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Case report

FETAL ACHONDROPLASIA- ULTRASONOGRAPHIG FEATURES (CASE REPORT)

ФЕТАЛНА АХОНДРОПЛАЗИЈА-УЛТРАЗВУЧНИ КАРАКТЕРИСТИКИ (ПРИКАЗ НА СЛУЧАЈ)

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Abstract

Introduction. Achondroplasia is the most common non-lethal skeletal dysplasia and the main cause for dwarfism in humans.
Case presentation. A 27-year-old pregnant woman came into our hospital in the third trimester of pregnancy with a medical report of short fetal limbs (<5 percentile). Our US exam revealed rhizomelic shortening of the limbs, with frontal bossing, depressed nasal bridge and a trident hand. These findings were highly-suggestive for achondroplasia which was confirmed by DNA testing for FGFR3 mutation after a well-adapting male baby was born.
Conclusion. Achondroplasia displays US features that raise a suspicion for the disease prenatally.

Keywords: achondroplasia, shortening of the limbs, frontal bossing, trident hand, FGFR3 mutation

Апстракт

Вовед. Ахондроплазија е најчестата форма на скелетна дисплазија и основна причина за џуџест раст кај луѓето.
Приказ на случај. 27 годишна бремена жена во трет триместар од бременоста дојде во нашата болница со медицински наод за кратки фетални екстремитети (<5 перцентила). Нашиот УЗ преглед утврди постоење на ризомеличен тип на скратување на екстремитетите, испакнатост на челниот предел, аплатирање на коренот на носната пирамида и „трозаба" дланка. Овие УЗ наоди побудија сериозно сомневање за постоење на фетална ахондроплазија, што (по раѓањето на витално машко бебе) беше и потврдено со ДНК анализа на FGFR 3 генот.

Заклучок. Ахондроплазијата пројавува УЗ карактеристики кои, уште во пренаталниот период, будат сомнеж за постоење на болеста.

Клучни зборови: ахондроплазија, скратување на екстремитетите, челно испакнување, трозаба дланка, FGFR 3 мутација.

Introduction

Achondroplasia is the most common and the best known non-lethal skeletal dysplasia [1]. The prevalence of the disease differs between the regions from 1 per 10 000 to 1 per 30,000 births [1,2]. The systematic review in 2020 found worldwide prevalence of 4.6 cases per 100,000 births [3] giving around 250,000 affected persons worldwide [4]. In our hospital, reviewed data from the past 10 years (2011-2020), revealed only 2 cases of suspected skeletal chondrodysplasias at birth (of which only one was DNA confirmed as a real achondroplasia) among 34,578 deliveries.
Achondroplasia is a genetic disorder caused by fibroblast growth factor receptor 3 gene (FGFR 3) mutation [5-7] which displays autosomal dominant inheritance pattern. The vast majority of the mutations are "de novo" paternal point mutations [8,9], and only 20% are mutations inherited from an already affected parent. This has implications in terms of genetic counseling the couple. It is important to emphasize to the couple that the recurrence rate in case of "de novo" mutation is very low-less than 1% [10]. On the other hand, with one affected parent, there is a 50% chance for transferring the disease to the offspring [11].
There are two types of achondroplasia. The homozygote type is clinically insignificant, because it is lethal in utero or during early infancy as a result of severe pulmonal hypoplasia [12]. The heterozygote type, contrariwise, despite obvious phenotypical appearance has near normal life expectancy. Some studies, however, dispute this claim, arguing that the life expectancy is

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up to 10 years shorter [13] primarily due to cardiovascular implications.

The main clinical feature in heterozygous achondroplasia (FGFR3 mutation prevents converting cartilage to bone) is dwarfism due to rhizomelic shortening of the limbs [11,14]. Intelligence is not affected. Deviation from the normal growth pattern of the fetal limbs starts after the 22th week of pregnancy and it aggravates over time [15,16]. In addition to the limb shortening, the fetal skeleton displays (in various proportion) some other signs, such as: frontal bossing, depressed nasal bridge, collar-hoop sign, trident hand, macrocephaly etc. [15,17,18]. These US findings can raise a suspicion for the disease and facilitate prenatal diagnosis by conducting invasive or non-invasive DNA testing. Having a diagnosis before the birth is of great importance: it gives the parents an opportunity to decide whether to continue or to terminate the pregnancy and allows the obstetrician to manage the perinatal period adequately.

