Egyptian Journal of Radiology and Nuclear Medicine

CASE REPORT

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Prenatal imaging and whole-exome sequencing identify novel tetratricopeptide repeat domain 7A mutation in foetus with gastrointestinal atresia: a case report

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Abstract

Background: Tetratricopeptide repeat domain 7A (*TTC7A*, chromosome 2p21) is a highly conserved structural motif essential for multiprotein scaffolding and cell survival. Fewer than 60 cases of *TTC7A* deficiency have been reported globally. It produces multisystemic disease phenotypes which are lethal in two-thirds of patients, with a median survival age of 12 months. It is predominantly detected postnatally, often rendering medical and surgical interventions futile.

Case presentation: We report the antenatal sonographic and magnetic resonance imaging characteristics of a novel phenotype of *TTC7A*-deficiency presenting with gastrointestinal atresia. This has never been previously documented. The diagnosis was confirmed via whole-exome next-generation sequencing, thus facilitating prompt initiation of management and prolonging viability.

Conclusions: Novel insight into the prenatal morphological characteristics of *TTC7A*-deficiency phenotypes expands knowledge of this rare condition. Furthermore, antenatal recognition facilitates targeted investigation, genetic counselling, and earlier multidisciplinary intervention to prolong viability of this predominantly lethal condition.

Keywords: Foetal imaging, Intestinal atresia, *TTC7A* mutation, Genotype–phenotype correlation, Whole-exome sequencing, Case report

Background

Tetratricopeptide repeat domain 7A (*TTC7A*, chromosome 2p21) is a highly conserved structural motif essential for multiprotein scaffolding. It is imperative in maintaining cell haemostasis, polarity, signalling, immune dynamics, and survival. Autosomal recessive mutations in *TTC7A* produce rare multisystemic disease phenotypes associated with significant morbidity and mortality [1, 2]. Heterogeneous gastrointestinal and immunological disease manifestations include multiple intestinal atresia, very early onset inflammatory bowel disease, aberrant intestinal villi architecture, apoptotic enterocolitis, and profound primary or combined immunodeficiency. There are often associated extraintestinal features related to the hair and skin [2].

To date, fewer than 60 cases of *TTC7A* deficiency, with over 20 distinct disease-causing mutations, have been reported globally [3]. *TTC7A* dysfunction is lethal in two-thirds of patients, with a median survival age of 12 months [1–3]. It is predominantly detected postnatally at which point medical and surgical interventions

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are often deemed futile. These include immunoglobulin infusion, haematopoietic stem cell transplantation, enterectomy, and/or organ transplant. Here, we describe a unique case of a *TTC7A*-deficiency phenotype detected on antenatal imaging and confirmed postnatally via whole-exome next-generation sequencing, thus facilitating prompt initiation of management and prolonging viability.

Case presentation

A healthy 33-year-old gravida 4 para 1–1 woman conceived her fourth pregnancy through in vitro fertilisation. She was in a consanguineous relationship with a second cousin—they had no family history of genetic or chromosomal disorders. The patient had no comorbidities and no prior surgical procedures. She had previously experienced a foetal death in utero at 35 weeks of gestation secondary to acute parvovirus infection. She had never smoked, consumed alcohol, or used illicit substances. She had no known hazardous environmental exposures. This current pregnancy was high risk for aneuploidy on combined first trimester screening (Trisomy 13:112, Trisomy 18 1:50, Trisomy 21 1:142, nuchal translucency 3.7 mm, Free βHCG 1.34 MoM, PAPP-A 1.98 MoM, PLGF 1.12 MoM). Maternal serum testing for cystic fibrosis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex viruses were negative. The patient initially declined further invasive and non-invasive prenatal testing as she intended to continue the pregnancy regardless of any findings. She opted for serial image-based monitoring.

