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FAMILIAL BENIGN RECURRENT INTRAHEPATIC CHOLESTASIS RESPONSE TO URTHODOXYCHOLIC ACID

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ABSTRACT

Introduction: Benign recurrent intrahepatic cholestasis (BRIC) is characterized by episodes of liver dysfunction called cholestasis**.** Episodes of cholestasis can last from weeks to months, and the time between episodes, during which there are usually no symptoms, can vary from weeks to years. The first episode of cholestasis usually occurs in an affected person's teens or twenties. An attack typically begins with severe itchiness followed by jaundice a few weeks later**. Case study:** A 23 years old Sudanese male presented to us at ELmek Nimer university hospital complain of generalized itching, constipation, yellowish discoloration of sclera and he passed dark urine, with recurrent attack of similar conditions during the last 5 years with extensively investigations to kwon what are the cause of his jaundice, also with multiple trial of management without any improvement. Based on his condition and positive family we diagnosed him as familial benign recurrent intrahepatic cholestasis. Start treatment with Urthodoxycholic acid with dramatic response and improvement in his condition and liver function test. **DISCUSSION:** Mutations in the ATP8B1 gene cause benign recurrent intrahepatic cholestasis type1 (BRIC1), and mutations in the ABCB11 gene cause benign recurrent intrahepaticcholestasis type 2 (BRIC2). These two genes are involved in the release of bile, a fluid produced by the liver that helps digest fats. **Conclusion**: The present case is support the use of Urthodoxycholic acid for the treatment of cholestatic liver diseases, and showed excellent out come in the treatment of familial benign recurrent intrahepatic cholestasis.

KEYWORDS: intrahepatic cholestasis, jaundice, Urthodoxycholic acid.

INTRODUCTION

Benign recurrent intrahepatic cholestasis (BRIC) is characterized by episodes of liver dysfunction called cholestasis. During these episodes, the liver cells have a reduced ability to release bile. Because the problems with bile release occur within the liver, the condition is described as intrahepatic cholestasis. Episodes of cholestasis can last from weeks to months, and the time between episodes, during which there are usually no symptoms, can vary from weeks to years. The first episode of cholestasis usually occurs in an affected person's teens or twenties. An attack typically begins with severe itchiness, followed by yellowing of the skin, mucus membrane and eyes (jaundice) a few weeks later. Other general signs and symptoms that occur during these episodes include a vague feeling of discomfort, irritability, nausea, vomiting, and a lack of appetite. A common feature of BRIC is the reduced absorption of fat in the body, which leads to excess fat in the feces (steatorrhea). Because of a lack of fat absorption and loss of appetite, affected individuals often lose weight during episodes of cholestasis. BRIC is divided into two types, BRIC1 and BRIC2, based on the genetic cause of the condition. The signs and symptoms are the same in both types. This condition is called benign because it does not cause lasting damage to the liver. However, episodes of liver dysfunction occasionally develop into a more severe, permanent form of liver disease known as progressive familial intrahepatic cholestasis(PFIC). BRIC and PFIC are sometimes considered to be part of a spectrum of intrahepatic cholestasis disorder of varying severity. Ursodeoxycholic acid (UDCA; 3, 7-dihydroxy 5_-cholanic acid) is a hydrophilic bile acid that is increasingly used for the treatment of various cholestatic disorders.[1,2] It is normally present in human bile, albeit in a low concentration of only about3% of total bile acids. It is the major bile acid in black bear's bile, which has been used in Chinese traditional medicine for the treatment of liver diseases.[3] First reports on the effects of UDCA in patients with liver diseases came from Japan as early as 1961.3 Since 1989, a number of controlled trials on the use of UDCA in primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) were published in the Western literature.[4] To date, UDCA is widely used for the treatment of PBC for which it is the

only drug approved by the U.S. Food and Drug Administration (FDA).

