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A novel case report of benign recurrent intrahepatic cholestasis-associated USP53 genetic mutation in a Pakistani girl

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Abstract

Benign recurrent intrahepatic cholestasis is an autosomal recessive disorder presenting with intermittent episodes of cholestatic jaundice. The initial episode of benign recurrent intrahepatic cholestasis tends to occur within the first two decades of a patient's life. Episodes can occur unprompted but can often be precipitated by infections or pregnancy. We report an interesting case of a 13-year-old girl presented with recurrent intrahepatic cholestasis. The patient has a unique homozygous USP53 genetic mutation, the first patient to present with this mutation within the South Asian region. The patient was initially misdiagnosed as a case of autoimmune hepatitis, and when presenting to our set-up was diagnosed as a case of benign recurrent intrahepatic cholestasis. The patient has since been managed on medication and remains regular in follow-up, responding well to treatment.

Keywords

Paediatrics, gastroenterology/hepatology, USP53, BRIC, novel mutation

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Introduction

Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive disorder presenting with intermittent episodes of cholestatic jaundice. The emergence of genetic testing has served to reclassify the cholestatic diseases. There are certain genetic mutations, namely ATP8B1 (BRIC1; OMIM # 24330) and ABCB11 (BRIC2; OMIM #605479), that are commonly associated with BRIC.[1] Both mutations cause cholestasis by impeding the function of the bile export pump, which actively transports bile into canaliculi. The USP53 (OMIM * 617431) is an emerging mutation, considered to sway a paradigm toward an increasing number of patients presenting with BRIC.[2]

Familial intrahepatic cholestasis can be divided into three groups, namely BRIC, progressive familial intrahepatic cholestasis (PFIC) and intrahepatic cholestasis of pregnancy. BRIC is a rare disorder characterized by the unusual presentation of recurrent episodes of cholestatic jaundice with no resultant liver damage.[3] The initial episode of BRIC tends to occur within the first two decades of a patient's life. Episodes can occur unprompted but can often be precipitated by infections or pregnancy. The duration of each episode can vary from weeks to months.[4] The diagnostic criteria as proposed by Luketic and Shiffman can be utilized to ascertain BRIC at the presenting illness. It delineates at least two episodes of jaundice separated by a symptom-free interval lasting several months to years; laboratory values consistent with intrahepatic cholestasis; severe pruritus secondary to cholestasis, liver-histology demonstrating centrilobular cholestasis; normal intrahepatic and extrahepatic bile ducts confirmed by cholangiography and absence of factors known to be associated with cholestasis, (i.e., drugs, pregnancy).[5]

Episodes that persist for longer periods with no intervention can lead to the development of coagulopathies and haemorrhagic tendencies due to vitamin K malabsorption.[3] The resolution of these episodes is indicated by the unanticipated and instantaneous cessation of anorexia and pruritus followed by the more gradual tapering of jaundice. Symptoms presentation tends to differ across patients but remains

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Table 1. Timeline of events preceding the diagnosis of BRIC.

Episodes	Date (DD/MM/YYYY)	Age of onset	Triggers	Duration (weeks)	Severity	Period till the next episode (month)
1	15-October-2022	12	Unknown	4	Moderate	~1
2	27-November-2022	12	Unknown	5	Severe	~3
3	05-February-2023	12	Viral illness	4	Severe	~1
4	14-March-2023	12	Acute gastritis	6	Mild	~1
5	08-April-2023	13	Fever	5	Moderate	~1
6	07-August-2023	13	Unknown	6	Mild	~4

BRIC: Benign recurrent intrahepatic cholestasis.

accordant to episodes within the same individual.[6] The hallmark of BRIC and other familial causes of intrahepatic cholestasis is that Gamma Glutamyl Transferase (GGT) remains normal or mildly elevated along with increased serum bilirubin and alkaline phosphatase.[7] GGT release is linked to cholangiocyte damage that is often caused by increasing levels of toxic bile salts within the bile.

