Bilateral congenital cataracts in an infant with Klinefelter syndrome

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Congenital cataract is one of the most treatable causes of visual impairment and blindness during infancy, with an estimated prevalence of approximately 2.5:10,000 infants under the age of 1 year. Congenital cataract can be observed with certain chromosomal abnormalities, such as trisomies, deletions, translocations and Turner syndrome. In Klinefelter syndrome, however, ocular complications and cataract are not commonly encountered, so reports in the literature are very rare.

In this manuscript, we present a 3-month-old male infant who had congenital cataracts. Chromosomal analysis revealed that his karyotype was 47,XXY. He did not show any of the main clinical signs of Klinefelter syndrome because of his very young age. To the best of our knowledge, our patient is only the second-ever case reported in the literature in which congenital cataracts have been found in an infant with a nonmosaic 47,XXY karyotype. The aim of the present report is to both describe the ocular abnormalities that can sometimes be found in Klinefelter syndrome and to emphasize the importance of performing a karyotype analysis in order to rule out chromosome abnormalities in patients with congenital cataracts.

Key words: Klinefelter syndrome, congenital cataract, karyotype analysis, infant.

Klinefelter syndrome (KS) occurs in about 1:1000 males and is the most frequent chromosomal aberration in males[1]. It is not easy to diagnose Klinefelter syndrome in young children because of the absence of significant physical manifestations before puberty. The characteristic findings in KS are small testes, azoospermia and increased LH and FSH levels, all of which can be observed in nearly all Klinefelter patients; in addition, other features such as hypogonadism, gynecomastia, increased height, sparse facial and body hair, learning disabilities, psychiatric complications, an increased risk of diabetes and metabolic syndrome, abdominal obesity and autoimmune diseases have been found in various cohorts of KS patients[2-4]. Furthermore, osteoporosis, thromboembolic disease and an increased risk of cancer have also been observed[5].

Klinefelter syndrome was first described in 1942, and since then numerous diseases have been found to be associated with KS. Some of these include ocular diseases, such as diffuse choroidal atrophy[6] and colobomas of the iris and choroid[7]. Recently, juvenile glaucoma and optic disc pit with macular detachment have been described in KS[8].

In this report, we present a 3-month-old male infant with atypical findings for Klinefelter syndrome. To the best of our knowledge, this is only the second reported case in the literature in which congenital cataracts have been found in an infant with the 47,XXY karyotype.

Case Report

A 3-month-old male infant was admitted to our hospital due to prolonged jaundice and opacification of the lenses. He was born at 38 weeks as the first child to parents who were fourth-degree cousins. His birth weight

was 2900 g. He was delivered by caesarean section due to fetal distress after a normal pregnancy that was free of complications. A prenatal ultrasound examination that had been performed at an outside medical center was normal. Additionally, there was no family history of metabolic or genetic disease.

On physical examination, the patient's weight was found to be 3400 g (25th-50th percentile), with a height of 50 cm (10th-25th percentile), a cranial circumference of 36 cm (25th-50th percentile) and an anterior fontanel size of 2x2 cm. Furthermore, the patient displayed a facies with a broad forehead, upslanting palpebral fissures, bilateral leukocorias, a depressed nasal bridge, bilaterally low-set ears and a short neck. Red reflex was absent bilaterally. Genital hypoplasia was not observed. The patient's appearance at the age of 10 months is shown in Fig. 1.

All of the routine laboratory tests, including prolonged hyperbilirubinemia tests, thyroid function tests, and those measuring plasma and urine aminoacids, urine-reducing substances, and ammonia and lactate levels, were found to be normal. TORCH screening and VDRL-RPR were both normal. His testicular volume was consistent with prepubertal levels. A hearing test was normal. Echocardiography detected a secundum atrial septal defect. Renal ultrasonography and cranial magnetic resonance imaging were all found to be normal.

Upon ophthalmic examination, the presence of leukocoria in the pupillary area of both of his eyes was found to be related to anterior polar cataract that closed the entire optic axis. Corneal diameters were found to be normal,

