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A Hispanic Girl with Cornelia de Lange Syndrome and 45,X/46,XX Karyotype

Abstract

Numerous chromosomal rearrangements, including the X chromosome, have been reported in individuals with Cornelia de Lange syndrome (CdLS) as possible responsible of CdLS phenotype, somatic, growth, and cognitive abnormalities. I here describe the case of a Hispanic girl with most of the major features of CdLS, whose cytogenetic analysis reported loss of the X chromosome consistent with a diagnosis of Turner syndrome.

Keywords: CdLs; NIPBL; EEG; MRI

Case Report

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Abbreviations: CdLS: Cornelia de Lange Syndrome; NIPBL: Nipped-B-like

Introduction

Cornelia de Lange Syndrome (CdLS) is a developmental disorder, inherited in an autosomal dominant manner [1,2] or an X-linked manner [3], characterized by craniofacial dysmorphism, limb abnormalities, growth failure, and intellectual disability [4,5]. More than two dozen of CdLS phenotype cases have been associated with chromosomal abnormalities involving several chromosomes, including the X chromosome. Mutations in the Nipped-B-like (NIPBL), SMC1A and SMC3 genes have been detected in about 50%, 5% and 1% of patients with CdLS, respectively [1-3]. I here present the case of a six year-old Hispanic girl with most of the features associated with CdLS that was discovered to have loss of the X chromosome, 45, X, consisting with Turner Syndrome.

Case Report

A six year-old, Hispanic girl with chronic gastroesophageal reflux is brought to the clinic for a second opinion regarding growth failure and poor weight gain. Born by Cesarean section at 36 weeks gestation due to maternal hypertension, her birth weight was 2160 g and length 43.9 cm, both under 5th percentile according to gestational age. Neonatal period complicated with jaundice requiring hospitalization for one week. The medical history also reported head size of 29.7 cm (microcephaly). There was not exposure to medications, cigarettes, alcohol, or illicit drugs. An upper gastrointestinal radiographic series at 4 weeks of age, done because a reported apparent life threatening event with cyanosis, showed gastroesophageal reflux, but no other abnormalities. She was admitted once at 5 years of age due to a urinary tract infection.

Patient sat at 10 months, walked at 3 years, and was diagnosed with mild to moderate bilateral sensorineural hearing loss at 2.5 year old during a speech delay evaluation. A global developmental delay was noted at 6 months of age. Her weight, height, and head circumference have remained between the 3rd and 5th percentiles. Patient wear glasses because Myopia and had nasolacrimal duct stenosis during infancy.

Her evaluation had also included multiple laboratory tests, including CBC, measurement of electrolytes, urinalysis, thyroid function tests, cystic fibrosis, celiac disease screening. She had been also evaluated by pediatric neurologist who ordered a brain MRI and an EEG, which were both within normal limits, and patient was diagnosed with diffuse cerebral dysfunction in the form of attention deficit hyperactivity disorder. A psycho educational evaluation reported to have an intellectual disability with IQ of 65. There is no history of self- injurious behavior. An echocardiogram revealed no structural or functional heart abnormalities, and pelvic ultrasound and a renal ultrasound were both normal.

Family History

Patient is an only child. Her mother has Hypertension. The father quit school in sixth grade, and has no history of chronic diseases. There is no other family history of birth defects or mental retardation. Consanguinity was denied.

Physical Examination

At physical examination the 6 year-old girl's weight of 14.1 kg, height of 1.1 m, and head circumference of 46 cm were below the 5th percentile. Physical findings included multiple dysmorphic features including synophrys, arched eyebrows, long eyelashes, low set posteriorly rotated ears, depressed nasal bridge, small upturned nose, widely spaced teeth with high arched palate, micrognathia, and the neck appears short with peculiarly low hairline (Figure 1). Patient had small hands and feet, with syndactyly of the first and second right toes. Hand length of 7.0 cm and feet length of 16.2 cm, both under the 5th percentile for age. Excessive body hair or hirsutism was also present involving temporal regions and arms.

