Endocrine Abnormalities in Mosaic Trisomy 16 Adolescent: A Case Report

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ABSTRACT

Chromosomal trisomy presents with a range of clinical manifestations, from subtle to life-threatening conditions that include trisomy 16, the most common aneuploidy in first trimester abortions. Most cases are linked to maternal complications and spontaneous abortions, typically detected prenatally. Infants who survive with trisomy 16 often have mosaic variants and may exhibit various anatomical and metabolic abnormalities, though a trisomy 16 diagnosis does not guarantee the presence of such abnormalities. We share the case of a 15-year-old boy who has mosaic trisomy 16. He was diagnosed after birth and showed mild symptoms without any major anatomical issues. However, he did experience several metabolic problems, such as insulin resistance, obesity, hormonal imbalances, and vitamin D deficiency. This report highlights the diverse clinical characteristics of trisomy 16, comparing them to previously reported cases.

INTRODUCTION

Trisomy 16 happens when the chromosome 16 bivalents separate too early during the first stage of maternal meiosis.[1] Trisomy 16 mosaicism occurs when there is a post-zygotic loss of chromosome 16, which helps some parts of the trisomic embryo. One of the most frequent reasons for trisomy 16 is uniparental disomy.[2] Mosaicism found during amniocentesis has been closely linked to fetal death, birth defects, and fetal anomalies, as well as intrauterine growth restriction.[3,4] We report the case of a 15-year-old boy who came to our outpatient department with signs that pointed towards Klinefelter syndrome. After conducting a chromosomal study, we discovered that he has trisomy 16 mosaicism.

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CASE PRESENTATION

A 10-year-old boy of South Asian descent came to our outpatient department 5 years ago with several health concerns. He had been experiencing bilateral gynecomastia, which was first noticed 2.5 years prior, as well as small genitalia and delayed developmental milestones. The boy was also obese and displayed aggressive behavior. At the time of the visit, he measured 160 cm in height and had a body mass index (BMI) of 16, with a z-score of 2.46. His mother was 29 years old when she gave birth to him.

The clinician suspected Prader-Willi syndrome and referred him to pediatric endocrinology for further evaluation. Laboratory tests revealed the following: levorotatory thyroxine 0.88 ng/dl, thyrotropin 2.36 uIU/ml, serum cholesterol at 174 mg/dl, serum triglycerides at 100 mg/dl, serum high-density lipoprotein (HDL) cholesterol 41 mg/dl, serum low-density lipoprotein (LDL) cholesterol 120 mg/dl, very low-density lipoprotein cholesterol 20 mg/dl, fasting plasma glucose 77 mg/dl, serum cortisol 5.70 µg/dl, testosterone 7.1, and serum insulin levels ranging from 66 to 90 µU/mg (see Table). The screening for Prader-Willi syndrome was negative. In response to the elevated insulin, HDL, and LDL levels, the pediatric endocrinologist prescribed metformin 500 mg, to be taken half a tablet in the morning and half a tablet in the evening.

The patient returned to the outpatient department 1 month later. At this visit, his BMI was 33.6. Noticing the worsening of his clinical symptoms and complaints, the clinician suspected Klinefelter syndrome. He ordered a variety of tests, including complete blood cell count, follicle-stimulating hormone, luteinizing hormone, testosterone levels, and karyotyping. See results

