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Rare Association of Cat Eye Syndrome and Mullerian Agenesis: Third Reported Case

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ABSTRACT

Introduction: Cat-eye syndrome is a rare genetic disease with extremely diverse phenotypes. Its most common manifestations include ocular coloboma, anal atresia, preauricular skin tags and pits.

Case report: We report the third case of Cat-eye syndrome associated to Mullerian agenesis in a 28 years-old female, to highlight the possibility of a link between partial trisomy or tetrasomy of chromosome 22 (specifically of the region 22q11) and Müllerian agenesis.

Discussion and Conclusion: In patients with CES, the short arm (p) and a small part of the long arm (q) of chromosome 22 are present three or four (trisomy or tetrasomy) times rather than twice in every cell of the organism. Schinzel et al, described in 1981 the first case of Cat eye syndrome associated to Mullerian agenesis in their series of 11 patients with CES. The second case of Müllerian agenesis in a patient with CES was reported by AlSubaihin et al. This rare association is suggesting that there may be genes in or near the 22q11 CES critical region that are important for normal mullerian development.

Key words: Cat-eye syndrome – Mullerian agenesis – Malformations – Genetic analysis

INTRODUCTION

Cat-eye syndrome (CES), also referred to as Schmid-Fraccaro syndrome, or chromosome 22 partial tetrasomy or chromosome 22 partial trisomy, is a rare genetic disease with an estimated prevalence of between 1 in 50,000 and 1 in 150,000 individuals [1,2].

The syndrome was named 'Cat Eye' due to the typical ophthalmological finding of vertical colobomas of the iris in few patients, it may be absent in 40-50% of cases [2].

In 1965, Schachenmann et al. identified the genetic basis of CES through a case of a child with polymalformative syndrome with vertical coloboma and other congenital anomalies, genetic analysis noted the presence of a small supernumerary bi-satellited marker chromosome (sSMC) derived from chromosome 22. The ultimate result is a trisomy or partial tetrasomy of chromosome 22, specifically of the region 22pter to 22q11.1 [3,4]. The proximal region of the (q) arm of chromosome 22 includes genes responsible for typical ophthalmologic findings [4].

It is a particularly complex disorder, with extremely diverse phenotypes; most common manifestations include ocular coloboma, anal atresia, preauricular skin tags and pits, cardiac malformations, renal malformations, facial dysmorphia and mild to moderate intellectual disability [5].

To our knowledge, only two cases of CES with Müllerian agenesis were reported in the literature. Here, we report the third case of this association to highlight the possibility of a link between partial trisomy or tetrasomy of chromosome 22 (specifically of the region 22q11) and Müllerian agenesis.

CASE REPORT

Female patient of 28 years-old, the fourth daughter of a healthy and non-consanguineous parents, with no family history of malformation. She was born by normal delivery, weighing 2000g, had neonatal respiratory distress requiring a short hospitalization in neonatology department. Parents noted ocular abnormalities at her first year of life, the initial ophthalmological examination noted bilateral coloboma of the iris, the parents were informed about the necessity of a general malformation check up (not performed). Neuropsychomotor development was normal, the patient didn't present an intellectual disability, she was performing good at school without learning difficulties. At the age of 12 years, the parents noted a growth retardation comparing to siblings and classmates, and consulted a pediatrician, a first paraclinical work-up included; Cerebral MRI that showed Chiari malformation, Standard radiography revealed a thoracic kyphosis, Ultrasonography noted uterine agenesis with ectopic left kidney, no cardiac malformation was shown. The patient underwent a procedure to remove skin tags anterior to both ears. She didn't have a regular follow up after, she consulted different doctors for primary amenorrhea, then consulted in our department for the same reason.

On clinical examination, her height and weight were respectively 142cm and 61 kg with a BMI of 30.25 kg/m^2, blood pressure and heart rate were normal. Eye examination showed bilateral microcornea, iris and choroidal vertical coloboma (Figure 1) with decreased visual acuity. The patient presented auricular dysmorphia with bilateral pits, tags and bilateral scars from previous skin tags excision (Figure 2), and otorhinolaryngologic evaluation diagnosed bilateral moderate hearing loss. Tanner stage was P5S5, the external genitalia were normal female with no clitoromegaly, no vaginal orifice was visualized.

