Trisomy 18: review of the clinical, etiologic, prognostic, and ethical aspects

Trissomia 18: revisão dos aspectos clínicos, etiológicos, prognósticos e éticos

Trisomía 18 (síndrome de Edwards): revisión de los aspectos clínicos, etiológicos, pronósticos y éticos

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ABSTRACT

Objective: To review the clinical, etiological, diagnostic, and prognostic characteristics of trisomy 18 (Edwards syndrome).

Data sources: Scientific articles in the MedLine, Lilacs, and SciELO databases were searched using the descriptors 'trisomy 18' and 'Edwards syndrome'. The research was not limited to a specific time period and included all articles in such databases.

Data synthesis: Edwards syndrome is a disease characterized by a broad clinical picture and a very reserved prognosis. There are descriptions of more than 130 different anomalies, which can involve virtually all organs and systems. Its findings are the result of the presence of three copies of chromosome 18. The main chromosomal constitution observed among these patients is a free trisomy of chromosome 18, which is associated with the phenomenon of nondisjunction, especially in maternal gametogenesis. Most fetuses with Edwards syndrome die during the embryonic and fetal life. The median of survival among live births has usually varied between 2.5 and 14.5 days.

Conclusions: Knowledge on the clinical picture and on the prognosis of Edwards syndrome patients is of great importance regarding the neonatal care and the decisions about invasive treatments. The speed to have a confirmed diagnosis is important for making decisions about medical procedures. Often, interventions are performed under emergency conditions, without many opportunities for discussion, and they involve difficult medical and ethical issues.

Key-words: chromosomes, human, pair 18; trisomy; chromosome aberrations; survival analysis; prognosis.

RESUMO

Objetivo: Revisar as características clínicas, etiológicas, diagnósticas e prognósticas da trissomia do cromossomo 18 (síndrome de Edwards).

Fontes de dados: Foram pesquisados artigos científicos presentes nos portais MedLine, Lilacs e SciELO, utilizando-se os descritores 'trisomy 18' e 'Edwards syndrome'. A pesquisa não se limitou a um período determinado e englobou artigos presentes nestes bancos de dados.

Síntese dos dados: A síndrome de Edwards é uma doença caracterizada por um quadro clínico amplo e prognóstico bastante reservado. Há descrição na literatura de mais de 130 anomalias diferentes, as quais podem envolver praticamente todos os órgãos e sistemas. Seus achados são resultantes da presença de três cópias do cromossomo 18. A principal constituição cromossômica observada entre estes pacientes é a trissomia livre do cromossomo 18, que se associa ao fenômeno de não disjunção, especialmente na gametogênese materna. A maioria dos fetos com síndrome

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de Edwards acaba indo a óbito durante a vida embrionária e fetal. A mediana de sobrevida entre nascidos vivos tem usualmente variado entre 2,5 e 14,5 dias.

Conclusões: O conhecimento do quadro clínico e do prognóstico dos pacientes com a síndrome de Edwards tem grande importância no que diz respeito aos cuidados neonatais e à decisão de instituir ou não tratamentos invasivos. A rapidez na confirmação do diagnóstico é importante para a tomada de decisões referentes às condutas médicas. Muitas vezes, as intervenções são realizadas em condições de emergência, sem muita oportunidade de reflexão ou discussão, e envolvem questões médicas e éticas difíceis.

Palavras-chave: cromossomos humanos par 18; trissomia; aberrações cromossômicas; análise de sobrevida; prognóstico.

RESUMEN

Objetivo: Revisar las características clínicas, etiológicas, diagnósticas y pronósticas de la trisomía del cromosoma 18 (síndrome de Edwards).

Fuentes de datos: Fueron investigados artículos científicos presentes en los portales MedLine, Lilacs y SciELO, utilizando los descriptores "trisomy 18" y "Edwards syndrome". La investigación no se limitó a un periodo determinado y abarcó artículos presentes en estas bases de datos.

