# Contents

## Weekly Volume 26 Number 15 April 21, 2020

### OPINION REVIEW

**1683** Determining the role for uric acid in non-alcoholic steatohepatitis development and the utility of urate metabolites in diagnosis: An opinion review  
*Brennan P, Clare K, George J, Dillon JF*

### REVIEW

**1691** Torque teno virus in liver diseases: On the way towards unity of view  
*Reshetnyak VI, Maev IV, Burmistrov AI, Chekmazov IA, Karlovich TI*

**1708** Blood-based biomarkers for early detection of esophageal squamous cell carcinoma  
*Chu LY, Peng YH, Weng XF, Xie JJ, Xu YW*

### MINIREVIEWS

**1726** Spontaneous porto-systemic shunts in liver cirrhosis: Clinical and therapeutical aspects  
*Nardelli S, Riggio O, Gioia S, Pazzono M, Pelle G, Ridola L*

**1733** Update on quinolone-containing rescue therapies for *Helicobacter pylori* infection  
*Mori H, Suzuki H*

### ORIGINAL ARTICLE

#### Basic Study

**1745** DNAH17-AS1 promotes pancreatic carcinoma by increasing PPME1 expression via inhibition of miR-432-5p  
*Xu T, Lei T, Li SQ, Mai EH, Ding FH, Niu B*

**1758** PTEN-induced kinase 1-induced dynamin-related protein 1 Ser637 phosphorylation reduces mitochondrial fission and protects against intestinal ischemia reperfusion injury  
*Qasim W, Li Y, Sun RM, Feng DC, Wang ZY, Liu DS, Yao JH, Tian XF*

#### Case Control Study

**1775** Value of long non-coding RNA Rpph1 in esophageal cancer and its effect on cancer cell sensitivity to radiotherapy  
*Li ZY, Li HF, Zhang YY, Zhang XL, Wang B, Liu JT*

#### Retrospective Study

**1792** Prevalence, clinical characteristics, risk factors, and indicators for lean Chinese adults with nonalcoholic fatty liver disease  
*Zeng J, Yang RX, Sun C, Pan Q, Zhang RN, Chen GY, Hu Y, Fan JG*
| Page | Title                                                                                      | Authors                                                                                       |
|------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| 1805 | Validation of the six-and-twelve criteria among patients with hepatocellular carcinoma and performance score 1 receiving transarterial chemoembolization | Wang ZX, Li J, Wang EX, Xia DD, Bai W, Wang QH, Yuan J, Li XM, Niu J, Yin ZX, Xia JL, Fan DM, Han GH |
| 1820 | Chemoprevention of gastric cancer development after *Helicobacter pylori* eradication therapy in an East Asian population: Meta-analysis | Sugimoto M, Murata M, Yamaoka Y                                                              |
| 1841 | Refractory very early-onset inflammatory bowel disease associated with cytosolic isoleucyl-tRNA synthetase deficiency: A case report | Fagbemi A, Newman WG, Tanyge SG, Hughes SM, Cheesman E, Arkwright PD                         |
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Refractory very early-onset inflammatory bowel disease associated with cytosolic isoleucyl-tRNA synthetase deficiency: A case report

Andrew Fagbemi, William G Newman, Stuart G Tangye, Stephen M Hughes, Edmund Cheesman, Peter D Arkwright

BACKGROUND
Aminoacyl tRNA synthetases/ligases (ARSs) are highly conserved enzymes involved in attaching amino acids to tRNA promoting protein synthesis. Although deficiencies of ARSs localized to the mitochondria classically present with neuropathology, the clinical features of cytosolic ARS deficiencies are more variable. They have previously been associated with neonatal hepatitis, but never with early-onset inflammatory bowel disease.

CASE SUMMARY
A nine-year-old Bangladeshi boy presented with neonatal liver failure and deranged clotting, transaminitis and cholestasis. His parents were first cousins. Two older brothers and a sister were well. The patient suffered from loose stools from early infancy which became more troublesome and persistent from five.
A child aged 3 years old with ten bloody motions a day. Repeated endoscopies showed persistent pancolitis, which was refractory to mesalazine, corticosteroids, azathioprine, sirolimus and anti-TNF (adalimumab) therapy, but has improved recently with subcutaneous methotrexate. Whole Genome Sequencing revealed a novel pathogenic missense variant (c.290A > G) in the cytosolic isoleucyl-tRNA synthetase gene, leading to an amino acid substitution (p.Asp97Gly). Pathogenic variants in other genes associated with inflammatory bowel disease (IBD) (ADAM17, EGFR, FOXP3, IL10RA, IL10RB, IL21R, NCF4, STAT3) were excluded. Cytokine assays demonstrated markedly elevated IL-2, IL-5, IL-13, IL-9 and IL-10 by the patient’s CD4+ T-cells, while IL-17A, IL-17F, IFNβ were lower, and TNFα not significantly different when compared to healthy controls.