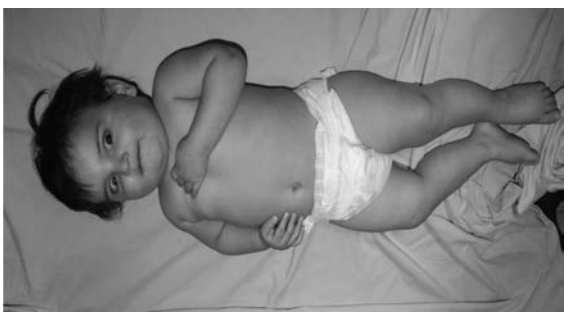
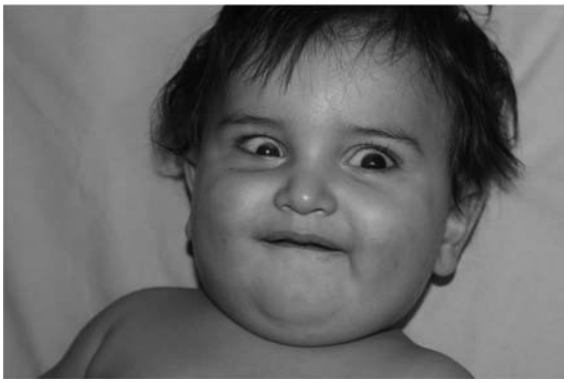


Fig. 1. (a) The patient's appearance at the age of 10 months, showing a facies with a broad forehead, upslanting palpebral fissures, bilateral lens opacity, a depressed nasal bridge, bilaterally low-set ears and a short neck.



(b) Bilateral leucocoria at the age of 10 months

and there was no pupillary or iris pathology. Additionally, his pupillary dilation was fairly good. Intraocular pressure was measured with a Tonopen and was 17/18 mmHg (OD/OS). Due to the fact that the retina could not be viewed clearly, B-scan ultrasonography was performed, and the findings were normal except for increased bilateral lens echogenicity. Cataract extraction and an anterior vitrectomy were first performed on the right eye and then, one week later, on the left eye. The preoperative appearance of the right eye is shown in Fig. 2. A postoperative fundus examination was found to be normal. As a result of the visual deprivation sustained in the first few months, bilateral nystagmus eventually developed.

Chromosome analysis performed on cultured leukocytes using GTG banding techniques showed a 47, XXY karyotype based on the 20 metaphases analyzed (Fig. 3).

Discussion

Klinefelter syndrome is considered to be the most common sex-chromosome disorder in males. The most widespread karyotype in affected patients is 47,XXY. While the clinical features manifested in KS are variable, the most frequently observed characteristics are tall stature, narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, an absence of spermatogenesis, androgen deficiency and normal to slightly decreased verbal intelligence. Indeed, some of these features can be so weakly pronounced that some patients are only diagnosed in adulthood due to infertility[5].

Although KS is a well-known syndrome, a more systematic knowledge about the long-

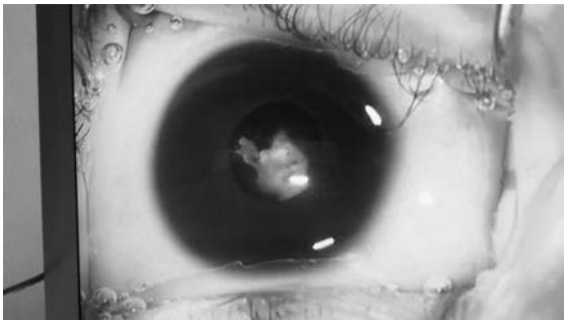


Fig. 2. The preoperative appearance of the right eye as seen at 3 months of age.

term outcome was absent until the last decade, when the results of nationwide epidemiological studies were reported[9]. While KS has been associated with various ocular anomalies, such as diffuse choroidal atrophy[6] and colombas of the iris and choroids[7], ocular irregularities are not a classical feature of KS. Recently, Muniesa Royo et al.[8] reported a 34-year-old KS patient with loss of vision in his left eye, bilateral ocular hypertension and optic disc pit with serous macular detachment in the left eye[8]. It is known that strabismus, impaired vision and refractive errors are more prevalent in a number of conditions associated with intellectual disability[10]. Interestingly, Qureshi et al.[11] reported an 8-year-old patient with a KS variant 49,XXXXY karyotype who had high myopia, which had not previously been reported in association with this condition.

The prevalence of congenital and infantile cataracts has been reported to be approximately 2.5:10,000 by the age of 1 year. While many of these cataracts are congenital, in certain cases it can be difficult to establish the exact age of onset with certainty[12]. Congenital and infantile cataracts have a diverse etiology. All three types of Mendelian inheritance have been reported for cataract; however, autosomal dominant transmission seems to be the most frequent. Congenital cataracts most commonly occur secondary to genetic and metabolic diseases (such as diabetes, galactosaemia, hypoglycaemia, galactokinase deficiency and some lysosomal storage diseases), intrauterine infections (TORCH infections) or trauma; less commonly, they may occur as a side effect of certain medications or radiation exposure[13, 14].

