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BRIEF COMMUNICATION

Unusual Presentations of Trisomy 21

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Abstract Trisomy 21 is the most common aneuploidy in liveborn infants. Most of the soft markers for trisomy 21 are non-specific and transient. We present 2 cases which had abnormalities which are very rarely associated with Down's syndrome. In the first case, the patient had bilateral congenital cataract along with an absent nasal bone. In the second case, the patient had severe asymmetric fetal growth restriction at 20 weeks with other multi-system abnormalities. With detailed ultrasound scanning and thorough investigation, we could diagnose trisomy 21 even with such unusual presentations.

Keywords Trisomy 21 · Congenital cataract · Severe fetal growth restriction · Down's syndrome · Aneuploidy · Karyotype

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Introduction

Chromosomal abnormalities occur in 0.1–0.2% of live births and the most common aneuploidy among live born infants is trisomy 21 (Down's syndrome) [1].

The soft markers associated with trisomy 21 are:

1st Trimester: increased nuchal transluscency, absent/hypoplastic nasal bone, reduced, absent or reversal of "a" wave in the ductus venosus and tricuspid regurgitation.

2nd Trimester: increased nuchal fold thickness, echogenic intracardiac focus, ventriculomegaly, echogenic bowel, shortened femur and humerus, pyelectasis and an aberrant right subclavian artery (ARSA).

We present case reports of two fetuses who had abnormalities which are very rarely associated with Down's syndrome.

Case 1

Mrs XYZ, 28 year old primigravida came at 22 weeks of pregnancy for her routine anomaly scan to the Department of Fetal Medicine, New Civil Hospital, Surat. She did not have any relevant past or family history of any congenital disorder or congenital cataract in family. She had no previous ultrasound scans done.

On the anomalies scan we observed: A prominent coronary sinus in the cardiac 4 chamber view, 4 vessels in the 3 vessel view with one vessel on the left of the pulmonary artery suggestive of persistence left SVC, absent nasal bone in the facial profile view (Fig. 1a) and bilateral extremely dense echogenic lenses suggestive of congenital cataracts (Fig. 1b). No other anomaly was detected in the detailed anomaly scan.

2nd trimester ultrasound based risk for trisomy 21 was 1 in 168.

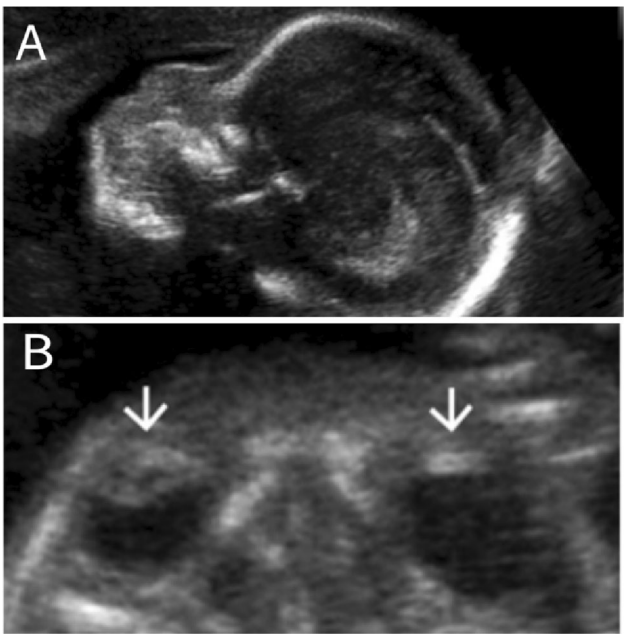


Fig. 1 **a** Facial profile showing absent nasal bone. **b** Orbits showing bilateral cataract

Suspecting congenital infection to be the cause of congenital cataract and in view of the increased risk of trisomy 21, the couple was counseled for amniocentesis.

TORCH Panel PCR was done which was negative for rubella and other infections.

Fetal karyotype was positive for trisomy 21 (Fig. 2).

TORCH PANEL BY DNA PCR

Specimen Description: Sample quality is optimum for the test.

TEST	RESULT	REF. RANGE
Toxoplasma PCR	Not Detected	Not Detected
Rubella PCR	Not Detected	Not Detected
CMV PCR	Not Detected	Not Detected
HSV Type 1 PCR	Not Detected	Not Detected
HSV Type 2 PCR	Not Detected	Not Detected

COMMENTS : Sample is Negative by DNA amplification for TORCH Panel.

CHROMOSOME ANALYSIS

Specimen description : Sample quality is optimum for the test.

CYTOGENETICS REPORT

METAPHASES COUNTED	: 20	CULTURE TYPE	: FIBROBLAST CULTURE
METAPHASES ANALYZED	: 20	BANDING TECHNIQUE	: GTG
METAPHASES KARYOTYPED	: 10	BANDING RESOLUTION	: 400

RESULTS

KARYOTYPE : 47,-,+21

COMMENTS : The karyotype report is enclosed herewith and is abnormal.

There is an extra chromosome 21 found in all the metaphases studied. Such chromosome complement is associated with Down syndrome.