Liver biopsies during episodes shows centrilobular cholestasis with bile deposition in canaliculi, hepatocytes and Kupffer's cells. Additionally, hepatocyte degeneration, necrosis, portal and parenchymal inflammation may also be seen. The resulting changes completely settle on their own between episodes.[5] Genetic testing is often utilized for further corroboration and assertion of the disease.[8]

We report an interesting case of an adolescent girl presented with recurrent intrahepatic cholestasis. The patient has a unique homozygous USP53 genetic mutation, the first patient to present with this mutation within the South Asian region.

Case report

A 13-year-old female child, being treated as 'autoimmune hepatitis' for 6 years at another facility, presented to our Emergency Room with complaints of jaundice, vomiting, generalized body itching, abdominal pain and loose stools for the past 2 weeks. The episode of jaundice started abruptly and was progressively worsening. She also had non-bilious, non-projectile vomiting containing food particles. There had been a total of seven episodes that occurred over the course of 2 weeks. Additionally, she had abdominal pain, loose chalky stools along with dark urine. She also complained of generalized body itching and fatigue.

A diagnosis of autoimmune hepatitis was made about 6 years ago when she presented with an episode of similar complaints. The family reported recurrent episodes of jaundice since she was 6 years of age. These typically tended to start abruptly, last for a few weeks, gradually increase and resolve spontaneously with no residual symptoms. There was usually a jaundice-free interval that lasted for a few months. This interval had been progressively decreasing based on the frequency of hospital visits (refer to Table 1). It was based on clinical judgement and an autoimmune profile which showed anti-LC1 antibodies to be borderline positive was done at a peripheral lab with a substandard set-up. All other causes of liver disease were ruled out including viral hepatitis and Wilson's disease was ruled out by normal serum ceruloplasmin and normal 24-h urinary copper. Anti-smooth muscle antibody was weakly positive. Serum IgG was within normal limits. Family history is positive for jaundice and gallstones on the maternal side. The parents are in a consanguineous marriage. On further interviewing, medical history revealed that the patient had been on steroids for the past 5 years, and the dose was increased whenever she had an incidence of jaundice and then it was tapered off. Azathioprine and ursodeoxycholic acid were added to her medications 2 months ago.

Examination revealed a Cushingoid face and buffalo hump. Scleral icterus was noticed, and the skin was yellow. Scratch marks were observed all over her body, especially on her limbs. Abdominal examination revealed stria on inspection. Generalized tenderness was appreciated on palpation. The patient reported an increase in pain while palpating the right upper quadrant. The liver was mildly enlarged on palpation. She was afebrile and vitally stable. Abdominal ultrasound revealed a slightly enlarged liver with fatty infiltration and an absent gallbladder owing to a cholecystectomy done 2 years ago. Her laboratory workup is shown in Table 2.

The patient was managed conservatively and was discharged once the symptoms resolved. However, she kept presenting to the hospital with similar complaints until 8 months later when her symptoms were reassessed. The diagnosis of autoimmune hepatitis was questioned because of the pattern of jaundice, cholestatic findings of the laboratory reports. A repeat autoimmune profile was done at our tertiary care set-up, with the appropriate lab equipment. It relayed a negative autoimmune profile (refer to Table 3), thus directing our diagnosis away from autoimmune hepatitis. A liver biopsy was advised but was not carried out. Genetic testing of the whole exome sequence revealed a homozygous USP53 mapped to 4q26 mutation confirming the diagnosis of BRIC. The child was put on Rifampin 150 mg once a day and Ursodeoxycholic acid 250 mg twice daily and steroids were slowly tapered off. The child responded well to treatment.

Table 2. Laboratory values during episodes of cholestasis.