Congenital cataracts can also occur in some chromosomal abnormalities such as trisomies

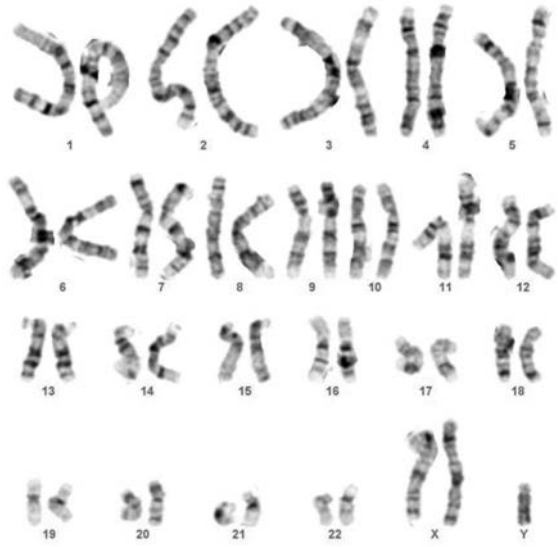


Fig. 3. G-banded karyogram of the patient, showing a 47,XXY karyotype.

(13, 18, 21), deletions (5p, 18p, 18q), translocations (3;4, 2;14) and Turner syndrome, but are not a usual finding in KS. Pamuk et al.[15] reported a 25-year-old 49,XXXXY syndrome patient with autoimmune diabetes, bilateral cataracts and glaucoma, but concluded that because of the patient's age, the cataracts were related to diabetes. In our case, given the absence of any metabolic or systemic disease, the cataracts seem to be associated with the chromosomal anomalies that were diagnosed at infancy.

Congenital cataracts can occur in association with a number of genetic syndromes that primarily affect other parts of the body, such as the kidneys (Lowe, Alport and Hallerman–Streiff–Francois syndromes), the skeletal system (Smith–Lemli–Opitz, Weill-Marchesani and Stickler syndromes), the central nervous system (cerebro-oculo-facio-skeletal, Marinesco–Sjogren, Meckel-Gruber and Zellweger syndromes), the musculoskeletal system (myotonic dystrophy) or the dermis (Cockayne syndrome, incontinentia pigmenti and ichthyosis), or that may cause other anomalies, such as digital (Bardet-Biedl and Rubenstein-Taybi syndromes) or dental anomalies (Lenz syndrome) [13,16].

Congenital cataracts are also genetically heterogeneous. Approximately two-thirds of bilateral congenital cataracts are related to

genetic causes. It is known that different mutations in the same gene can cause similar cataract patterns or that the same mutation in a single gene can lead to different phenotypes. To date, more than 25 loci and genes on different chromosomes have been associated with congenital cataract[17]. Recently, a 2-month-old infant with Klinefelter syndrome and a unique combination of ocular abnormalities, including microphthalmia, cataracts and malformed pupils, was described by Juhn et al[18]. In their report, the authors hypothesized that mutations in the BCOR gene (BCL6 co-repressor) located in Xp11.4 may cause cataract and micropthalmia. In some Klinefelter syndrome patients, increased BCOR gene expression due to the extra X chromosome may result in cataracts[19]. There were both similarities and differences between our case and that reported by Juhn et al[18]. While both patients had bilateral anterior polar cataract, the previous case had bilateral microphthalmia and irregular bridges of iris stroma that adhered to the lens capsules. Our patient, however, had isolated cataract without any other ocular pathologies. After the cataract surgeries, both cases had nystagmus related to late surgical treatment.

Cataract produces prolonged visual deprivation that causes irreversible loss of vision. It is estimated that approximately 200,000 children worldwide are blind from cataract[20]. Treatment for bilateral cataract should be given according to the density of the lens and the closing of the visual axis. If surgery is necessary, it is imperative that it be performed early enough to better ensure that the damage from congenital cataracts is minimized[21]. Ideally, the best time for surgery is during the 4^{th}-6^{th} weeks[22] in unilateral cataracts and the 6^{th}-8^{th} weeks[23] in bilateral cataracts. In our patient, as in the previously reported case, nystagmus, resulting from delays in treatment, was observed.

In conclusion, although congenital cataract has a diverse etiology, it is important to perform a karyotype analysis in order to rule out chromosome abnormalities. On the other hand, the exceptional case of our patient emphasizes the need for careful and detailed ophthalmologic examination of all patients diagnosed with Klinefelter syndrome. Finally, an increased awareness of Klinefelter syndrome, and its potential for ophthalmologic complications, may aid in early diagnosis that will, in turn, allow for more effective treatment and genetic counseling.

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