Síntesis de los datos: La síndrome de Edwards es una enfermedad caracterizada por un cuadro clínico amplio y pronóstico bastante reservado. Hay descripción en la literatura de más de 130 anomalías distintas, que pueden implicar a prácticamente todos los órganos y sistemas. Sus hallazgos son resultantes de la presencia de tres copias del cromosoma 18. La principal constitución cromosómica observada entre estos pacientes es la trisomía libre del cromosoma 18, que se asocia al fenómeno de no disyunción, especialmente en la gametogénesis materna. La mayoría de los fetos con síndrome de Edwards evoluciona a óbito durante la vida embrionaria y fetal. La mediana de sobrevida entre los nacidos vivos tiene usualmente variado entre 2,5 y 14,5 días.

Conclusiones: El conocimiento del cuadro clínico y del pronóstico de los pacientes con el síndrome de Edwards tiene gran importancia en lo que se refiere a los cuidados neonatales y a la decisión de instituir o no tratamientos invasivos. La rapidez en la confirmación del diagnóstico es importante para la toma de decisiones referentes a las conductas médicas. Muchas veces, las intervenciones son realizadas en condiciones de emergencia, sin muchas oportunidades de reflexión o discusión, e implican cuestiones médicas y éticas difíciles.

Palabras clave: cromosomas humanos par 18; trisomía; aberraciones cromosómicas; análisis de sobrevida; pronóstico.

Introduction

Trisomy 18 was first described in 1960 by Edwards *et al*, who reported a newborn with multiple malformations and cognitive impairment[1]. Interestingly, unlike Down syndrome, the syndrome had never been recognized as a distinct clinical entity until then[2]. Edwards *et al* reported a "new trisomy syndrome", which was first named as "17-18 trisomy". That occurred due to the difficulties in differentiating the pair of autosomal chromosomes[1]. By that time, autosomal chromosomes were classified based on the length and the position of the centromere, and were subdivided into categories assigned by letters from A to G[3]. Shortly after the description of the syndrome, in 1960, Smith *et al*[4] showed that the additional chromosome was the chromosome 18. In the following years, several other different chromosomal constitutions associated with Edwards syndrome (ES) were reported, such as trisomy 18 mosaicism, double aneuploidy (i.e., trisomy 18 associated with other numerical changes of autosomal and sexual chromosomes) as well as structural anomalies, such as translocations.

ES is one of the most frequent autosomal trisomies observed at birth, second only to Down syndrome (trisomy of the chromosome 21). Its importance lies on its high prevalence, estimated from 1: 3600–1:8500 live births in different areas of the world, such as North America, Europe and Australia[5-10]. In trisomy 18, a predominance of affected females is observed, in the ratio of almost 1 male to 2 females[7,11-13]. Some authors, however, have reported an equal frequency of genders in fetal evaluations[9], mainly before the 18th gestational week[14].

Clinical Manifestations

ES is characterized by variable clinical manifestations, with involvement of multiple organs and systems. More than 130 different anomalies have been reported in the literature, which may affect virtually all organs and systems, none of which is pathognomonic of trisomy 18[2,15-18]. 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.

Neurological findings

Mental retardation is frequent and usually severe in this syndrome. The hypotonia, observed in the neonatal period, is followed by hypertonia. The cry is weak and the response to sounds is reduced. Suction difficulties are common. Severe cognitive and motor development dysfunction is the rule[16,17,19]. Nevertheless, individuals with ES usually reach some degree of psychomotor maturity and keep learning continuously[19]. Interestingly, cases of trisomy 18 mosaicism with normal intelligence have been reported[20].

Growth

Low birth weight is common, and followed by failure to thrive. The hypoplasia of the subcutaneous, fat, and skeletal muscles is characteristic[2,16,17]. Growth curves specific for trisomy 18 patients can be found in the literature[21].