Laboratory workup	Reference range	15/10/22	27/11/22	05/02/2023	14/03/2023	08/04/23	07/08/23
LFTs							
SGOT (U/L)	⩽32	43	38	40	54	64	59
SGPT (U/L)	⩽33	16	21	23	26	35	49
Alkaline phosphate (U/L)	⩽468	661	508	507	576	491	543
Total bilirubin (mg/dL)	⩽1.2	34.82	6.63	5.86	17.93	8.79	5.07
Direct bilirubin (mg/dL)	⩽0.30	31.86	4.86	4.51	13.38	7.22	4.69
Gamma G.T. (U/L)	⩽40	21	22	22	21	19	24
CBC							
WBC (/μL)	4000–10500	10990	12,020	10,880	9940	10,320	8650
RBC (m/μL)	3.8–5.8	5.19	4.44	5.21	5.18	5	5.24
Haemoglobin (g/dL)	12.0–15.0	13.3	12.3	12.5	13.1	12.7	13.6
HCT (%)	35–45	39.7	38.4	39.7	40.6	39.9	40.9
MCV (fL)	78–95	76.5	86.5	76.2	78.4	79.8	78.1
MCH (pg)	26–32	25.6	27.7	24	25.3	25.4	26
MCHC (g/dL)	32–36	33.5	32	31.5	32.3	31.8	33.3
Platelets (/μL)	150,000–400,000	507,000	431,000	437,000	551,000	544,000	386,000
Neutrophils (%)	50–60	76	69	66	65	60	48
Lymphocytes (%)	35–40	14	22	25	25	32	41
Monocytes (%)	1–4	6	7	5	7	5	8
Eosinophils (%)	1–2	4	2	3	3	3	3
Basophils (%)	0–0.75	0	0	1	0	0	0
RDW (%)	11.5–14.0	20.9	15.4	19.1	20	13.2	13.8
Haematology							
Prothrombin time (s)	9.5–11.5	30.2					
INR (internalised normal ratio) (s)	0.8–1.3	2.74					

At her last clinical visit, Cushingoid features have begun to resolve and the time between episodes has increased. The patient is showing signs of improvement with the medical management ascribed to her.

Reference ranges are per the patient's age and gender.

Table 3. Immunological investigations.

Immunological investigation	
Celiac disease predisposing HLA (DQ2/DQ8) autoantibodies	Negative
Deaminated gliadin peptideantibody IgA	Negative
Deaminated gliadin peptideantibody IgG	Negative
T – transglutaminase IgA antibody	Negative
T – transglutaminase IgG antibody	Negative
Serum endomysial IgA	Negative
Anti AMA-M2 antibodies	Negative
Anti M2-3E antibodies	Negative
Anti Sp100 antibodies	Negative
Anti PML antibodies	Negative
Anti gp210 antibodies	Negative
Anti LKM-1 antibodies	Negative
Anti LC-1 antibodies	Borderline
Anti SLA/LP antibodies	Negative
Anti Ro-52 antibodies	Negative

Discussion

This is the first patient presenting with a novel USP53 genetic mutation within the South Asian region, confirming the diagnosis of BRIC. There is limited data available on the incidence of BRIC. Case reports have mentioned patients with recurrent episodes of normal GGT cholestasis for which there were no associated precipitating factors.[8] Our patient had episodes similar to the ones described in the literature and subsequently underwent a cholecystectomy due to sludge present in the gallbladder. The hallmark of BRIC is that GGT remains normal is evident from the liver function tests of our patient. When reviewing scholarship reporting USP53-associated BRIC, patients were seen to have normal GGT similarly.[2,9] (refer to Table 4)

USP53 is affiliated to a family of ubiquitin-specific proteases that may uniquely contribute to progressive liver disease. Mutations in USP53 have in very recent literature been associated with early-onset cholestasis.[10] In mice, USP53 has been indicated to approximate and interact with Tjp2 (ZO-2). TJPs are cytoplasmic proteins that seem to link intrinsic membrane-tight junction proteins to the cytoskeleton.[8] Variants of TJP2 have been foregrounded to present within a spectrum of liver phenotypes, from familial hyperchloremia to severe and progressive cholestatic liver disease.[11]

Table 4. A literature review depicting patients with USP53 Associated BRIC summarized in a table.

