Prenatal diagnosis of rare fetal anomalies – a case report

Diagnostyka prenatalna rzadkich zaburzeń rozwojowych płodu – opis przypadku

Piotrowski Krzysztof[1], Constantinou Maria[2], Patalan Jacek[3], Waloszczyk Piotr[4], Celewicz Zbigniew[3], Kałużewski Bogdan[2], Mędrek Krzysztof[1], Zajączek Stanisław[1]

[1] Cytogenetics Unit, Department of Pathology, Pomeranian Medical University, Szczecin, Poland
[2] Department of Medical Genetics, Medical University, Lodz, Poland
[3] Department of Foeto – Maternal Medicine, Szczecin, Poland
[4] Department of Forensic Medicine, Pomeranian Medical University, Szczecin, Poland

Abstract

Hereby we present a case of a pregnancy in which careful dysmorphology of the fetus in subsequent sonographic evaluation resulted in detection of a very rare anomaly. It allowed explanation of the fetal phenotype, compared then with that of the newborn and estimation of genetic risk for the next pregnancies in this family.

Key words: **ultrasound diagnosis** / **malformations** / **cryptic aberration** /

Streszczenie

Przedstawiono przypadek ciąży, w której dzięki wnikliwej analizie dysmorfologicznej płodu w kolejnych badaniach USG zainicjowano szereg unikalnych badań genetycznych, które doprowadziły do wykrycia bardzo rzadkiego zaburzenia u dziecka. Pozwoliło to wyjaśnić zarówno fenotyp płodu, następnie żywo urodzonego dziecka, jak i ocenić ryzyko genetyczne występujące w tej rodzinie w kolejnych ciążach.

Słowa kluczowe: **ultrasonografia** / **badania genetyczne** / **fenotyp** / **płód** / / **ryzyko** / **ciąża** /

Adres do korespondencji:
Stanisław Zajączek
Cytogenetics Unit, Department of Pathology, Pomeranian Medical University
Poland, 70-115 Szczecin, Połabska 4
tel./fax: 48 91 466 15 65
e-mail: upc@sci.pam.szczecin.pl

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Introduction

Golden standard of routine prenatal cytogenetic analysis is a detection of aneuploidies and other relatively great span of structural chromosomal abnormalities. Major limitation of diagnosis is a low resolution in amniocyte's metaphase banding pattern, referring to aberration larger than 5-10 kb, while more subtle aberrations may remain undetected. Recently, some new molecular cytogenetic techniques have been introduced (FISH, MLPA, Micro-array e.t.c.), which make it possible to detect smallest genomic imbalances. These, relatively new methods may be applied also in prenatal diagnosis, but for the reasons of low accessibility, higher costs and time consumption, they are employed in limited number of laboratories and to date are not introduced in routine diagnostics. Therefore only selected gravidas may be qualified to this high resolution methods [1].

The prior step to selection of distinctive cases to this new unique cytogenetic analyses should be a refined ultrasound examination and the next step is a correlation of the results with a differential analysis of possible phenotypes and syndromes.

Aim of the study

We present a very rare case of fetus with visible malformations during prenatal sonographic examination. Followed by a multistep cytogenetic analyses by M-FISH and mCGH. Despite of normal routine amniocyte's karyotype we identified subtle unbalanced aberration due to father's very delicate reciprocal balanced translocation, resulting in unbalanced fetal karyotype with high genetic risk for next possible pregnancies.

Case report

Gravida, fetus and neonate

A 31-years old women was referred at 13th+5 week of pregnancy for prenatal diagnosis due to previous four undiagnosed early pregnancy losses. During non-invasive screening we found: cystic hygroma (13,3 mm), cardiac insufficiency (abnormal DV flow), multiple bone anomalies (malformation of feet and hands) and abnormally extended median abdominal wall.

Biochemical markers (PAPPA 0,8 MOM and free β HCG 1,2 MOM) did not increase the risk of major trisomies, however cystic hygroma was a main indication for amniocenthesis, especially due to higher risk of monosomy X. In the 16th week of gestation, before an amniocenthesis ultrasound scans showed also: hypoplastic left heart syndrome with CoA, and perimembraneous VSD, kidneys defects (polycystic kidneys), symmetrical shortening of all long bones, feet and hand deformation, mild retrognathia, with slightly regressing cystic hygroma. Hence standard cytogenetics analyses revealed normal karyotype of the fetus with an unusual constellation of malformations, which did not correspond to any common syndrome to us, we decided to introduce more subtle genetic analyses.

