Case **report**

PRENATAL DIAGNOSIS OF WOLF-HIRSHHORN SYNDROME - CASE REPORT

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Abstract

Wolf-Hirschhorn syndrome (WHS, MIM 194190) is caused by the loss of the genetic material of the distal segment of chromosome 4p. We present a case of the fetus diagnosed in the second trimester of pregnancy by genetic amniocentesis which was prompted by abnormalities detected on ultrasound.

Key words: *Wolf-Hirshhorn syndrome, Prenatal diagnosis, genetic ultrasound, deletion 4p*

DEFINITION

Wolf-Hirschhorn syndrome (WHS, MIM 194190) is caused by the loss of the genetic material of the distal part of the short arms of chromosome 4. It is a rare disorder, with the estimated frequency of 0.2:10,000 births. We present the case of the second trimester fetus diagnosed by amniocentesis, which was prompted by abnormalities detected on ultrasound (early-onset IUGR, heart defect and dysmorphism).

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CASE REPORT

A 27-years-old patient underwent the first trimetster ultrasound screening scan at 13 weeks. The result of the screening was classified as normal, although nuchal translucency was around the 90th centile. No other suspicious signs were noticed at that moment, although retrospectively micrognathia can be identified in the images obtained at that time. The next scan at 20th week revealed significant IUGR and a suspicion of ventricular septal defect, therefore the patient was offered genetic amniocentesis. Initially the patient refused invasive testing and looked for the second opinion scan elsewhere, which failed to confirm the findings. The next scan at our institution confirmed the findings and additionally the overriding aorta was noticed. The patient agreed to have the amniocentesis performed and as a result 4p deletion was noted on GTG banding [46,XX,del(4)(p15.2) karyotype], which is diagnostic of the Wolf-Hirschhorn syndrome. The parental karyotypes were normal, so the deletion was a *de novo* event. The child was born by cesarean section at term in our institution and had typical health problems: low birth weight, major feeding difficulties etc. The child expired short before cardiologic surgery, for which she had been scheduled for, was performed.

DISCUSSION

Many prenatally diagnosed cases of Wolf-Hirschhorn syndrome have been described.[1] Frequent abnormality on

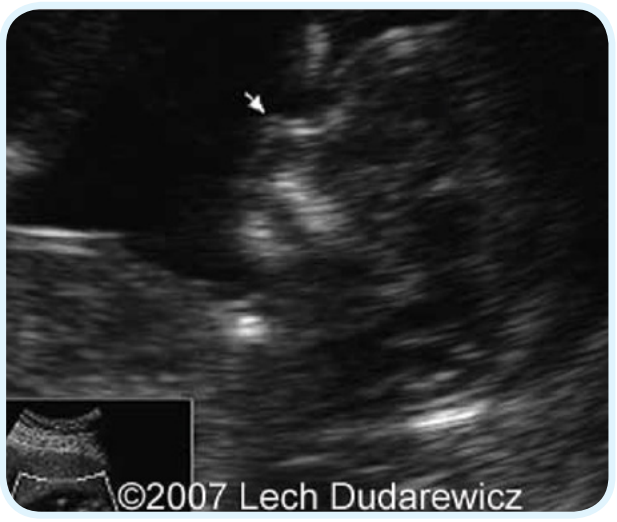

Foto 1. 13 weekend of pregnancy. Fetus face profile.

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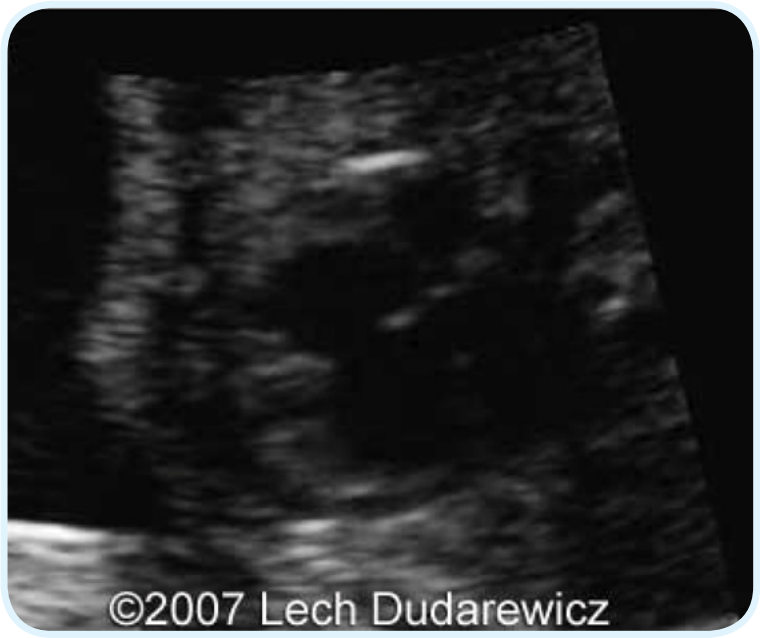

Foto 2. 20 weekend of pregnancy - ventricular septal defect.