Skull and face

The skull of patients with ES is dysmorphic, with narrow bifrontal diameter and prominent occipitus; enlarged fontanels and microcephaly may be present. The face shows a triangular shape, and the forehead is high and wide. Palpebral fissures are narrow, the nose and mouth are small, the palate is narrow and high, and there is micrognathia. The ears are dysplastic and low-set, resembling faun ears, and may be associated with preauricular tags. Cleft lip is reported in 5% of cases, and cleft palate in other 5%. Choanal atresia may also be present[2,13,16,17].

Less frequent anomalies include wide fontanels, hypoplasia of the supracilliary ridges, Wormian bones, eye abnormalities such as corneal opacities, microphtalmia, coloboma, cataract, glaucoma, blue sclera, oblique or narrow palpebral fissures, epicanthic folds, ptosis, abnormally thickened eyelids, abnormally long or sparse eyelashes, blepharophimosis, hypertelorism, strabismus and nystagmus[2,16,17].

Thorax and abdomen

Short neck with excess hair, short sternum, small nipples, umbilical or inguinal hernia and/or diastasis of the rectus muscles, narrow pelvis and limitation of the hip abduction may be noticed. The chest may be relatively wide, with or without widely spaced nipples. Other findings include incomplete ossification of the clavicle, hemivertebrae, fused vertebrae, scoliosis, rib anomalies, pectus excavatum and hip dislocation[2,16].

Extremities

Typically, the fists are clenched, with overlapping of the second over the third and of the fifth over the fourth fingers[2,16,17] (Figure 1). The distal crease of the fifth finger

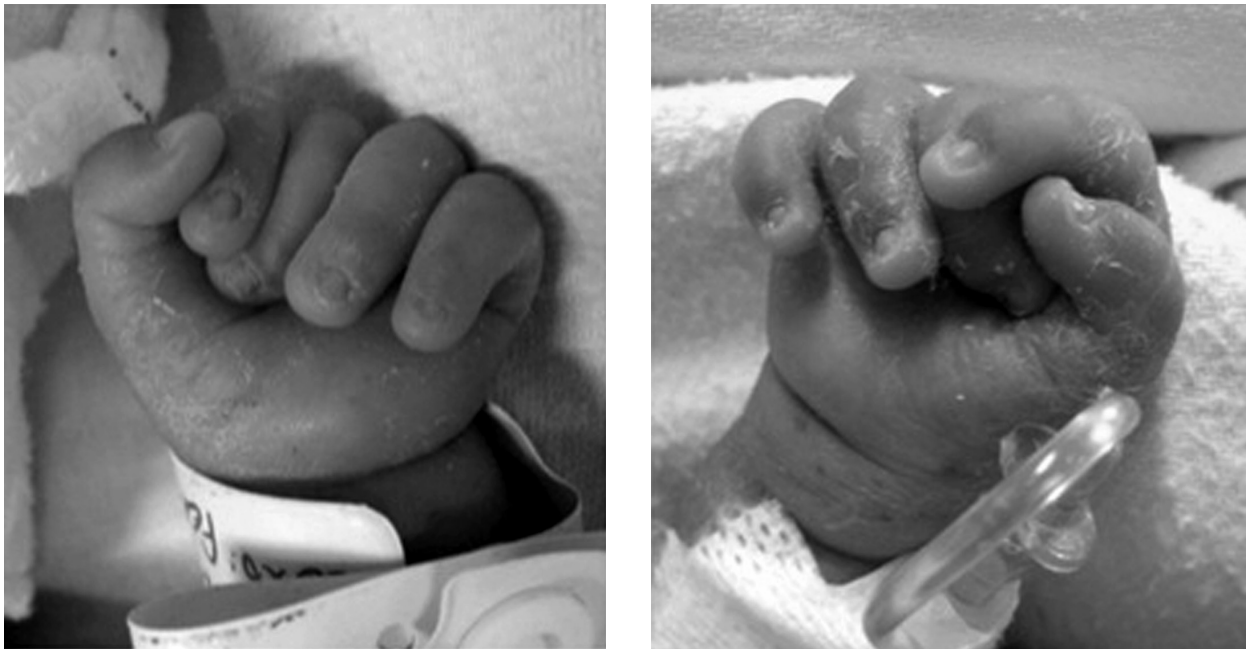

Figure 1 - Hands of a patient with Edwards syndrome. Note the clenched fists with overlapping fingers and the hypoplasia of the nails

