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HEPATITIS B INFECTION LEADING TO SUB-ACUTE LIVER TRANSPLANT: A CASE STUDY

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Abstract:

This research paper tries to inform about the unfamiliar and lethal outcomes of missing a simple hepatitis B vaccination and being infected with viral diseases. We have tried to compile various symptoms, ways of transmission, preventive measure and progression of hepatitis B. This is a case study of a 32 year old lady who had symptoms of muscle pain joint pain, jaundice and weakness. Her early symptoms were clearly showing association with significant liver disease leading to liver failure due to viral hepatitis B although she had no relevant medical history. Her symptoms progressed rapidlyuntil liver failure and required immediate liver transplant. We present various symptoms, clinical factors that may have influenced her progression to sub-acute liver failure as described in the literature.

Keywords: Sub-acute liver failure, hepatitis B risk factors and causes, hepatitis B virus, cirrhosis, hepatocellular carcinoma,transmission (horizontal and vertical),Asterixes, hepatic encephalopathy

Introduction: Human race is prone to number of life threatening viral disease and Hepatitis B is one of them. Hepatitis has five different strains, Hepatitis A,B, C, D and E.Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It can be acute as well as chronic and puts people at high risk of death. If HBV lasts more than six months it becomes chronic in nature. Hepatitis B is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma,in the world and WHO estimates that more than 500 million people worldwide are persistently infected with different varients of the hepatitis virus like (HBV) hepatitis B and/or hepatitis C virus (HCV) (Rehermannand Nascimbeni 2005) and cause about 1 million deaths all over the world.According to WHO Hepatitis B is common in Western and African regions of the world with more than 6. 2% while in Regions of Eastern Mediterranean, Asian Region and

some regions of Europe, 3.3%, 2.0% and 1.6% of the population is infected, respectively and Americas with 0.7% of the population is infected (Lee 1997).

Talking about its transmission it includes both horizontal as well as vertical routes. Horizontal includes transmission in early years (likelesions, sanitary habits, bites etc.) and horizontal transmission in adults (throughmedical procedure exposure, sexual contact, intravenous drug use). Vertical transmission through close contact and sanitary habits from mother to child or generation to generation (Brian et. al. 2004). But the exact comparison of HBV varies due to difference in the population, selection of markers, temporal variation and many other reasons. The lack of awareness about this deadly disease is one of the reasons that it is still considered lethal because of its severe outcomes like liver cirrhosis (scarring of liver) that impair livers ability to function(Liver failure). A subtype called acute liver failure is a clinical condition shutting down of important functions of liver takes place which affect the most of body system metabolism. When that occurs, a liver transplant is necessary to sustain life. Other complications that can occur are hepatocellular carcinoma, Kidney disease and inflammation of blood vessels. This is so as vaccination is still not been implemented in all countries or its execution is not properly done, thus reservoir hosts and different means of infections is maintained and thus transmission is still a great problem to deal with.

After the HBV infection the recovery rate is high in adults in acute stage only and very few develop the chronic form while infants and the children are more prone developing the chronic form of infection. Full recovery from this infection is still not possible but medication helps to reduce the effectiveness of the viral DNA to some extent and reduce the harmful after effects. The only prevention is the vaccination for HBV.A highly protective and 98-100% effective and safe vaccineagainst hepatitis B is available in the market and in government hospitals it is available at free or minimal prices. A simple Preventive measure like vaccination against hepatitis B infection avert or decreases the development of complications including the development of chronic disease and liver cancer. This vaccine can be taken in total of three doses with in a period of six months. Also if a person gets infected by HBV can prevent the further infection by getting the preventive treatment that includes Immunoglobulin vaccine within 24 hours.

The various symptoms that are helpful self diagnose and rush to expert may vary from mild to severe .The incubation period of this virus is about 1 to 6 months after infection has taken place. Symptoms may include Jaundice (yellowing of skin and cornea), dark pale to brown coloured urine, Joint and muscle pain, abdominal pain, loss of appetite, weakness, fatigue, fever, nausea , vomiting and increased sensitivity to smell.

Hepatitis B infection is spread through various common ways. One such way is sexual contact and having unprotected sex with someone who is infected, having more than one sexual partner. The virus can pass throughsaliva, blood, semen or vaginal secretions. Sharing of infected needles, accidental needle pricks for health care workers, from infected mother to new born childduring childbirth, blood transfusions. Risk increases if we live in areas where the HBV is more common. This virus can survive outside the body on various surfaces for about 7 days.

