CASE REPORT

Treatment for tuberculosis in a patient with Dubin-Johnson syndrome

Meena Alpana,¹ Mradul Kumar Daga,² Sunita Aggarwal,² Anand Nidhi¹

¹Department of Internal Medicine, Maulana Azad Medical College, New Delhi, India

²Department of Medicine, Maulana Azad Medical College, New Delhi, India

Correspondence to
Dr Meena Alpana, alpana.meena@outlook.com

Accepted 27 July 2015

SUMMARY

Dubin-Johnson syndrome (DJS) is an autosomal recessive disorder characterised by conjugated hyperbilirubinemia resulting from mutations of ABCC2/MRP2 gene. The beneficial effects of ursodeoxycholic acid (UDCA) and rifampicin were found to be complementary in the treatment of cholestatic liver disease secondary to DJS. We present a case of a young woman with tubercular meningitis. She was started on modified antitubercular therapy in view of conjugated hyperbilirubinemia. However, reinitiation of rifampicin resulted in redevelopment of jaundice. Liver biopsy was suggestive of DJS. The patient was started on rifampicin along with UDCA. There was improvement in hyperbilirubinemia and a full course of antituberculous therapy without further worsening of the disorder was possible. This is a rare case of DJS with tuberculosis, showing beneficial effects of rifampicin and UDCA combination therapy, which so far has been considered doubtful. It is uncertain what the level of efficacy of therapy is in various MRP2 gene mutations.

BACKGROUND

Dubin-Johnson syndrome is a rare autosomal recessive disorder characterised by chronic predominantly conjugated hyperbilirubinemia. This syndrome results from absence of ABCC2/MRP2 protein in the canalicular hepatocyte membrane because of mutations of ABCC2/MRP2 gene.¹ The combination therapy of rifampicin and ursodeoxycholic acid (UDCA) has been postulated to be complementary in treatment of cholestatic liver disease.² However, there are few studies documenting such effect. We present a case of Dubin-Johnson syndrome with tubercular meningitis showing significant therapeutic and symptomatic improvement of hyperbilirubinemia and cure of tuberculosis.

CASE PRESENTATION

A 35-year-old woman presented to the emergency room with high-grade intermittent fever of 15 days duration, associated with jaundice for the past 7 days. She had a history of one episode of generalised tonic-clonic seizure followed by alteration of sensorium. There were associated symptoms of headache, nausea, vomiting and photophobia. There was no history of abdominal pain, or bladder or bowel disturbances. The patient did not have a history of bleeding from any site, or rashes or insect bite.

There was a history of recurrent jaundice during two conceived pregnancies, which resolved after

delivery. There was no history of tuberculosis, blood transfusion, drug abuse or addiction.

On examination, the general condition of the patient was poor. Blood pressure was 126/70 mm Hg, pulse 72 bpm, temperature 100.6°F. On general physical examination, hirsutism was noted and icterus was present. No clubbing, cyanosis, pallor or lymphadenopathy was noted. Respiratory and cardiovascular system examination was normal. On neurological examination, the patient was in an altered state and agitated, with neck rigidity; Kernig's sign was positive. Tone, power, and deep and superficial reflexes were normal. Fundus showed evidence of papilloedema. No cranial nerve deficit was noted. Abdomen examination was negative for organomegaly or free fluid.

INVESTIGATIONS

Investigations revealed haemoglobin of 10.1 g/dL, white cell count 6400 cu mm³, platelet count 1.85 cu mm³ and erythrocyte sedimentation rate 18 mm/h (0–15 mm/h). Liver function panel showed conjugated hyperbilirubinemia (total bilirubin of 5.5 mg/dL (0.3–1.3 mg/dL) and direct bilirubin 3.7 mg/dL (0.1–0.4 mg/dL)), alanine transaminase 34 U/L (7–41 U/L), aspartate transaminase 57 U/L (12–38 U/L) and alkaline phosphatase 252 U/L (non-pregnancy: 33–96 U/L). Serum total protein and albumin were 6.9 mg/dL (6.7–8.6 g/dL) and 2.9 mg/dL (3.5–5.5 g/dL), respectively. Serum urea was 16 mg/dL (7–20 mg/dL), creatinine 0.6 mg/dL (0.5–1.2 mg/dL), serum total calcium 10.1 mg/dL (8.7–10.2 mg/dL) and phosphate 3.6 mg/dL (2.5–4.3 mg/dL). A lumbar puncture was performed to rule out meningitis, and revealed a total cell count of 160, which was predominantly lymphocytic with raised protein of 224 mg/dL (15–50 mg/dL), and was tested positive for TB-PCR. Chest X-ray was suggestive of miliary pattern of tuberculosis in the lungs. Ultrasound of the abdomen was normal. Brain MRI revealed early hydrocephalous with increased leptomeningeal enhancement along basal cisterns and tentorium.

Gene mutation data and urinary coproporphyrin isomer excretion could not be assessed due to non-availability of resources.

TREATMENT

The patient was started on modified antitubercular treatment because of deranged liver panel, with ethambutol, levofloxacin and streptomycin along with cerebral decongestants. She improved symptomatically over a month and liver function tests

CrossMark

To cite: Alpana M, Daga MK, Aggarwal S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211123

returned to normal levels. Isoniazid was subsequently reintroduced, with the patient tolerating it well. However, on reintroduction of rifampicin, her liver function deranged again in the form of conjugated hyperbilirubinemia (a rise from total bilirubin of 1.1–4.2 mg/dL and direct bilirubin rise from 0.4 to 3.2 mg/dL) with normal enzymes.

