Plurimalformative syndrome associating trisomy 18 and omphalocele. Case report and review of the literature

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Abstract

Trisomy 18 or Edwards syndrome is a rare chromosomal anomaly, associated with mild to severe intellectual disabilities and multiple congenital anomalies. Trisomies 18 and 13 are lethal, only 5–10% of patients surviving the first year of life. Although prenatal biological and ultrasound investigations are mandatory and free and the detection rate of chromosomal abnormalities is high, the birth of children with no real chance at a normal life being thus avoided by therapeutic abortion, the parents of the here presented child did not benefit from medical examination or prenatal tests, unfortunately the case of many families in Romania. The policy of limiting medical intervention in newborns with Edwards syndrome due to the broad spectrum of severe congenital malformations, severe mental retard and reduced life expectancy is unanimously accepted, but yet difficult to apply from an ethical point of view. That is why very important for both healthcare providers and families to have accurate and detailed knowledge of survival, disease course, and quality of life so that they can make fully informed decisions regarding care of these babies. The particularity of this case is the association of multiple congenital anomalies in a male newborn with trisomy 18, almost all apparatus and systems being affected, with the presence of an omphalocele and complete right labiopalatine cleft, which are less frequent at children with trisomy 18.

Keywords: trisomy 18, omphalocele, plurimalformative syndrome.

Introduction

Trisomy 18 or Edwards syndrome is a rare chromosomal anomaly associated with severe intellectual disabilities and multiple congenital anomalies, with an incidence of 1/3000–1/8000 newborns, 80% of them being girls [1]. Children with trisomy 18 are usually low birth weight, with craniofacial dimorphism, microcephaly and micrognathia, low implanted ears, skeletal or renal anomalies, and cardiac malformations. Multiple studies demonstrated a longer survival for girls with trisomy 18 compared to boys, and also a racial influence, with a longer survival for black race children. Although any woman presents the risk of having a child with such an anomaly, the advanced maternal age is correlated more frequently with the incidence of this condition [2]. At 12 weeks of gestation, the relative prevalence of trisomy 18 to 21 and of trisomy 13 to 21 is of 1/3, 1/7, respectively, while at birth, the same rates are of 1/12, 1/28, respectively. Trisomies 18 and 13 are lethal and the miscarriage rate or fetal death between 12–40 weeks of gestation is about 80%, the median age of survival being 10 days for trisomy 13 and 14 days for trisomy 18 [3]. Only 30% of these children survive the neonatal period and 5–10% the first year of life [3, 4], the most frequent cause of death being acute cardio-respiratory failure due to associated cardiac malformations, which are met in 70–100% of the cases [5]. It is obvious that the prognosis of these patients depends on different treatment strategies, especially during the neonatal period, because most of the congenital malformations can be now successfully treated. It is not clear yet how the modern aggressive treatment may influence the survival rate in trisomy 18, the main impediment to answer these questions being the policy of implementing a minimal treatment in patients with such anomalies [6].

The aim of this paper is to present a case of plurimalformative syndrome and trisomy 18 and to discuss about the incidence of similar chromosomal anomalies, diagnosis and prevention possibilities, prognosis of such cases, issues of medical and surgical therapy that might be raised, and also ethical dilemmas. It is very important for both healthcare providers and families to have accurate and detailed knowledge of survival, disease course, and quality of life so that they can make fully informed decisions regarding care of these babies [7], the here presented case demonstrating the multitude of malformations associated with this syndrome and its fatal course despite intensive neonatal resuscitation measures.

Patient, Methods and Results

We studied the case of a newborn with plurimalformative syndrome, using to support the diagnosis of trisomy 18 family history records, detailed clinical examination, imaging and lab investigations, genetic checkup, anatomopathological elements. For publishing this case, photographs included, parental consent and the approval of hospital ethics committee were obtained. The data were processed using the specialized module of Microsoft Excel application.

On October 14, 2010, at 01:24 a.m., a male child aged
about two hours born at “Cuza-Vodă” Maternity Hospital, Iassy, Romania, was referred to our clinic with the following diagnosis: plurimalformative syndrome, right complete labiopalatine cleft, bilateral external beam hemimelia forearm and hand, omphalocele, congenital bilateral undescended testis, small for gestational age newborn.