Case description:

A 32 year old woman went from sudden normal life to hepatitis b infection and ended up in the liver transplant. A resident of Jammu region of Jammu and Kashmir territory, India a research scholar, a mother of one child was living her normal life with no serious medical

history except mild constipation. Suddenly she complained of muscle pain and joint pain in the last days of May 2020. On consultation with doctor was advised to take muscle relaxant and to have some tests done (Uric acid and LFT). The test were normal with little rise in billirubin (3.5) and little itching. So the physician recommended Udimarin-300, syrup Livpress and plenty ofglucose and suggested to have USG done and to repeat liver functioning test (LFT).The USG showed hepatomegaly (size 165 mm) and rest everything was accurate. Along with this Hepatitis B antigen test was performed that came out to be reactive. On 13th of May,2020 billirubin raised to 8 with Hb 10.5.After that the patient showing symptoms like Jaundice, severe itching, and muscle pain was advised to perform various test (repeated USG, IgM anti HBc, IgM Anti HAV, IgM Anti HEV, LFT, INR,PTI and repeat the LFT, INR and PTI weekly. So test results were positive for surface antigen for hepatitis A and Hepatitis B, and negative for IgM anti HBc, IgM Anti HAV, IgM Anti HEV. LFT, INR,PTI were 2.2, 1.15,15 respectively, BP (100/73) . The hepatologist suggested TAF (started on 17-05-2020and was continued) and some other medicines (TAF0.25mg daily, Heparex 400,Udiliv 450 etc))and immediately administered 3 vitamin K injections one after the other on the interval of one day . Family screening for HBV antigen for both paternal and in laws was also done and the husband was found positive with very high viral load (48000 IU/ml), maximum Billirubin 5.8, INR (1.26) and PT (17), SGOT (1712), SGPT (3390), GGT(124.7).The positive thing that came out was that his Anti-Hbc-IgM (Hep. B core antibody) and Anti-HBs-IgM (Hep. B surface antibody, ELISA) were positive and declared resolved after within aperiod of five months without any treatment.

After this the patient was shifted to DMC hospital, Chandigarh and was admitted there for we and all the parameters came to normal and was discharged with some medication. But after 22 days all the parameters started rising with billirubin(6.7), INR (1.6), PT (20), SGOT (985), and SGPT (790). The patient was again admitted and the conditioned worsened with days complaining of vomiting, extreme nausea, decreased appetite, icterus, weakness. The total proteins had decreased to 5.9 with albumin (2.7). All the tests were repeated on daily basis along with LFT, RFT, Electrolyte levels, fasting sugar along with Anti HBc-IgM (found non reactive), HEV (non reactive), HBV DNA ($11.69*10^2$ IU/ml decreased due to TAF), Hepatitis BE Ag (reactive) and Ab (non reactive), USG . The doctors were confused over irregular pattern of billirubin, SGOT, SGPT. So they went for hepatitis Deltastrain antigen, along with Liver biopsy (TJLB-Trans Jugular Liver Biopsy) in order to rule out the possibility of autoimmune hepatitis. Also various test like COOMBS direct test, COOMBS indirect test, blood cultur, urine culture, SCRUB TYPHUS, LEPTOSPIRA (ELISA), Anti HIV were done. All above mentioned tests were negative except COOMBS direct (+). Hb, electrolytes were declining tremendously. The USG whole abdomen showed hepatomegaly (170 cm) with fatty infiltration of liver, thickened gall bladder wall and few periportal lymph nodes. The Liver Biopsy report suggestedpresence of portal tracts showing bile ductular proliferation and dense infiltration by chronic inflammatory cells seen as lymphocytes and few plasma cells. The liver parenchyma showed marked ballooning degeneration with confluent necrosis leading up to submassive necrosis. The liver parenchyma is also infilterated with same infilteration. No signs of steaosis, emperipolesis, interface hepatitis, granuloma, or malignancy was seen .Thus suggesting Acute Hepatic injury. Also HBe Ag has become negative and Anti HBe positive. HBV viral load was significantly decreased. The patient was administerd with daily 100 ml of Albumin I/V injection Tab TAF was shifted to Tab- Entacavir 0.5mg daily, lactulose high bowel wash, Hepaford sachet thrice a day etc. Meanwhile in between oedema symptoms were seen for about 4-5 days but was treated timely. Asterixes(trembling lateral extremities) was observed as a sign of **hepatic encephalopathy** in the third week of August. This was due to increased ammonia level as the

liver was unable to metabolize the ammonia into urea and thusthat impaired the functioning of brain cell. This also resulted in the delayed response of nervous system and affecting the memorising ability. The condition was worsened and the doctors remarked that the patient was likely to go into cirrhosis and there was high risk of liver failure. So the doctors suggested to shift the patient to the specialised liver institute for further case management. The delaying of tests reports due to COVID-19 condition also contributed for making things more serious.

