VARIABLE PROGNOSIS IN TRISOMY 18 (EDWARDS SYNDROME) – 3 CLINICAL CASES PRESENTATION

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Abstract

Trisomy 18 (Edwards syndrome) occurs in 1/3000 to 1/8000 births and it is the second frequent autosomal aneuploidy with a characteristic clinical aspect, easily recognizable in the neonatal period. The severity of the anomalies conditions the life expectancy and the life span varies from 2 weeks to one year of life, only 5-10% surviving beyond the first year of life. Yet, in the literature there are reported cases with variable survival. The purpose of this article is to present 3 cases diagnosed with trisomy 18 with variable survival.

Key words: trisomy 18, cytogenetics, survival

Introduction

Edwards syndrome described in 1960, by Edwards et al and Smith et al, is a plurimalformative syndrome with an occurrence on 1/3000 to 1/8000 live births, this incidence being influenced by the application of prenatal diagnostic. An important part of the fetuses with trisomy 18 die during the pregnancy, only a small part come to term [1] The ratio between sexes is 0,9 male : female, females being more affected with trisomy 18 than males [2].

In the clinical tableau there are multiple malformations with a specific pattern of signs that allow an early diagnosis in the neonatal period, including growth deficiency, microcephaly, micrognathia, prominent occiput, clenched hands, congenital heart defects, kidney abnormalities.

The median life span as reported in literature varies from 2.5–14.5 days [3, 4, 5].

We present 3 situations of trisomy 18 where: the first patient, a male died at 9 months old, the second case, a female still alive, being 4 years.

Cases presentations

Clinical data as well as the family and pregnancy history of the patients are presented in Table 1. For all our cases the physical evaluation was consistent with trisomy 18. All patients underwent karyotyping by GTG banding in the Genetic Laboratory of the University of Medicine and Pharmacy "Victor Babes" Timisoara. For all the three cases investigated, the cytogenetic analyses were carried out and metaphase spreads were obtained by 72-hr-culture of peripheral blood lymphocytes using standard techniques. For all patients the chromosomal imbalance revealed three chromosomes 18 in all the metaphases visualized (Figure 1-3). In the second case, because the patient survived after 1 year, for exclusion of a possible cryptic mosaic FISH analysis was performed. The FISH analysis using CEP18 (Spectrum Green) probe showed three signals corresponding to chromosome 18 in all 50 metaphases and 250 nuclei evaluated (Figure 4).

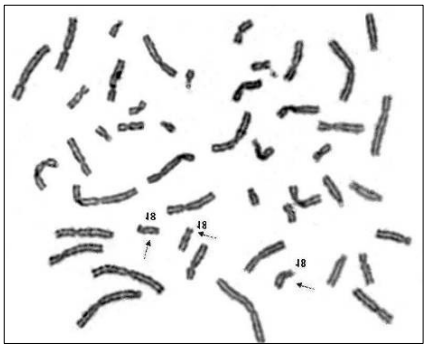

Figure 1. Patient 1 – metaphase showing 3 chromosomes 18.

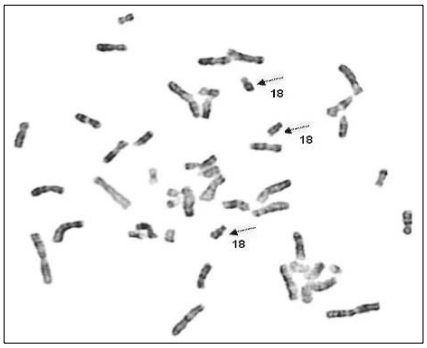

Figure 2. Patient 2 – metaphase showing 3 chromosomes 18.

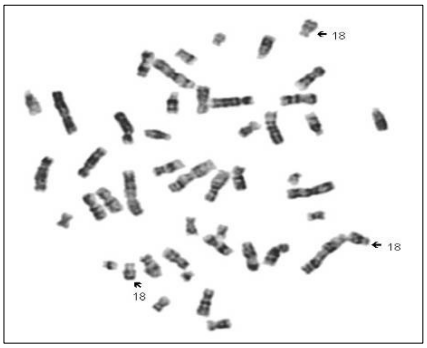

Figure 3. Patient 3 – metaphase showing 3 chromosomes 18.

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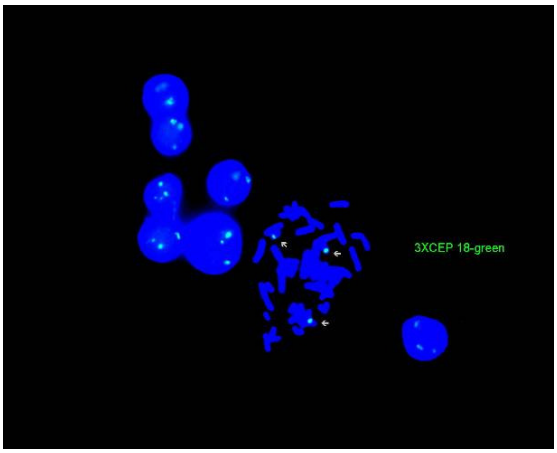

Figure 4. Patient 2 - FISH analysis showing 3 signals for chromosome 18.

