CHARACTERISATION OF A 19-YEAR-OLD «LONG-TERM SURVIVOR» WITH EDWARDS SYNDROME

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Summary: Characterisation of a 19-year-old «long-term survivor» with Edwards Syndrome: Trisomy 18 is the second most frequent autosomal aneuploidy affecting about 1 in 8,000 newborns. Similar to trisomy 13 more than 90% of the patients die within the first year. Main causes of death are failure of vital organ function, in most cases of brain, heart, kidney, and gut, sometimes combined with severe infections. The degree to which essential organs are affected at birth and the clinical course differ considerably. Unknown genetic factors and various environmental effects are most likely involved. A less severe course of Edwards syndrome can be caused by a partial trisomy due to a deletion of the extra chromosome 18 or somatic mosaicism with a trisomic and a normal cell-line in the patient. In this report conventional chromosome analysis, FISH, and QF-PCR have been performed on a 19-year-old female patient with trisomy 18 to investigate a large number of cells including non-mitotic cells from various different tissues. This study supports evidence for an apparently pure form of trisomy 18 in this 'long-living' patient with Edwards syndrome.


INTRODUCTION

The clinical syndrome of trisomy 18 was first described in 1960 by Edwards and colleagues (2). As many as 90% or more of children with trisomy 18 die within the first year of life (9). Some of them survive beyond that period, only a few live into their late teens (8). «Long-term survivors» in this context are usually defined as patients surviving more than one year of age (10). Patients with trisomy 18 present complex medical problems as severe growth deficiency, poor motor activity with increased muscle tone, massive neurologic dysfunction, abnormal craniofacial profile, multiple cardiac defects, short sternum, hernias, radial hypoplasia, and marked lanugo. Birth weight is usually low, ultrasound examination in pregnancy frequently shows decreased fetal activity, polyhydramnios, small placenta and single umbilical artery (7). The incidence for this second most common autosomal trisomy (only trisomy 21 occurs more frequently) is 1 in 8000 births (1). The sex ratio in newborns is 4 girls/1 boy (1). It seems that patients who show a mosaic of normal and trisomy 18 cell-lines have much better chances to survive their childhood than those with pure trisomy 18 (3). In the present study we describe a 19-year-old female patient with a pure trisomy 18.

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CASE REPORT

The patient was born at term with a birth weight of 2,140 grams, birth length of 48 cm, and OFC of 32 cm as the only child of a 24-year-old mother and 30-year-old father. The parents are unrelated and both of Caucasian origin. Because of general dystrophy, craniofacial anomalies such as dolichocephaly and low set ears, and further dysmorphic signs including a mild form of bilateral hexadactyly of both hands the patient was diagnosed with Edwards syndrome. Initial cytogenetic analysis of 17 G-banded metaphases from a lymphocyte culture was performed a few days after birth. A cardiac problem could not be found. In the following years she did not thrive well but had no life-threatening crisis. At the age of 5 years she was treated because of recurrent urinary tract infections. A small extra horseshoe kidney and her right non-functional kidney were surgically removed. Since then no new urinary infections occurred. In early infancy there were feeding problems, but with tube feeding at the age of 7 years, she started to gain weight and developed by the age of 8 years a massive obesity. Dietary measures normalised her body weight. She was never able to sit or to articulate but she responded well to visual, acoustic and tactile stimuli and liked to play and communicate at a low level with her parents and other known persons.

We examined the proband at an age of 18 years. She had a body length of approximately 134 cm (difficult to measure because of joint contractures and scoliosis; 3rd centile = 152 cm), weight of 28.5 kg (3rd centile = 44 kg) and a head circumference of 51 cm (3rd centile = 51.4 cm). She had facial anomalies with midface hypoplasia, micrognathia, broad and bulbous nose, short philtrum, and low set ears with an external auditory canal stenosis (Fig. 1). In addition there was strabismus divergens, a protruding tongue, widely spaced teeth, scoliosis and kyphosis, and bilateral contractures of the upper and more severe of the lower limbs, with a fixed pronation position of the feet. Both hands had a partial rudimentary postaxial hexadactyly. Puberty with pubarche and menarche was reached at about 14 years, but she did not have a hypertrophic clitoris or hypoplastic labia majora. There was nearly a complete absence of breast development. Osteoporosis was diagnosed by radiological examinations. She was frequently suffering from asthma and was treated with salbutamol and corticoids. Presumably due to cortisone related side-effects she repeatedly developed skin lesions like eczema, in particular of her lower arms with itchy, difficult to treat, skin irritations. A few weeks after her 19th birthday the patient had a fracture of her right upper arm caused by a mild trauma. Although she received non-surgical treatment, she died from pneumonia as a complication at an age of 19 years and 3 months. Permission for necropsy was not given.
Figure 1A and B:
The patient at the age of 18 years. Note scoliosis, kyphosis and contractures of the upper and lower limbs with a fixed pronation position of the feet (Fig. 1A). Dysmorphic facial features include midface hypertelorism, broad and bulbous nose, short philtrum, and low-set ears (Fig. 1B).
Technique Investigations