CASE STUDY

A 23 years old Sudanese male presented to us at ELmek Nimer university hospital complain of generalized itching, constipation, yellowish discoloration of sclera and he passed dark urine, he 's condition started 6 years ago with recurrent attack of similar condition with frequency hospital admission and multiple drugs used. On examination patient was deeply jaundice Figure [1,2-Aand 2-B], with generalized scratching marks over all his body, vital signs were normal, cardiovascular system, chest, and Central nervous systems were normal. Abdominal examination there was no organomegally or ascetics. He was thoroughly and extensively investigated during his course of management, but his all investigations *complete blood count with peripheral blood picture,* [Table-1], *Immunological investigations*[Table-2], *Autoimmune hepatitis disease screening* [Table -3], *Iron profile* [Table-4], *Renal function test*[Table-5], *Diabetic Profile*[Table -6], *Serial abdominal ultrasounds*[Table-7] were normal. His Liver Function Test showed high serum billirubin Figure [3], both direct[conjuacated] Figure [4], and indirect[unconjuacated] billirubin, Figure [5], but direct billirubin all the time is more high than indirect billirubin , liver enzyme mainly alkaline phosphates was high Figure [6,7,8and9], [Table -8], others protein Figure [10], albumin Figure [11], and globulin Figure [12], were normal. *Viral screening test were negative except positive for CMV-IgG* [Table -9], *Prothrombin Profile* [Table -10], and Direct Coombs test [direct agglutination test DAT] is negative. *Magnetic resonance Cholangiopancreatography(MRCP) showed,* Common bile duct and both hepatic ducts presented normal caliber with no evidence of filling defect or signs of obstruction. Gall Bladder is mildly contracted with on filling defect. Liver is normal in size and intensity with no focal lesion or dilated intra-hepatic bile ducts. Pancreas is normal in size and texture with no evidence of solid mass, Pseudocyst or peripancreatic fluid collection. Pancreatic duct appear normal *Figure* [13-14-and15]. Also during this period of his management Endoscopic retrograde cholangiopancreatography [ERCP] Figure [16], was done and stent was inserted [on the second day of december2/12/2014] with little improvement of liver function test but unfortunately it was impaired again. In spite of all these investigations no any definite diagnosis. While when he managed in our hospital his mother and his sister came to visit him accidently we found that both of them were have jaundice and we investigated them with typical liver function test similar to our patient. So we put familial benign recurrent intrahepatic cholestasis is one of the differential diagnosis. On 5th day of October 2015 we diagnosed him as familial benign recurrent intrahepatic cholestasis in base of family history, evidence of cholistasis features clinically and laboratory, which showed no evidence of others causes of jaundice in this young male with recurrent attack of jaundice and positive family history. On this evidence we started treatment with Urthodoxycholic acid with dramatic response and improvement in both his clinical condition and his liver function test. Unfortunately 6 month [on twenty first of June 2016] later patient stop the treatment by himself again his condition was deteriorated and became deeply jaundice, on 26th of June 2016 patient developed massive upper gastrointestinal bleeding and malaena, upper GI endoscopy was done and showed erosive antral gastritis without fundal varies. On 13th of March 2017patient developed night blindness and most probably due to vitamin A deficiency because its fat-soluble vitamin he received vitamin A supplementation, fortunately he showed complete recovery within two to three weeks.

DISCUSSION

BRIC is a rare disorder. Although the prevalence is unknown, this condition is less common than the related disorder PFIC, which affects approximately 1 in 50,000 to100, 000 people worldwide.

Mutations in the *ATP8B1* gene cause benign recurrent intrahepatic cholestasis type1 (BRIC1), and mutations in the *ABCB11* gene cause benign recurrent intrahepatic cholestasis type 2 (BRIC2). These two genes are involved in the release of bile, a fluid produced by the liver that helps digest fats.

The *ATP8B1* gene provides instructions for making a protein that helps to control the distribution of certain fats, called lipids, in the membranes of liver cells. This function likely plays a role in maintaining an appropriate balance of bile acids, a component of bile. This process, known as bile acid homeostasis, is critical for the normal secretion of bile and the proper functioning of liver cells. Although the mechanism is unclear, mutations in the *ATP8B1* gene result in the buildup of bile acids in liver cells. The imbalance of bile acids leads to the signs and symptoms of BRIC1.

The *ABCB11* gene provides instructions for making a protein called the bile salt export pump (BSEP). This protein is found in the liver, and its main role is to move bile salts out of liver cells. Mutations in the *ABCB11* gene result in a reduction of BSEP function. This reduction leads to a decrease of bile salt secretion, which causes the features of BRIC2.The factors that trigger episodes of BRIC are unknown.

Some people with BRIC do not have a mutation in the *ATP8B1* or *ABCB11* gene. In these individuals, the cause of the condition is unknown. Both types of BRIC are inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Some people with BRIC have no family history of the disorder. These cases arise from mutations

in the *ATP8B1* or *ABCB11* gene that occur in the body's cells after conception and are not inherited.

Ursodeoxycholic acid (UCDA) is increasingly used for the treatment of cholestatic liver diseases. Experimental evidence suggests three major mechanisms of action: (1) protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, resulting from modulation of the composition of mixed phospholipid-rich micelles, reduction of bile acid cytotoxicity of bile and, possibly, decrease of the concentration of hydrophobic bile acids in the cholangiocytes; (2) stimulation of hepatobiliary secretion, putatively via Ca2_- and protein kinase C-_–dependent mechanisms and/or activation of p38MAPK and extracellular signal-regulated kinases (Erk) resulting in insertion of transporter molecules (*e.g.*, bile salt export pump, BSEP, and conjugate export pump, MRP2) into the canalicular membrane of the hepatocyte and, possibly, activation of inserted carriers; (3) protection of hepatocytes against bile acid–induced apoptosis, involving inhibition of mitochondrial membrane permeability transition (MMPT), and possibly, stimulation of a survival pathway. In primary biliary cirrhosis, UDCA (13-15 mg/kg/d) improves serum liver chemistries, may delay disease progression to severe fibrosis or cirrhosis, and may prolong transplant-free survival. In primary sclerosing cholangitis, UDCA (13-20 mg/kg/d) improves serum liver chemistries and surrogate markers of prognosis, but effects on disease progression must be further evaluated. Anticholestatic effects of UDCA have also been reported in intrahepatic cholestasis of pregnancy, liver disease of cystic fibrosis, progressive familial intrahepatic cholestasis, and chronic graft-versus-host disease. Future efforts will focus on definition of additional clinical uses of UDCA, on optimized dosage regimens, as well as on further elucidation of mechanisms of action of UDCA at the molecular level**.**