and, less frequently, of the third and fourth fingers may be lacking. Analysis of the dermatoglyphics usually shows a pattern of increased arches at the digital pulps of six or more fingers. Single palmar crease and clinodactyly of the fifth fingers may also be present[2,16]. The nails are hypoplastic. Clubfoot and prominent calcaneus are common, and there may be rocker-bottom (or rocking chair) foot. The hallux is shortened and dorsiflexed. Syndactyly of the second and third toes is also a common finding[2,16,17]. Less frequent anomalies include syndactyly of the third and fourth fingers, polydactyly, ectrodactyly, thumb aplasia and hypoplasia/aplasia of the radius[16,17].

Genitals

Cryptorchidism, clitoral hypertrophy with hypoplasia of the labia majora and ovaries are common. Hypospadia, micropenis, ovarian or gonadal dysgenesis, and bifid uterus may also be observed[2,16,17].

Skin and cutaneous annexes

Redundancy of the skin, hirsutism of the forehead and the back, prominent cutis marmorata and hemangiomas can be observed. Hypomelanosis of Ito and skin abnormalities along the Blaschko´s lines have also been described[2,16,17].

Internal organs malformations

Central nervous system malformations occur in nearly 30% of cases, with frequent cerebellar hypoplasia, heterotopy of the granule cells in the white matter, and anomalies of the corpus callosum. Other abnormalities include hydrocephalus, anencephaly, myelomeningocele, facial palsy, Arnold-Chiari malformation, arachnoid cysts and periventricular heterotopia of the brain[16,17].

Congenital heart defects are often described and are considered almost a rule. The frequency of heart defects reported in autopsies and echocardiography studies is similar (usually greater than 90%)[9,10,17,21-23]. A wide spectrum of heart defects is reported in patients with ES, with most individuals presenting with multiple defects. Ventricular septal defects and patent ductus arteriosus were described in the original report of Edwards *et al*[1], and are considered as major anomalies, frequently described in the literature. Polivalvular heart disease (characterized by the involvement of two or more atrioventricular and/or semilunar valves) is considered by some authors as a characteristic finding, which has been described in some case series of patients with ES in 100% of cases[13,17,22,24].

Regarding the intra-abdominal organs, several types of renal abnormalities have been observed, the most frequent being the horseshoe, polycystic, ectopic or hypoplastic kidneys, renal agenesis, hydronephrosis, hydroureter and ureteral duplication[16,17,22]. Malformations of the digestive system include esophageal atresia with or without tracheoesophageal

Table 1 - Frequently observed anomalies in patients with trisomy 18, based on Marion *et al*[15]; Hodes *et al*[16] and Kinoshita *et al*[17]

Alterations
Growth
Failure to thrive
Central nervous system
Neurodevelopmental delay
Hypertonia
Skul and face
Prominent occipitus
Micrognathia
Dysplasic, low-set ears
Microcephaly
Thorax
Widened spaced nipples
Heart deffects
Ventricular sept defects
Patent ductus arteriosus
Patente foramen ovale
Polivalvular heart disease
Abdomen
Umbilical/inguinal hernia
Ectopic pancreas
Meckel´s diverticulum
Urogenital
Cryptorchidism
Prominent clitoris
Renal deffects
Horseshoe kidney
Cystic kidneys
Limbs
Hypoplastic nails
Camptodactyly of the fingers
Clubfoot
Prominent calcaneous
Dorsiflexed halux
Rocker-bottom foot
Syndactyly of the second and third toes

fistula, omphalocele, pyloric stenosis, extra-hepatic biliary atresia, ileal atresia, Meckel´s diverticulum and intestinal malrotation. Thyroglossal duct cyst, hypoplastic gallbladder, gallstones, abnormal liver lobulation, heterotopic pancreas, incomplete fixation of the colon, agenesis of the appendix, accessory spleen, cloacal exstrophy, diaphragmatic eventration, diaphragmatic hernia, imperforate or misplaced anus can also be observed.