The gravida did not agree to terminate the pregnancy. In next sequence of sonographic evaluations we did not detect any new anomalies, only progression of intrauterinal growth restriction.

After uneventful pregnancy preterm delivery of a boy occurred at 36th week (2130g, 40 cm, Apgar 6,6,7). After a birth, the boy had a collapse and needed respiratory care. Mother did not agree for only palliative treatment, demanded full therapy, therefore prostin was applied. Paradoxical, bad reaction to prostaglandins therapy with no response of arterial duct was observed, with progressively worsening condition. This reaction was totally different than expected. Consequence of polycystic kidneys was a renal insufficiency which disqualified cardiosurgery. The child died at 40th day of life.

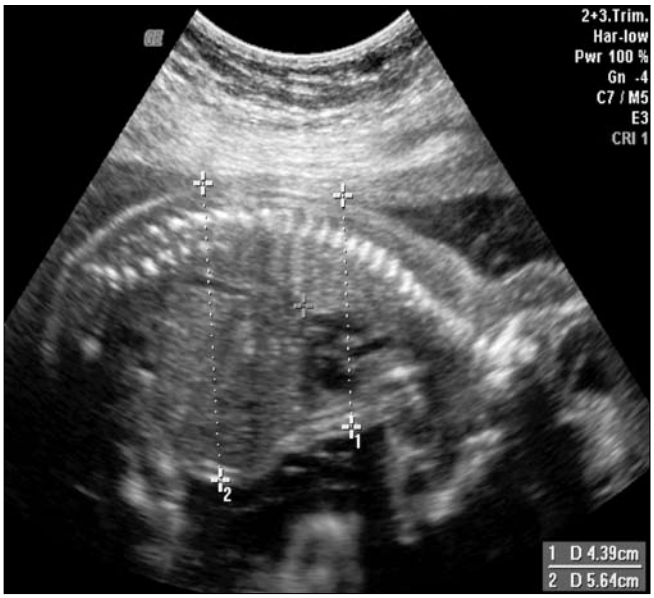

Figure 1. 16 weeks of gestation: comparison of abdomen and chest diameter.

Figure 2. 16 weeks of gestation: rocker bottom foot.

Autopsy confirmed all detected anomalies: and in the heart showed also two additional structures, first was a fiber-like connection between aortal Co with TP, second was a vassel lying on the right side aside typical location of DA.

There may be several interpretations of this situation:

a) duplication of DA with hypoplasia of one,
b) atypical anastomoses between aorta and pulmonary artery and hypoplastic DA,
c) fibrous strand connecting region of the CoA with TP and normal DA on the right side.