Case presentation

A 27-year-old G2P1 woman was referred to our hospital after US finding of long bones shortening. Her first pregnancy went well and she delivered, 2 years ago, a healthy male baby weighing 3230 g and 51 cm tall. The patient denied a history of a short stature among hers, or her partner's family members. The patient's medical history, as well as paternal age were uneventful too. Regarding the obstetrical history, the US exam at 13th and 20th week showed normal fetal growth pattern. A deviation in terms of limbs shortening was first noticed at 34 gestational week, which was the woman's first US examination after the second trimester anomaly scan. The deviation was remarkable (<5 percentile).

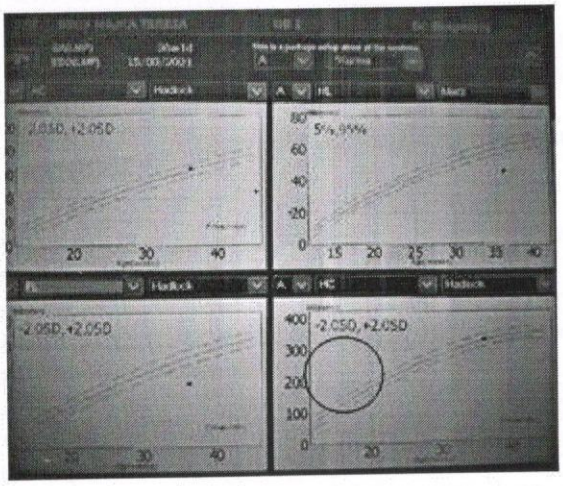

Fig 1. Long bones shortening

The patient came into our hospital in 36+ 1/7 week of gestation. Our US examination showed the following:

- All of the long bones measures were below 5 percentile. Proximal limb expressed more severe shortening on its upper portion, i.e., rhizomelic type of shortening (humerus adequate for 26+week while radius and ulna for 30+ week). The distal limb was equally affected (all three bones had measures adequate for 26+ week of gestation) (Figure 1).

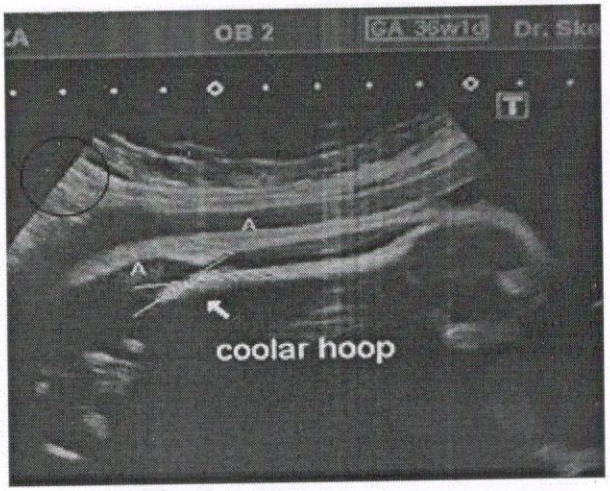

Fig 2. "Collar-hoop" sign

- Besides shortening, the femur also displayed "collar-hoop" sign. We measured the femoral proximal diaphysis-metaphysis angle of 149º (Figure 2).

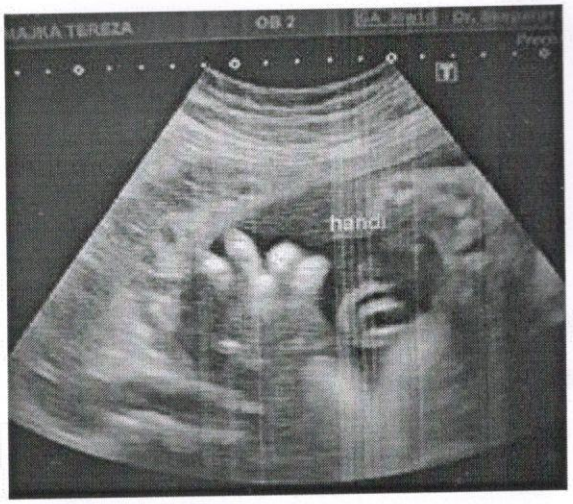

Fig 3. Tri-dent hand

- The hands and the fingers didn't appear significantly smaller. However, the presence of a trident hand was notified (Figure 3).
- The fetal head was bigger than average regarding the gestational age (BPD and HC above 90 percentile), but still the head did not reach criteria for macrocephaly (BDP and HC <95 percentile). The fetal profile displayed depressed nasal bridge and frontal bossing above (Figure 4).

