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DIAGNOSTIC DILEMMA OF BENIGN RECURRENT INTRAHEPATIC CHOLESTASIS IN PAPUA NEW GUINEA: A CASE REPORT

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ABSTRACT:
The first reported case of Benign Recurrent Intrahepatic Cholestasis (BRIC) in the South Pacific region proved to be a major clinical challenge at the Port Moresby General Hospital in Papua New Guinea. Given the rarity of the disease, it took over a decade of nonspecific medical interventions and patient distress before an actual diagnosis was made and appropriate treatment administered. The patient endured five bouts of the debilitating cholestatic episodes ranging from periods of three to six months durations prior to actual diagnosis of the disease condition was made. Diagnosis was based on pathognomic clinical presentations and the laboratory exclusion of other related conditions. Anti-cholestatic treatment combinations for BRIC administered during a sixth cholestatic episode had remarkable response. Subsequent pre-icteric symptoms were effectively managed with a periodic treatment protocol with resultant patient been symptom free for over a period of ten years to date (2007 – 2018). The positive management outcome of this case has established a better preventative therapeutic approach for BRIC.

Keywords: Benign recurrent intrahepatic cholestasis, jaundice,
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INTRODUCTION:

Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive disorder characterized by recurring episodes of cholestatic jaundice and pruritus [1]. Symptoms resolve spontaneously without any significant liver damage. This syndrome was first described by Summerskill and Walshe in 1959 [2], and further reports described its characteristic early onset in 80% of the cases [3]. By 2009 there have were about 100 cases reported around the world [4, 5]. Follow-up cases from 17 to 50 years have shown lack of progression to end stage liver disease [6-8]. These recurring episodes which vary from a couple of weeks up to six months have had significantly detrimental effects on the quality of life of the patients.

Based on the genetic mutations two forms of BRIC have been reported. BRIC1 has a single gene mutation on *ATP8B1*, an aminophospholipid transporter, while BRIC2 involves a mutation in *ABCB11*, a bile salt exporter pump [9, 10]. In contrast, more severe phenotypes called progressive familial intrahepatic cholestasis types 1 and 2 (PFIC1 and PFIC2), which have mutations on the same genes with severe deficiencies of the transporters and tend to cause chronic end-stage liver damage which is fatal [4, 11]. BRIC is usually diagnosed after excluding PFICs and all other possible causes of hyperbilirubinaemia and elevated liver enzymes, coupled with the pathognomic clinical manifestations of recurrent jaundice and pruritus with intervals of total clinical and biochemical remission [12]. We report a case of adult onset of BRIC in Papua New Guinea (PNG) that proved to be a diagnostic dilemma and furthermore, report on the establishment of an effective non-invasive treatment approach.

CASE REPORT:

In 2007, a 33 year-old male who was asymptomatic presented to the Medical Science Research Centre, at the School of Medicine and Health Sciences, University of Papua New Guinea, with a prior history of five episodes of recurrent jaundice, associated with severe pruritus, impaired sleep, dark urine and pale stool. Each attack had lasted between 3 to 6 months with intervals of 1- 4 years of complete clinical and biochemical remission. During the first 4 episodes between 1996 and 2003, he was managed by a team of surgeons in collaboration with physicians both in PNG and Australia as a case of "cholestasis of unknown origin" as no possible cause could be determined after series of routine biochemical, radiological and surgical tests. As such, trials of steroids, antibiotics and vitamin K were administered with no clinical or biochemical response. Hence, he was just observed in-hospital until clinical remission and discharge on all occasions.

The initial episodic attack occurred at the age of 20 years in 1996, prior to which he had an uneventful childhood and adolescence. During all the attacks (the initial five) the laboratory results for Liver Function Tests (LFT) showed markedly elevated transaminases and total bilirubin with predominant conjugated bilirubin (Table 1). The haemoglobin results were normal (between 14.4 to 16.5 g/dL), with normal Activated Partial Prothrombin Time *(*APTT) and prothrombin time (PT). Viral Hepatitis A and B, Human immunodeficiency virus (HIV), Coombs test and alpha fetoprotein were all negative; thus possible infective, autoimmune or malignant causes were excluded. Ultrasound reports showed stones in the gall bladder with no signs of obstruction in the billiary tree and a normal echotexture of the liver. These findings were further confirmed by CAT scan in 2003 following a fourth cholestatic episode. During the fourth attack in 2003, he

re-presented to the Greenslopes Private Hospital in Brisbane, Australia, where he had an endoscopic cholescystectomy done because of the presence of gall bladder stones despite any evidence of obstruction. A liver biopsy also done showed diffuse bile plugging but no associated parenchymal damage or inflammation and was reported to be in favour of early extrahepatocytic cholestasis. The patient had a fifth cholestatic attack in 2005 which lasted for several months.

Table 1: Peak values of liver function tests for the patient during each episode of BRIC and the response to treatment.