**CONCLUSION**

This case report provides evidence that recessive mutations in cytosolic isoleucyl-tRNA synthetase are a novel monogenic cause of IBD, which should be considered, particularly in infants and children with a history of neonatal hepatitis and very early-onset IBD poorly responsive to treatment.

**Key words:** Inflammatory bowel disease; Hepatitis; Gene; Cytosolic isoleucine tRNA synthase

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Core tip: Consider cytosolic isoleucyl-tRNA synthetase in children presenting with neonatal hepatitis and refractory very early-onset inflammatory bowel disease. This case report provides evidence for a novel monogenic cause of inflammatory bowel disease that should be considered, particularly in patients with very early-onset, poor response to treatment and a history of neonatal hepatitis.

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**INTRODUCTION**

Aminoacyl tRNA synthetases/ligases (ARSs) are a group of 20 ubiquitously expressed, highly conserved enzymes involved in attaching each specific amino acid to a tRNA to promote protein synthesis. ARS deficiencies localized to the mitochondria have been known for 40 years and classically present with lactic acidosis, encephalopathy, failure to thrive and global developmental delay. Clinical features of cytosolic ARS deficiency are more variable[1,2]. In 2016, three unrelated individuals harboring compound homozygous variants in cytosolic isoleucyl-tRNA synthetase (IARS) [p.(Arg418)(Ile1174Asn), p.(Arg254)(Pro437Leu) and p.(Val370Gly)(Asn992Asp) (MIM: 600709)] were reported[3]. The patients suffered growth and developmental delay, sensorineural hearing loss, muscular hypotonia, diabetes mellitus, hepatic dysfunction with steatosis and fibrosis, and zinc deficiency. A further individual with compound heterozygous for the missense substitutions p.(Arg739Cys)(Phe556Ser) with microcephaly, growth and developmental delay and neonatal cholestasis was described in 2017[4] and a seven year old boy compound heterozygous for p.(Gln671fs)(Thr69Ile) has also been reported with hepatopathy, hypotonia, intellectual disability and growth retardation[5,6]. Here, we present a child with cytosolic IARS deficiency, whose main clinical feature was refractory inflammatory bowel disease (IBD), hitherto not previously described in other patients with IARS deficiency.
CASE PRESENTATION

Chief complaints
A nine-year-old Bangladeshi boy born in the United Kingdom presented with poor feeding, weight loss, drowsiness due to neonatal liver failure with deranged clotting, transaminitis and cholestasis.

History of present illness
The patient suffered from loose stools from early infancy and was commenced on an amino acid formula from the age of two months with initial improvement. His diarrhea has been much more troublesome since the age of five years old with ten bloody stools a day.

History of past illness
The patient was free from other medical history.

Personal and family history
His parents were first cousins. Two older brothers and a sister were well.

Physical examination
On examination, he was microcephalic, with normal weight, height and gross motor development. He was clubbed with mild hepatomegaly.

Laboratory examinations
Serum orosomucoid concentration was persistently raised [1736–2685 mg/L (normal range 300–1200 mg/L)], as was his ESR [28–140 mm/h (normal range 4–10 mm/h)]. C-reactive protein was normal. Since the neonatal period, his liver function tests, including gamma-glutamyl transferase have been normal. Fecal calprotectin is intermittently elevated (peak 393 mcg/g), although the latest level is normal at 50 mcg/g. Plasma zinc concentration was normal at 17.2 mol/L (10–18 mol/L).

Imaging examinations
Abdominal ultrasound showed no signs of hepatosplenomegaly, but the liver had diffusely increased echogenicity consistent with fatty change, possibly related to weight gain associated with chronic corticosteroid use.

Further diagnostic work-up
Liver biopsy showed hydropic degeneration of hepatocytes (Figure 1A). There was no evidence of mitochondrial DNA depletion and plasma lactate was normal. Repeated endoscopy at 6, 7 and 8 years old showed persistent chronic inflammation in the cecum, and pancolitis with diffuse inflammation, superficial ulceration, distortion of the crypt architecture and crypt abscess formation, in a distribution similar to that found in ulcerative colitis (Figure 1B). There were no inflammatory changes in the esophagus, stomach and duodenum, nor were there any granuloma to suggest Crohn’s disease.