CONCLUSION

The present case is *support that* familial benign recurrent intrahepatic cholestasis present in twenties decade of life and it affect both male and female. Also the condition is benign and not progress to cause liver cirrhosis. The present case is *also support the use of* Urthodoxycholic acid for the treatment of cholestatic liver diseases, and showed excellent out come in the treatment of familial benign recurrent intrahepatic cholestasis from this we add another use of Urthodoxycholic acid. Figure [17]

Table 1: Hematological investigations
Hematology profile:

	02/12/2014	10/05/2015	12/08/2015	21/12/2015	22/06/2016	Normal range
Hbg/dl	11.8g/dl	13 g/dl	13.2 g/dl	9.4 g/dl	13.1 g/dl	12-16
Hb%					90%	
RBCs	4.21mili/cumm	4.5 mili/cumm	5.52 mili/cumm	3.27 mili/cumm	4.03 mili/cumm	3.8-5
PCV	33.8%	40%	41.3%	29.6%	37.1%	36-46
RBCs indices						
MCV	80.3fl	89 fl	74.8 fl	90.6 fl	92.1 fl	78-98
MCH	28.0pg	28 pg	23.9 pg	28.7 pg	32.4 pg	27-32
MCHC	34.9 g/dl	32 g/dl	32 g/dl	31.8 g/dl	35.1 g/dl	30-37
RDW	13.8%			14.9%		
Platelet Count	407cells/cumm	296000 cells/cumm	450000 cells/cumm	408000 cells/cumm	444000 cells/cumm	150000-450000
MPU	6.6			7.6		
WBCs	5.2 cells/cumm	9000 cells/cumm	7.2 cells/cumm	8.7 cells/cumm	18.900 cells/cumm	4000-11000
WBCs differential count						
Segmented Neutrophils	62.9%[3.3]	72%	52%	76.7%[6.7]	83.9%	
lymphocytes	28%[1.5]	19%	34%	15.6%[1.7]	11%	
Monocytes	9.1%[0.5]	09%	10%	7.7%[0.7]	4.1%	
Eosinophils			4%		0.4%	
Basophils					0.6%	
Peripheral Blood picture						
RBCs		Normocytic normochromic cells	Normocytic normochromic, target cells		Normocytic normochromic cells	
WBCs		Normal morphology	Normal morphology		Neutrophilia	
Platelets		adequate	adequate		adequate	
ESR			13mm/2h			

Normal range: Haemoglobin (12.0-16.0)g/dl, RBCS (3.8-5.0)milli cells/cumm, TWBC (4.000-11000) cells/cumm, PCV (36-46.0), MCV (78.0-98.0) FL, MCH (27.0-32.0) pg, MCHC (30.0-37.0)g/dl, platelet count (150.000-450.000) cells/cumm.

Table 3: Autoimmune Hepatitis Disease Screen.

Anti mitochondrial antibody [AMA-M2 3E]	Negative
Anti Smooth Muscle antibody[ASMA]	Negative
LKM-1	Negative

Table 2: Immunological investigations.

ANA profile:

Antigen	Result
RNP/Sm	Negative
Sm	Negative
SS-A native(60KDa)	Negative
Ro-52 recombinant	Negative
SS-B	Negative
Scl-70	Negative
PM-Scl100	Negative
Jo-1	Negative
Centromere B	Negative
PCNA	Negative
dsDNA	Negative
Nucleosomes	Negative
Histones	Negative
Ribosomal-P-protein	Negative
AMA-M2	Negative
ANA global IIF	Negative

Table 4: Iron Profile.

	Result	Reference range
Ferritin	977 ng/ml	28-365ng/ml
Iron	72 ug/dl	40-140ug/dl
TIBC[Total Iron binding capacity	257 ug/dl	200-400ug/dl

Table 5: Renal Profile.

	06/07/2013	02/12/2014	26/6/2016	12/3/2017	Normal range
Blood urea			29 mg/dl	23 mg/dl	[15-45mg/dl]
S creatinine	0.6 mg/dl	0.6 mg/dl	0.55mg/dl	0.6 mg/dl	[0.4-1.4mg/dl]

Table 6: Diabetic Profile.

	02/06/2013	02/12/2014	10/04/2015	21/06/2016	12/3/2017	Normal range
Random blood sugar	116mg/dl	108 mg/dl	134mg/dl	247mg/dl	82 mg/dl	< 180mg/dl

Table 7: Serial Abdominal Ultrasounds Were Done with Different Expertise Doctors Reviled.