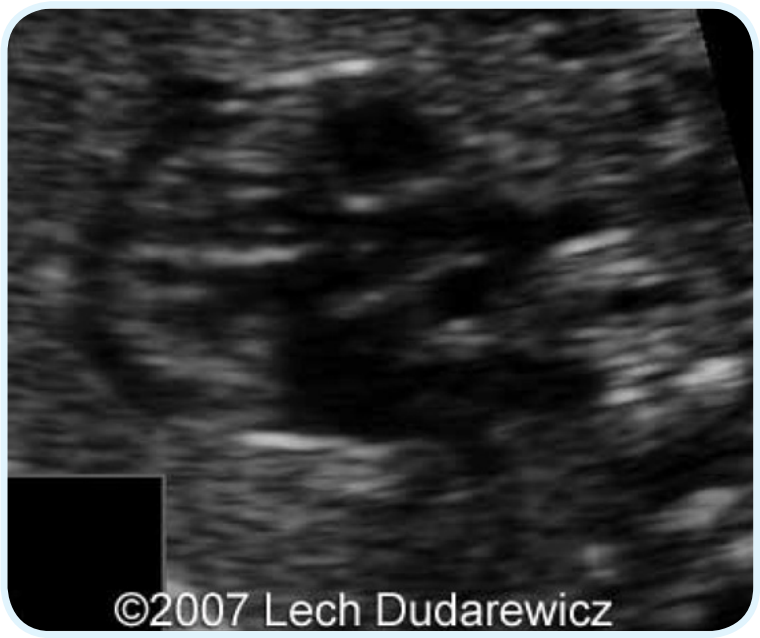

Foto 3. 25 weeks of pregnancy - ventricular septal defect and aorta overridding.

first trimester examination is increased nuchal translucency. [2] Although nuchal edema is a very unspecific sign, with wide differential diagnosis, it warrants karyotyping, which leads straight to the diagnosis. Other frequently cited signs of the Wolf-Hirschhorn syndrome are heart defects, characteristic facial dysmorphism (Greek helmet – like forehead and nose), ambiguous genitalia in boys (tulip sign) and constant and early IUGR. It is estimated, that heart defects are present in 30-55% of neonates with WHS, but there is no data available on the frequency of heart defects in fetuses. The most common heart defects are ventricular and septal defects, which are amenable to surgery with favorable outcome. [3] The facial dysmorphism observed in WHS is very characteristic, often compared to the appearance of the Greek helmet, which is caused by the presence of the broad and prominent forhead, hypertelorism (too widely set orbits, present in 74% of WHS patients) prominence of the glabella and presence of the widened, beak-like nose. In addition to that, anti-Mongoloid configuration of the eyelids and anomalies of the ears can be found. Micro/retrognathia may be found in the excess of 80% of patients with this entity. [4] Much more often than in the general population cleft lip and palate occurs, the palate is narrow and high-vaulted in about 57% of the affected, and among other defects, clubfoot, diaphragmatic hernia or agenesis/hypoplasia of the corpus callosum can be found. [5] The IUGR is early and can be demonstrated around mid-gestation in more thaan 90% of fetuses, in fact some authorities consider IUGR a constant feature of this disorder. It is worth to point out, that detection of early IUGR warrants karyotyping, fetal echocardiography and calls for the particular scrutiny of the fetal face, as in the favorable fetal position it should be possible to detect the facial dysmorphism characteristic of the Greek helmet and suspect the diagnosis before the karyotype is known.

In the postnatal period microcephaly is present in about 90% of patients with WHS.

Hypospadias and other urogenital system abnormalities are a common feature in WHS patients, their prevalence is estimated at about 60% of male neonates. The more severe forms are detectable by ultrasound. Two thirds of WHS patients are female, which suggests higher lethality in male fetuses. [6]

Anomalies associated with WHS, which are very difficult, virtually impossible to detect by ultrasound currently comprise: coloboma of the eye and diminished muscular tension. [7] Milder forms of hypospadias may also be very difficult to diagnose by ultrasound, unless the fetus urinates while the imaging plane is aligned with the abnormally directed jet of urine of the fetus with hypospadias.

