Original Article

CLINICAL CHARACTERISTICS OF A SAMPLE OF PATIENTS WITH CAT EYE SYNDROME

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ABSTRACT

Objective. cat eye syndrome is considered a rare chromosome disease with a highly variable phenotype. the objective of this paper was to describe the clinical characteristics of a sample of patients with cat eye syndrome who were seen at our service.

Methods. this is a retrospective analysis of a sample of six patients with diagnoses of cat eye syndrome. all of these patients' karyotypes exhibited the presence of an additional marker chromosome, inv dup(22)(pter->q11.2::q11.2->pter). one patient also exhibited mosaicism with a lineage that had a normal chromosomal constitution. clinical and follow-up data were collected from the patients' medical records. fisher's exact test was used to compare the frequencies observed in our study with figures given in the literature ($P<0.05$).

Results. the main abnormalities observed were preauricular tags and/or pits and anal atresia (both observed in 83% of cases). coloboma of the iris, an important finding with this syndrome, was observed in two cases (33%). congenital heart disease was detected in four patients (67%) and the main defect found was interatrial communication (75%). uncommon findings included hemifacial microsomia combined with unilateral microtia and biliary atresia. just one of these patients died, from chylothorax and sepsis.

Conclusion. the phenotype observed in cat eye syndrome is highly variable and may be superimposed on the phenotype of the oculo-auriculo-vertebral spectrum. although these patients usually have good prognosis, including from a neurological point of view, we believe that all patients with the syndrome should be assessed very early on for the presence of cardiac, biliary and anorectal malformations, which may avoid possible complications in the future, including patient deaths.

Key words: Human chromosome pair 22. Mosaicism. Goldenhar syndrome. Facial asymmetry.

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Introduction

Cat eye syndrome, also known as Schmid-Fraccaro syndrome (OMIM 115470), is considered a rare chromosome disease with an estimated incidence of 1 in every 50,000-150,000 live births (Berends et al., 2001). It is caused by partial tetrasomy of chromosome 22 which is the result of a supernumerary dicentric marker chromosome with satellites at the ends, inv dup(22)(pter->q11.2::q11.2->pter). This, as its description states, involves duplication of the entire short arm of chromosome 22 (p) plus part of its long arm (q), as far as band 11. It is now known that this band contains regions of low copy repeats (LCRs) which predispose it to rearrangements, including the marker chromosome observed in cat eye syndrome (Heather et al., 2002). Clinically, the disease is characterized by the presence of multiple malformations, primarily involving the eyes, ears and anorectal and urogenital systems. Notwithstanding, the phenotype that has been observed is highly variable and includes descriptions of very mild cases (Berends et al., 2001; Rosias et al., 2001).

Therefore, in response to the scarcity of studies of the disease

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in Brazil (Belangero et al., 2009), the objective of this paper is to describe the clinical characteristics of a sample of patients with cat eye syndrome who were seen at our service.

Methods

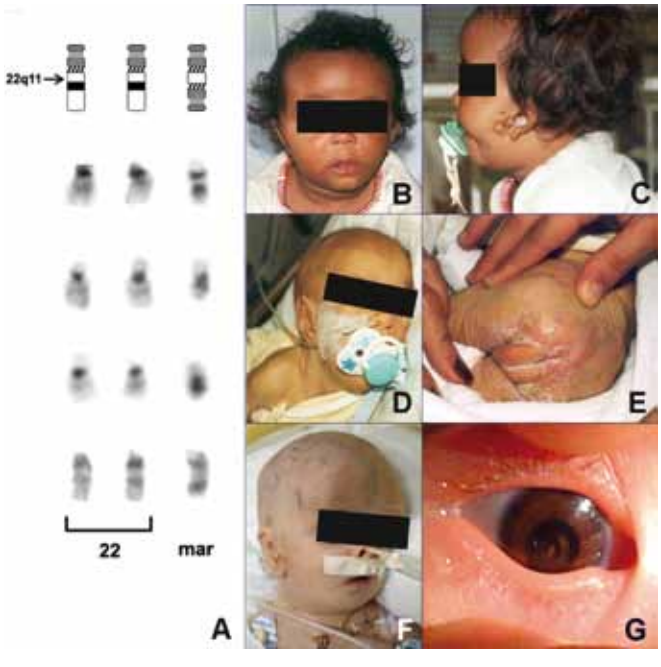
This is a retrospective analysis of a sample of six patients with diagnoses of cat eye syndrome who were referred to the Clinical Genetics Department because of anal atresia, preauricular tags and/or preauricular pits, associated with other malformations. All of these patients' karyotypes exhibited the presence of an additional marker chromosome, similar to the dicentric chromosome found in the partial tetrasomy 22: inv dup(22)(pter->q11.2::q11.2->pter) (see Figure 1). One patient also exhibited mosaicism with a lineage that had a normal chromosomal constitution: 47,XX, inv dup(22)(pter-->q11.2::q11.2->pter)[30]/ 46,XX[14]. In three cases it was possible to karyotype the patients' mothers and in one case the father was karyotyped, with normal results in all four cases.