Authors	Age of patient	Gender of patient	Country	Year of publication	Clinical presentation
Ateş et al.[9]	16 years	Male	Turkey	2023	He presented with a normal serum GGT level while having repeated episodes of cholestasis since the age of 6 months.
Alhebbi et al.[2]	4 months	Male	Japan	2020	The patient presented in a coma. On further examination, he was found to have a cerebral haemorrhage. He had a normal GGT level coupled with itching.
Alhebbi et al.[2]	7 years	Male	Japan	2020	The patient presented at the age of 18 months with the complaints of repeated episodes of jaundice and itching. He was found to have a normal GGT. level. These episodes came on after the patient had suffered from an infection and would resolve after treatment with ursodeoxycholic acid.
Alhebbi et al.[2]	6 months	Female	Japan	2020	The patient presented to the hospital with jaundice and itching. She had normal GGT levels. Her condition resolved after treatment with ursodeoxycholic acid

BRIC: Benign recurrent intrahepatic cholestasis; GGT: Gamma Glutamyl Transferase.

A prospective cross-sectional study was done on neonates presenting with cholestasis in a tertiary care centre in Pakistan.[12] This singular study delineates how an increasing trend is seen in the prevalence of PFIC within the Pakistani population. An amalgam of factors was found to contribute to the spectrum of cholestasis prevalent in this region. Among genetic and metabolic etiologies, PFIC was found to be the leading cause, followed by galactosemia and neonatal iron storage disease. Other causes were grouped into idiopathic neonatal hepatitis, obstructive, infectious and endocrine causes.[12] Knowledge and awareness of BRIC are of particular importance because of the lack of research publications and documentation within this region. It poses a worrying advent regarding misdiagnoses. Genetic testing has revolutionized diagnosis; as indicated by the initial misdiagnosis of the child with autoimmune hepatitis.

To make a diagnosis of BRIC an autoimmune profile tends not to be required.[5] Anti-LC1 antibodies which were found to be borderline positive in our patient were suggestive of a possible diagnosis of autoimmune hepatitis. Our literature review, however, found that a positive Anti-LC1 antibody, rather than a borderline positivity is associated with autoimmune hepatitis type 2. Henceforth, a borderline positivity is non-specific to establishing a diagnosis of autoimmune hepatitis, further directing us to the final diagnosis of BRIC for this patient.[13]

Supportive treatment is initiated to relieve episodes and pre-empt further complications. It is well postulated that bile acid retention can lead to pruritus, which is often seen in patients with BRIC. Episodes that persist for longer periods with no intervention can lead to the development of coagulopathies due to vitamin K malabsorption.[14] This is evident in the deranged INR of our patient which was later resolved after supplementation with vitamin K. Cholestyramine limits the number of bile acids circulating in the body by binding to them and enhancing the amount excreted through the faeces. Rifampin reduces bile acid concentrations within the hepatocytes, reducing pruritus.[15] During periods of exacerbation, rifampicin causes an alleviation of symptoms and ameliorates biochemical parameters. Rifampicin is henceforth, comfortably considered first-line therapy.[16] BRIC is benign in nature, with no progression to end-stage liver disease.[17] It is imperative that patients be counselled accordingly, with special emphasis on how without treatment a recurrence and exacerbation in episodes of BRIC can be seen.

Conclusion

The study underscores an interesting case of a 13-year-old girl presenting as a case of BRIC caused by a novel USP53 genetic mutation. BRIC remains a disease that is sparsely researched and published in the Pakistani population. An amalgam of factors can contribute to this, primarily limitations associated with awareness, knowledge and the ability to diagnose the rare condition. Further research is required to elaborate on the intricacies involved with BRIC, its diagnosis, prognosis and treatment options. Our reported case serves to supplement, augment and enrich discourse about this scarcely reported condition.

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Author contributions

T.E.K. Manuscript write-up; reference writing; editing and proofreading; S.F. Manuscript write-up; reference writing;

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Informed consent

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