The most frequent anomaly in the organs of the immune system is the atrophy or hypoplasia of the thymus. The decreased lymphocyte count in the spleen, lymph nodes and intestinal tract has also been described. Agenesis or segmentation defects of the right lung, thyroid or adrenal hypoplasia may be present[2,16,17], as noted in Table 1.

Several neoplastic diseases have been occasionally reported in individuals with ES and include Wilms´ tumor[25] and hepatoblastoma[26].

Pathophisiology

It is important to note that the abnormalities presented by the patients result from the additional genetic material of the chromosome 18, and there is controversy in the literature regarding the critical region for the syndrome[27]. For instance, the region 18q21.1→qter is considered critical by some authors, as its duplication is enough to result in the ES phenotype[28]. Other authors consider the 18q12 as the critical region. According to Boghosian-Sell *et al*, there are two critical regions, a proximal (18q12→q21.2) and a distal one (18q22.3→qter), which act together to produce the typical phenotype of the trisomy 18[27].

The less severe, nonspecific phenotype of patients with mosaicism seems to be related to the proportion of normal cells in the organism of the affected individual. However, some authors have not observed this association. In some instances, patients with trisomy 18 may present unusual clinical manifestations, making the diagnosis a challenge[18]. The discrepancies in the phenotype can even be observed between monozygotic twins[29].

Etiology

In ES, as well as in other trisomies, maternal age is usually older[6,9,13,17,30]. There is no doubt in the literature that this is the most important predisposing factor for the non-disjunction of the chromosomes in the process of cell division. Most cases of trisomy 18 occur due to the *de novo* meiotic non-disjunction of the maternal meiosis phase II. Interestingly, in other trisomies the defects commonly occur during the meiosis phase I[31].

Chromosomal translocations can happen as new anomalies (*de novo*) or can be transmitted within a family. The chromosomal mosaicism, in the other hand, is always a post-zygotic event. The main cause is the mitotic non-disjunction that can occur in any phase of the embryogenesis or development[32].

Diagnosis

The clinical features of ES are very singular, and it is rarely confused with other conditions. Marion *et al*[15] developed a scoring system aiming to optimize its identification in the neonatal period. Their goal was to create a method to help the physician with no specific training in clinical genetics and dysmorphology to differentiate the newborns with the syndrome from other children with multiple congenital defects[15].

The diagnosis of ES is usually confirmed by the karyotype test showing either partial or complete trisomy of the chromosome 18. More recently, other techniques such as the fluorescent *in situ* hybridization (FISH) and the comparative genomic hybridization (CGH) have been used to detect patients with trisomy 18, especially in specific situations such as the rapid diagnosis of newborn babies or prenatal diagnosis. The first descriptions on the use of these techniques date back to the mid-eighties. The FISH test can also be performed in tissues fixed in formalin and embedded in paraffin[33]. The sequencing of fetal DNA molecules in the maternal blood has also emerged as an accurate and non-invasive form of prenatal diagnosis[34].

About 90 to 95% of patients with ES have the chromosomal constitution of free trisomy of the chromosome 18; less than 10% present a translocation that involves the chromosome 18 which results in the trisomy, or mosaicism, which shows the chromosomal constitution of a lineage of trisomy 18, usually associated with a normal lineage. Double aneuploidy, i.e., the presence of a chromosomal constitution of trisomy 18 associated with another aneuploidy (for instance, of the chromosome X) is considered rare.