RECURRENCE : After the diagnosis of a child with trisomy, the recurrence risk for future pregnancies is about 1% when the mother is under 30 years of age. For women who are over 30 years old, the risk is based on age.

Fig. 2 Result of TORCH panel and karyotype of amniotic fluid

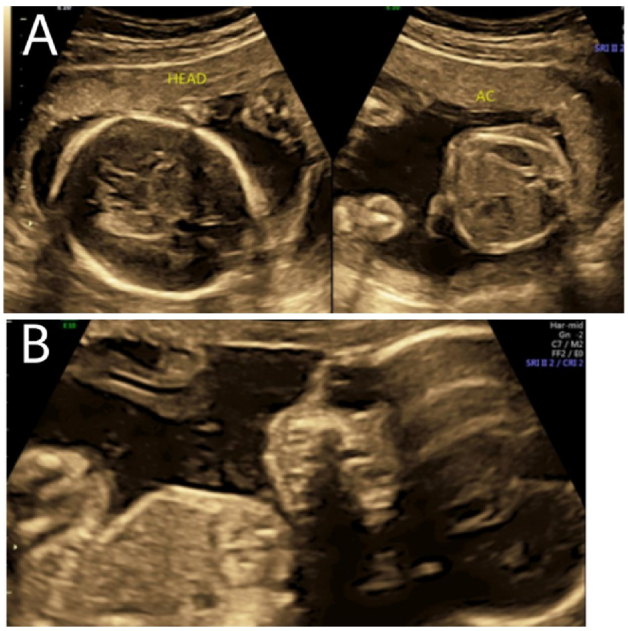


Fig. 3 **a** Striking disparity between abdominal circumference and head circumference. **b** Fetal overview showing big head and small abdomen

Case 2

A 23 year old primigravida presented for a second opinion anomaly scan at 20 weeks. She had no significant past or family history. There was no history of consanguineous marriage. Her antenatal period was uneventful.

Her anomaly scan showed severe asymmetric fetal growth restrictions with an abdominal circumference lag of 4 weeks (Fig. 3a, b), micrognathia with wide set protruding eyes (Fig. 4a), inferior vermian hypoplasia (Fig. 4b), small echogenic kidneys and unilateral right talipes (Fig. 4c). Maternal and fetal doppler were normal.

Based on the above finding of severe early asymmetric IUGR, Fetal triploidy was suspected. The couple was counseled for amniocentesis and prenatal testing. In view of unfavourable prognosis the couple decided to terminate pregnancy. Karyotype of the abortus was suggestive of trisomy 21 (Fig. 5).

Discussion

Case 1

The incidence of congenital cataract in neonates ranges from 1 to 6 in 10,000 live births [2]. Congenital infection (especially rubella, toxoplasmosis and cytomegalovirus) are found in 30% of cases of congenital cataract. Genetic syndromes are found only in 10% of cases. The outcome of