	06/07/2013	09/12/2013	01/12/2014	16/08/2015	16/08/2015
Liver	Average size, regular surface, regular outline, with homogenous echo pattern and no focal lesions or cysts detected	Normal size, echogenicity. No focal lesions, or periportal fibrosis or dilated bile ducts	An average size, regular surface, regular outline, with homogenous echo pattern, and no focal lesions. No intra or extra hepatic billiary radical's dilatation	Normal No intra or extra hepatic billiary radical's dilatation	Average size, homogenous echo pattern, and no focal hepatic masses. No intrahepatic billiary radical's dilatation
Gall Bladder	Pyriform, distended, average size, no masses but showed septa. Neither calculi nor polyps were detected with average wall thickness with presence of mud	appear contracted	pyriform , distended, average size, no masses or septa	normal	small shrunken with thickened wall, dilated cystic duct no stones seen
CBD	normal measure 5 mm		average caliber 4.5 mm	normal	dilated [0.86 cm]
spleen	normal	normal	normal	normal	normal
kidneys	normal	normal	normal	normal	normal
pancreas	normal	normal	normal	normal	normal
Para-aortic lymph nodes	normal	normal	normal	normal	normal
ascites	No	No	No	No	No
Pelvic organs	normal	normal	normal	normal	normal

Table 8: Liver Function Test.

	25/5/ 2013	**2/6 2013**	**11/6 2013**	**6/7/ 2013**	**13/7/ 2013**	**12/12/ 2013**	**8/9/ 2014**	**2/12/ 2014**	**8/12/ 2014**	**13/12/ 2014**	**21/12/ 2014**	**12/8/ 2015**	**17/9/ 2015**	**5/10/ 2015**	**29/4/ 2016**	**21/6/ 2016**	**24/6/ 2016**	**26/6/ 2016**	**12/3/ 2017**	**4/ 2**
Protein				7.1		8.1	6.8	8.1		6.8				6.6		5.7	5.2	5.8	7.8	8.
Albumin				4.5		3.7	3.4	4.1		3.8				3.3		2.9	2.8	2.9	3.6	3.
Globulin						4.4	3.4											2.9	4.2	5.
Total Bilirubin	17.7	29.8	26.4	33.6	18.3	42.4	29.38	27	11.2	6.8	3.2	22	11.4	19.84	6.1	35.5	26.8	20.28	44.55	0.
Direct Bilirubin	11.8	20.2	17.6			28.8	18.1					15.9	8.4	15.84	2.8	30.3	21.4	12.5	33	0.
Indirect Bilirubin	6.9	9.6	8.8			13.6	11.28					6.1	3	4	3.3	5.2	5.4	7.78	11.55	0.
S.ALP	226	342	319	381.6	388.2	235	183	247	173	180.2	118	326	179	182		419	309	217	315	12
S.AST	35	39	39	129.5		57	53	100	37.9	53.2	27	61	51	36		121	36	23	36	14
S.ALT	31	27	34	118.6		60	72	46	45	67.9	51.5	70	51	23		151	54	26	27	10
GGT				116.8	190			82	28.5	62.3	35.4	28								

Normal range

Protein {6.7-8.7) g/dl, Albumin (3.8-5.0) g/dl, Globulin (2.9-3.7)g/l. Total Bilirubin (up to 1mg/dl), Direct Bilirubin(up to 0.25mg/dl), Indirect bilirubin(up to 0.75mg/dl), serum Alkaline phosphates [ALP](50-130 u/l), Serum aspartate aminotransferase[AST] (up to 35u/l), serum Alanine aminotransferas[ALT](up to45u/l), Gamma -glutamyl transpeptidase [GGT](11-50u/l).

Table 9: Viral Screen.

Viral	Result
HCV AB	Negative
HBV[HBs Ag]	Negative
HAV	Negative
CMV-IgG	Reactive
EBV-IgG	Negative

Table 10: Prothrombin Profile.

	02/06/2013	06/07/2013	02/12/2014	13/12/2014	10/05/2015	17/11/2015
Prothrombin time	19.9 second	24.2second	14.3second	14.3second	23 second	12.2second
Prothrombin control	14.0 second	12.3second	13.8second	13.8second	14second	13 second
INR	1.44	2.25	1.07	1.07	1.7	0.91

Figure [2-B] now on management with ursodeoxycholic acid

Figure [2-A] during management with ursodeoxycholic acid

Figure [1] before start treatmen with ursodeoxycholic acid

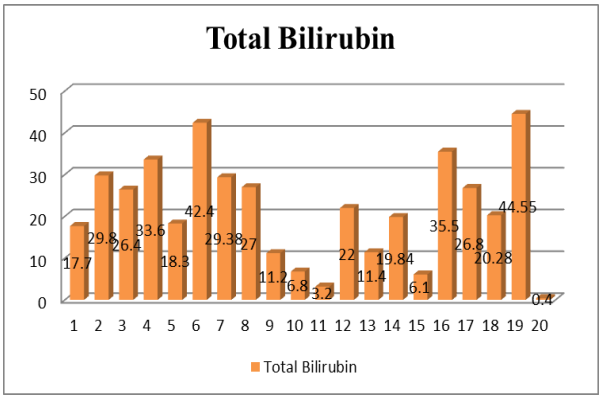

Figure [3].

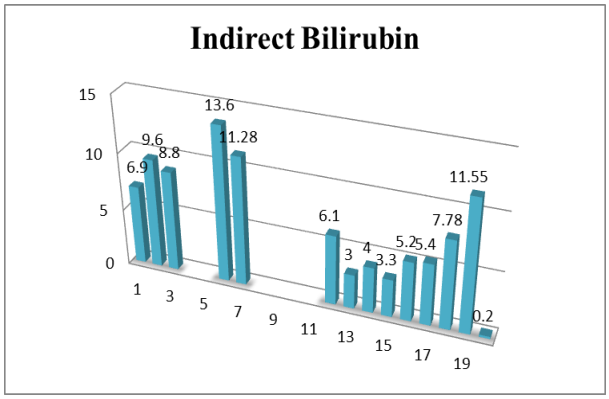

Figure [5].