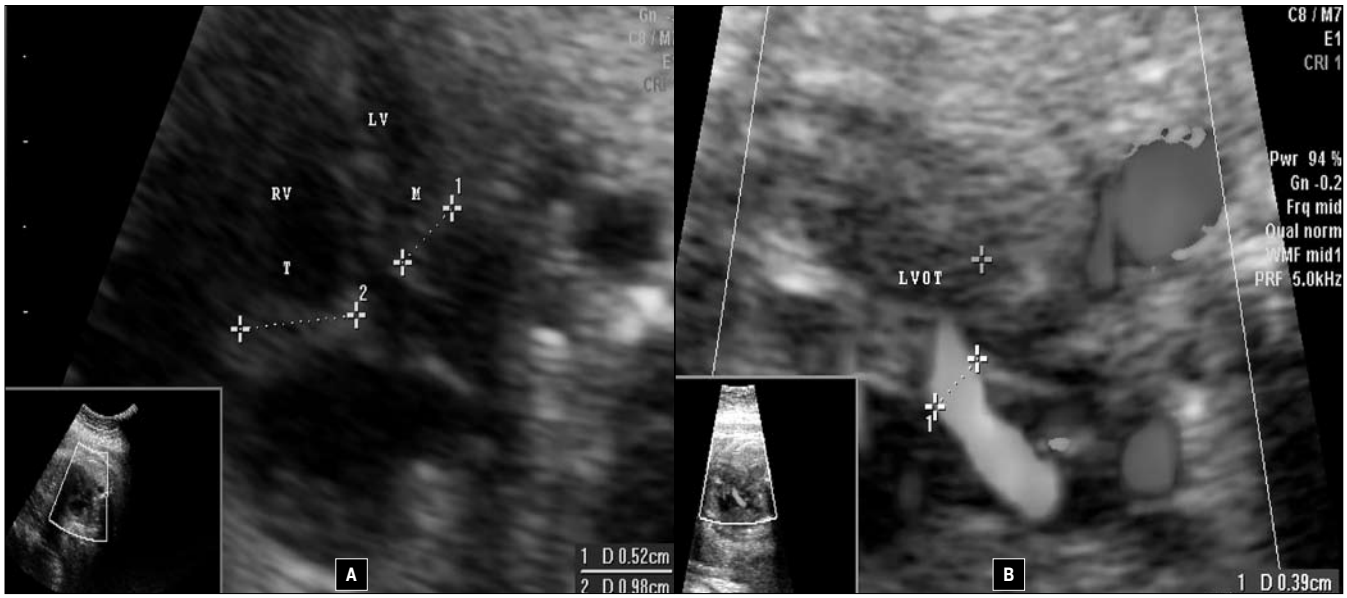

Figure 3. 20 weeks of gestation: The heart. **A** – four chamber view demonstrating hypolastic left heart syndrome. **B** – LVOT demonstrating CoA.

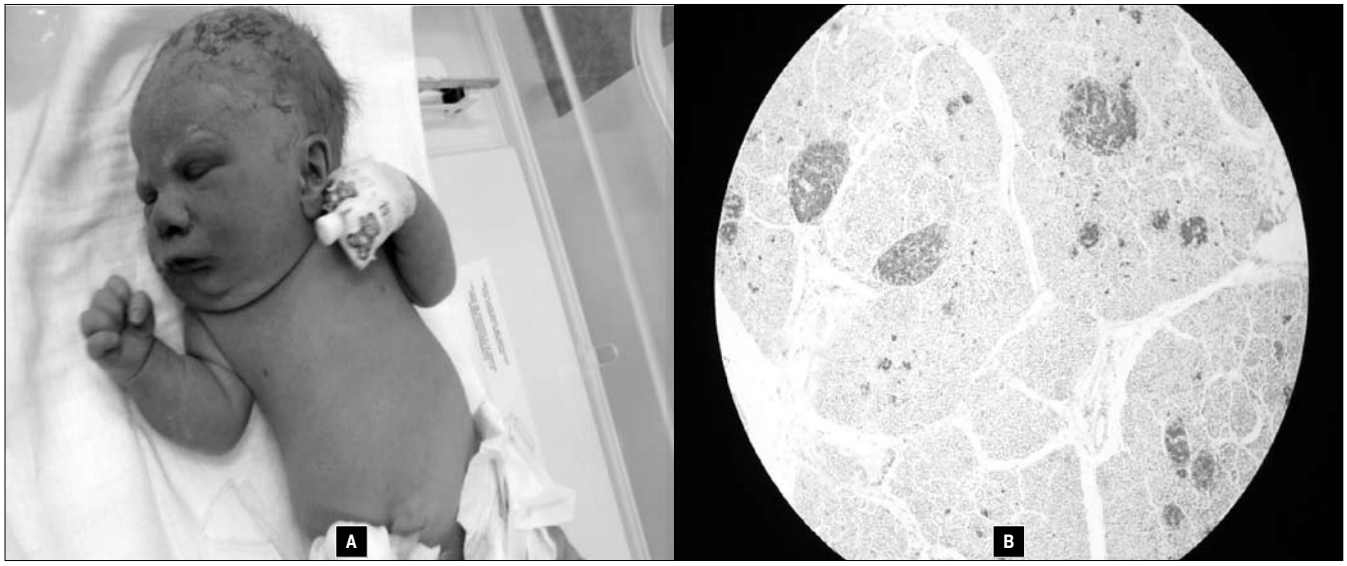

Figure 4. A – Body build, big abdomen, wide spaced nipples and facial dysmorphies; low-set ears, hypoplastic eyebrow, prominent glabella, broad and flat nose, broad nasal root and long and flat philtrum. Short webbed neck; hypoplastic nails. **B** – The histopathology analyses shows hyperplasia of pancreas isles.

Only a hypothesis may clarify clinical paradoxical reaction to prostaglandin. Perimembranous VSD as well as polycystic kidneys and hydronephrosis was also confirmed. According to our knowledge such an unusual coexistence of cardiac anomalies have not been described so far. Anomalies which were not detected in sonography were uretheral and urachal hypoplasia and polysplenia. Histological investigation detected hyperplasia of pancreatic isles.

Genetic analyses

Standard karyotype analyses of amniocytes was performed at 15th week with resolution of 450 – 650 kb and showed normal male karyotype. Despite of this results, we decided to employ the methods with greater resolution.