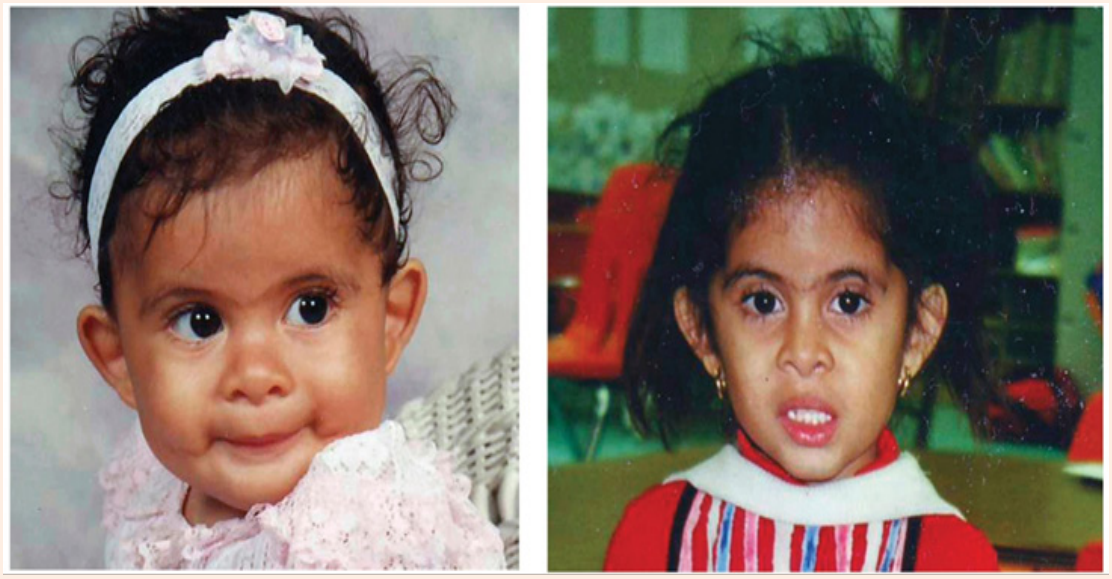

Figure 1: Photograph of patient at 12 months and 6 years of age, respectively.

Cytogenetic Analysis

Cytogenetic evaluation revealed an abnormal mosaic karyotype 45, X (12)/46, XX (8) (Figure 2). The first cell line, seen in 8 of 20 cells scored was 46, XX, a normal female karyotype (Figure 2(a)). The second cell line, seen in 12 of 20 cells scored was 45, X, a female karyotype missing one copy of the X chromosome (Figure 2(b)). No evidence of chromosome 3 or 5 abnormality was detected in this analysis.

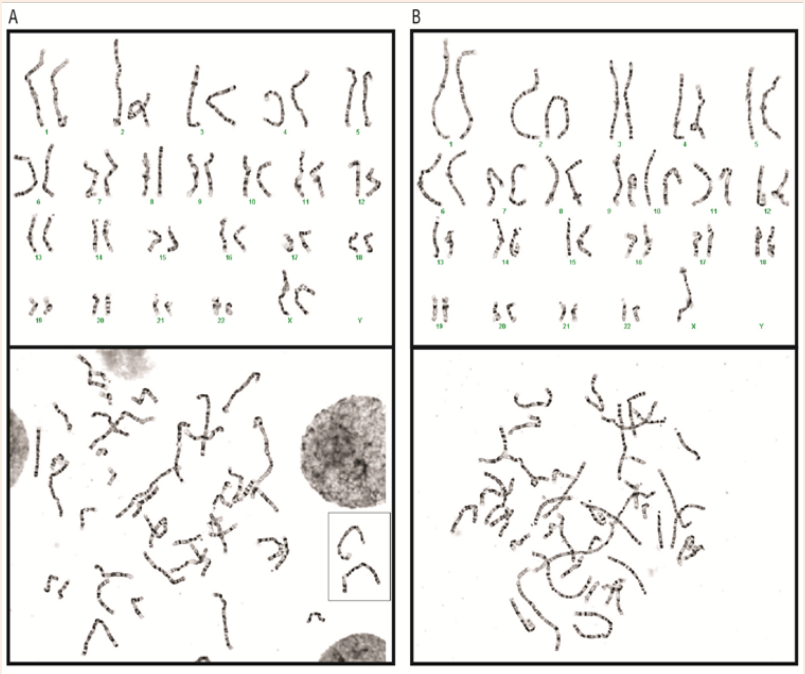

Figure 2: Cytogenic evaluation revealing (A) a normal female Karyotype 46, XX, seen in 8 of 20 cells scored and (B) an abnormal female Karyotype 45, X, seen in 12 of 20 cells scored.