On biological tests; complete blood count, renal and hepatic functions were normal. Hormonal tests showed; FSH : 5.5 UI/L, LH : 6.87 UI/L, Estradiol : 50 pg/ml, Prolactin : 11,51 ng/ml, Cortisol :2 3 µg/dl, TSH : 4,26 mUI/L

Radiological tests; An abdominal-pelvic MRI was performed (Figure 3) showing a complete uterine and vaginal agenesis associated with left renal ectopy (pelvic) and right renal agenesis related to Mayer-Rokitansky-Küster-Hauser Syndrome type 2, both ovaries were visualized: the left measured 5 x 2.1 cm and the right measured 5,2 x 1,3 cm.

A post-natal Karyotype of a peripheral blood sample was performed for a possible genetic etiology for the bilateral microcornea and coloboma, and also the preauricular ear tags and pits. The analysis showed : partial tetrasomy of chromosome 22 47 XX, + marker [50]: presence of a small supernumerary chromosome marker in all mitoses observed and analyzed. The appearance of this chromosome is consistent with a small supernumerary chromosomal marker derived from chromosome 22 (sSMC 22), suggesting strongly the diagnosis of Cat -Eye syndrome. further evaluation of genetic composition of this marker with fluorescence in situ hybridization (FISH) or microarray techniques were recommended but the patient refused in view of financial constraints.

Currently the patient is 30 years old, she graduated at the age of 24 years old and worked as a kinesitherapist. A multidisciplinary follow up is maintained.

Figure 1: Bilateral microcornea, iris and choroidal vertical coloboma in our patient

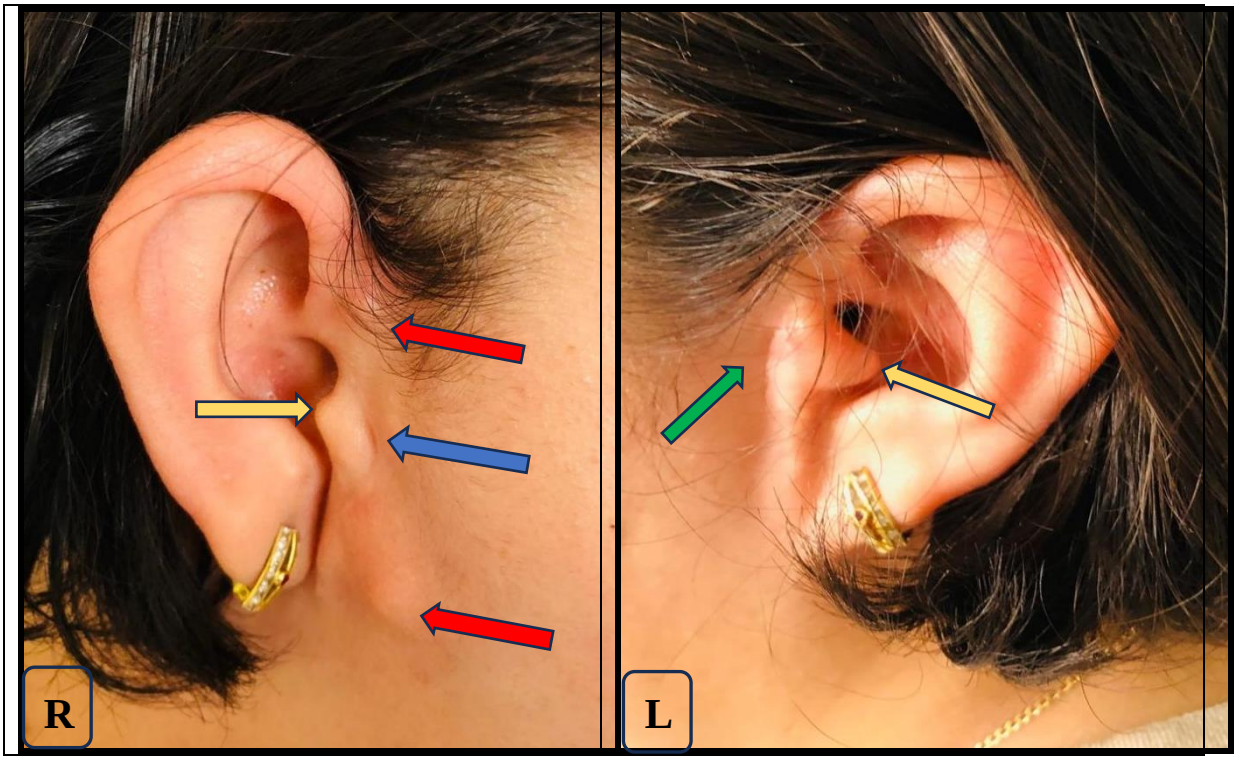

Figure 2: Auricular abnormalities in our patient: Red arrow: pre-auricular tags, Blue arrow : Pits, Yellow arrow : hypertrophic tragus, Green arrow : scar of prior tags excision.