WHS patients are characterized by severe retardation of the psychomotor development and abnormally low muscular tension. In 47 % of patients epilepsy is present, having a tendency to withdraw with time. Most often the attacs start between the fifth and 23-rd months of postnatal life, and tend to cease between three and eleven years. There are severe feeding problem, often necessitating even gastrostomy placement, associated with severe growth and nourishment problems, descirbed in 80% of children with this diagnosis. Growth problems are accompanied by scoliosis in 66% of the affected persons.

About 85-90% of cases are caused by a *de novo* deletion, whereas in 10-15% of cases parental chromosomal rearrangement with chromosome 4 involvement constitutes

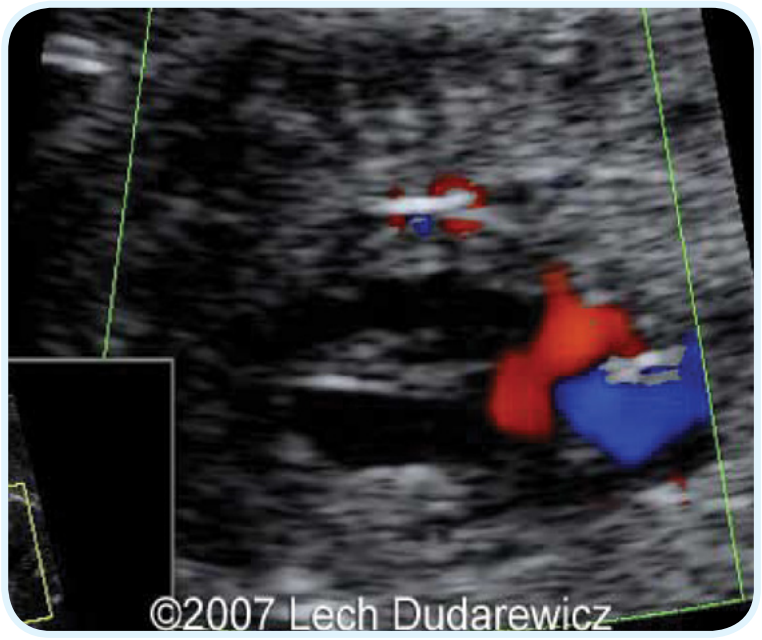

Foto 4. 25 weeks of pregnancy - ventricular septal defect

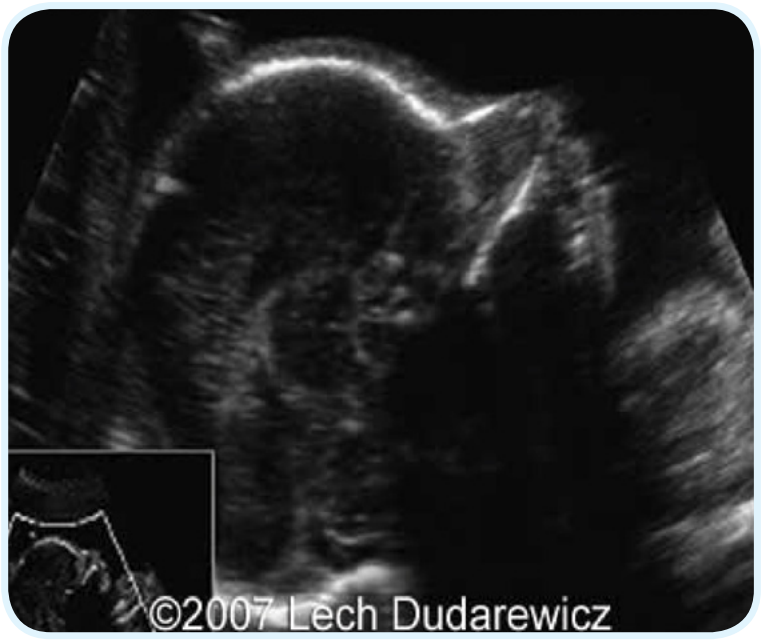

Foto 5. 25 weeks of pregnancy - abnormal fetyszystów face profile with micrognathia.

the origin of the disease. *De novo* deletion is associated with a low (but not negligible: parental gonadal mosaicism must be born in mind) recurrence risk, typically stated at not higher than 1%, while in the presence of parental chromosome 4-involving structural aberration the risk of recurrence is high. Every couple with WHS offspring in the anamnesis should obtain professional genetic counseling, with targeted prenatal diagnosis in future pregnancies, taking into consideration all options, including invasive prenatal diagnosis even using specific FISH probes, or other molecular methods, bearing in mind discreet, non-specific and late-onset ultrasound signs and presence of cases with cryptic deletions.