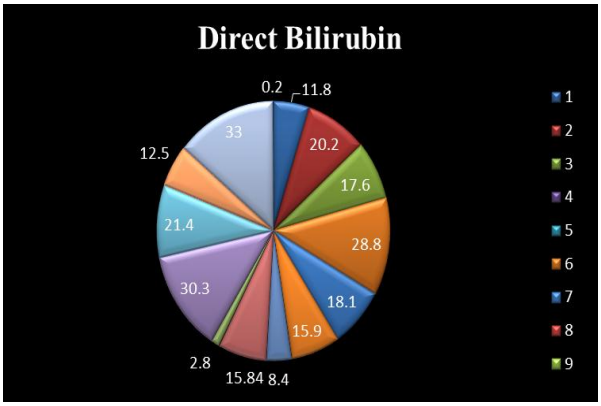

Figure [4].

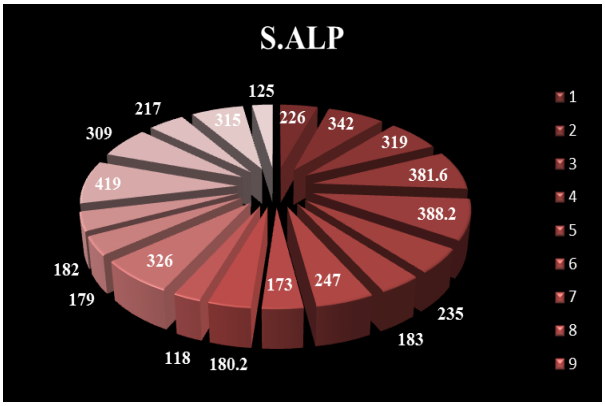

Figure [6]: Serum Alkaline phosphatase{S.ALP}.

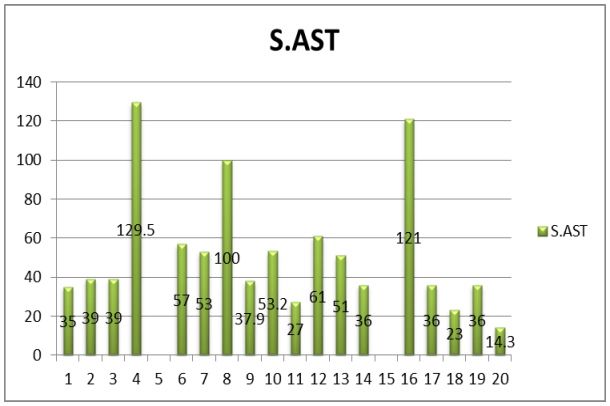

Figure [7]: Serum Aspartate aminotransferas {S.AST}.

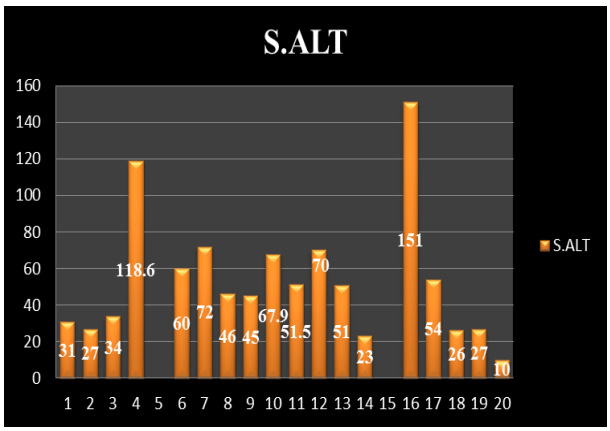

Figure [8] Serum Alanine aminotransferas {S.ALT}.

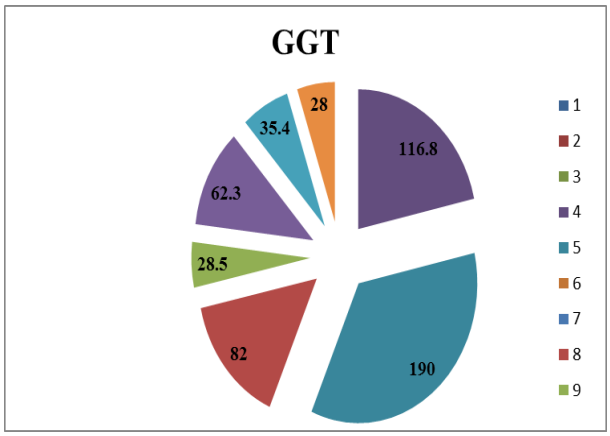

Figure [9]: Gamma – glutamyl transpeptdase {GGT}.