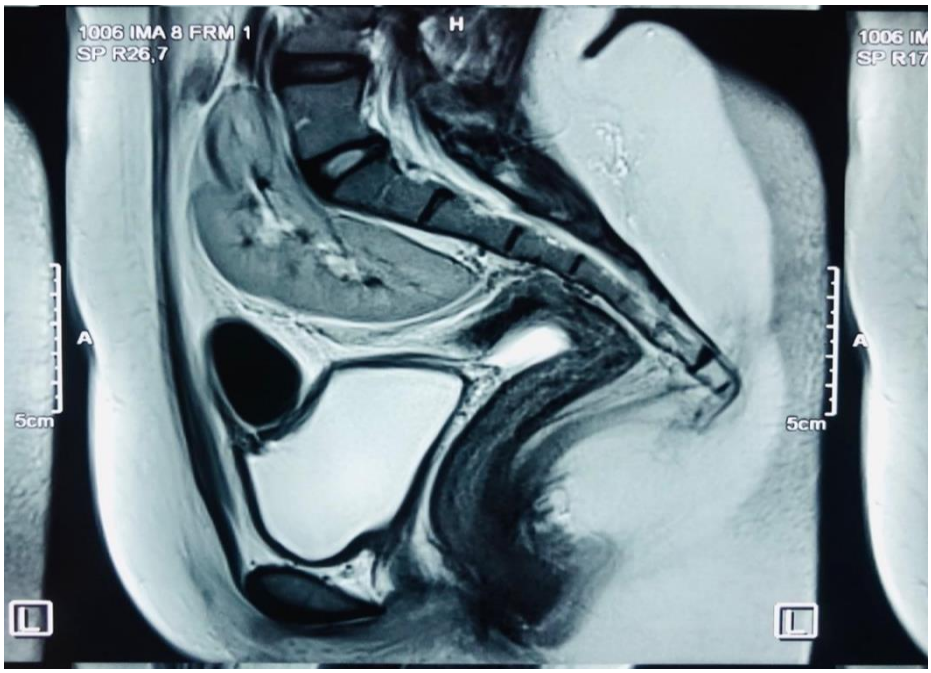

Figure 3: Sagittal MRI view showing total uterine and vaginal agenesis with a solitary left pelvic kidney

DISCUSSION

CES is a genetic disorder that affects various parts of the body. Its principal clinical features include anorectal (anal atresia with fistula) and urogenital malformations, ocular coloboma, preauricular skin tags and/ or pits, and congenital heart defects (frequency ranging from 50% to 63%: anomalous pulmonary venous return…). Minor features include down-slanting palpebral fissures, hypertelorism, skeletal malformations, dysplastic ears, micrognathia, and microphthalmia… [5,6,7]. Neuropsychological development can be normal to severe retardation, other neurological characteristics such as ocular motility disorders, hearing difficulty, spasticity, ataxia, and seizures are frequent [6,8].

Coloboma from which the name of cat eye syndrome was derived, is due to failure to close a fissure in the lower part of the eye during early development. It may involve the iris, choroid and the retina. The affection of the vison depends on the presence of choroid and retina involvement leading to blindness in some patients [9].

Clinical presentation of CES can vary greatly from patient to patient [5]. The classical triad of symptoms in patients with CES comprises iris coloboma, anal atresia, and preauricular skin tag or pit [5]. However Only 41% of reported cases show these signs and less than 10% of patients present all these three major clinical features [6]. Our patient had coloboma and preauricular pits and tags, no anorectal abnormalities were found, she was diagnosed also with Chiari malformation which is a rare anomaly, it was previously reported in 22q11 deletion syndrome and in a patient with 22q11 duplication [10].

CES is seen in patients with proximal duplication of the long arm of chromosome 22, partial tetrasomy (22pter-22q11), duplication-inversion (22pter-22q11), and partial trisomy (22pter-22q11) [11]. The partial tetrasomy of chromosome 22 is due to a supernumerary dicentric marker chromosome with satellites at the ends. It is thought that the formation of the small extra Inv dup 22 chromosome is facilitated by recombination between low copy repeats during meiosis [2].