The patient was further evaluated for isolated conjugated hyperbilirubinemia. Serum ceruloplasmin, antinuclear antibody, antiliver–kidney microsome type 1 (LKM1), smooth muscle autoantibodies, antineutrophil cytoplasmic antibodies, HbsAg, antihepatitis C virus and HIV 1&2 were negative; 24 h urinary copper was normal; serum luteinising hormone, follicle-stimulating hormone and testosterone levels were also normal.

The patient underwent a liver biopsy for a definitive diagnosis, which was highly suggestive of Dubin-Johnson syndrome (figure 1).

On the basis of the results of the liver biopsy and clinical disease, the treating physicians were faced with a dilemma of starting a novel therapy with rifampicin and UDCA. Considering the limitation of resources at our centre, where MRP2 gene mutation testing could not be conducted, the possibility of initiating this therapy was discussed, explaining its pros and cons to the patient's guardians. After obtaining their positive consent, the decision of starting the therapy was made.

As the patient's bilirubinaemia settled, isoniazid was again reintroduced followed by rifampicin along with UDCA. The patient was kept under close watch for any declining liver function tests and ultrasound of the abdomen was repeated initially weekly for 3 weeks followed by once monthly.

OUTCOME AND FOLLOW-UP

The patient improved symptomatically, in terms of improved appetite and weight gain, and she became afebrile. There were no signs or symptoms of worsening of disease. She completed

her therapy for disseminated tuberculosis successfully without redevelopment of jaundice.

DISCUSSION

Dubin-Johnson syndrome is an autosomal recessive disorder that is caused by a mutation in the gene responsible for the human canalicular multispecific organic anion transporter (cMOAT) protein.^{1 3} It is also called MRP2. This protein mediates ATP-dependent transport of certain organic anions across the canalicular membrane of the hepatocyte. A defect in cMOAT (MRP2) protein results in the impaired hepatobiliary transport of non-bile salt organic anions and is thought to be responsible for conjugated hyperbilirubinemia and for the accumulation of hepatocellular pigment. Most patients are asymptomatic. Subclinical cases can become evident during pregnancy, use of contraceptive pills or intercurrent illness. Dubin-Johnson syndrome is a benign disorder and does not require any specific therapy.

UDCA and rifampicin have both been used as treatments for cholestasis and appear to act partly by nuclear receptor-mediated changes in gene expression. UDCA improves biochemical indices of cholestasis, namely, serum alkaline phosphatase activity, bilirubin and primary bile acids. UDCA lowers the biliary cholesterol saturation index by stimulating the expression of the canalicular phospholipid transporter ABCB4/MDR3. UDCA also stimulates CYP3A4/CYP3A11 expression in human hepatocytes, while CYP7A1, the key enzyme system for bile acid synthesis, is downregulated.⁴ Rifampicin is known to interfere with hepatic elimination of endogenous compounds and xenobiotics, because of substrate of ABCC2. However, it is one of the first-line drugs of antitubercular therapy, necessitating its use in the current case. Furthermore, rifampicin also enhances bile acid detoxification as well as bilirubin conjugation and excretion, as reflected by increased expression of CYP3A4, UGT1A1 and MRP2.² In patients with chronic cholestatic diseases, rifampicin improves pruritus and decreases serum concentrations of bile acids and bilirubin. The beneficial effects of rifampicin and UDCA were therefore complementary in the treatment of cholestatic disease. However, considering the adverse effects of this combination therapy in patients with impaired MRP2 expression, a genetic study to identify MRP2 mutation is advisable to guide for response to therapy.⁵

Learning points

- ▶ Dubin-Johnson syndrome is a rare disease and its treatment poses a great challenge in serious illnesses and pregnancy.
- ▶ This is a rare case showing the additive effects of rifampicin and ursodeoxycholic acid in management of tubercular meningitis in a patient with Dubin-Johnson syndrome.
- ▶ It is uncertain what the level of efficacy of therapy is in various MRP2 gene mutations.

Contributors MA is the chief author and investigator of this case report and takes full responsibility for its final submission. AN proofread the report. MKD and SA supervised, proofread and guided in the management of the patient and writing of the report.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Figure 1 (A) Patient liver biopsy showing multiple areas of granulated pigment. (B) Fontana-Masson stain.

REFERENCES

- 1 Paulusma CC, Kool M, Bosma PJ, *et al.* A mutation in the human canalicular multispecific organic anion transporter gene causes the Dubin-Johnson syndrome. *Hepatology* 1997;25:1539–42.
- 2 Marschall HU, Wagner M, Zollner G, *et al.* Complementary stimulation of hepatobiliary transport and detoxification systems by rifampicin and ursodeoxycholic acid in humans. *Gastroenterology* 2005;129:476–85.
- 3 Toh S, Wada M, Uchiyama T, *et al.* Genomic structure of the canalicular multispecific organic anion-transporter gene (MRP2/cMOAT) and mutations in the ATP-binding-cassette region in Dubin-Johnson syndrome. *Am J Hum Genet* 1999;64:739–46.
- 4 Fickert P, Zollner G, Fuchsichler A, *et al.* Effects of ursodeoxycholic and cholic acid feeding on hepatocellular transporter expression in mouse liver. *Gastroenterology* 2001;121:170–83.
- 5 Corpechot C, Ping C, Wendum D, *et al.* Identification of a novel 974C-->G nonsense mutation of the MRP2/ABCC2 gene in a patient with Dubin-Johnson syndrome and analysis of the effects of rifampicin and ursodeoxycholic acid on serum bilirubin and bile acids. *Am J Gastroenterol* 2006;101:2427–32.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow