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INTENSIVE CARE OF NEWBORN WITH EDWARDS SYNDROME – CASE REPORT

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Case report

Key words: Edwards syndrome, intensive care, survival

Summary. ***Introduction.*** Edwards syndrome is the second most common autosomal chromosome anomaly in humans, with a prevalence of 1: 6,000–1: 8,000 in live births. The syndrome includes a recognizable pattern of major and minor anomalies, and prominent psychomotor and cognitive impairments. It carries an increased risk of neonatal and infant mortality. More than 50% of children die in the first week of their life, and less than 10% of them survive until the age of one year. The approach to the treatment of such patients has so far caused many controversies among pediatricians. Whereas some believe that the use of intensive therapy prolongs survival, others believe that it has no long-term effect and due to the severe psychomotor and cognitive impairment its application is not justified. ***Case report***. A female newborn, born on January 11th, 2014, immediately after birth, was transferred to Neonatal Intensive Care Unit of Department of Pediatrics, University Clinical Hospital Mostar, because of hypotonia, pale-grayish color of the skin, deficient spontaneous motor skills and respiratory insufficiency. Clinically, the newborn showed phenotypic characteristics typical of Edwards syndrome. Immediately upon receipt the patient was intubated and connected to mechanical ventilation. The same day diaphragmatic hernia was diagnosed and a corresponding surgery was performed. Cytogenetic findings confirmed complete trisomy 18. Heart echography showed VSD input type (size 8 mm), ASD II (5 mm), PDA (3 mm). Further diagnostic examination showed other congenital malformations with less clinical importance. After stabilization, the patient continued post-intensive treatment with cardiac therapy and physiatric treatment. After being discharged, the patient was repeatedly hospitalized, among other things due to the development of pulmonary hypertension and its complications. The child died in June 2016 of heart failure at the age of two years and six months. ***Conclusion***. The application of intensive treatment had a certain impact on our patient's survival. It has also been shown that intensive care is followed by cardiovascular events as major mechanisms of death, as opposed to non-invasive approach where high percentage of deaths are associated with central apnea.

Introduction

Edwards syndrome (trisomy 18) is the second most common autosomal chromosome anomaly in humans, with a prevalence of 1: 6000 to 1: 8000 in live births, while the overall prevalence is 1: 2500 to 1: 2600, due to the high incidence of abortions and fetal loss after prenatal diagnosis (1). More than 95% of affected children have a complete trisomy 18 whereas others are affected because of parental translocation, or mosaicism. The syndrome includes recognizable pattern of large and small abnormalities, increased risk of neonatal and infant mortality and prominent psychomotor and cognitive impairments. The main features are: small face, craniofacial dysmorphia, hypoplastic mandible, low-lying auricles, and characteristic flexion contractures of fingers, short sternum and anomalies of the heart, kidneys and digestive tract. The clinical picture has more than 100 symptoms and signs. Congenital heart defects occur in almost all newborns with this syndrome (in 95–99% of cases), they have a wide range of appearance and are often combined in the same patient. According to the order of frequency these are: VSD, valvular heart defects, infundibular pulmonary stenosis, AVSD, TOF and double output of blood vessels from the right ventricle. As in the case of Down's syndrome, the transposition of great vessels or the inversion at any level (cardiac or visceral) are not described, which seems to be characteristic of these trisomies. The diagnosis may be suspected based on impaired ultrasound findings or maternal serum screening, and postnatally, based on phenotype. In both cases, the diagnosis is confirmed with cytogenetic analysis (2–4). The main causes of mortality are central apnea, heart failure due to cardiac malformations, respiratory insufficiency due to hypoventilation, aspiration, upper airway obstruction, and combinations of these and other factors (including decisions related to aggressive intensive care). It is impossible to give the prognosis during pregnancy and neonatal period (1). More than 50% of children die in the first week of life, and less than 10% of them live past the first year of life (4).

Case report

A female newborn, the fourth child of six pregnancies (previously two miscarriages), was born on January 11th 2014 at the Department of Gynecology, University Clinical Hospital Mostar. The course of pregnancy in the first trimester was normal, but in the fourth month of

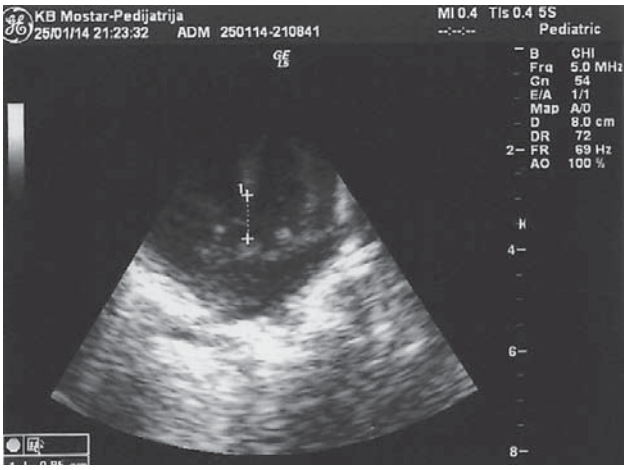

Figure 1. ECHO: The view of VSD inlet

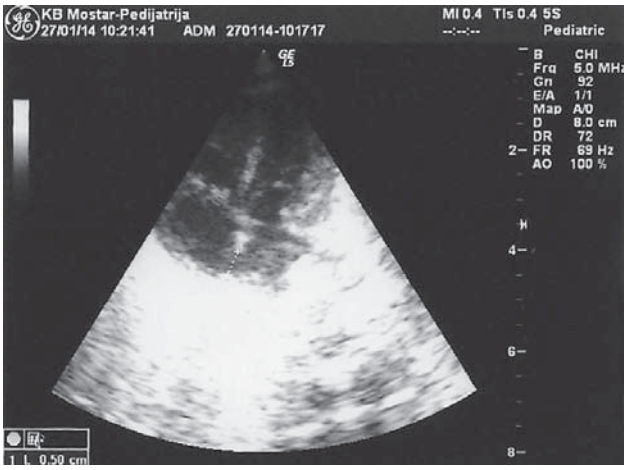

Figure 2. ECHO: The view of ASD II

pregnancy the mother had vaginal bleeding. Diagnosis of placenta praevia totalis was established, and Mg and Gynipral administered. Childbirth occurred 11 days after the due date (due date January 1st 2014), naturally, without complications. The newborn had birth weight of 2 810 g, length of 52 cm, Apgar score 7/8. Clinically, the newborn showed phenotypic characteristics typical of Edwards syndrome: microcephaly, wide open fontanelle, wide forehead, small face, hypertelorism, epicanthic fold, narrow and short opened eyelids, ptosis, small nose and mouth, micrognathia, low-lying auricles, short neck with excess wrinkled skin, hypoplastic chest, short sternum, increased hairiness on the back, changes on extremities – clenched fist with a typical position of fingers where the second finger overlies the third and the fifth overlies the fourth, contracture of fingers, hypoplasia of radius, dislocation of hips, dorsal flexion of thumb, partial syndactyly of 2nd and 3rd toe. Weakened respiratory movements and pale-grayish color of skin were noticed after the birth. The clinical condition stabilized after brief ventilation with Ambu mask and blood oxygen saturation level rose. The newborn was transported with transport incubator to the Neonatology and Neonatal Intensive Care Unit, in Pediatrics Clinic.

On receipt the newborn was hypotonic, with pale-grayish color of skin, deficient spontaneous motor skills and respiratory insufficiency – on arrival SpO_2 89–91%. After primary stabilization, the decrease in hemoglobin oxygen saturation was still visible, and the patient was intubated and put on mechanical ventilation. ABS of capillary blood on admission: pH 7,166; PCO_2 86,4 mmHg; PO_2 39,6; SO_2 73,3%; $CHCO_3$ 30,5 mmol / L; BE –1,6 mmol / L. On admission and several times during the stay samples for control ABS, laboratory and microbiological tests were taken. Radiologic examination (X-ray babygram) on the first day showed diaphragmatic hernia. The surgical procedure of diaphragmatic hernia was performed on the same day using general endotracheal anesthesia. The planned surgery and postoperative period passed without complications. The necessary supportive antibiotic and other supportive therapy with adequate sedation was provided. On several occasions, the newborn received plasma and red cell concentrate. After 3 days the patient was extubated and removed from mechanical ventilation, which she tolerated by taking respiratory therapy and inhalations. She was fed on tube. Echography of the heart and great vessels *(Figure 1, Figure 2)* showed the following congenital heart defects: inlet VSD type (size 8 mm), ASD II (5 mm) and PDA (3 mm), which are stable due to taking corresponding cardiotonic (Digoxin salt. 1x1 drop per os, every day), and diuretic (Lasix 2x1 mg orally, every other day). Abdominal ultrasound showed hypoplastic right kidney with pyelectasis, left kidney bigger with extended channel system intrarenal. Ultrasound of the brain and EEG were normal. Bilateral atresia of ear was established by a specialist *otorhinolaryngologist* otoscopic examination. Cytogenetic findings *(Figure 3)* confirmed the diagnosis of trisomy 18 on January 27th. Using GTG – banding method, the following cytogenetic findings were obtained from blood sample: female karyotype complete trisomy 18 – Sy Edwards (47, XX, + 18). Post-intensive period passed without complications. A specialist physiatrist performed examination and the patient was already involved in physiatrist's treatment during the stay at the Clinic. Parents received detailed information regarding the diagnosis of Edwards syndrome, and the child was released to home treatment on April 7th 2014. Therapy on discharge: Lanitop salt. 1x1 drop p.o.; Lasix 2x1 mg p.o./every other day; Vitamin D3 salt. 1x4 drops p.o. The appointments were made for control examinations of children's cardiologist, nephrologist, neuropediatrician and physiatrist, and the instructions about vaccination were given to the parents.

Later, the patient was repeatedly hospitalized because of gastroenteritis, infection of the respiratory system, and complications associated with the development and progression of pulmonary hypertension. Over time cardiac treatment was expanded and the following medications were added to the previous therapy: Aldactone, Enalapril powder and Propanolol. The patient regularly