Parameters LFT	**Normal values**	***Episodes: Year & Month***					
		1: 1996 Nov	2: 1998 Dec	3: 1999 Nov	4: 2003 Nov	5: 2005 Nov	6: 2008 Mar
Total Bilirubin (µmol/L)	**2-22**	410	530.7	87.7	14	112	53
Conjugated Bilirubin (µmol/L)	**0-14**	309	502	69.4	4.2	97	40
ALP* (U/L)	**24-168**	90	113	71	59	128	78
AST# (U/L)	**30-50**	60	1136	57	44	219	86
ALT§ (U/L)	**30-50**	47	1428	128	127	468	136
GGTΨ (U/L)	**12-58**	ND	ND	ND	36	191	60
PT ♠ (seconds)	**12**	13	ND	ND	ND	ND	ND
APTT@ (seconds)	**32**	36	ND	ND	ND	ND	ND

Liver Function Tests (LFT); *Alkaline Phosphatase (ALP), #Aspartate Transaminase (AST), §Alanine Transaminase (ALT), ΨGamma Glutamate Transpeptidase (GGT), ♠Prothrombin Time (PT), @Activated Partial Prothrombin Time (APTT), Not Done (ND)

The 2008 attack (sixth episode) occurred during the course of our investigations. Physical examination revealed deep jaundice with pronounced scleral icterus, increased skin pigmentation and generalised excoriations secondary to severe pruritic itching. He had no signs of spider naevi, palmar erythema, thenar atrophy to suggest hepatocellular failure. Laboratory analysis showed elevated levels of bilirubin and transaminases (Table 1). Genetic screening for *ATP8B1* and *ABCB11* did not reveal any mutations for PFIC1 or PFIC2 on the hot spots suggesting a mutation in other sites not screened. Hence, fulfilling the Tygstrup Diagnostic Criteria [13] based on the pathognomic clinical manifestations and biopsy results the patient was diagnosed and managed as a case of BRIC. Patient was commenced on a combination of Ursodeoxycholic acid (UDCA) and Rifampicin

that was well tolerated; after one month of treatment the laboratory results and clinical examination of the patient showed marked improvement (Table 2).

Table 2: Depicting the Liver function Test parameters and the initiation, duration and response for treatment of the sixth episodic attack.

LFT	Weekly dates on which patient was initially commenced on treatment						
	Week 1 (4/4/08)	Week 2 (1/5/08)	Week 3 (7/5/08)	Week 4 (13/5/08)	Week 5 (21/5/08)	Week 6 (18/6/08)	Week 7 (15/7/08)
T/Protein (g/L)	80	ND	ND	79	76	74	74
Albumin (g/L)	39	35	35	36	39	40	42
AST (U/L)	86	41	ND	45	55	27	21
ALT (U/L)	136	39	31	41	39	19	20
ALP (U/L)	78	80	84	77	69	45	40
GGT (U/L)	60	ND	ND	49	64	32	20
T/Bil (µmol/L)	53	479	444	332	191	42	19
Conj/ Bil (µmol/L)	ND	ND	ND	308	ND	20	15

Liver Function Tests (LFT); Alkaline Phosphatase (ALP), Aspartate Transaminase (AST), Alanine Transaminase (ALT), Gamma Glutamate Transpeptidase (GGT), Total Bilirubin (T/Bil), Conjugated Bilirubin (Conj/Bil), Total Protein, Not Done (ND)