In patients with CES, the short arm (p) and a small part of the long arm (q) of chromosome 22 are present three or four (trisomy or tetrasomy) times rather than twice in every cell of the organism [2]. The proximal part of the long arm of chromosome 22 (22pter-22q11.2) is currently estimated to be about 2.1 Mb, it is the critical region for chromosomal rearrangements because it contains several repetitive genomic segments, it includes also genes which are responsible for the cat eye [2,9,12].

Two types of the small supernumerary marker chromosome (sSMC) have been described, according to the size and rupture site. Type 1 includes only the critical region of the CES, and type 2, reported in only a few cases of CES, includes both the CES and DiGeorge syndrome critical regions [13]. Therefore, the sSMC may vary in molecular size, but a direct correlation between CES phenotypes and the size of the supernumerary region has not been identified [7,11]. The other limitation to performing phenotype–genotype correlation is somatic mosaicism. Previous studies have shown that the rate of mosaicism can be markedly variable between tissues in the same patient, and have demonstrated the existence of germinal mosaicism in CES [13]. Also, no correlation has been established between disease severity and the degree of mosaicism in CES [3].

Genetic anomalies related to CES, appear spontaneously, in which case the karyotypic analysis of the parents is normal. A few cases may be due to a balanced translocation in either parent, in which case the recurrence rate is elevated [2].

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also referred to as Müllerian aplasia or Müllerian agenesis, is a congenital disorder that affects females and is defined by the agenesis or absence of

uterus and superior part of the vagina. These individuals have a normal karyotype (46, XX) and generally normal ovarian function. It is classified into two types: Type I is characterized by uterovaginal aplasia, while Type II is also associated with extragenital anomalies, most commonly renal (30-40%), skeletal, atrial and cardiac. The frequency of type I and type II MRKH syndrome is 56–72% and 28-44%, respectively. The reported incidence rate of MRKH syndrome is around 1/5,000 live births [14,15].

genetic background of MRKH is poorly studied, however several interesting genetic findings emerged following the advent use of chromosomal microarray. The most reported chromosomal regions and the possible genes implicated in MRKH sd are: 1q21.1 (RBM8A gene), 1p31-1p35 (WNT4 gene), 7p15.3 (HOXA gene), 16p11 (TBX6 gene), 17q12 (LHX1 and HNF1B genes), 22q11.21, and Xp22 [14,15].

Schinzel et al [16], described in 1981 the first case of cat eye syndrome associated to Mullerian agenesis in their series of 11 patients with CES. It was a 32-year-old female. Anomalies noted at birth or thereafter included: hypertelorism, downslanting palpebral fissures, exotropia, bilateral epicanthic folds, inferior coloboma of the left iris and choroid, a left preauricular pit, low nuchal hair line. She presented also complex cardio-vascular malformation operated at the age of 18, Anal atresia with a recto-vestibular fistula required surgery at 7 months and again at 6 years.

She had agenesis of the vagina, hypoplasia of the uterus and rudimentary tubes, but normal ovaries, absence of the left kidney and mild hydronephrosis of the right kidney, malrotation of the gut. Breasts, axillary and pubic hair were normal postpubertal.

The second case of Müllerian agenesis in a patient with CES was reported by AlSubaihin et al [12], in a 16-year-old girl presented with bilateral colobomata, primary amenorrhea and absence of the uterus and upper vagina on pelvic MRI. Microarray analysis showed tetrasomy of the pericentromeric region of chromosome 22 diagnostics of CES.

We report herein the third case of this rare association, suggesting a possible extension of CES manifestations to include mullerian agenesis, implicating additionally, that there may be genes in or near the 22q11 CES critical region that are important for normal mullerian development.

There is no specific therapy for this syndrome. Treatments generally focus on the management of symptoms and may require surgery to correct ocular abnormalities, and other malformations cardiac, renal, anal…) as well as speech therapy, language therapy, special education and other supportive measures [5].

The global prognosis is favorable, including for those with intellectual disability. However, early detection of malformations and therapeutic guidance is essential, especially regarding congenital heart disease and anorectal malformation, which may require surgical treatment [4].

CONCLUSION

In conclusion, we highlight through our case report, this extremely rare association of CES and Müllerian agenesis. Implicated genes of MRKH syndrome include the 22q11 region suggesting the possibility of a potential association between CES critical region 22q11 abnormalities and genital malformations especially Mullerian agenesis. Additional case reports of this association are necessary to identify the link between genes residing in 22q11 region and MRKH.

Declaration by Authors

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