Fortnightly foetal anatomy ultrasound scans from 20 to 24 weeks of gestation demonstrated non-progressive moderate small bowel dilation (7-12 mm) and echogenicity within the bowel tissue consistent with a blockage in the distal small bowel (Fig. 1). Amniotic fluid index (AFI), foetal Doppler measurements, and foetal movements remained reassuring and within normal limits throughout. At 26 weeks of gestation, there was an acute reduction in small bowel dilation to less than 3 mm, an increase in echo-free intra-abdominal fluid, and reduced peristalsis on obstetric ultrasound (Fig. 1). Subsequent foetal magnetic resonance imaging (MRI) confirmed a moderate volume of ascites coupled with decreased small bowel dilation (Fig. 2). This was suggestive of a bowel perforation, stenosis, and/or atresia of the proximal ascending colon. Mild cerebral ventricle asymmetry was simultaneously noted with no significant ventriculomegaly. Between 28 and 31 weeks of gestation, absent peristalsis and a gradual increase in echo-free ascites with free loops of small bowel in the intra-abdominal fluid were observed on serial ultrasound scans (Fig. 3).

Postulated underlying aetiologies (including metabolic disorders, infection, rare chromosomal pathologies), management options, and prognoses were routinely and extensively discussed with the patient in a multidisciplinary environment. Genetic counsellors noted the unusual anatomical features and hypothesised an underlying metabolic storage disorder such as Niemann–Pick disease or trisomy 21 with erythroblastic component which could only be confirmed postpartum. Paediatric surgeons deemed intrauterine scope and surgery unnecessarily risky in the setting of uncertain aetiology and recommended postnatal surgical review. The potential for unforeseen and sudden stillbirth was discussed with the patient. She was informed to seek immediate medical attention if she experienced reduced or absent foetal movements.

Amniocentesis and prenatal array studies at 32 weeks of gestation, following foetal corticosteroid coverage, were performed: no abnormalities or infections were detected. At 33 weeks of gestation, the mother developed acute symptomatic polyhydramnios characterised by dyspnoea and generalised abdominal pain. There was a simultaneous increase in foetal ascites raising suspicion for mirror syndrome. Amniodrainage of 1400 ml of fluid reduced AFI from 35 to 27 cm and was sent for DNA storage testing. The antenatal course was further complicated at 34 weeks of gestation by pregnancy-induced hypothyroidism and obstetric cholestasis. The mother was admitted for monitoring, serial bloods, daily ursodeoxycholic acid, and twice daily cardiotocography. Delivery via caesarean section was scheduled for 36 weeks of gestation in coordination with obstetricians, anaesthetists, neonatal intensivists, and paediatric surgeons.

An uncomplicated caesarean section for pathological cardiotocography following preterm labour was performed at 35 + 3 weeks of gestation. A live 3600 g female infant with Apgar scores of 3, 7, and 9 at 1, 5, and 10 min of age was delivered and admitted to the neonatal intensive care unit. The newborn had absent bowel sounds, abdominal distention secondary to 500 ml of ascites, and severe mid-to-distal gastrointestinal atresia. At three days old, she received a stoma with total parenteral nutrition. She was not suitable for small bowel transplant due to profound combined immunocompromise. The infant received palliative care and succumbed to rhinovirus infection at 8 months of age.

Next-generation whole-exome sequencing of neonatal DNA on the Illumina NextSeq Sequencing System uncovered a homozygous pathogenic variant of the *TTC7A* gene on chromosome 2p21 (OMIM 609,332; c.1404delG). This causes an autosomal recessive immunodeficiency