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Discussion

Cornelia de Lange Syndrome was named in honor to Cornelia de Lange [6,7], a Dutch pediatrician who described two female patients with similar features in 1933. The syndrome is sometimes referred to as Brachmann-de Lange Syndrome because Dr Brachmann had also described a similar patient in 1916 [8]. Cornelia de Lange Syndrome is a congenital syndrome, meaning that the signs may be recognized at birth or shortly thereafter [9]. The prevalence is difficult to estimate because there are classic or severe and milder phenotypes and the array and severity of associated symptoms may be very variable from case to case [5,10]. Most patients have the characteristic facial features including arched eyebrows growing together in the middle (synophrys), long eyelashes, low set ears, high palate, small widely teeth, small upturned nose, depressed nasal bridge, micrognathia and short neck with low hairline, but only the classic cases present with more striking limb involvement (from micromelia or small hand to oligodactyly or missing digits) and severe cognitive impairments with overall IQs ranging from 30 to 85. Growth failure with weight and height under 5th percentile is present in over 95% of patients since newborns throughout life. In addition, hirsutism is present in more than 80% of cases with other superimposed conditions such as gastroesophageal reflux, sensorineural hearing loss, ocular, cardiovascular, and genitourinary problems frequently added [4,5,10,11].

Loss of the X chromosome is consistent with a diagnosis of Turner Syndrome. However 45, X has been reported in this patient, whose phenotype resemble a Cornelia the Lange Syndrome [12,13]. Prior to the cytogenetic analysis report and identification of a mosaic pattern with 45, X/46, XX in this girl, a diagnosis of Cornelia de Lange was the most possible diagnosis. In this patient there are many phenotypic features which overlap between CdLS and Turner Syndrome, including growth failure, short neck with low hairline, and low set and differently shaped ears.

There have been several reported cases of patients carrying a clinical diagnosis of CdLS in whom chromosomal abnormalities have been found [1-3,12-17]. The diagnosis of CdLS is clinically based. At present there are only three genes known to be associated with CdLS: Nipped-B-like (NIPBL), SMC1A (formerly SMC1L1), and SMC3 [1-3]. Mutations in NIPBL and SMC3 are considered to have an autosomal dominant pattern of inheritance, while SMC1A mutations have an X-linked pattern of inheritance [1-3]. X-linked CdLS appears to affect males and females similarly [2,3]. In many of the cases of CdLS the cause is unknown and occurs in people with no history of the condition in their family.

Many signs and features are not specific to Turner Syndrome or to CdLS, making it difficult to determinate if the chromosome abnormalities are the cause of the CdLS phenotype or just co-incidental diagnosis etiologically unrelated. Therefore, it is very important to do a definite and pronto diagnosis in order to provide an appropriate management and genetic counseling.

Conclusion

I have reported the case of a six year-old Hispanic female patient with many of the classic signs of CdLS, including craniofacial features, growth failure, intellectual disability, limb abnormalities, hirsutism, and gastroesophageal reflux, who after cytogenetic analysis was found to have loss of the X chromosome, consistent with a diagnosis of Turner Syndrome. Loss of chromosomal material (i.e. 45, X) has been previously reported in patients whose phenotype resembled Cornelia de Lange syndrome [12,13]. Given that etiologically unrelated chromosomal abnormalities may be present in individuals with CdlS, it is important to clearly identify them in order to carefully evaluate the correct diagnosis. These concluding diagnoses with chromosome studies were of significant benefit to the patient and family for proper genetic counseling.

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