Table. Patient's Laboratory FIndings 2017 – 2022

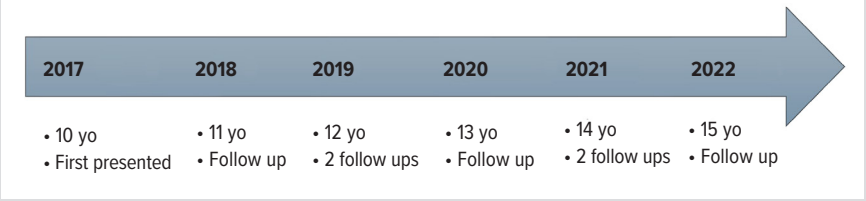
Variables	Ref Range	2017	2018	2018 + 2 months	2019	2020	2021	2021 + 5 months	2022
Fasting blood glucose	3.3 – 5.6 mmol/L	4.30	4.80	4.50	4.80	4.70		4.40	4.10
	65 – 100 mg/dL	77.0						(79.0)	
HBA1C	4.0% – 6.5%	–	–	5.0	-	–			5.7
Serum insulin	2 – 25 µU/mL	66.90	–	–	58.70	15.16	51.01	13.60	36
Serum cholesterol	< 200 mg/dL	174	–	–	–	–			
Serum triglycerides	< 150 mg/dL	100	–	–	–	–			
Serum LDL	< 100 mg/dL	120	–	–	–	–			
Serum VLDL	< 30 mg/dL	20	–	–	–	–			
Serum HDL	≥ 40 mg/dL	41	–	–	–	–			
Serum T4	0.89 – 1.76 ng/dL	0.88	–	–	1.02	–	1.78		
Serum thyrotropin	0.34 – 5.6 µIU/mL	2.36	–	–	2.47	–	3.28		
Serum cortisol	AM: 4.3 – 22.4 µg/dL								
	PM: 3.1 – 16.66 µg/dL	5.7	–	–	–	–			
Serum testosterone	6 – 27 nmol/L	7.1	–	–	–	–	9.71		14.2
Serum FSH	0.0 – 6.0 mIU/mL	0.22	–	–	–	–			
Serum luteinizing hormone	1.0 – 3.5 mIU/mL	0.10	–	–	–	–			
Total lung capacity	4.0 – 11.0 x 109/L	–	10.9	–	–	7.9			11.6
Red blood cells	4.50 – 5.50 x 1012/L	–	5.4	–	–	6.1			5.86
Hemoglobin	13.0 – 17.0 g/dL	–	11.2	–	–	12.0			12.4
Hematocrit	40% – 50%	–	36.6	–	–	40.6			40
Mean corpuscular volume	83.0 – 101.0 fL	–	67.0	–	–	66.6			68.8
Mean corpuscular hemoglobin	27.0 – 32.0 pg	–	20.5	–	–	19.7			21.2
MCHC	31.5 – 35.0 g/dL	–	30.2	–	–	29.6			30.8
Platelets	150 – 400 x 109/L	–	432	–	–	342			178
Neutrophils	40% – 80 %	–	65	–	–	60			70
Lymphocytes	20% – 40 %	–	25	–	–	32			25
Eosinophils	1% – 6 %	–	04	–	–	04			02
Monocytes	2% – 10 %	–	06	–	–	04			03
Serum calcium	8.6 – 10.2 mg/dL	–	9.3	–	–	–			
Serum 25-hydroxy vitamin D	> 30 ng/mL	–	6.62	–	–	–	36.09		
Total bilirubin	3 – 18 µmol/L	–	12.0	–	–	–			
Serum alkaline phosphatase	< 645 U/L	–	260	–	–	–			
Serum alanine aminotransferase	< 42 U/L	–	29.0	–	–	–			
Serum uric acid	200 – 420 µmol/L	–	370	–	–	–			567
Serum urea	3.3 – 7.5 mmol/L						3.3		
Serum creatinine	62 – 120 µmol/L						54		
Serum sodium	3.5 – 5.1 mmol/L						4.5		
Serum potassium	135 – 145 mmol/L						139		
Growth hormone (basal)	6 – 15 mIU/L								0.18
Growth hormone (after exercise)	> 20 mIU/L								1.30
Serum follicle-stimulating hormone	1.3 – 19.3 IU/L								3.6
Serum luteinizing hormone	1.2 – 7.8 IU/L								10.4

Abbreviations: ref, reference; HBA1C, hemoglobin A1c; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; T4, free levorotatory thyroxine; FSH, follicle-stimulating hormone; MCHC, mean corpuscular hemoglobin concentration.

in Table. The karyotyping report revealed that he had mosaic trisomy 16, specifically 47,XY + 16 [12]/46,XY [08] (see Figure 2).

The finding of mosaicism in this patient was unexpected, as it did not align with his symptoms. Two months after his initial visit, he was prescribed metformin (500 mg, twice daily), dietary modifications for anemia, exercise, psychiatric

Figure 1. Timeline of Patient's Age During Follow-ups



Abbreviation: yo, years old.

All lab results are presented in the Table.

counseling for autism and behavioral issues, and further lab tests (fasting blood sugar, hemoglobin A1c, uric acid, alanine aminotransferase, vitamin D, and cortisol). Based on his lab results, he was given vitamin D injections and continued on metformin. A month later, his thyroid and fasting glucose levels were normal but insulin remained elevated, leading to an increase in his metformin dosage to 750 mg and continued vitamin D supplementation.

Over time, the patient's weight increased, and he returned with similar complaints. Lab results showed elevated insulin, and metformin was maintained at 750 mg. Later, due to persistent behavioral concerns, a psychiatrist prescribed Adablizer. A year ago, after presenting with aggression, obesity, and hand pain, he underwent tests for bone age, thyroid function, testosterone, and was referred to a neurologist. Despite some improvement in labs, elevated glucose and insulin levels led to adjustments in his treatment, including metformin and vitamin D.

