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Case Report: Description of a Patient with Trisomy 22 in Inbred Line

Leandro Gutiérrez[1], Flavia Leveroni[1], Cristina Mayer[2], Jorge Doldán[2], Amada Rolón[1], Ana Melnichuk[1], Alejandro Laudicina[3], Sonia Bageston[2] and Alberto Fenocchio[1]

1. Laboratory of Human Genetics and Cytogenetic, School of Natural, Chemistry and Exact Sciences, National University of Misiones, Posadas, Misiones N3300MLL, Argentina

2. Laboratory of Cytogenetic, Dr. Ramón Madariaga Hospital, Posadas, Misiones N3300MLL, Argentina

3. Lexel SRL, División In Vitro, Buenos Aires City, Buenos Aires C1135ABO, Argentina

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Abstract: Long arm trisomy of chromosome 22 or cat eye syndrome (OMIM#115470) is a disease with an enormous variability of clinical features, ranging from minor malformations like hypertelorism, to major ones, as congenital heart and renal disorders, combined with variable growth retardation. The authors report a case of a newborn female with clinical features of cat eye syndrome with trisomy 22 in inbred line, who died 35 days after birth. The clinical features at the time of diagnosis were: left preauricular appendix, low-set ears, hypertelorism, mongoloid palpebral apertures, right-sided microphthalmia, left-sided anophthalmia, cleft lip and palate, short neck, anomalous pulmonary venous return, severe lung hypertension, hyperechogenic little kidneys and clinodactyly of the fifth finger on the left side. Cerebral ultrasound showed dilatation of both lateral ventricles, with a callosum corpus difficult to evaluate. The cytogenetics diagnostic was made from peripheral blood by conventional cytogenetics techniques in two different laboratories, and confirmed by fluorescent *in situ* hybridization.

Key words: CES (cat eye syndrome), Smith Fraccaro Syndrome, trisomy 22.

1. Introduction

A great variety of clinical disorders are associated either with increased or decreased gene dosage [1]. In 1886 Haab described the clinical association between anal atresia and coloboma. Later, it was demonstrated that patients with these symptoms had a small extra acrocentric chromosome. In 1977, Bhuler and Hsu demonstrated that the extra genetic material was the chromosome 22. In subsequent years, this condition began to be recognized as CES (cat eye syndrome) or Smith Fraccaro Syndrome [2]. CES (OMIM#115470) is a disease with enormous clinical features variability, from minor malformations like: hypertelorism, preauricular tags, low-set and malformed ears, anti-mongoloid palpebrals fissures, microphtalmia and short neck, to major ones such as congenital heart and renal disorders, ocular coloboma, anal atresia, craniofacial and skeletal malformations all combined with variable growth retardation and learning disabilities [3-5]. Most frequent features include coloboma of iris, renal abnormalities and imperforate anus, although the most consistent features are preauricular skin pits and/or tags [6, 7]. Cytogenetically, most of the CES cases are associated with the presence of a supernumerary chromosome, consisting of a bisatellited and dicentric chromosome 22 with an inverted duplication, leading to a tetrasomy of a region that expands from p arm to 22q11.2 [2, 3, 5, 8]. However, Meins et al. reported a CES case with long arm partial trisomy of chromosome 22 derived from a translocation t(11;22) or from an interstitial

Corresponding author: Leandro Gutiérrez, M.Sc., research fields: human genetics and cytogenetics. E-mail: leandrogutierrez82@gmail.com.

duplication of 22q11.2 [3, 9, 10]. Whereas, total trisomy of chromosome 22, were reported only as mosaicism cases [2, 11]. Recently, others 22q11.2 rearrangements have been recognized and may result in CES phenotype such us proximal 22q duplication [12]. This case provides new data into the phenotypic and cytogenetic variability of CES and 22q associated disorders.

2. Materials and Methods

We describe a newborn female, arising from the genetic services of Ramón Madariaga Hospital of (Posadas, Misiones, Argentine), with clinical features suggestive of CES (Table 1), who died 35 days after birth. The patients had a non-contributory family history and parental chromosome analyses were not requested (Fig. 1).

Standard cytogenetic analysis was carried out on peripheral blood lymphocytes in the cytogenetic laboratory of Ramon Madariaga Hospital. A high resolution was done at the Cytogenetic and Human Genetics Laboratory (University of Misiones) in order to confirm the trisomy. A total of fifty metaphase plates were analyzed.

FISH confirmation studies were also done on the same peripheral blood lymphocytes culture used for the standard cytogenetic analysis. Enumeration probes for chromosome 22 and for chromosome 13 (as control) were used (LIVe Probes, Lexel *in Vitro*).

3. Results and Discussion

An important subset of cases are associated with a SMCs (supernumerary marker chromosome) derived from chromosome 22, and some reports suggested that may cause CES if they involve the proximal region of chromosome 22q with a trisomy or tetrasomy of the cat eye critical region [8, 13].

Classical CES is always characterized by the presence of a dicentric and bisatellited small inv/dup(22)(q11) supernumerary marker chromosome. Thus, patients with CES usually have a partial tetrasomy of a chromosome 22 region that expands from p arm to 22q11.21 region [8, 13, 14]. The case described here exhibited a complete trisomy on chromosome 22, associated with principal features of CES: coloboma, anal atresia, left preauricular appendix, low-set ears, hypertelorism, right-sided microphthalmia, left-sided anophthalmia, cleft lip and palate, short neck, anomalous pulmonary venous return, severe lung hypertension, hyperechogenic little kidneys and clinodactyly of the fifth finger (Table 1). Cerebral ultrasound showed dilatation of both lateral ventricles, with a callosum corpus difficult to evaluate.