DIFFERENTIAL DIAGNOSIS

The ascertainment of early IUGR with accompanying micrognathia and heart defect warrants fetal karyotyping as the first diagnostic step. Deepening the diagnosis may involve also the in-depth, level III ultrasound, targeted at "genetic" markers and combined with fetal echocardiography. Actually the diagnosis of WHS may be entertained basing upon the ultrasound findings, but in most cases it is reached by the cytogeneticists, excluding the cases with cryptic deletions, undetectable by classis karyotyping. The role of the sonologist, basing upon the characteristic constellation of dysmorphic findings and congenital defects may be crucial in the mentioned above group of patients with microdeletions. At present, in leading centers, molecular methods of genetic prenatal diagnosis begin to be the standard of care in the group of fetuses with abnormal phenotype and normal classical cytogenetics.

The differential diagnosis of WHS in the prenatal period encompasses other cases with IUGR, nuchal thickening, heart defects and micrognathia, so it is broad. Particularly trisomy 18 should be taken in consideration, the main differentiating feature being overlapping clenched fingers that are virtually a constant feature of trisomy 18 from 18 weeks of gestation on, and not typical of Wolf-Hirschhorn syndrome, it should be rememberd however, that this feature may not be present earlier. Also a very rare Pitt-Roger-Danks syndrome, which is caused by a smaller size deletion 4p16.3 and as the consequence of the smaller amount of genetic material loss, presenting with only part of the Wolf-Hirschhorn syndrome spectrum, should be born in mind.[8] Also 5p deletion and embryonic or fetal infections should be considered.

PROGNOSIS

The prognosis involving the psychomotor development in WHS patients is utterly unfavorable, as 100% of the affected children present with severe or deep intellectual handicap. A small proportion of patients however reach developmental milestones higher than previously thought possible, and even are able to walk independently or speak using single words or even simple phrases.

The prognosis as to the survival is problematic, as about 35% of liveborn neonates die within first two years, mainly because of feeding complications. The mortality seems to be correlated with the size of the cytogenetic deletion. The life expectancy is unknown, although patients as old as 40 years have been described.

Prenatally, the WHS diagnosis should be considered an indication for termination of pregnancy, if diagnosed before

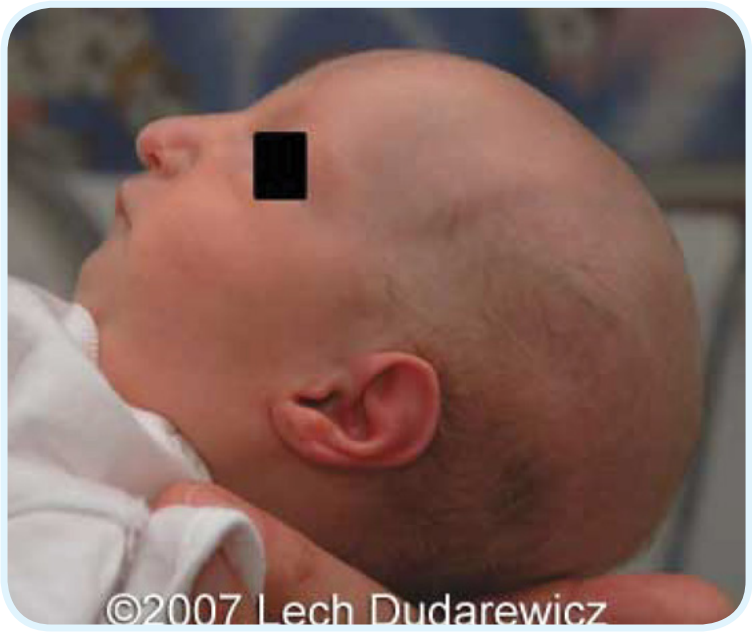

Foto 6. Abnormal neonate face profile with micrognathia.

Foto 7. Front neonate face with dysmorfia

viability. After this time we feel, that the standard obstetrical care should not be altered, although the pregnancy should undergo III level specialist care, with anticipation of all typical/possible perinatal and neonatal problems.

TEACHIN POINT

Wolf-Hirschhorn syndrome is a disease amenable to diagnosis by ultrasound, its signs being sometimes so discreet, that can be noticed only in the second trimestar of pregnancy. The basis of the diagnosis is cytogenetics, supplemented by the newer molecular techniques.

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