In view of the very early-onset of the disease and its poor response to immunosuppressive medication, an underlying genetic cause was considered. Whole genome sequencing performed as part of the United Kingdom 100000 Genome Project revealed a homozygous c.290A > G, p.(Asp97Gly) variant in cytosolic IARS (encoded by IARS1, NM_013417). Parents were both heterozygous as were two unaffected siblings with the other unaffected sibling wild type. The variant was absent in the gnomAD database of about 140000 controls and scored by in silico predictors (MutationTaster 0.99; CADD score 32) to be pathogenic. The aspartic acid residue at this position is conserved to Caenorhabditis elegans and the variant lies in the IleRS core domain, where other disease-causing variants have been identified[7]. Variants in other genes associated with IBD (ADAM17, EGFR, FOXP3, IL10RA, IL10RB, IL21R, NCF4, STAT3) were screened and no potentially pathogenic variants were found.

Immune phenotyping was determined by flow cytometry. Mucosal-associated invariant T-cells cell and natural killer cell frequencies were reduced, comprising < 0.2 and 1% of lymphocytes, respectively (range: 1%–15%). Greater than 60% of the patient’s CD4+ and CD8+ T cells were of a naïve phenotype, reflecting the young age of the patient. T-cells, total B-cells as well as B-cell subsets (transitional, naïve, memory, class switching) were within normal range. Release of Th1, Th2, Th17 and Treg pathway cytokines (IL-2, IL-4, IL-5, IL-9, IL-10, IL-13, IL-17A, IL-17F, TNFa and IFNβ) that may be deranged in IBD were assayed by cytotometric bead array (Becton Dickinson) after 5-d stimulation of purified memory CD4+ T cells with anti-CD2/CD3/CD28 monoclonal antibodies. Secretion of some inflammatory (IL-2, IL-5, IL-13, IL-9) and immune regulatory (IL-10) cytokines by the patient memory CD4+ T-
Figure 1  Histology and blood leukocyte cytokine profile of patient with cytosolic isoleucyl-tRNA synthetase deficiency. A: Liver histology showing hydropic change, but no classic apoptosis of the hepatocytes; B: Pancolitis, with diffuse increase in inflammatory cells, cryptitis and crypt abscess formation. High power insert: A few apoptotic epithelial cells seen, but within normal limits, c/cytokine profile; C: Cytokine secretion from peripheral blood leukocytes of patient with isoleucyl-tRNA synthetase deficiency compared with healthy donor. HD: Healthy donor; IARS: Isoleucyl-tRNA synthetase.

cells was markedly elevated, while IL-17A, IL-17F, IFNβ were lower and TNFα not significantly different compared to healthy donors (Figure 1C).

**FINAL DIAGNOSIS**

Transient neonatal hepatitis and refractory very early-onset IBD due to cytosolic isoleucyl-tRNA synthetase.

**TREATMENT**

His IBD was refractory to additional zinc supplementation, as well as immune modulation with mesalazine, corticosteroids, azathioprine, sirolimus and anti-TNF therapy (adalimumab). Recent treatment with subcutaneous methotrexate has led to reduction in his stool frequency to 4 – 5 stools/d with no blood or mucous.

**OUTCOME AND FOLLOW-UP**

Nine-year-old boy with chronic IBD (ten bloody watery stools/day and abdominal pain) despite normal plasma zinc concentration and most standard immune modulatory therapy. His symptoms have recently improved with the addition of subcutaneous methotrexate. Vedolizumab infusions are being considered as a further steroid-sparing immunomodulator. Informed written consent was obtained to report on this case from the child’s parents.

**DISCUSSION**

This is the first report of a homozygous variant in cytosolic IARS associated with refractory very early-onset IBD. The fact that this variant is novel, is predicted to
result in an amino acid substitution from aspartate to glycine at a highly conserved residue, and segregates with the phenotype in the family, indicates that it is disease causing. Supportive evidence from additional cases and functional enzyme assays would be helpful in definitively confirming the role of the IARS gene in very early-onset IBD. Assays are unfortunately not currently available. This case report will hopefully lead to additional patients with very early-onset IBD due to variants in the IARS gene being reported by other clinicians.

ARSs may be associated with T-cell dysfunction[8,9] as seen in our patient, but the lack of improvement with most immunsuppressant drugs suggests that other inflammatory pathways are involved. The high IL-10 level is in keeping with an ineffectual compensatory Treg response rather than a defect in this pathway. There is some suggestion that sirolimus, which blocks mammalian target of rapamycin complex 1 may ameliorate the disease, but use of sirolimus in our patient made no difference to his clinical course[8,9].

Maintaining optimal zinc levels may also help optimize aminoacyl-tRNA synthetase activity, but our patient had normal plasma zinc concentrations and zinc supplements did not help ameliorate his IBD. It is possible that there are defects in cell turnover and resultant barrier dysfunction of gut mucosa leading to microbe-induced inflammation particularly in the colon. Broad-spectrum antibiotics may help for severe exacerbations.

CONCLUSION

This case report provides evidence for a novel monogenic cause of IBD that should be considered, particularly in patients with very early-onset, poor response to treatment and a history of neonatal hepatitis.

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