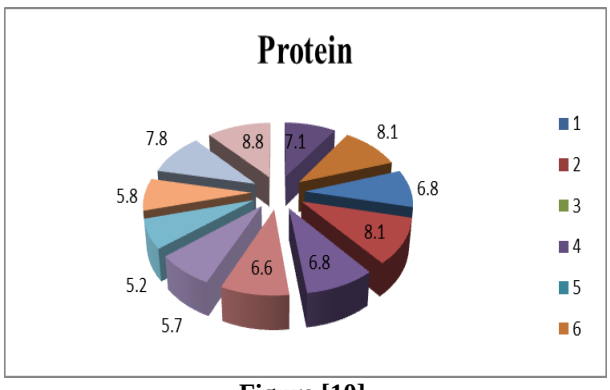

Figure [10].

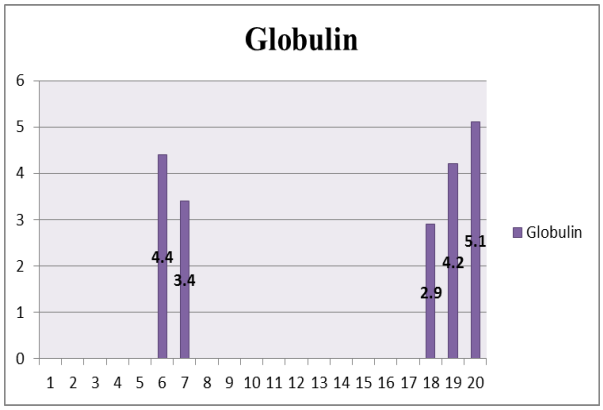

Figure [11].

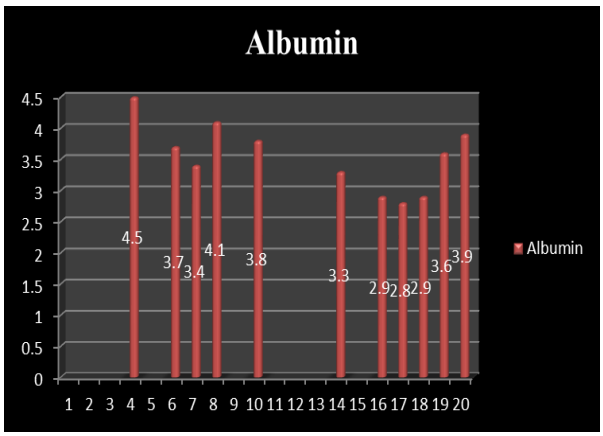

Figure [12].