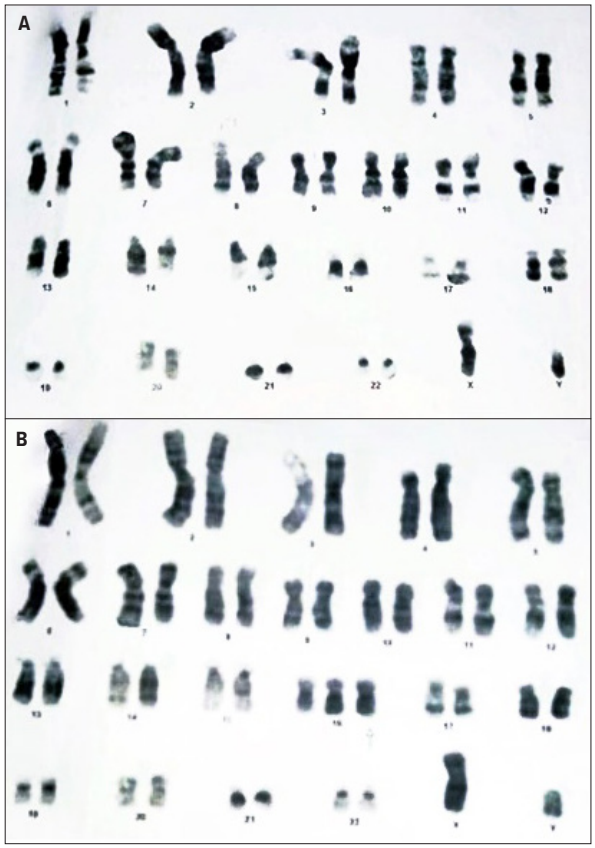
DISCUSSION

In this case report, the patient received a diagnosis of trisomy 16 mosaicism after birth at the age of 10, confirmed through blood karyotyping. Excluding earlier cases identified before chromosome banding techniques were available, there are just five documented cases of trisomy 16 mosaicism diagnosed postnatally. The limited number of cases makes it challenging to predict a specific phenotype, and establishing a clear connection between genotype-phenotype, the degree of mosaicism, and the severity of symptoms remains difficult.[5] The effects of trisomy 16 mosaicism can range widely, from neonatal loss to a relatively mild phenotype with normal development. In between these extremes, individuals may experience issues such as intrauterine growth restriction, preterm birth, aortic coarctation, craniofacial differences, orofacial clefts, heart defects, kidney dysplasia, imperforate anus, and various other anomalies.[3,5-10] Patients with trisomy 16 mosaicism experience a wide range of outcomes, highlighting the diverse nature of mosaic chromosome abnormalities.[5]

Our patient, a school-aged child, presented with mild to moderate clinical features not typical of mosaic trisomy 16. He showed rapid growth (height and BMI above the 99th percentile), small genitalia, bilateral gynecomastia, and aggressive behavior later diagnosed as autism spectrum disorder. Lab results indicated insulin resistance and signs of metabolic syndrome. There was no significant prenatal history, though he had delayed developmental milestones. Initially suspected of having Klinefelter syndrome, a cytogenetic study confirmed mosaic trisomy 16. These clinical features had not been associated with mosaic trisomy 16 before and may result from an undiagnosed recessive condition linked to a parental mutation on another chromosome.

As mentioned in previous studies, there are numerous instances of children with mosaic trisomy 16 who have been diagnosed with a normal phenotype and have shown positive long-term outcomes, with many of them attending school.[5,9-11] In fact, in about 20% of cases, pregnancy outcome is absolutely normal,[7] which points to the existence of bias in publications, with more severe and complicated cases of mosaic trisomy receiving disproportionately higher interest in published literature.[5,9] This also suggests that mosaic trisomy 16 is underdiagnosed. Many cases, such as the one reported in Ousager et al,[10] Rieubland et al,[5] and our case were missed prenatally and, even at birth, and were diagnosed later.

Figure 2. Patient`s Karyotype Showing Trisomy 16 Mosaicism



A. Normal karyotype with 46 chromosomes.
B. Trisomy 16 with 47 chromosomes.

CONCLUSIONS

In summary, we shared a case of mosaic trisomy 16 that presents clinical features distinct from those previously documented. Confirming this diagnosis can be beneficial for parents considering future pregnancies. Additionally, further research on the long-term outcomes and clinical characteristics of mosaic trisomy cases is needed to enhance our understanding of mosaic trisomy 16 syndrome.

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