The first reports of prenatal diagnosis of trisomy 18 date to the early 70´s. Currently, the suspicion of ES in the neonatal period can be done by fetal ultrasound (including the nuchal translucence), biochemical analysis (showing reduced levels of human chorionic gonadotropin, alpha-fetoprotein and unconjugated estriol in the maternal serum during the first

and second gestational trimesters), and confirmed by fetal chromosomal analysis obtained by chorionic villus puncture and amniocentesis[35].

Fetal echocardiography, especially when performed by the 20th gestational week, can detect heart defects suggestive of trisomy 18. It is considered an essential method for the diagnosis of the syndrome, once the echocardiographic finding of heart defects is considered the most sensitive for the diagnosis of the syndrome after the 16th gestational week. Other common manifestations reported during pregnancy can be observed in Table 2. Szigeti *et al* report that perinatal autopsy can provide additional information in fetuses with ES and may help the diagnosis[37]. According to Viora *et al*, the modern ultrasound examination is clearly highly sensitive (sensitivity > 90%) to detect fetuses with this syndrome[36].

In Brazil, the identification of patients with trisomy 18 during prenatal care is especially important for planning the birth, since termination of pregnancy is not legally allowed (it may only be permitted in cases of risk to the mother´s life or when there is a history of sexual violence)[38].

Table 2 - Abnormalities that can be observed at ultrasound in fetuses with trisomy 18, based on Viora *et al*[36]

Abnormalities detected on ultrasound
Polydramnius/oligohydramnius
Intrauterine growth restriction
Single umbilical artery
Central nervous system
Abnormally shaped head (strawberry or lemon shape)
Dandy-Walker malformation
Choroid plexus cysts
Neural tube deffects
Micrognathia
Cystic hygroma or lymphangiectasy
Omphalocele
Esophageal atresia
Heart defects
Renal anomalies
Limbs anomalies
Clenched fists with overlapping fingers
Radius abnormalities
Rocker-bottom foot
Clubfoot

The frequency of cesarean deliveries is quite high in pregnancies of fetuses with ES, ranging from 48 to 90%[6,9,12,13,23,30] and some studies particularly highlight this aspect[12]. Interestingly, few maternal complications during pregnancy have been reported. Preeclampsia has been described in 12.5 to 17% of mothers of fetuses with ES[17,22,30]. Preterm birth, with low birth weight and low first and fifth minutes Apgar scores are also frequent among children with ES[6,9,13,17,21,30].

Differential diagnosis

The differential diagnosis of ES is relatively wide, and includes conditions such as the fetal akinesia sequence (also called Pena-Shokeir syndrome type I), and Patau´s syndrome. Due to the defects of the hands, some cases may be misinterpreted as the so-called distal arthrogryposis type I. Other conditions to be considered in the differential diagnosis, due to the overlapping of some malformations, are the CHARGE syndrome, previously named as CHARGE association (*Coloboma, congenital Heart defects, choanal Atresia, Retardation of growth, Genital and Ear abnormalities*) and the VACTERL association (*Vertebral defects, Anal atresia, Cardiac malformations, Tracheoesophageal fistula with Esophageal atresia, Renal dysplasia, and Limb anomalies*).

Prognosis

Most of the fetuses with ES do not survive to the end of the gestational period. Those who are born alive have a poor prognosis. The median survival reported in the literature ranges from 2.5 to 14.5 days. In general, 55–65% of the affected newborns die during the first week, 90% in six months, and only 5–10% reach the end of the first year of life[5-11,13,24,30,39-41], as shown in Table 3.

The findings of Lin *et al*[13], in agreement with Weber[11], Carter *et al*[5], Baty *et al*[21], Root and Carey[8], Embleton *et al*[9], Rasmussen *et al*[10] and Niedrist *et al*[24] suggest that the girls with ES have greater chances of being born alive and survive for longer periods than the boys. Moreover, some cases of ES seem to have a longer survival due to a chromosomal constitution of mosaicism[10].

