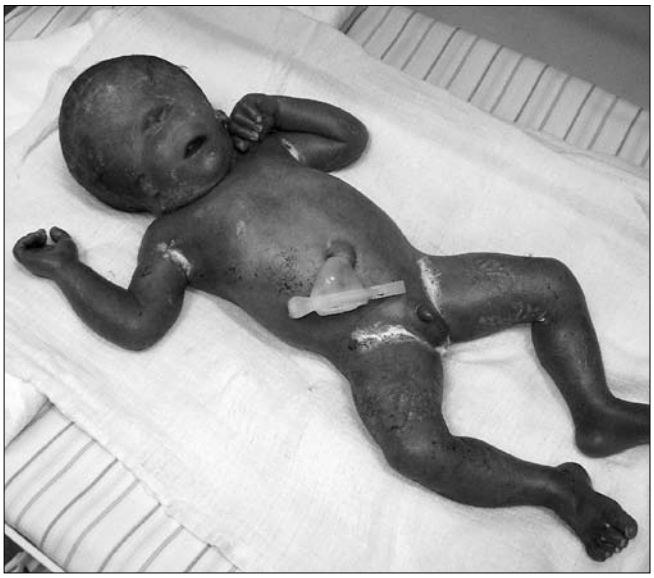
Case report

The patient, 30 weeks gestation of her second pregnancy, was referred to our hospital after initial diagnosis of hydrocephalus in a municipal hospital. The first pregnancy had progressed without complications and ended with a birth of a healthy newborn. Anamnesis and family history were unremarkable. The father of the child has diabetes. The patient had been managed in obstetrics out-patient clinic from 16 weeks gestation and had five check-ups before being referred to the hospital. Ultrasound test revealed cephalic longitudinal lie of the fetus, esophageal atresia, hydramnion, schizencephaly and cyclopia. Fetal pulse measured by CTG was oscillating about 140 beats per minute. Due to fetal lethal defects, pharmacological induction of labor was carried at the request of the mother. After several hours a male fetus was born. The newborn showed vital signs, the examination revealed heart rate of 20-30/minute. He was not breathing, the muscular tone was diminished. The child weighed 1270grams and was 35cm in length. The cranial circumference was 27cm, and the chest circumference 24cm. Physical examination showed a high forehead with a single centrally localized eye, atresia of the nasal conchae which were located at the mouth level, lack of a nose, the anterior fontanel 3x3cm, separation of the sagittal suture, posterior fontanel 2x2cm. (Picture 1 and 2).

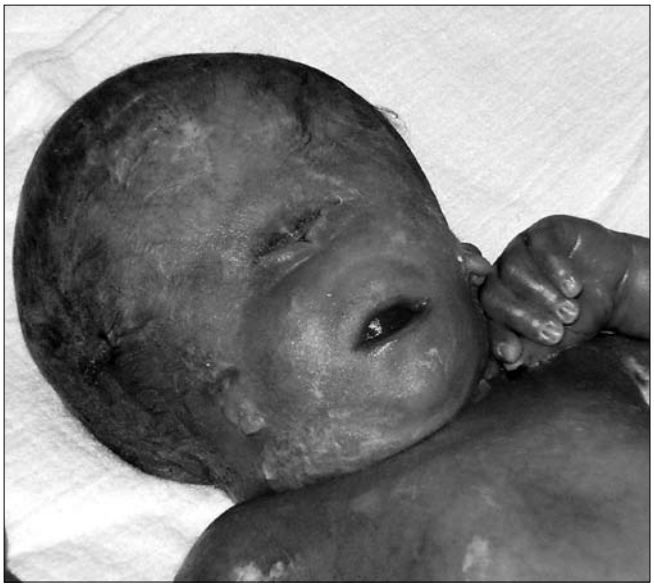
The ultrasound examination of the head revealed a single big fluid-filled area and the lack of structures presenting cerebral tissue echogenicity. In the anterior frontal projection a centrally located eye bud was visible. The ultrasound imaging of the abdominal cavity showed no evident organic changes. After two hours of life lack of breathing, peripheral cyanosis, no peripheral pulse and no heart action were noted. Due to the state of the child, no resuscitation was attempted and the child was declared dead.

The histopathological examination revealed normal cranial bones, almost complete lack of cerebral hemispheres (there was only a cerebral tissue fragment found, with dimensions 3x2x1 cm with convolutions and sulci, covered with leptomeninx). The cerebellum and the medulla were normal, apart from the recognized features of encephalomalacia.

The case described differs slightly from the cases of the most frequently occurring single-cell prosencephalon forms presented in literature. The lack of similarity is connected mainly with the complete absence of the nasal tube commonly localized above the single eye and with the structure and generally the presence of ears.



Picture 1. A newborn with cyclopia.



Picture 2. The facial skeleton of a newborn with cyclopia.

Discussion

Diagnosis of cyclopia is especially difficult and the diagnostically and economically best method continues to be searched for. The role of ultrasound diagnostics in the case of cyclopia needs to be estimated. With modern ultrasound imaging techniques, diagnosis of holoprosencephalon in the first trimester should not be difficult [16, 18, 19, 28, 29].

Despite common knowledge that many developmental eye defects are detectable with the help of amniotic fluid analysis, in case of the described pathology the examination is not performed as it is not precise enough for cases of holoprosencephaly. It also carries the possibility of complications for the mother and the fetus and in the general practical and economical dimension gives place to proper embryonal ultrasound techniques. An experienced doctor performing ultrasound examination is able, as early as in the first trimester of the pregnancy, to estimate precisely the structures of the eyes on adequate fetal life stages. Already at about 10-11 weeks gestation the orbits may be examined, the lens can be visualized in week 14 and the eye-lids can be examined in week 16. Embryonal ultrasonography enables to detect also other eye pathologies apart from cyclopia, such as microphthalmia or complete lack of eyes [29].

Every obstetrician managing a pregnant patient, especially one with risk factors, should bear in mind the possibilities of abnormal fetal development including cyclopia. Special attention should be paid to proper diagnosis of this pathology at the earliest possible stage of fetal life. Also prophylaxis during pregnancy is a key issue and it should include prohibition of alcohol intake during conception time and pregnancy.

Detailed anamnesis regarding drugs taken (salicylates) or diseases connected with cholesterol metabolism disorders occurring in the family should be collected. The strongest emphasis should be laid on early ultrasound diagnostics of this pathology and that patients suspected of fetal facial skeletal defects be referred to centers qualified in prenatal examinations.

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