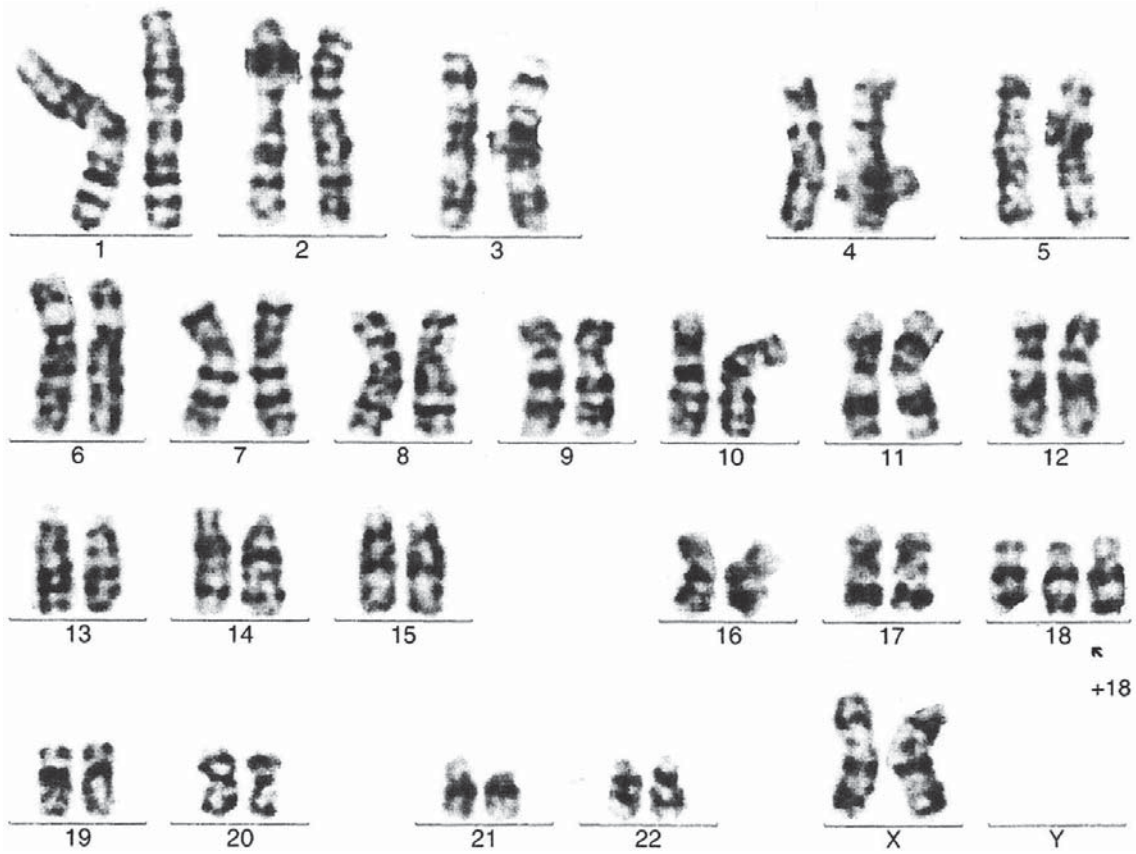

Figure 3. Cytogenetic findings (GTG – banding method): female karyotype, full trisomy 18 (47, XX, + 18)

attended controls and was taking prescribed medications. The last control in our Clinic was in August 2015, after which parents and the patient moved abroad. Exitus Letalis took place in June 2016 due to a heart failure at the age of two years and six months.

Discussion

In 2008 and 2009, 495 diagnosis of Edwards syndrome were established in England and Wales, out of which 92% prenatally. Out of this total, 339 pregnancies resulted in abortion, 49 had the following outcomes: stillbirth / miscarriage / fetal death; there were 35 live births and 72 with unknown outcomes (5). Most recent studies report a median survival of 3–14.5 days, a percentage of survival after 24 hours of 60%–75%, after 1 week of 40%–60%, after 1 month of 22%–44%, after 6 months of 9%–18%, and after 1 year of 5%–10% (6–8). The only study known to us for survival of patients with Edwards syndrome after the second year of life states that it is less than 4% (12). Researches linking to prevalence and survival of patients with Edwards syndrome by gender showed a higher prevalence at birth in females compared to males (F: M%, 60,4:39,6). However, this difference is not present if ratio is calculated among fetuses from aborted pregnancies (F. M% 48,3:51,7) (9). Moreover, the incidence of fetal death is higher for males compared to females (10,11). Furthermore, female newborns have a better survival rate compared to males (7,8).

Based on these data, it can be concluded that the outcome of patients with Edwards syndrome is difficult to predict during pregnancy and neonatal period. The reason lies in the fact that this population is so variable and the syndrome can be presented in various combinations of congenital defects. The clinical presentation may vary from easier to more severe forms. Our case is interesting because of the length of our patient's survival, although severe congenital malformations were found there, including congenital heart defects that are never operated due to their poor prognosis in Edwards syndrome. This case report systematically presents all medical diagnostics and procedures used in the treatment, so we could understand their impact on the length of survival in our and other patients with Edwards syndrome. So far the approach to the treatment of liveborn infants with Edwards syndrome has caused a lot of conflicting opinions in medical society, mostly because of poor prognosis and the lack of data relating to the efficacy of treatment. Does the application of intensive therapy have an effect on the length of survival?

A previous research from Japan suggests that it has. The authors reviewed detailed clinical data of 24 patients with complete trisomy 18, who were admitted to the Neonatal Intensive Care Unit of Nagano Children's

Hospital, undergoing intensive treatment in the period from 1994 to 2003. Cesarean section, resuscitation by intubation, and surgical operations were performed on 16 (67%), 15 (63%), and 10 (42%) of the patients, respectively. Mechanical ventilation was required by 21 patients (88%), and 6 (29%) of them were extubated. Survival rate at the age of 1 week, 1 month, and 1 year was 88%, 83%, and 25%, respectively. Survival beyond 2 years (4%) was similar to the 5–10% usually reported as 1-year survival rate. Median survival time was 152,5 days.