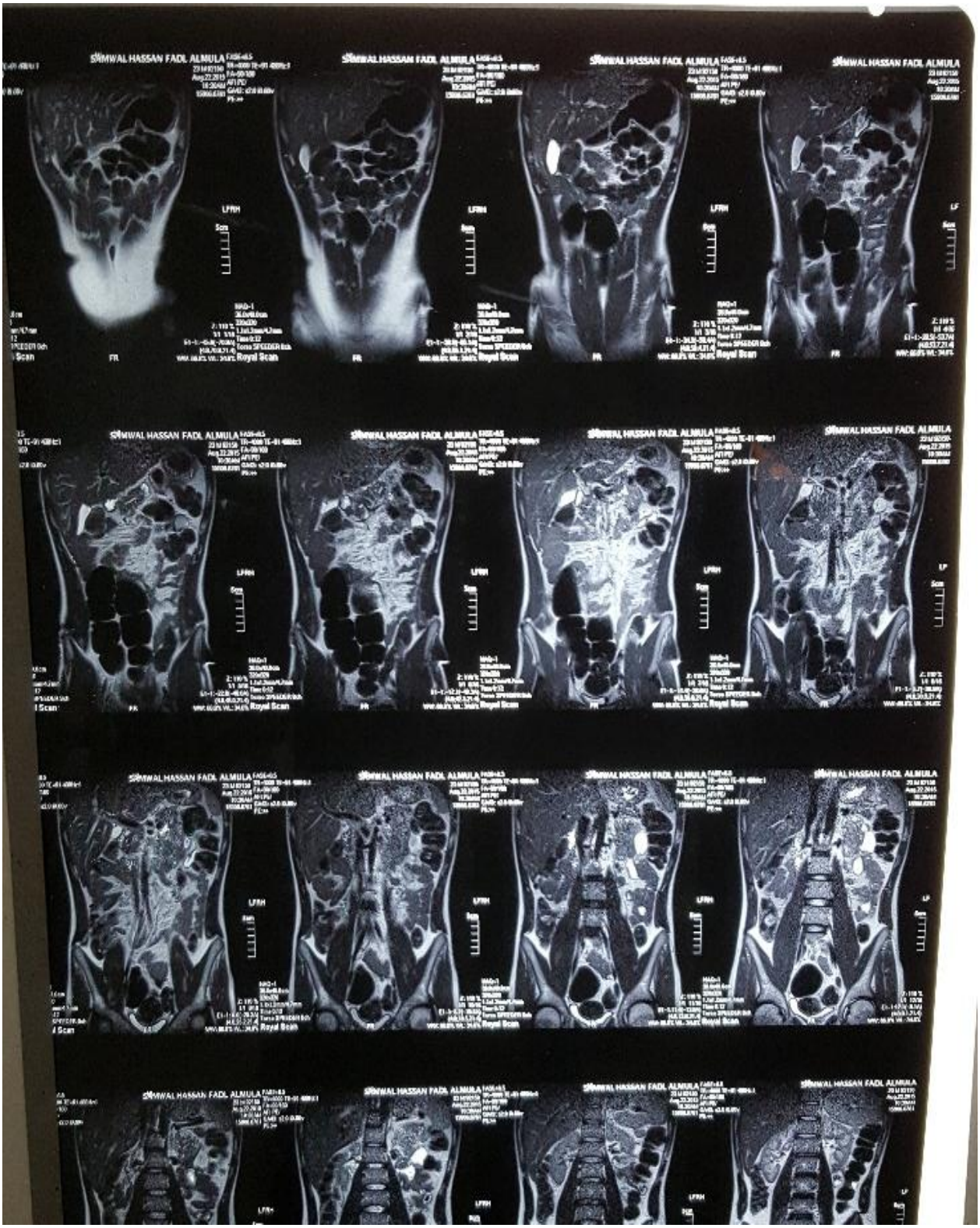

Figure 13: Magnetic resonance Cholangiopancreatography [MRCP] CORONAL VEIW.

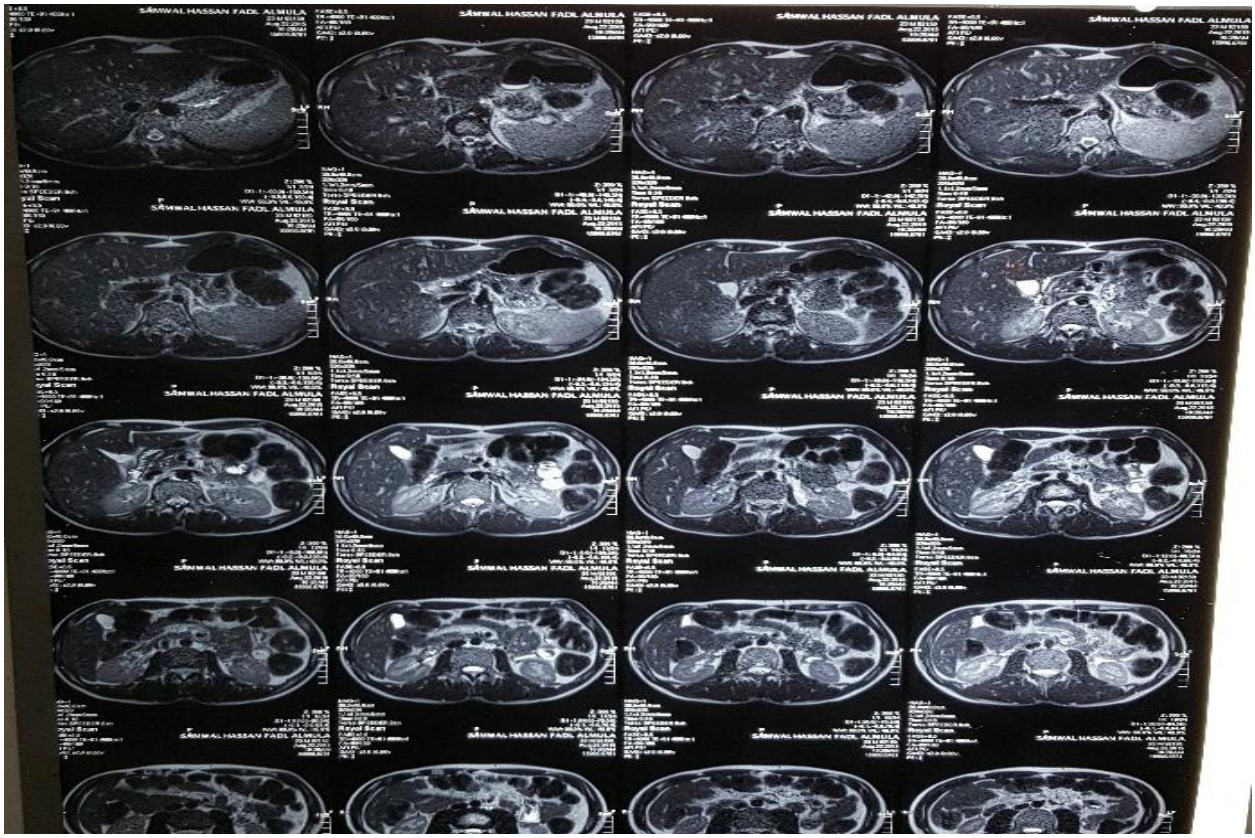

Figure 14: ***Magnetic resonance Cholangiopancreatography*** **[MRCP] AXIAL T2-WEIGHTED VEIW.**