First step was M-FISH analysis of amniocytes' mataphases, which was performed with use of a 24-XCYTE set of probes (Metasystems). DNA isolation from a culture of amniocytes was performed by the automatic isolating system (Roche). Microarray-CGH was performed with use of the Agillent Human Genome CGH Microarray Kitt 2,44k. The high resolution 60-mer oligonucleotyde based microarray was used which allowed genome wide survey and typing of molecular aberrations with resolution of ~75kb. mCGH investigation (2,44 OLIGO m-CGH Agilent) showed deletion of 5.7 Mb of 15q26.1qter and 22.5 Mb duplication of 3q26.33qter, confirmed then by M-FISH interpretation with use of telomeric probes (Tel Vision 3qSO and 15qSO). Results of all cytogenetic analyses was defined finally as: 46XY, ish der (15)t(3;15)(qter+,qter-)pat.

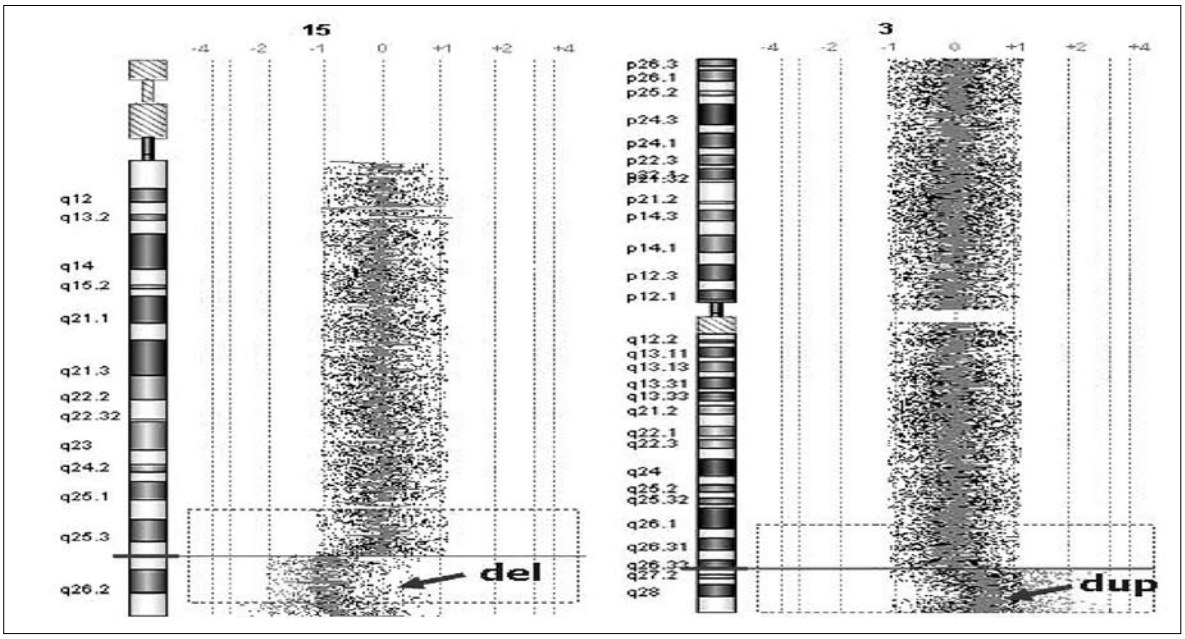

Figure 5. Genetics analyses – 15q26.1-qter loss and 3q26.33-qter gain were identified by aCGH.

Further investigations performed in both parents detected normal standard karyotype in a mother, while the father carried balanced subtelomeric translocation 46,XY,ish t(3;15)(qter-qter+;qter+qter-) without any clinical symptomes.

It is needed to be emphasized that discovery of paternal chromosomal aberration and determination of future family high genetic risk was possible only as a result of previously determined anomalies in the fetus.

Discussion

Small subtelomeric aberration are well known and relatively frequent cause of neuropsychological retardation with coexisting structural anomalies of the children. Their span is at most cases too small for routine prenatal detection. Similar imbalances may be frequently generated if a parent is a carrier of a very small balanced, undetectable aberration. This situation generate high genetic risk for all future pregnancies.

Diagnosis of this type of aberrations is troubleshooting, particularly due to the very small extent aberration, variability and complex fetal phenotypes and for this reason, their prevalence among fetuses remains unknown, similarly to relatively low frequency in postnatal diagnosis. Despite of the small size, subtelomeric regions include great number of clusters of different genes, hence the aberrations of them generate great load of clinical phenotypes.