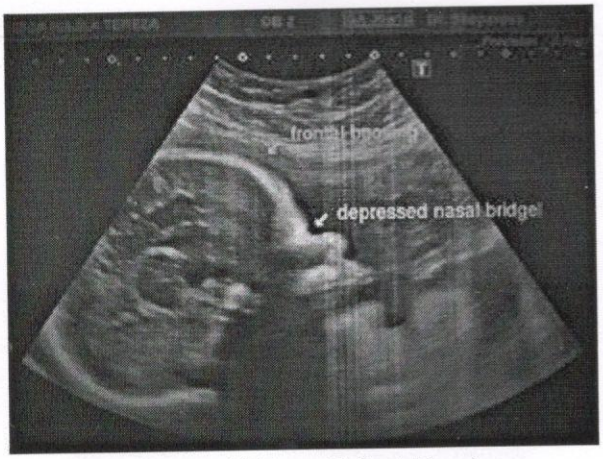

Fig. 4. Depressed nasal bridge with frontal bossing

- Abdominal circumference was within the normal range, but the fetal chest compared to the abdomen on sagittal plane appeared narrow (Figure 5).

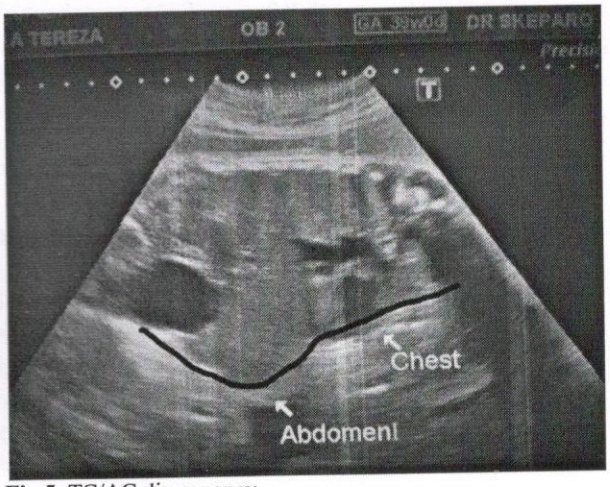

Fig 5. TC/AC discrepancy

- Polyhydramnios was also present. AFI equaled 170 mm, which was above 95 percentile regarding the gestational age.
- Uterine blood flow was uncompromised (mean PI 0.8).

Based on US findings, a suspicion for fetal achondroplasia was made. Proceeding to prenatal testing was offered to the patient. She declined the procedure. A regular antenatal care was carried out until spontaneous onset of labor occurred.

At 40+1/7 week of gestation, the woman gave spontaneous vaginal birth to a male baby weighing 2970 g and 47 cm tall. The initial inspection revealed correlation between our US findings and phenotypical appearance of the newborn. The baby had prominent forehead and flattened nasal bridge (Figure 6). His limbs were smaller than normal with obvious rhizomelic shortening of proximal one, thorax was a bit narrower than expected (circumference of 310 mm), which was emphasized by the baby's frog belly (Figure 7). The trident hand was present (Figure 8).