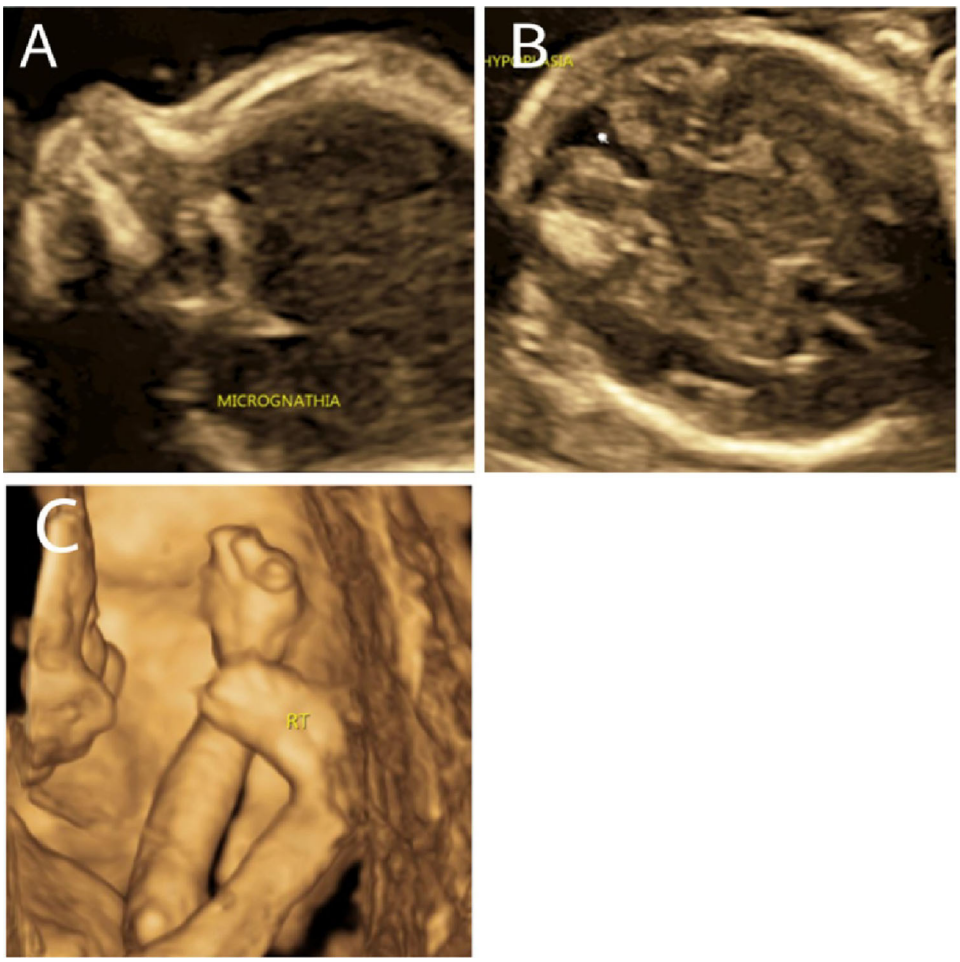


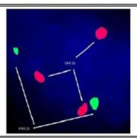
Fig. 4 **a** Facial profile showing micrognathia. **b** Posterior fossa showing vermian hypoplasia. **c** Right talipes

Fig. 5 Karyotype of abortus

CHROMOSOME ANALYSIS (FISH)

FISH INVESTIGATION FOR	:	Aneuploidy detection of chromosomes 13, 18, 21, X and Y.
METHOD	:	By Fluorescence in situ Hybridization (FISH)
PROBES USED	:	Vysis AneuVysion DNA probe kit for chromosome 13, 18, 21, X and Y.

RESULTS



	1ST HYBRIDIZATION (LSI)		NO. OF CELLS ANALYZED	INTERPRETATION
	GREEN	ORANGE		
Chromosome	13	21		
SIGNALS PER CELL	2	3	25	TRISOMY 21

2 Green and 3 Orange signals in each cell show normal diploid status for chromosome 13 and TRISOMY OF CHROMOSOME 21 respectively.

	2ND HYBRIDIZATION (CEP)		NO. OF CELLS ANALYZED	INTERPRETATION
	AQUA (Blue)	--		
Chromosome	18	SEX CHROMOSOMES		
SIGNALS PER CELL	2	2	25	Normal

2 Aqua (Blue) signals show normal diploid status for chromosome 18. (Sex chromosomes signals not shown.)

RESULT : nuc ish 13q14(RB1×2)[25],nuc ish(SE18×2)[25],nuc ish 21q22(D21S65×3)[25]

INTERPRETATION : Trisomy 21 found in all the interphase cells studied.

LIMITATIONS OF FISH : *FISH is used to quickly rule out the most common chromosomal abnormalities i.e. Trisomy 13, 18, 21 and numerical sex chromosome disorders within 2-3 days. The accuracy of this test is about 99%. Structural abnormalities like translocations, deletions and abnormalities of other chromosomes cannot be ruled out by FISH. Cytogenetics should be carried out for this.*

fetuses with congenital cataract depends on the associated syndrome. Our suspicion of congenital rubella infection as the leading cause of congenital cataract in a developing country was obvious, however the rubella PCR reports suggested otherwise.

The first antenatal diagnosis of congenital cataract in Down's syndrome was reported by Romain et al. [3] in 1999. They reported a case of a 45 year old woman who underwent amniocentesis for advanced maternal age which indicated trisomy 21. Subsequently, the fetus developed congenital cataract at 24 weeks.

The frequency of diagnosing congenital cataract in a fetus with trisomy 21 is only 1 out of 700 cases of Down's syndrome [4]. A thorough routine examination of the fetal face and orbits contribute towards this rare association.

Case 2

The patient was referred for a second opinion anomaly scan. The patient had no soft markers which are routinely associated with trisomy 21. Severe asymmetric early-onset FGR made it highly suspicious for triploidy. The karyotype of trisomy 21 was unusual.

Genetic causes contribute to 5–20% of FGR, especially in early onset growth restricted fetuses. Genetic causes include triploidy, trisomy 18,13,16 and 21. Out of these, trisomy 18 is associated with a more severe FGR compared to trisomy 13 or 21 [5].

Early onset FGR or severe asymmetric FGR is not a common feature of Down's syndrome. Chromosomal anomalies most commonly associated with early onset FGR are trisomy 13,18, Triploidy, Chromosome 4p deletion syndrome and chromosome 12p tetrasomy [6]. Additionally, submicroscopic chromosomal anomalies (22q11.2 microduplication syndrome) and single gene disorders (often associated with minimal ultrasound findings) are most commonly associated with early and severe fetal growth restriction [7].

Non-placental mediated growth restricted fetuses include those with structural and chromosomal/genetic anomalies (trisomies 13 and 18; genetic conditions such as Russel Silver syndrome), congenital infections (rubella, cytomegalovirus, toxoplasmosis) and inborn errors of metabolism [8].

Literature suggests that early onset asymmetric FGR is not routinely associated with trisomy 21, which makes this case a very rare one.

A detailed protocol based survey of fetal anatomy with a high level of suspicion for aneuploidies and invasive testing facilitate a diagnosis of chromosomal anomalies like trisomy 21 even when they have a very unusual presentation.

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