In the other hand, long term survival (in a few cases, longer than two decades) is well documented, even in the absence of mosaicism, mostly in non populational studies (most of them, case reports). However, it is important to note that these patients usually present with severe neurodevelopmental delay and high dependency[42].

Table 3 - Data on survival of patients with trisomy 18 born alive according to studies from different countries

Author	Weber [11]	Carter *et al*[5]	Young *et al* [6]	Goldstein e Nielson [7]	Root e Carey [8]	Embleton *et al*[9]	Brewer *et al*[39]	Rasmussen *et al*[10]	Niedrist *et al*[24]	Lin *et al*[13]	Imataka *et al*[40]	Hsiao *et al*[41]	Rosa *et al*[30]
n	192	43	21	76	64	34	84	114	161	39	179	31	31
Country	USA	Australia	United Kingdom	Denmark	USA	England	Scotland	USA	Switzerland	Taiwan	Japan	Taiwan	Brazil
	%	%	%	%	%	%	%	%	%	%	%	%	%
Birth	100	100	100	100	100	100	100	100	100	100	100	100	100
1 day	98	60	67	60	86	70	88	86	68	95	85	90	
1 week	89	35	32	44	45		43	63	40	46	69	58	
2 weeks	81	15		32	41			50	31	27		45	
1 month	72	11	18	21	34	15	25	39	22	16		32	52
2 months	53	8			22			30	17	11	36	14	32
3 months	38	5			20	6		21	14	5			23
4 months	30				14			19	12	5			19
5 months	23		0		9			12	9	3			
6 months	13	5		3	9			11	9	3	18	10	13
1 year	8	4			5	0	2	8	6	3	9	6	6
2 years	5	0			5				4	3		6	3
3 years	3				5				3	3		3	
4 years	2				5				2	3			
5 years	1				3				2	3			
6 years	0.3				3				1	3			
Median of SV (days)	70	5	2.5	6	4	3	6	14.5	4	6	UD	12	31

n: sample size; USA: United States of America; SV: survival; UD: undetermined

Tanigawa *et al* found that some ultrasound findings are associated to less than one month survival[43]. Such findings consist of severe polyhydramnios, lack of fluids in the stomach, major heart defects, and male gender. Gestational age on birth also seems to affect survival[8,10,24]. Some recent studies have shown survival rates lower than previously reported, possibly due to the less aggressive care of children with ES, related to the short survival expectancy[10].

In addition, previous studies have shown that the presence of congenital heart defects do not influence the survival of patients with ES[9,10]. More recently, Niedrist *et al* also found, in a Swiss cohort study, that heart defects have little or no influence on survival[24]. In the past, apnea and no therapeutical investment were considered the major causes of death[9]. According to Kaneko *et al*, patients older than one month usually die due to complications of the congenital heart defect (apnea is a common cause among neonates in the first week of life)[44]. However, recent studies indicate that congenital heart defects are the leading cause of death in intensive care patients[23,45]. Thus, intensive management, including heart surgery, can improve the survival of patients with the syndrome[45]. Indeed, studies that evaluated patients receiving neonatal intensive care have shown median survival longer than usual, ranging from 152.5 to 238 days[23,45].

Heart surgery is rarely performed in patients with ES. However, indications of heart surgery have been growing in the recent years. This seems to be related to a change in the behavior of healthcare providers towards greater acceptance on the autonomy of the parents regarding treatment decisions[44]. To date, there are no well-defined criteria of heart surgery indications in this group of patients. Most individuals survive to palliative and corrective surgeries. However, the risk of complications consequent to surgical corrections of the heart defects, as well as the risk of death from other causes, is high[46]. Therefore, as stated by Yamagishi, guidelines for the treatment of such patients are needed[46].