The following data were collected from patient records: age and sex, referring service, anthropometric measurements, parents' age at birth of patient, clinical characteristics observed on physical examination, results of supplementary tests and death/survival to date.

Fisher's exact test was used to compare the frequencies observed in our study with figures given in the literature, using PEPI to perform the calculations. Only results where $p<0.05$ were considered statistically significant.

The study was approved by the institution's Research Ethics Committee.

Figura 1 - Ideograma e cariótipo parcial por bandas GTG mostrando exemplos de cromossomos 22 citogeneticamente normais e de marcadores apresentados pelos pacientes. Notar que o ponto de quebra para a formação do cromossomo marcador ocorre na região 11 do braço longo (q) do cromossomo 22, levando a uma inversão duplicação do segmento pter->q11 (A). Características clínicas de alguns pacientes da amostra. Notar principalmente na microssomia hemifacial (B), apêndices e fossetas pré-auriculares (C, D e F), imperfuração anal (E), micrognatia (F) e coloboma de íris com epicanto (G) (B e C: paciente 2; D e E: paciente 3; F e G: paciente 5)



Results

Four of the six patients in the sample were female and two were male. Their ages at initial presentation varied from 5 days to 2 years and 6 months (mean of 234 days). Four of them had been referred by the pediatric surgery department, one by pediatrics and one by the pediatric cardiology department. Paternal ages varied from 36 to 50 years (mean of 41.2 years) and maternal age varied from 31 to 39 years (mean of 36 years). Birth weights varied from 2,178 to 3,640 g (mean of 2,896 g), length from 44 to 51.5 cm (mean of 47.9 cm) and head circumference from 32 to 36 cm (mean of 33.9 cm).

The patients and their clinical characteristics can be observed in Figure 1 and Table 1. The main abnormalities found were preauricular tags and/or preauricular pits and anal atresia (both observed in 83% of cases). Coloboma of the iris, an important finding with this syndrome, was observed in two cases (33%). Congenital heart disease was detected in four patients (67%) and the main defect was interatrial communication (75%). In terms of clinical progression, only one patient had died at data collection (patient 5). This fatality was the result of postoperative complications after surgery for congenital heart disease, with chylothorax and sepsis.

Discussion

Although the supernumerary marker chromosome derived from 22 can vary in molecular size, depending on the LCRs in the q11 region where the rearrangement occurs (whether they are more proximal or more distal), no direct correlation has yet been identified between cat eye syndrome phenotypes and the supernumerary region size (Mears et al., 1994; Berends et al., 2001).

Notwithstanding the small size of our case series, the phenotypes observed among our patients were no different from those that have previously been described in the literature. While this syndrome is known as cat eye syndrome because of the appearance of the iris, caused by vertical coloboma of the iris and choroid (which resembles a cat's iris), the most commonly observed malformations with this disease are preauricular pits and/or tags and anorectal malformations (Rosias et al., 2001). These were the principal findings among our sample, both observed in 83% of cases. In contrast, some of the malformations observed in this sample, for example biliary atresia, have rarely been described in the syndrome. Four out of 48 cases (8%) in a series described by Rosias et al. (2001) had this abnormality.

We were unable to locate any other descriptions in the literature of patients with cat eye syndrome and hemifacial microsomia combined with unilateral microtia (patient 2). Taking all of this patient's findings together with the preauricular tags/pits, presentation was highly suggestive of a clinical diagnosis

Tabela 1 - Características clínicas apresentadas pelos pacientes com a síndrome do olho do gato de nossa amostra