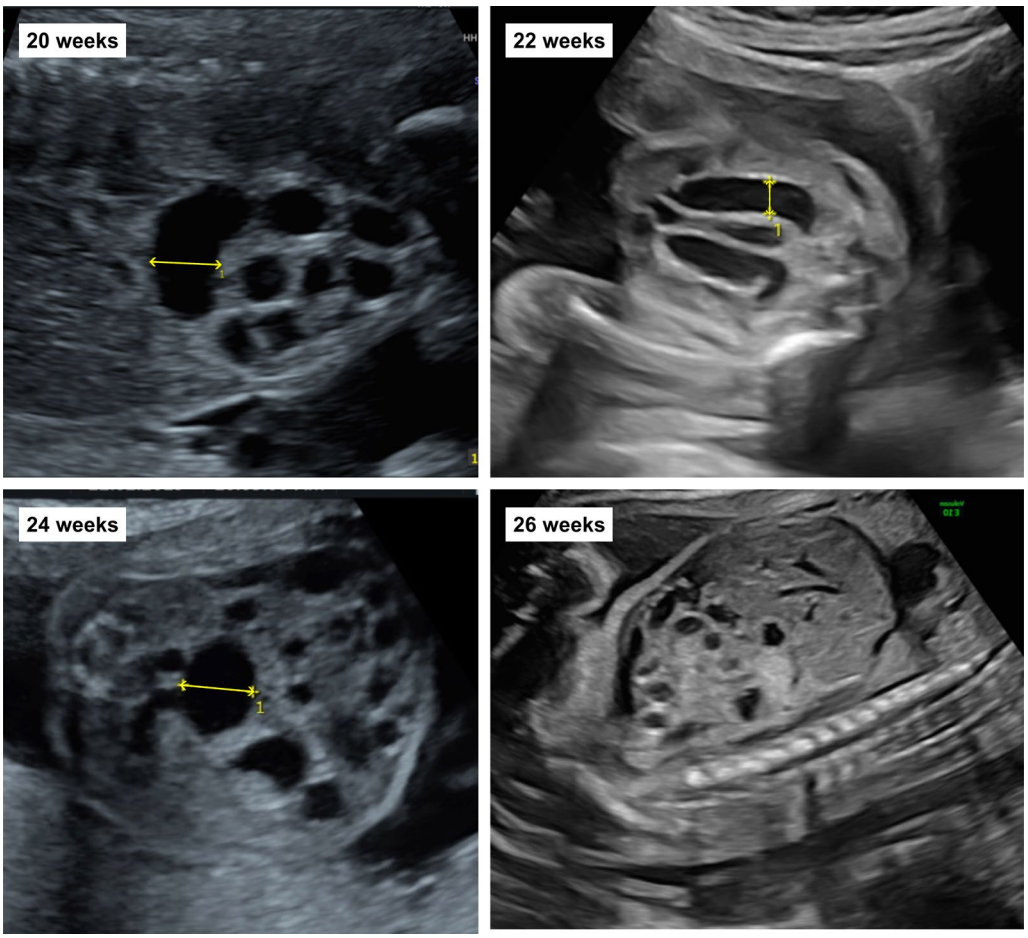

Fig. 1 Grayscale serial foetal morphology ultrasound scan images. 20 weeks of gestation: dilated small bowel (7-10 mm; yellow resonance arrow) and echogenicity within the bowel tissue. 22 weeks of gestation: persistent yet non-progressive small bowel dilation (8-10 mm). Overall stable foetal interval growth, foetal movements, and amniotic fluid index. 24 weeks of gestation: increase in small bowel dilation to 12 mm with mild oedema of the bowel tissue. 26 weeks of gestation: significant and acute reduction in small bowel dilation to 2-3 mm. There is no obvious peristalsis in the proximal gastrointestinal tract but echo-free fluid streaming within the bowel lumen is visualised. The stomach is normal with no polyhydramnios

syndrome with gastrointestinal defects. Our case is the fifty-third to ever be formally reported worldwide.

Discussion

Our case identified a novel deleterious biallelic mutation in tetratricopeptide repeat domain 7A (*TTC7A*, chromosome 2p21) using whole-exome sequencing. The associated gastrointestinal phenotype was documented antenatally using foetal morphology imaging. TTC7A is a highly conserved structural motif essential for multiprotein scaffolding. It is imperative in maintaining cell haemostasis and survival. Autosomal recessive mutations in *TTC7A* produce rare multisystemic disease phenotypes associated with significant morbidity and mortality [1, 2]. Heterogeneous gastrointestinal and immunological disease manifestations include multiple intestinal atresia, very early onset inflammatory bowel disease, aberrant intestinal villi architecture, apoptotic enterocolitis, and profound primary or combined immunodeficiency [2]. There are often associated extraintestinal features related to the hair and skin [2].

The pathophysiology of *TTC7A* deficiency is gradually being ascertained. TTC7A mediates multiprotein scaffolding to chaperone the enzyme phosphatidylinositol-4-kinase-3-α to the plasma membrane of gastrointestinal epithelial cells. Here, it catalyses the synthesis of phosphorylated phosphatidylinositol (PI4P) [4–6]. TTC7A deficiency produces subthreshold levels of PI4P which disrupts epithelial cell polarity, tight junction formation, signalling, and haemostasis. Subsequent cell apoptosis impairs gastrointestinal tract integrity and enables foreign antigen translocation into the lamina propria. An