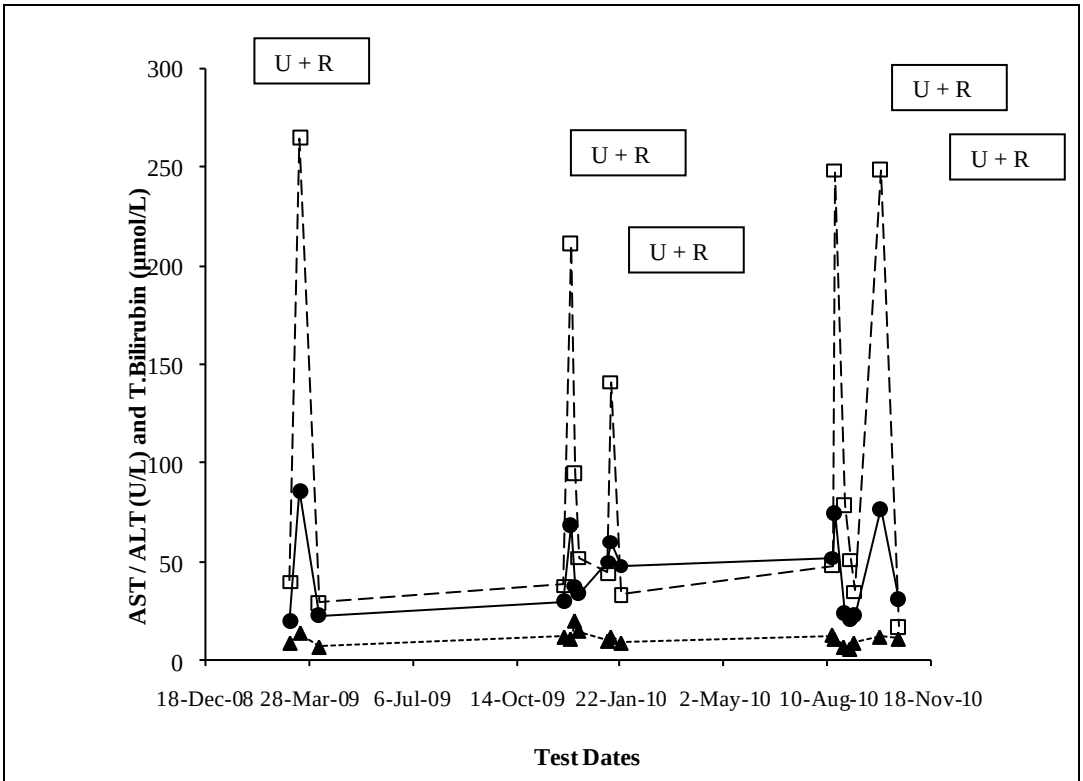

Figure 1. The Total Serum Bilirubin (▲), Alanine Transaminase (□) and Aspartate Transaminase (●) profiles in the patient during March 2009 and November 2010. Also showing U + R treatment (combined UDCA and Rifampicin) response during initial increase in transaminases.

During the subsequent two years (Nov, 2008 to Nov, 2010), the patient had five pre-icteric episodes. Upon the establishment of early symptoms of malaise, pruritus and associated elevated transaminases (particularly ALT), patient was consistently commenced on a two week course of UDCA and Rifampicin which effectively lowered the levels of transaminases and kept patient in remission (Figure 1). It has now been over ten years (2007 to 2018) since the management approach was established. Over the latter seven year period, he had only one course of the treatment.

DISCUSSION:

The management of BRIC is not definitive and has been generally to alleviate the debilitating effects of cholestasis. It includes treatment for pruritus relieve with bile acid sequestrants like cholestyramine, centrally acting opioid antagonists, antihistamines and/or rifampicin. It has also been managed with invasive procedures like nasobilliary drainage, extracorporeal albumen dialysis and occasionally liver transplantation [14]. Non-invasive preventative measures for cholestasis has never before been documented. Consistent will BRIC episodes, a pre-icteric phase associated with malaise, generalised pruritus and consisting of elevations in transaminases, particularly ALT and presumably serum total bile acids (not tested), always preceded hyperbilirubinaemia for this patient. As such, the early establishment of the pre-icteric phase guided the prompt administration of an intervention strategy which prevented the development and progression to actual clinical and biochemical pathognomic features of BRIC (Figure 1). Unfortunately, during the treatment and monitoring periods, the precipitating factors could not be ascertained, however, it was noted that the symptoms started mainly in the rainy periods. As such, upon the earliest onset of symptoms and confirmation with spikes in the transaminases, treatment with UDCA and rifampicin were initiated and continued for a period of two weeks, effectively preventing progression to clinical BRIC on all occasions (Figure 1). UDCA is a steroid bile acid which is FDA approved for use in primary biliary cirrhosis (PBC) and other cholestatic disorders despite its mechanism of action not being elucidated [15]. Moreover, recent reports indicate that it is used in ATP8B1 and ABCB11 deficiencies (BRIC1 and BRIC2) but has not shown any consistent effects [16]. In contrast, Rifampicin, which indirectly increases the 6α-hydroxylation of bile acids, that is subsequently glucoronidated and excreted in the urine reduces or abolish pruritus in mild forms of ATP8B1 and ABCB11 deficiency (BRIC1 and BRIC2) but not in severe forms (PFIC1 and PFIC2) [10]. The response to treatment thus, further confirms the BRIC diagnosis. The combination of these two medicines effectively prevents the progression of BRIC from the pre-icteric phase to the cholestatic episodes.

CONCLUSION:

Knowledge of BRIC is crucial as early recognition can avoid the performance of expensive and/or invasive diagnostic investigations and also the patient can be counselled regarding its benign nature. The effective preventative therapeutic approach used for this patient is a non-invasive method that can be utilised in BRIC cases. A pre-cholestatic treatment approach, which was of a short duration and effectively prevented cholestatic episodes on all occasions, was established. This approach seems to have prevented subsequent pre-cholestatic symptoms. As such, the anticipatory short course administration of UDCA and Rifampicin has proven to be successful, thus the administration will effectively limit, minimise or eliminate BRIC symptoms in patients on recurrent and prolonged medications during the long cholestatic bouts.

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