A Rare Double Aneuploidy Case (Down–Klinefelter)

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Abstract

Down's syndrome has its own dysmorphic findings and is accompanied by mental retardation and hypotonia. Klinefelter's syndrome is a syndrome caused by a numerical abnormality that affects male physical and cognitive development. This case reports a unique finding of 48,XXY, + 21 and a current literature review. A 4-month-old male patient presented with typical clinical features of Down's syndrome with hypothyroidism, atrial septal defect, ventricular septal defect, and patent ductus arteriosus without any phenotypic signs of Klinefelter's syndrome.

Keywords

- ▶ aneuploidy
- ▶ chromosome
- ▶ syndrome

Introduction

Down's syndrome and Klinefelter's syndrome are the most common chromosomal abnormalities in humans with an incidence of one in 770 live births for Down's syndrome and 1 in a 1,000 newborn males for Klinefelter's syndrome.¹ Phenotypic expression of any aneuploidy varies and depends on the number of extra chromosomes, degree of mosaicism, and their location in the whole body.²

Two chromosomal abnormalities rarely occur together. The first reported case of double aneuploidy was in 1959 by Ford et al,³ and several cases have been described since then. This is a case report of a 4-month-old patient with Klinefelter's syndrome and Down's syndrome due to possibly two meiotic nondisjunction events who presented with only clinical features of Down's syndrome.

Case Report

The patient was born at 38 weeks' gestation weighing 2.9 kg (10–25th percentile) with 48 cm length (10–25th percentile) and a 34-cm head circumference (25th percentile). This male patient was born to healthy unrelated parents as the first child of a 35-year-old father and a 36-year-old mother. He presented to our Clinical Genetics clinic with dysmorphological signs of Down's syndrome, including flat face, upslanting palpebral fissures, a flat nasal bridge with epicanthal

folds, small nose, micrognathia, microcephaly, low set ears with overfolded ear lobes, brachydactyly, bilateral single palmar creases, and sandal gap deformity, when he was 4 months old. He was at the 3rd percentile for height (55 cm), 3 to 10th percentile for weight (4.3 kg), and 3rd percentile for head circumference (35.5 cm). His physical examination revealed hypotonia and a grade 2/6 systolic murmur. An echocardiogram revealed that he had a small atrial septal defect, small ventricular septal defect, and patent ductus arteriosus. He also had hypothyroidism and had been receiving treatment with levothyroxine. A chromosome analysis showed the presence of nonmosaic 48,XXY, + 21. Parental karyotypes were both normal (► Fig. 1).

Conclusion

The double aneuploidy 48,XXY, +21 was first described in 1959,³ and the incidence is reported to be 0.4 to 0.9 per 10,000 male births.⁴ Most commonly, double aneuploidy occurs when two meiotic nondisjunction events happen from the same or different parental origins.⁵ The coincidence rate of Down's syndrome and Klinefelter's syndrome in the same patient is 0.098% in newborns, and it has been found to dependent on parental age.⁶ Advanced maternal age is one of the main risk factors for double aneuploidy, as it is for single chromosomal aneuploidies caused by parental nondisjunction during gametogenesis.⁷ According to literature review of

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Fig. 1 GTG-banded karyotype of the patient. The patient's karyotype reveals the presence of an additional 21 and X-chromosome (48, XXY, +21).

double aneuploidy cases, the majority of the mothers were younger than 35.^{5,6,8,9} The nonrandom aspect of double aneuploidy provides evidence that a hereditary predisposition to nondisjunction exists, with one chromosomal imbalance increasing the risk of another to occur.⁴ While the genetic analysis of other double autosomal trisomies usually showed a predominantly maternal origin, as in single trisomies,¹⁰ sex chromosomal trisomies can originate from either the mother or the father.¹¹ Theoretically, 50% of XXY cases could arise from an error in paternal meiosis I and the remaining from maternal meiosis I or II. Abnormal separation of chromosomes occurs frequently in older individuals because of chromosomal separation dysfunction related to the spindle apparatus and kinetochore.⁵

In patients with concurrent Down's syndrome and Klinefelter's syndrome, the characteristic features of Klinefelter's syndrome begin developing during late infancy and become apparent during puberty.⁴ Since the sexual development primarily depends on the presence of the Y chromosome, the 48,XXY, +21 individuals have male phenotype. Klinefelter's syndrome is a form of primary testicular failure with testicular hypotrophy and elevated gonadotropin plasma levels, and it is the most common form of male hypogonadism.¹² Our patient had undescended testicles. Though karyotype was indicated due to his clinical features of Down's syndrome, which is why a chromosome analysis was performed. According to the latest reported cases, there have been a few reported Down–Klinefelter's syndrome cases with cardiac defects.^{4,5,9,13} However, this is the first case report of Down–Klinefelter's syndrome accompanying both heart defects and hypothyroidism.

In conclusion, Down–Klinefelter's syndrome is a rare chromosomal abnormality. Patient present with physical

characteristics of Down's syndrome at birth and Klinefelter's syndrome features at during puberty. It is important to counsel families about recurrence risk for future pregnancies. A clinical geneticist evaluation is also recommended.

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Conflict of Interest

None.

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