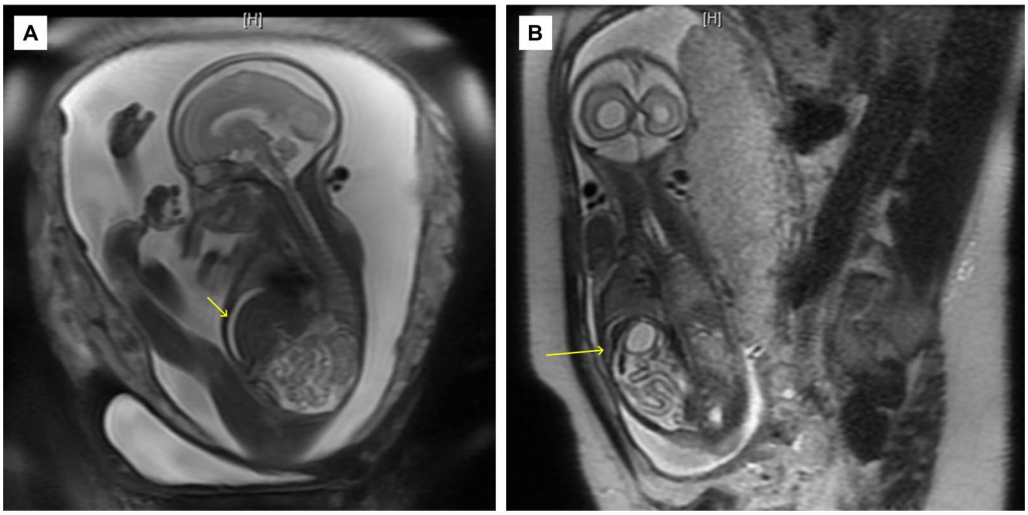

Fig. 2 Foetal magnetic resonance imaging (MRI) at 27 weeks of gestation. **A**: Axial MRI of fluid-filled loops of small bowels noted. There is a moderate volume of ascites with fluid overlying the liver (yellow arrow). **B**: Coronal MRI of a tubular structure containing high T1 signal at the inferior margin of the right hepatic lobe (yellow arrow). This is consistent with ascending colon atresia, stenosis, and/or perforation. There is no meconium visualised distal to this point. Mild cerebral ventricle asymmetry noted with no significant ventriculomegaly