The patient comes from an unmonitored pregnancy, natural birth, head presentation, gestational age 38 weeks, birth weight 1700 g, Apgar score 6 for one minute and 5 for five minutes, $\text{SaO}_2=90\%$ under head tent, length 44 cm, thoracic perimeter 34 cm, cephalic perimeter 32 cm, ponderal index 1.9.

From the family history records, we learned that the patient was an ethnic Rom, his mother was 38, gravida 15 and para 5, suffered from vitiligo, had an extrauterine pregnancy, not married, smoker one pack a day, disadvantaged social environment. The father, aged 37, had no history of disease. One sister, premature born at 36 weeks of gestation, 900 g weight at birth, died in 1996 of sepsis due to ulcerative necrotizing enterocolitis. The results of biological tests demonstrated leukocytosis, thrombocytopenia, and hepatocytolytic hemorrhage, hyperplasia of the islets of Langerhans in the pancreas was found (Figure 4), which is typical for trisomy 18, and karyotyping revealed 47,XY,+18 (presence of single lineage with free trisomy of chromosome 18). Karyotyping was performed in the Laboratory of Immunology and Genetics, “St. Spiridon” Emergency Hospital, Iassy, by the conventional G-banding method.

About 48 hours after admission, the patient developed acute cardiovascular and respiratory failure for which he was orotracheally intubated, and, despite all intensive care measures and resuscitation, he died on October 16, 2010, at 06:22 a.m.

A post-mortem examination (necropsy) was performed, the anatomopathological findings being: plurimalformative syndrome, complete right labiopalatine cleft and per oral level hemangioma, small ranula, congenital absence of the radius and both thumbs, short ulna, clenched hands, medium-sized omphalocele containing bowel loops, bilateral congenital undescended testes and micropenis. The internal organs were largely affected by stasis and edema, multiple malformations being detected: meningo-cerebral stasis and edema, intraventricular hemorrhage and dilatation, pulmonary stasis and outbreaks of collapse with incomplete segmentation of the right lung, dextrocardia with atrial septal and ventricular septal defects (Figure 2), and large ductus arteriosus, malrotation with common mesentery, annular pancreas, horseshoe kidney (Figure 3). Microscopically, biliary stasis, intestinal hemorrhage, hyperplasia of the islets of Langerhans in the pancreas was found (Figure 4), which is typical for trisomies associated with omphalocele. There were some others microscopically particularities found in this case: outbreaks of mucosal epithelium in the esophagus (Figure 5), outbreaks of hematopoiesis in the liver and kidney (Figure 6) and calcification in cerebral nerve tissue (Figure 7). The main cause of death was broncho-pneumonia (Figure 8).

Figure 1 – Plurimalformative syndrome.

Figure 2 – Dextrocardia with atrial and ventricular septal defects.
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Figure 3 – Horseshoe kidney.

Figure 4 – Hyperplasia of the islets of Langerhans in the pancreas (HE staining, ×100).

Figure 5 – Outbreaks of mucosal epithelium in the esophagus (HE staining, ×100).

Figure 6 – Hematopoiesis in the area of intrahepatic bile ducts (HE staining, ×200).

Figure 7 – Calcification in cerebral nerve tissue (HE staining, ×100).

Figure 8 – Bronchopneumonia (HE staining, ×100).