	PACIENTES						TOTAL
Achados	1	2	3	4	5	6	N= 6
Sexo	F	F	F	M	F	M	2M / 4F
Retardo de crescimento	+		+		+		3 / 6
Achados Neurológicos							
Hipotonia	+	+					2 / 6
Dilatação ventricular	+			NE	NE		1 / 4
Hipoplasia cerebral		+		NE	NE	+	2 / 4
RDNPM	+	+			NA	+	3 / 5
Crises convulsivas						+	1 / 6
Alterações craniofaciais							
Microcefalia	+					+	2 / 6
Microssomia hemifacial		+					1 / 6
Hipertelorismo / telecanto		+					1 / 6
Fendas palpebrais oblíquas para baixo		+	+			+	3 / 6
Pregas epicânticas	+	+		+		+	4 / 6
Coloboma ocular				+	+		2 / 6
Palato alto						+	1 / 6
Orelhas displásicas / baixo implantadas	+	+					2 / 6
Fossetas / apêndices pré-auriculares	+	+	+	+	+		5 / 6
Cardiopatia congênita							
Comunicação interatrial	+		+	+			3 / 5
Drenagem venosa pulmonar anômala total					+		1 / 5
Persistência do canal arterial			+		+		2 / 5
Comunicação interventricular				+			1 / 5
Persistência veia cava superior esquerda			+				1 / 5
Anormalidades abdominais							
Refluxo gastroesofágico						+	1 / 6
Atresia biliar ou cisto colédoco	+						1 / 6
Hérnia umbilical		+					1 / 6
Alterações urogenitais							
Agenesia renal			+	NE			1 / 5
Chordee curto	NA	NA	NA		NA	+	1 / 2
Anormalidades anorretais							
Fosseta sacral		+				+	2 / 6
Ânus imperfurado	+	+	+	+	+		5 / 6
Fístula retal		+		+	+		3 / 6

F: feminino; M: masculino; +: presente; NE: não avaliado; NA: não se aplica;

RDNPM: retardo de desenvolvimento neuropsicomotor

of oculo-auriculo-vertebral spectrum (OAVS), or Goldenhar syndrome (OMIM 164210) (Strömland et al., 2007; Engyz et al., 2007). Based on the results of our literature search, this is the first case description of a patient with cat eye syndrome and this phenotype. However, interestingly, we found a report in the literature of other patients with the OAVS phenotype and cytogenetic abnormalities involving the addition of part or the whole of chromosome 22. These included trisomy of chromosome 22 in mosaic (Pridjian et al., 1995), the supernumerary chromosome der(22)t(11;22) (Engiz et al., 2007) and duplication of the long arm of chromosome 22 (Hathout et al., 1998). Furthermore, in some of the cases described by Berends et al. (2001) there was facial asymmetry/hypoplasia of one hemiface. Notwithstanding, we cannot rule out the possibility that this finding is associated with the chromosomal mosaicism exhibited by the patient, in which areas of hyperplasia and hypoplasia may occur (Woods et al., 1994).

The frequency of heart defects observed in our sample (67%) was statistically similar to that of other series described in the literature, ranging from 50% to 63% (Berends et al., 2001; Rosias et al., 2001). However, as Rosias et al. (2001) and Berends et al. (2001) have rightly pointed out, these frequencies may have been affected by bias, since mildly affected patients may escape detection. The main heart defect described among people with cat eye syndrome is total anomalous pulmonary venous connection (29% to 43%), although this was only detected in one of the patients in our sample (25% of the cases with congenital heart disease). The most common malformation in our series was interatrial communication (75%), which has been described in around 30% of previous samples, and persistent ductus arteriosus, in 14% of the patients with the syndrome (Berends et al., 2001; Rosias et al., 2001). We observed persistence of the left superior vena cava in one of the patients in our sample, which is an uncommon finding (Berends et al., 2001). On the other hand, another common defect - tetralogy of Fallot - was absent from our series although it is described in around 8% to 14% of cases (Berends et al., 2001; Rosias et al., 2001). Rarer malformations include abnormalities of the aorta (such as interruption of the aortic arch), pulmonary stenosis, tricuspid atresia, hypoplastic left heart syndrome, mitral valve, atrial or ventricular hypoplasia and single ventricle (Berends et al., 2001; Rosias et al., 2001; Belangero et al., 2009).

With relation to neurological findings, structural anomalies of the central nervous system are observed with low frequency among people with cat eye syndrome. Examples include cerebral hypoplasia (present in patients 2 and 6 of our sample) and cerebellar atrophy and micropolygyria (Berends et al., 2001; Rosias et al., 2001). Delayed neuropsychomotor development is reported in around 50% of patients (Berends et al., 2001) and was observed in three of the five patients in our sample who were assessed (60%). In turn, mental development ranges from normal to severely impaired (Berends et al., 2001; Rosias et al., 2001). That feature cannot be adequately assessed for this sample because of the young ages of our patients.

Patients with cat eye syndrome usually have good prognosis. The complications primarily responsible for those deaths that do occur are heart failure, liver failure/biliary atresia, bronchopneumonia and sepsis (Rosias et al., 2001), as was observed in the only patient who died from our sample.

Conclusion

The phenotype observed in cat eye syndrome is highly variable and may be superimposed on the OAVS phenotype. Although these patients usually have good prognosis, including from a neurological point of view (when mental deficiencies are present they are usually mild to moderate) (Berends et al., 2001), we believe that all patients with the syndrome should be assessed very early on for the presence of cardiac, biliary and anorectal malformations. Some of these may need early intervention and treatment which can avoid possible complications in the future, including patient deaths.

Conflicts of interest: No conflicts of interest declared concerning the publication of this article.

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