Table: Patients' data at birth.

	Patient 1	Patient 2	Patient 3
Parents age	mother 30 years old father 38 years old	mother 34 years old father 36 years old	mother 39 years old father 39 years old
Consanguinity	no	no	no
Family history	Second child	First child	3 spontaneous abortions
Pregnancy history	No investigations were done	Nothing relevant	Growth retardation
Age of gestation at birth	37 weeks	39 weeks	37 weeks
General data	weight 2330 g head circumference 31 cm length 48 cm	weight 2450 g head circumference 32 cm length 47 cm	weight 1770 g head circumference 31cm length 42 cm hypotonia
Craniofacial	prominent occiput, hypertelorism, short palpebral fissures, low set, malformed ears, small oral opening, micrognathia (Figure 5)	slightly prominent occiput, narrow bifrontal diameter, hypertelorism, short palpebral fissures, low set, malformed ears, high arched palate, microstomia, micrognathia, short neck (Figure 6)	prominent occiput, narrow bifrontal diameter, hypertelorism, short palpebral fissures, low set, malformed ears, microstomia, micrognathia, short neck (Figure 7)
Hands and feet	arthrogryposis, clenched hands with the index finger overriding the middle finger and the fifth finger overriding the fourth finger, rocker-bottom feet, hypoplasia of nails	clenched hands, syndactyly of finger 4 and 5 bilaterally, rocker-bottom feet, hypoplasia of nails	clenched hands with the index finger overriding the middle finger and the fifth finger overriding the fourth finger, simian crease, syndactyly of finger 2 and 3, short hallux, rocker-bottom feet, hypoplasia of nails
Cardiac	heart murmur and at the transthoracic echocardiogram a ventricular septal defect was discovered	ventricular septal defect, atrial septal defect, pulmonary hypertension, ventriculomegaly	atrial septal defect, anomalous tricuspid valve, enlarged right ventricle, enlargement of right atrium, enlarged pulmonary vein
Genital			Hypoplasia of labia major with prominent clitoris
Renal	no signs of renal malformations		
Central nervous system	minor enlargement of posterior horns of the lateral ventricles and agenesis of corpus callosum		intraventricular cerebral bleeding, severe ischemic encephalopathy

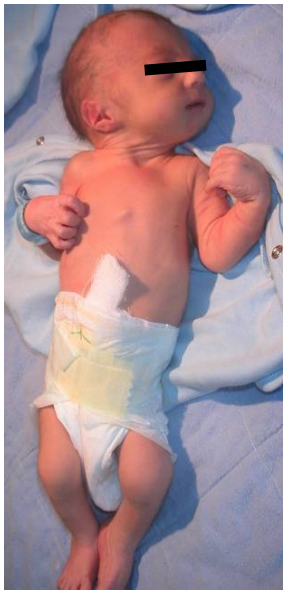

Figure 5. Patient 1 at birth.

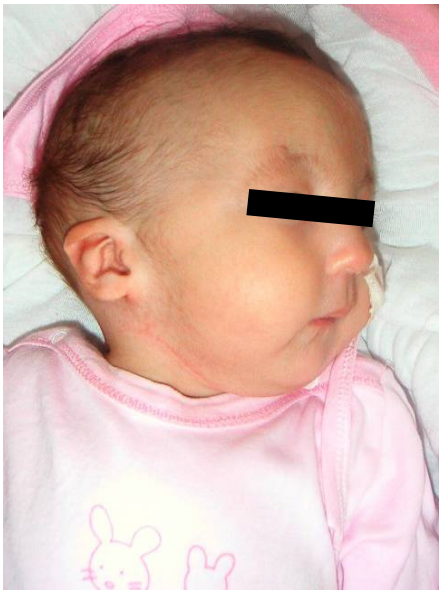

Figure 6. Patient 2 facial aspect.

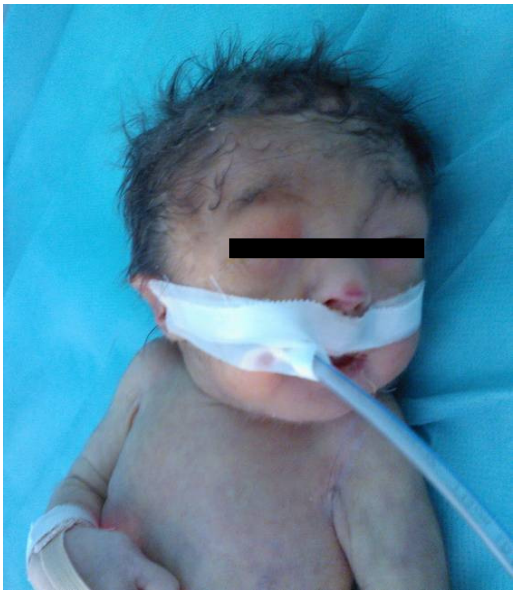

Figure 7. Patient 3 dysmorphism at birth.