Discussion

The particularity of the presented case consists in the association in a male newborn with trisomy 18 not screen prenatally of multiple congenital malformations, almost all apparata and systems being affected. More than 130 different anomalies have been reported in different studies, and virtually all organs and systems may be affected, but none is pathognomonic of trisomy 18. The most frequent phenotypic characteristics of the syndrome, according to the topography, consist of: neurological findings, growth disturbances, malformations of the skull, face, thorax, abdomen, limbs, genitals, skin, skin annexes, and internal organs [8], our patient presenting all these anomalies, bilateral radial aplasia, omphalocele and labio-maxillo-palatine cleft included, present in but 5–10% of cases [9, 10]. Although some studies report a characteristic association of omphalocele with neural tube defects in patients with trisomy 18 [10, 11], this was not the case with our patient. Su et al., in 2007, reported a similar case of trisomy 18, but in a female newborn with Dandy–Walker malformation and Meckel diverticulum [12]. The percentage of associated malformations differs from one study to another, depending on the time of diagnosis (pre- or post-natal) and also on the group of studied patients, whether or not dead fetuses and stillbirth were included. There are too few articles describing pathological characteristics at the microscopic level, and here we outlined some microscopic features.
The tragedy of giving birth to such a child could be relatively easily avoided by performing routine tests in the first and second trimester of pregnancy, followed by therapeutic abortion. The screening for the prenatal detection of trisomy 21 is insured by a series of tests which include maternal age, fetal nuchal translucency (NT) thickness, maternal serum free ß-hCG and pregnancy-associated plasma protein A (PAPP-A) levels between 11 and 13 weeks of gestation, with a detection rate of approximately 90% and a false positive results rate (FPR) of 5% [13, 14]. A good consequence of the screening for trisomy 21 is the early detection of trisomies 18 and 13, which are on the second and third most commonly diagnosed chromosomal anomalies. At 11–13 weeks of gestation, the relative prevalence of trisomy 18 and 13 to trisomy 21 is 1/3 and 1/7, respectively. All these trisomies are associated with advanced maternal age (like in this case), increased NT and decreased PAPP-A levels in maternal serum, but in trisomy 21 ß-hCG is high, while in trisomies 18 and 13 it is low. If we take into account the fetal heart frequency (FHR) and the specific algorithms for trisomies 18 and 13 combined with the algorithm for trisomy 21, approximately 90% of fetuses with Down syndrome and approximately 95% of those with trisomy 13 and 18 can be detected with a false positive result rate of 3.1% [15]. Although prenatal biological and ultrasound investigations are mandatory and free and the detection rate of chromosomal abnormalities is high, the birth of children with no real chance at a normal life being thus avoided by therapeutic abortion, the parents of the here presented child did not benefit from medical examination or prenatal tests, unfortunately the case of many families in Romania.

Trisomies 18 and 13 are lethal and miscarriage or fetal death rate between 12–40 weeks of gestation is approximately 80%. That is why it raises the problem of exposing mothers to the risk of invasive tests in the first trimester of pregnancy and then to the early decision of terminating it, taking into account the fact that most trisomies 18 and 13 can be identified only echographically in the second trimester of pregnancy, thus avoiding the exposure to invasive tests in the first trimester. Anyway, most mothers prefer the screening to be done as soon as possible, and besides this, therapeutic abortion is safer in the first than in the second trimester of pregnancy [16]. An accurate characterization of the fetal chromosomal defects has implications in the couple decision regarding the continuing of the pregnancy or elective abortion and brings important information for the future reproductive options in order to give birth to a healthy baby [17].

Recent studies have shown a poorer survival of these patients than reported in literature in the previous decades, leading some authors to the conclusion that the patients with trisomy 13 and 18 recently born receive from the start a less aggressive treatment due to the bad prognosis at birth [16]. Our patient survived only two days despite intensive therapeutic measures. The policy of limiting medical intervention in newborns with Edwards syndrome due to the large spectrum of severe congenital malformations, severe mental retard and reduced life expectancy is unanimously accepted, but yet difficult to apply from an ethical point of view [7]. Ethical problems arise from the significant differences in the results of some studies on morbidity rate, therapeutic abortion or medical interventions applied to these patients [4, 18, 19]. The absence of cytogenetic confirmation in newborns suspected of trisomy 18 who need emergency medical intervention or another intensive care maneuver makes this decision even more complicated. That is why some authors recommend intensive treatment at least during the first two weeks in all newborns suspected of Edwards syndrome, until cytogenetic confirmation, this approach being in line with parents’ wishes, and avoiding any conflict [7]. This approach is valid in Romania, our patient benefiting all possible investigations and therapeutic support, although the Edwards syndrome was suspected at birth and confirmed by karyotyping three weeks later.

Conclusions

All these data are useful to family doctors, geneticists, obstetricians, neonatologists, pediatric surgeons, anesthesiologists, pediatricians, etc. who come in contact with patients affected by such chromosomal anomalies or deal with counseling families who are about to give birth to or have a child with trisomy 13 or 18.

Acknowledgments

For publishing the data and photographs of this patient, parental informed consent and written approval, as well as the approval of the hospital ethics committee were obtained.

References

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Received: February 6, 2013

Accepted: February 25, 2014