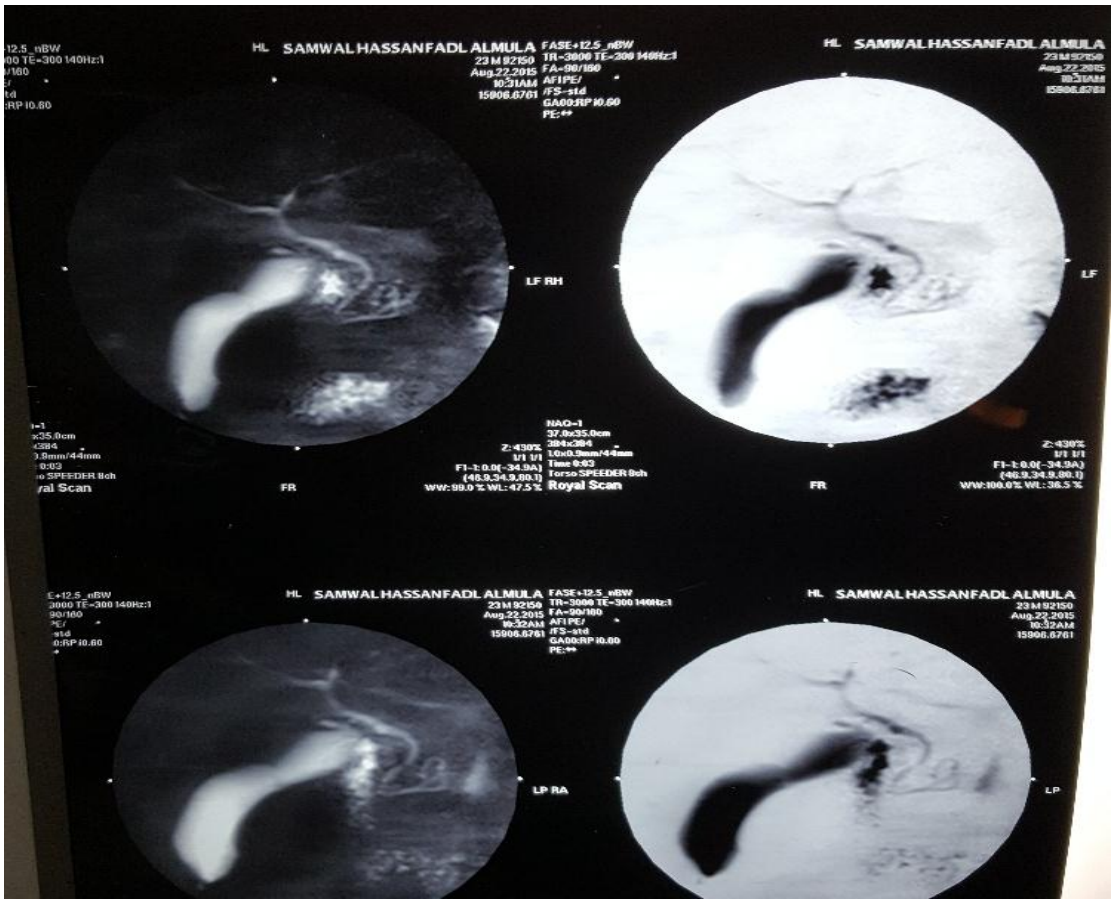

Figure [15] ***Magnetic resonance Cholangiopancreatography[MRCP]CORONAL MAXIMUM INTENSITY PROJECTION.***

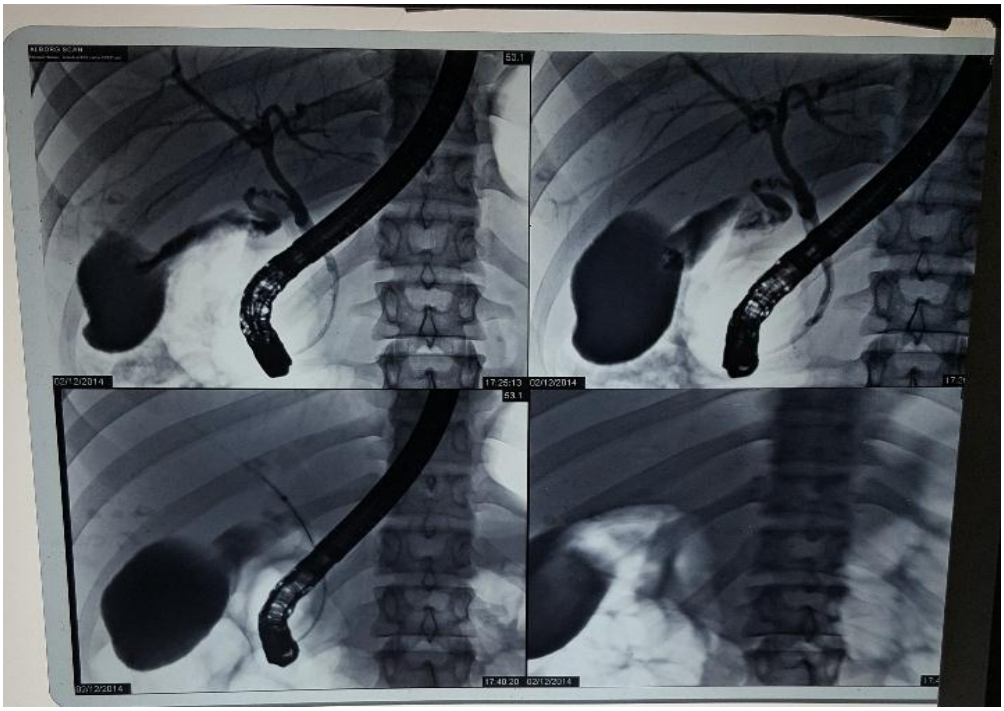

Figure 16: Endoscopic retrograde cholangiopancreatography{ERCP].

Figure [17].

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