Patient 1 died at age of 9 months, cause of death being respiratory failure. Patient 2, in evolution (Figure 8) developed severe mental retardation, she can sit and hold her head and she is tube feed. On the psychiatric side, she acquired only a few simple words as mama, papa. An intraoral clinical examination revealed a narrow high-arched palate and anterior open bite. The patient remains under our supervision. Due to the cardiac malformations in the third case the prognostic was very poor and the child survived only 3 days.

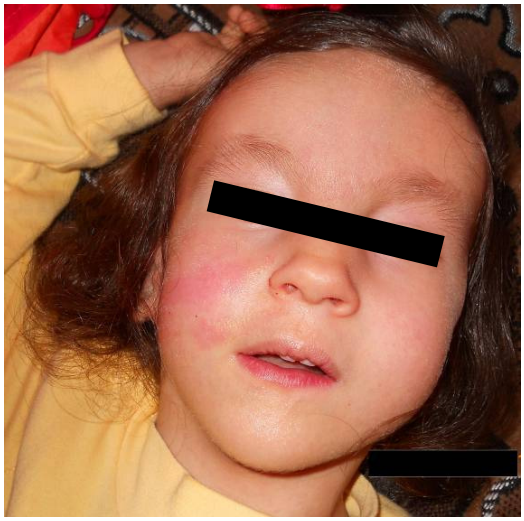

Figure 8. Patient 2 dysmorphism at age of 3 years and 7 months.

Discussions

Aneuploid syndromes are characterized by phenotypic variability and it is also well documented the overlapping of some clinical manifestations between these syndromes. For the numerical chromosomal aberrations there are key features present in all patients, but there is also a wide heterogeneity of clinical manifestations and a large variability as regards of the patient's outcome and evolution. Due to these characteristics of the aneuploid syndromes it is difficult to establish a correlation between the aberrations of a certain chromosomal region and the clinical features and is practically impossible to make a prediction about the evolution or prognosis.

Our patients present many physical stigmata of trisomy 18 that are the visit card of this syndrome: prominent occiput, short palpebral fissure, microretrognathia, clenched

hands, and rocker-bottom feet. The presented patients have a common set of manifestations found in 50% or more of patients with trisomy 18 as the specific craniofacial aspect, clenched hands, and cardiac anomalies. Additionally, patient 3 presents several hand and feet anomalies as syndactyly of finger 2 and 3, short hallux, simian crease and also genital anomalies that were reported in less than 50% of trisomy 18 patients and were not found in the other two cases reported here.

It is interesting that among the patients with trisomy 18 that survived, some of them had sever cardiac anomalies like Fallot tetralogy and yet reached the age of 20 years [7].

In a study done by Weber in 1967, it was showed that in female patients with trisomy 18 the survival rate is better than in males [4], observation sustain by other reports, [5] but there are other studies that infirm this supposition [8]. There is a diversity regarding the severity of organ malformation as well as of the clinical outcome. The causes of death and of the prolonged survival are not clear yet, there are genetic and epigenetic factors that interfere with the genetic load of the chromosome 18. The common causes of death are most often apneic spells, cardiac failure, or respiratory insufficiency, congenital heart malformations being the major cause of death [7, 9]. The literature presents that the infections are a frequent cause of morbidity and of mortality in older patients.

Cytogenetically it is important to exclude the mosaicism although no precise correlation between the degree of mosaicism and survival was reported [4, 10].

The first report about cases of trisomy 18 with long survival was done in 1978 by Smith who reviewed six patients with survival beyond 10 years and added another case [11].

To the best of our knowledge in the literature we found several individual cases of trisomy 18 patients that had a longer survival, above one year of life: 6 years Raczkowski's case [12], 8 years Querioz' patient [13], 13 year Mehta's case [14], 14 years Hinojal's patient [15], 15 years Simon-Bautista's case [16], 19 years Petek's case [17], 20 years Kelly's patient [7], 50 year in Bhanumathi's case [18]. Other cases with long survival associated Wilms'tumor: 1 year old, Geiser's case [19], 1.9 years old Miller's case [20], 4.7 years old, Wang-Wuu's case [21], 5 and 9 years old, Faucett's patients [22], 5.8, 8.7 and 13.9 years old, Olson's patients [23], 9.4 years old, Anderson's case [24], 13 years old, Karayalcin's patient [25], 21 years old Shanke's case [26].

As specified by other authors, we sustain the remark that trisomy 18 is not universally lethal. Patient 3, who is still alive will be followed periodically at our department. At prenatal diagnosis, in the cases with abnormal ultrasound findings and/or abnormal biochemical screening for trisomy 18 it is necessary to perform cytogenetic analysis from amniotic fluid. The risk for trisomy 18 implies counseling the parents as regard of giving birth to a trisomic fetus. For the parents, the decision of having the child in these conditions implies a degree of risk that should be taken in consideration.

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