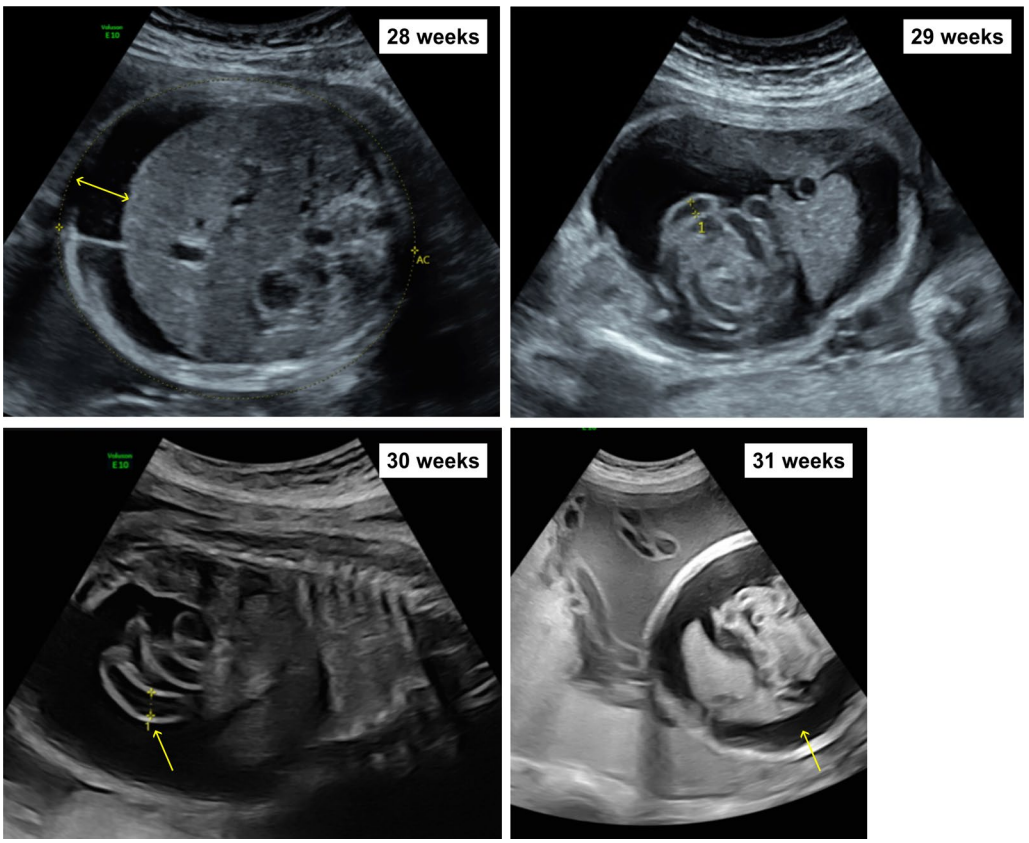

Fig. 3 Grayscale serial foetal morphology ultrasound scan images. 28 weeks of gestation: Increased ascites (16 mm, yellow resonance arrow) in the abdominal cavity coupled with decreased small bowel dimensions (2-3 mm) consistent with bowel perforation. 29 weeks of gestation: Foetal appearance is unchanged with persistent large volume of free fluid in the abdominal cavity. 30 weeks of gestation: Volume of echo-free ascites significantly increased with free loops of small bowel seen floating within it (yellow arrow). The picture is unusual for a bowel perforation and raised further suspicion for atresia secondary to an underlying metabolic or chromosomal disorder. 31 weeks of gestation: Ascites further increased with acute concurrent rise in amniotic fluid index (23 cm) and hepatomegaly

oedematous inflammatory response ensues which obliterates the underlying anatomy [1]. This manifests as altered peristalsis, bowel distention or obstruction, ascites, and eventual necrosis and/or atresia [1–3, 7, 8]. We demonstrated this disease process and associated pathological features on antenatal imaging. These characteristics include small bowel dilation followed by acute reduction, an increase in echo-free intra-abdominal fluid, aberrant peristalsis, and generalised gastrointestinal oedema.

Published literature on TTC7A deficiency is sparse. Since 2013, only 53 genetically confirmed cases with over 20 distinct disease-causing mutations have been documented globally [1–3, 7, 9, 10]. All were diagnosed postnatally, contributing to delayed onset of management and a high infant mortality rate (~70%). *TTC7A* dysfunction is lethal in two-thirds of patients, with a median survival age of 12 months [1–3]. Surgical and medical management options have been trialled with varying degrees of improved viability and quality of life. These interventions include early total enterectomy, organ transplant, parenteral nutrition, haematopoietic stem cell transplant, immunosuppressives, steroids, biologics, and prophylactic immunoglobulins and antibiotics [1, 3, 9, 10]. Due to the pleiotropic nature of TTC7A deficiency, the establishment of set standards of care is ongoing.

Conclusions

TTC7A deficiency is a rare, and often lethal, multisystemic condition inherited in a monogenic autosomal recessive manner. Our case highlights key morphological characteristics of TTC7A deficiency that may be detected on routine foetal imaging. This knowledge facilitates antenatal recognition, thus enabling earlier multidisciplinary intervention to preserve gastrointestinal and immune function. It also provides insight into phenotype–genotype correlations to guide genetic counselling and the development of diagnostic genetic screening or in utero therapy.

Abbreviations

TTC7A: Tetratricopeptide repeat domain 7A; AFI: Amniotic fluid index; MRI: Magnetic resonance imaging; PI4P: Phosphorylated phosphatidylinositol.

Acknowledgements

We thank Dr. N. Luk and Prof. R. Ogle for contributing to the care of this patient and providing the accompanying sonographic and magnetic resonance images. We also thank the patient and her family for allowing us to share their case.

Author contributions

KB contributed to the study conception and design as well as writing the draft and final manuscripts.

Funding

No funding was obtained for this study. The authors received no financial support for the research, authorship, and/or publication of this article. This research did not receive any specific grant.

Availability of data and material

All data generated or analysed during this study are included in this article and are available at the Fetal Medicine Department at The Royal Prince Alfred Hospital, Sydney.

Declarations

Ethics approval and consent to participate

This manuscript is a human case report. Written informed consent was obtained from the study participant.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review on request.

Competing interests

The authors declare that they have no conflict of interest (financial, personal, or otherwise) regarding the publication of this case report.

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Received: 19 April 2022 Accepted: 31 May 2022
Published online: 07 June 2022

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