Chromosomal analysis was repeated at an age of 18 years from 100
GAG banded chromosomes from peripheral lymphocytes and again tri-
omy 18 in all analysed metaphases was found. High resolution chro-
mosomal banding showed no structural anomalies of chromosome 18 in
any of the 20 investigated metaphases. FISH analysis using a chromo-
some 18 painting probe (Vysis) showed no additional anomalies.

In order to analyse the distribution of the trisomy 18 in various dif-
dent tissues (blood lymphocytes, urine sediment, hair roots), a large
number (200) of interphase nuclei of nucleated cells from whole blood
and cells from urine sediment were analysed using the AneuVision ane-
uploidy detection kit (Vysis) (Fig. 2). The metaphases and nuclei were
analysed with a Zeiss axiophot microscope equipped with a cooled CCD
camera (Photometrics). Digitalised images were captured by the Cyto-
Vision Ultra System from Applied Imaging International Ltd. Due to the
small amount of available nucleated cells from some tissue samples we
also performed QF-PCR to further exclude the presence of a minor, tis-
sue-specific mosaicism. A skin biopsy was not performed because of her
unexpected death. A total of 42 hair roots were randomly collected from
the whole capillitium and were divided into two tubes. DNA was
extracted in 50 μl DNA-isolation buffer (Qiagen) according to the sup-
plier. Sedimented cells from two aliquots of 10 ml urine were used for
DNA isolation essentially as described above for hair root cells. QF-PCR
was performed on DNA obtained from blood cells, hair roots and cells
from urine sediment. PCR primers and conditions were used as
described by Pörtl and co-workers (5). The product was analysed on an
ABI 3100 Genetic Analyser (Applied Biosystems). Cytogenetic, molecu-
lar-cytogenetic as well as molecular data revealed a common result of a
pure trisomy 18 in all tissues analysed.

Figure 2:
FISH with CEP 18
(purple), mapping to the
chromosomal band
18p11.1-q11.1, and CEP X
(green), mapping to the
chromosomal band
Xp11.1-q11.1. Hybrid-
isation signals are
present on all three chro-
mosomes 18 and both
cromosomes X (green).
DISCUSSION

Greve and colleagues (1993) (3) reported on a 16 1/2-year-old female patient with an initial diagnosis of pure trisomy 18. A cytogenetic follow-up study, performed at an age of 15 years confirmed the previous results in lymphocytes. In fibroblasts however a low frequency mosaicism of 4% normal cells was found. These authors concluded that the extent and severity of abnormalities were related to a tissue-specific frequency of mosaicism. First reports from the pre-banding era did already suggest that mosaicism for trisomy 18 has a practical relevance (6). Studies on extra fetal tissue indicated that a selection process can be involved in mosaic formation (4). In the present study we used FISH and QT-PCR to analyse cells from whole blood, hair roots, and urine sediment in a female patient who was diagnosed with a pure trisomy 18 by routine cytogenetics in blood lymphocytes. Although no mosaicism was found in all tissues analysed, mosaicism at a lower percentage than detectable with the methods applied or present in other tissues of the patient can not completely be excluded. The clinically most important conclusion of this study is that the prognosis with regard to an extended life span for patients with a pure trisomy 18 can be relatively good when no life-threatening congenital anomalies which can not be treated are present at birth or during the first year. This information is therefore valuable for paediatricians, parents, and support groups and reports on further patients, with respect to the genetic and natural history of the syndrome, are needed.

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REFERENCES


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