In this study the authors also investigated pathophysiologically the reasons of death in patients who had intensive treatment, distinguishing the key factors associated with death and final mechanisms of death. The common key factors associated with death were congenital heart defects and heart failure, and pulmonary hypertension. On the other hand, the final modes of death were sudden cardiac or cardiopulmonary arrest and events related to progressive pulmonary hypertension. From these observations, it becomes clear that apnea and withdrawal of treatment could be considered the major cause of death when a patient with trisomy 18 was managed with purely comfort care. When a patient with trisomy 18 has intensive treatment, the common causes of death are altered, and survival does increase (12).

Reviewing data from literature, and comparing it to the usage of intensive therapy, the length of survival and mechanism of death in our case, we can assume that the equal correlation between these parameters was confirmed. An early application of intensive therapy in this group of patients has a significant impact on the extension of life expectancy and outcomes in neonatal and infant period. However, the equalization of mortality rates after the second year of life raises the question if the application of intensive therapy is justified, from the perspective of families of newborns who undergo aggressive medical procedures, and the quality of life that period of intensive and post-intensive care carries, but also from the perspective of the health care system that is additionally burdened by heavy financial expenses in such cases. The intention of this paper is to provide access to all available information on intensive treatment of patients with Edwards syndrome and to show what such treatment carries. These data should be used to help doctors in providing information to patients' families and in cooperation with them in decision about treatment options for each individual case.

Conclusion

The application of intensive care in newborns with Edwards syndrome has effect on survival in neonatal and infant period. It has no effect on survival rate of patients in the period after the second year of life but may have effect on pathophysiological modus of death.

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INTEZIVNO LIJEČENJE NOVOROĐENČETA S EDWARDSOVIM SINDROMOM – PRIKAZ SLUČAJA

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Prikaz slučaja

Ključne riječi: Edwardsov sindrom, intezivno liječenje, preživljenje

Sažetak. ***Uvod***. Edwardsov sindrom je druga najčešća autosomna kromosomska anomalija u čovjeka, s prevalencijom od 1:6000 – 1:8000 kod živorođene djece. Sindrom obuhvaća prepoznatljiv uzorak većih i manjih anomalija, te značajana psihomotorna i kognitivna oštećenja. Nosi povećani rizik od neonatalne i dojenačke smrtnosti. Više od 50 % djece umire u prvom tjednu života, a manje od 10 % ih doživi prvu godinu života. Pristup u liječenju ovakvih pacijenata dosad je u pedijatrijskoj zajednici izazivao dosta kontroverza, jer dok jedni smatraju kako primjena intezivne terapije produžuje preživljenje, drugi smatraju kako nema dugoročni učinak i s obzirom na teška psihomotorna i kognitivna oštećenja da njezina primjena nije opravdana. ***Prikaz slučaja***. Žensko novorođenče, rođeno 11.1.2014. premješteno je na JIL Klinike za pedijatriju SKB Mostar neposredno nakon poroda zbog hipotonije, sivoblijede boje kože, oskudne spontane motorike, respiratorno dekompenzirano. Klinički novorođenče je pokazivalo fenotipske karakteristike tipične za Edwardsov sindrom. Odmah po prijemu pacijentica se intubira i stavi na strojnu ventilaciju. Isti dan se dijagnosticira dijafragmalna hernija i napravi se operativni zahvat. Citogenetskim nalazom se potvrdi potpuna trisomija 18. Ehografijom srca nađu se VSD inlet tip (vel. 8 mm), ASD II (5 mm), PDA (3 mm). Daljom dijagnostičkom obradom nađu se i druge prirođene malformacije manje kliničke važnosti. Nakon stabilizacije postintezivno pacijentica nastavlja s kardiološkom terapijom i fizijatrijskim tretmanom. Nakon otpusta više puta hospitalizirana, među ostalim zbog razvoja plućne hipertenzije i njenih komplikacija. Dijete je umrlo u lipnju 2016. od posljedica srčanog zatajenja, u dobi od dvije godine i šest mjeseci. ***Zaključak***. Primjena intezivnog liječenja kod naše pacijentice imala je utjecaj na njeno preživljenje. Također, pokazalo se kako kod ove bolesti primjena intezivnog liječenja nosi kardiovaskularna zbivanja kao glavni mehanizam umiranja, za razliku od neinvazivnog pristupa gdje se visok postotak umrlih povezuje s centralnom apnejom.