CES diagnosis was suspected on the basis of craniofacial features (bilateral colobomata, auricular anomalies, hypertelorism) and anal atresia, associated with internal organ malformations. There were no characteristics of Pierre-Robin sequence. Cytogenetic analysis of the newborn showed an altered karyotype with 47, XX, +22 [16] and FISH studies confirmed the trisomy 22 in inbred line (Fig. 2). CES is mainly diagnosed by the presence of an extra marker chromosome identified by FISH and usually chromosome examination of both parents is also indicated [15]. Increasing numbers of aberrations identified within 22q11, show some clinical overlaps with CES. None of the major features of CES (coloboma, anal stenosis, preauricular pits/tags, genitourinary malformations, congenital heart defect) are specific for the syndrome and are also observed in other 22q11-related disorders. Among other features observed in CES patients, some are known, although

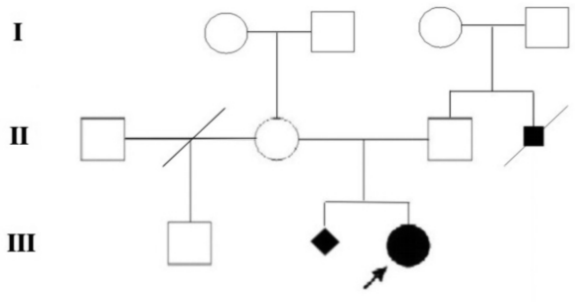

Fig. 1 Heredogram of the patient with CES.

Table 1 Birth and clinical data of the case report compared with the principal characteristic for CES described in the literature [15].

General birth and clinical data of the case	
Birth data	**Case**
Sex	Female
Gestionalage (weeks)	37
Weight (g)	1,940
Lenght (cm)	46
Major features	
Preauricular skin pigs/tags	Left preauricular tags
Anal atresia	+
Urogenital malformations	Hyperechogenic little kidneys
Ocular coloboma	+
Circulatory defects	Anomalous pulmonary venous return
Minor features	
Downslatingeye positions	Mongoloid palpebral apertures
Hypertelorism	+
Ear abnormalities	Low-set ears
Others	
	Severe lung hypertension
	Right-sided microphthalmia
	Left-sided anophthalmia
	Cleft lip and palate
	Short neck
	Clinodactyly

The presence of denotation (+) indicate presence of the characteristic.

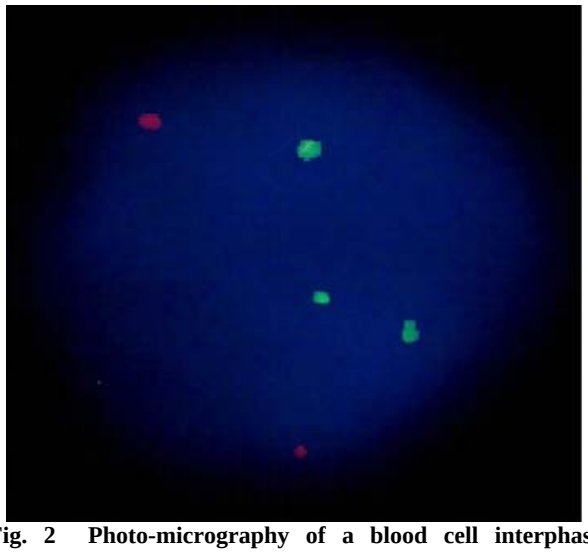

Fig. 2 Photo-micrography of a blood cell interphase showing three green hybridization signals corresponding to chromosome 22 and two red signals corresponding to chromosome 13 (LIVe Probes, Lexel *in Vitro*).

rarely described in CES, such as severe microtia and biliary agenesis. As far as the authors know, Pierre Robin sequence has never been described in CES, but micrognathia is a well known trait of CES [15].

In the literature there are descriptions of Pierre Robin sequence in patients with other aberrations of chromosome 22, mostly DG/VCFS [15, 17].

It is known that non-mosaic trisomy 22 is the second most common aneuploidy identified in spontaneous miscarriage [18]. Moreover, only a few live births cases of trisomy of chromosome 22 were described, always found in mosaicism and accompanied with reduced survival expectation (the patients die during the neonatal period) [4, 5, 11]. In the case reported here, the observed phenotype indicate CES. Cytogenetic and molecular cytogenetic analyses confirmed the presence of trisomy 22 in inbred line. Although all the cells analyzed in this study had the trisomy 22 (constitutional karyotype in blood cells), it is not possibly to exclude mosaicism in other tissues or a tetrasomy of 22q11 due to interstitial microduplication [18, 19].

Moreover, this case provides new information into the phenotypic and cytogenetic variability of CES and 22q associated disorders. In agreement with others reports, the authors suggest that careful clinical and molecular description of additional patients with these kind of disorders is necessary to understand the relationship between genotype and phenotype [8, 15, 17, 20]. However, clear delineation of the phenotypes associated with rearrangements of 22q11.2 cannot always be accomplished [8, 20].

4. Conclusion

Clinical and cytogenetic findings in this patient allow us to suggest a case of CES with a pure line trisomy of chromosome 22. However, mosaicism in other tissues or tetrasomy of 22q11.2 cannot be excluded.

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