In contrary to regular trisomies, where we have plain algorithms of their diagnosis, it is not possible to routinely diagnose all subtelomeric aberrations in every pregnancy. The detection requires complicated, time consuming and expensive methods of molecular and cytogenetic analyses (FISH, MLPA, microarray etc) which may be employed only in justified cases in reference laboratories [1, 2, 3, 4]. That puts the question of qualification to this higher level diagnosis. In our opinion, it is possible only by the carefull sonographic evaluations, performed by the sonographers with high skills both in image evaluation, but also with broad knowledge in possible syndromes of anomalies [5, 6, 7].

In our case the constellation of anomalies was not characteristic for common syndromes. In differential diagnosis at first we analysed possibility of skeletal anomalies like achodroplasia, achondrogenesis, but their symptomatology do not include additionally detected anomalies like heart and/or kidneys defects; another similar disease, which is osteogenesis imperfecta presents a number of malformations with multiple fractures, which were not detected in our case. We excluded also a thanatophoric dysplasia with typical clinical features: large skull with full forehead and low nasal bridge accompanied by a narrow thorax with short ribs. Finaly a diastrophic dysplasia has a wide range of skeletal malformations with demineralization of bones especially the sternum, but have no accompanying malformation of heart and kidneys [8].

Secondly we analysed group of known syndromes exhibiting heart defects. At first Di George syndrome doesn't show renal and bones anomalies, while frequently cleft palate is observed. In Williams syndrome both renal and bones anomalies are not characteristic similarly to other classic microdeletions.

Careful analyses of presented anomalies suggested, that probability of classical syndromes caused by well known microdeletions was low, but four previous pregnancy losses forced us to the effort and investigation of possible submicroscopic aberrations.

Performed analyses revealed not only an unbalanced aberration in the fetus, but also allowed detection of carrier status in father with great genetic risk in family.

Observed fetus represent of mixed phenotype, resulting from the sum of features of diagnosed two aberrations: small submicroscopic duplication of 3q and equally small deletion of the distal part of 15q.

To our knowledge, we present the first case of such mixed phenotype, identified prenatally, observed postnatally and in autopsy. In available literature only 25 cases are described with isolated deletion of 15q and 15 cases of isolated duplication of 3q. No case of these two aberrations in one individual has already been published [9, 10]. Observed phenotype has features of both anomalies: deletion of 15q has a characteristic signs: IUGR, triangular face with micrognathia, and malformations of extremities (proximally placed thumbs, cubitus valgus, brachydactyly and tapering of digits) – all this signs were found in sonographic analyses, excluding triangular face. [5, 11, 12]. Terminal duplication of 3q demonstrate many different facial dysmorphies, complex heart defect (VSD, ASD, malrotation and interrupted Ao, HLHS), polycystic kidneys with anomalies of urinaly tract, and polydactyly [13, 14, 15, 16, 17, 18, 19].

All this anomalies, excluding polydactyly and urethral anomalies we detected in prenatal sonographic evaluation.

The autopsy revealed also CoA with hypoplastic, non functional DA, and unusual anastomose [?] between PA and Ao. In our knowledge similar anomaly has not been described in literature yet, both in prenatal sonographic screening and particulary in a living child. Very unique finding were the atypical vessels between Ao and PA, with atypical response to prostaglandin [20]. We suggest, that this anastomoses [?] were a substitute of DA, without an expected reaction to PG.

In histological investigation hyperplasia of pancreatic islets was also detected. We can't verify if this hyperplasia maybe in this context interesting, that in 15q region, one of diabetogenic genes is localized, and hyperplasia of islets may be a result of haploinsuffitiency.

In medical history of our gravida four previous losses of pregnancies had been reported. After described case within following year the sixth pregnancy had been detected and then had been lost at 9th week of gestation, before invasive prenatal diagnosis was introduced. We assume this could be a result of harbouring genetic imbalance, associated with balanced translocation in father.

Conclusions

1. Qualification of particular pregnancies to such refined procedures must be made at the earlier USG level with carefully differential analysis of possible phenotypes and syndromes.
2. Our case demonstrates the necessity of advanced genetic analysis for proper performing of prenatal diagnosis. It may be achieved only by extraordinary and non-routine methods.
3. High familiar genetic risk in next pregnancies, based on paternal balanced carrier status, could be determined in this family only by use of M-FISH and mCGH.

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