Heart surgery can improve life expectancy, allow the hospital discharge and improve the quality of life of patients and their families[46]. Some limitations, however, can be observed among the studies that support these results, such as the small sample sizes and the selection of patients with less severe cardiac and extracardiac defects[44,46,47]. Yamagishi[46] and Muneuchi[47] have reported that selected individuals can benefit from the surgical correction of heart defects, and the indication of such procedure should be carefully individualized. Nevertheless, few studies have evaluated the effectiveness of heart surgery and the further quality of life in the long term follow up of patients with ES[47]. Thus, it is unclear whether heart surgery improves the prognosis of these individuals[46]. Patients with ES present several risk factors for developing sepsis, an important cause of death, which include low birth weight, prematurity, multiple malformations, associated with long intensive care stay and the consequent invasive procedures, which favor the development of infections.

In Brazil there are no specific guidelines on cardiovascular resuscitation of newborns with ES, neither in the delivery room nor later. However, according to the Neonatal Resuscitation Program of Sociedade Brasileira de Pediatria[48], medical decisions in the delivery room need to be supported by the prenatal diagnosis, and take into consideration the parents' wishes and the recent therapeutic advances. The 'wait to see' strategy before starting the resuscitation should be abandoned, as it may lead to deleterious consequences such as hypoxemia and hypotension, which further increase morbidity and mortality. As reported by Rosa *et al*[30], the prenatal diagnosis of ES in Brazil is still poor, which has important implications on the management of these patients. In their series of 31 consecutive patients evaluated in a referral hospital in southern Brazil, Rosa *et al* found that none of them had been diagnosed prenatally[30].

Interestingly, the choice for performing cardiopulmonary resuscitation can be influenced, for instance, by cultural factors. In the evaluation of patients born in Taiwan from 1991 to 2003, Hsiao *et al*[41] did not find any differences on survival between the genders in individuals with ES, and attributed this observation to the more frequent no consent for resuscitation for female newborns (bearing in mind that the male sex is favored in relation to the female sex among traditional Chinese families).

Genetic Couseling

The diagnostic and etiological evaluation of the syndrome are important not only for the adequate management of these individuals, but also for the proper genetic counseling of the families. In cases of free trisomy 18 there is no indication for the cytogenetic evaluation of the parents because, as previously stated, this anomaly results from the phenomenon of non-disjunction during the gametogenesis. Some authors suggest that there is a slight increased risk in further pregnancies, even for potentially viable trisomies, and that certain women present a predisposition for meiotic errors

in general. However, the recurrence of the same trisomy in another child has only rarely been reported, and the risk is considered virtually unknown. Some studies point a risk from 0.5% to less than 1%[21]. Those estimates were based mainly on the risk for nondisjunction, which was empirically calculated for trisomy 21.

Uehara *et al* found that none of the 170 women who had a child with trisomy 18 had the same anomaly repeated in a further pregnancy[49]. However, it is important to take into consideration the increased risk of trisomies with advancing maternal age. Moreover, one cannot rule out the possibility of gonadal mosaicism, especially in recurrent cases.

In the other hand, in cases of trisomy 18 due to translocation, the chromosomal analysis of the parents is indicated, in order to rule out the presence of a balanced chromosomal rearrangement in one of them. In that case, the risk of recurrence for the couple is increased, depending on the type of chromosomal anomaly. However, if the parental karyotypes are normal, it is assumed that the syndrome occurred due to a new (*de novo*) mutation, although the possibility of germinative mosaicism cannot be ruled out.

Conclusions

The knowledge of the clinical features and prognosis of patients with ES is of great importance regarding the neonatal care and the decision of performing invasive procedures, such as heart surgery or cardiopulmonary resuscitation. The early diagnostic confirmation is important for making medical decisions. Often, interventions are performed under emergency conditions, leaving little opportunity for reflections or discussion, and involve difficult medical and ethical issues.

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