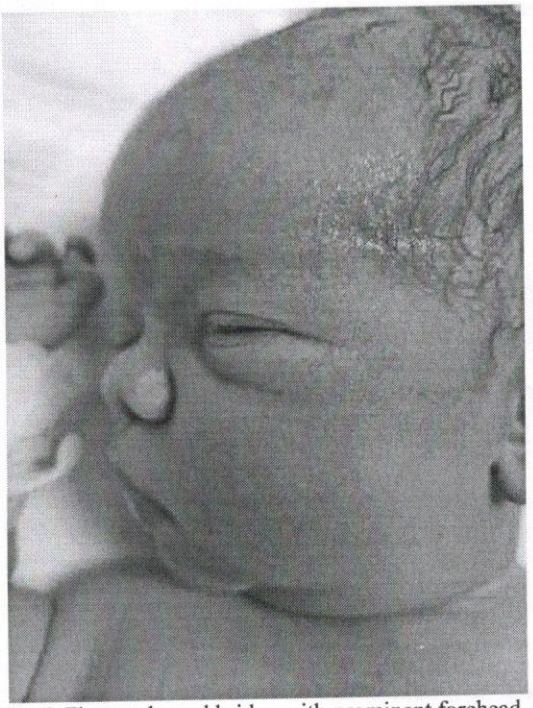

Fig 6. Flattened nasal bridge with prominent forehead

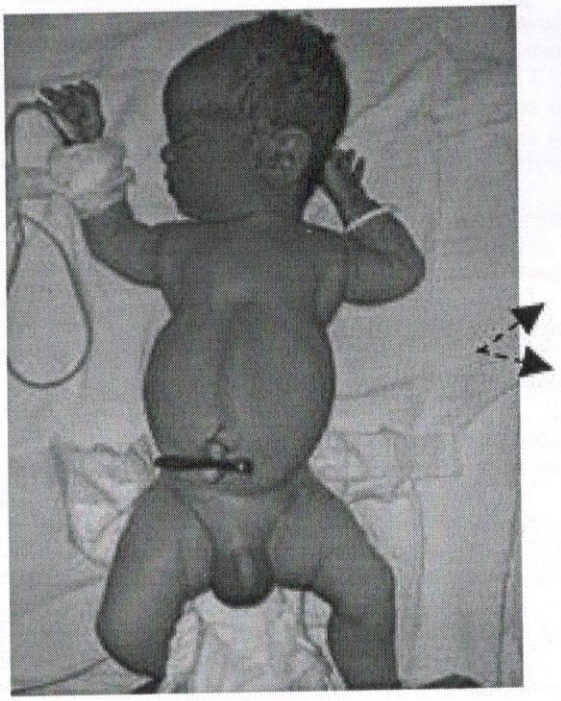

Fig.7. Rhizomelic limb shortening, narrowed thorax and frog bely

The blood samples were collected from the baby, the mother and the father and were sent to our National Research Center for Genetic Engineering and Biotechnology

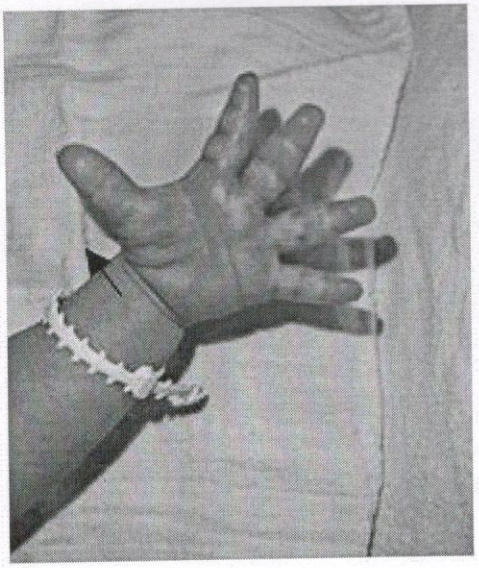

Fig 8. Tri-dent hand

(Macedonian Academy of Sciences and Arts) for molecular diagnosis. The analysis of newborn's DNA confirmed a mutation on FGFR3 gene in heterozygote manner with a pathological variant in exon 9 c.1138G>A, while the mother and the father had normal alleles for FGFR3 gene.

Discussion

Bone shortening in our case was notified in the third trimester of pregnancy which is typical for achondroplasia [18]. Unlike FGR, which also shows a deviation from the normal growth pattern in the third trimester, here the abdominal circumference and the uterine artery Doppler were within normal range, and oligohydramnios was not present. Moreover, we observed a moderate polyhydramnios which can be seen in 50% of achondroplasia cases [17]. Apart from the shortening, we revealed a "collar-hoop" sign on the femur which pretends to be one of the most prominent features of this entity [17].

The fetal head presented relative macrocephaly with depressed nasal bridge and prominent forehead, which are among the features of thanatophoric dysplasia, too [18]. However, unlike the later one, the fetal chest wasn't severely narrowed, and the long bones shortening wasn't brutal as it starts much latter in the pregnancy. Shortening of the ribs wasn't detected, too [18]. Trident hand, almost a pathognomonic sign for a skeletal dysplasia, was also observed.

DNA analysis of the newborn confirmed our suspicion, and showed the most frequent c1138G>A mutation on FGFR3 gene which is, along with c.1138G>C mutation, responsible for achondroplasia in 98% of the cases [9]. Lack of the parents' FGFR3-gene mutation, classified this case as "de novo" mutation in line with findings that 4/5 of achondroplasia cases are sporadic ones [9].

Conclusion

Achondroplasia expresses some features that can be detected by US examination in the late fetal period and accurately raises a physician's suspicion to the disease prenatally.

Conflict of interest statement. None declared.

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