Thus the patient was finally shifted to ILBS (Indian Institute of Liver and Biliary sciences) on 28th of August 2020 and she was immediately shifted to ICU. The case was handled by the India's most experienced hepatologist.All parameters were checked again with maximum values of INR(4.35), PT (47.5), BILLIRUBIN (18) , SGOT (1010), SGPT (680), ALP (190), GGT (790), total proteins(4.87), createnine (0.43), ammonia (382), urea (16), Na (130), K (0.43), Cl (100), HB (8.6), fasting blood sugar(149), Mg (1.2). Hyponateremia was observed with increased ammonia levels and significant encephalopathy. High INR indicative of possible acute liver failure. Consecutive four Plasma therapies were given to the patient in order to revive the patient'shealth but didn't work and final call for liver transplant was given. Live donor liver transplant (LDLT) was done. The live donor was her younger sibling with blood group O+ passing all parameters for the LDLT. So finally on 4th of September 2020, the surgery was performed which was a complete success. An explantof healthy liver (16*11*7 cm) and attached gall bladder (4*2 cm)weighing 780 gm was transplanted to the recipient. Along with that other procedures that were done were correction of liver necrotic areas, ascites of 2 litres, peri-hepatic and peri-lymphatic edema, arterial anatomy (type 1 Michel's- LHA and RHA from HAP, normal anatomy of hepatic veins. The recipient and the donor were kept under Intensive care monitoring and showed a good recovery rate with stabilizing parameters. The receipient was in ICU on vasopresser and ventilator support. Patient showed decreasing Lactate trend and inotropes were taperedand patient showed extubated on POD 1 (post operational day) and nasogastric feed was started, along with Tab Tacrolimus and injection methyl prednisolone was started. Oral diet was started on POD 2 and normal diet was built up to POD 4. The patient developed Tachypnoea on POD3 so and X-Ray was done showing B/L pleural infusion, that was managed by non invasive ventilation (NIV), incentive spirometry and chest physiotherapy.Left and right drains were removed on 6th and 12th PODS respectively. CMV viremia caused by cytomegalo virus on POD7 and was treated well with Valgan while cellcept was held for a week.Another complication that appeared after the transplant was Post-liver transplantation diabetes mellitus (PLTDM) and was managed immediately after the transplant procedure by the help of endocrinologist prescribimg with optimised doses of Insulin and Lantus. In this case this could be due to (i) due to high body mass index (BMI) (Yadav et al. 2013, Kuoet al.2010 , lizet al. 2016, Ling et al. 2016) (ii) pre transplant impaired fasting glucose (Cho et al. 2014, Salibaet al. 2007) (iii) immunosuppressive therapy with high-dose corticosteroids (Honda et al.2013, Hartog et al.2015) or calcineurin inhibitors (tacrolimus or cyclosporine) (Khalili et al. 2004, Kuoet al.2010 , Xueet al.2017, Ling et al.2017). (iv) Nonalcoholic steatohepatitis (NASH) (Lonardoet al. 2016).Doctors confirmed this as sub acute liver failure (O'Grady classification).

	Week1	Week	Week	Week	Week	Week	Week	Week8	Week9	Week1	Week1	Week1	Week1	Week1	Week1	Week1	Week1

		2	3	4	5	6	7			0	1	2	3	4	5	6	7
INR	1	1.2	2.8	1.4	1.24	1.26	1.24	1.43	1.52	2.1	2.8	1.98	2	2.8	3.2	4.16	4.35
PT	12.5	12.5	28	13.5	13.5	17.5	16	17.3	17.4	19.4	20.6	28	32	30	30	47	49.5
BILLIRUBIN	3.5	8.5	8	8.5	3.3	2.2	1.8	1.92	1.59	2.28	4.5	7.85	9.08	13	15	18	12.7
SGOT	1030	10035	10032	10045	10074	795	828	430	660	646	1311	1063	1065	1085	1011	1000	566
SGPT	800	10005	12800	12500	9113	847	702	450	511	550	590	563	790	641	788	680	320
ALP	102	150	440	444	157	153	383	227	257	281	199	320	191	200	190	128	132
GGT	-	-	-	48	160	220	360	540	649	688.5	570	688	650	780	790		
Total proteins	-	6.8	6.8	7.5	9.9	7.6	6.4	7.3	6.5	6.9	6.9	9.9	6.9	6.6	6.22	6.67	5.05
Albumin	-	4.2	4.2	4.35	4.21	3.9	3.7	3.8	3.4	3.2	3	3.2	2.71	2.6	3.76	2.94	2.94
Creatinine	-	-	-	-	-	-	-	-	-	-	-	0.63	0.73	0.87	0.95	0.58	0.5

Urea	-	-	-	-	-	-	-	-	-	-	-	12	11	12	13	16	15
Ammonia	-	-	-	-	-	-	-	-	-	-	-	170	180	190	200	238	382
Hb	10.5	10.5	10.5	10.5	10.6	10.6	10.7	10.7	10.7	10.8	10.8	10.9	10.7	10	10	8.5	9
Bld sugar fasting	90	92	90	110	97	95	95	97	92	92	90	91	120	125	132	160	149
Na	-	-	-	-	-	-	-	-	-	-	-	133	134	133	132	131	132
K	-	-	-	-	-	-	-	-	-	-	-	3.89	3.86	3.7	3.72	0.43	0.43
Cl												100	101	100	99	103	99

Table 1: Showing various clinical parameters regarding LFT, RFT, CBC and electrolytes on weekly basis from the appearance of symptoms to the day of liver transplant. (LFT-Liver functioning test, RFT-renal functioning test, INR-International Normalized Ratio,PT-Prothrombin Time, SGOT-Serum glutamic-oxaloacetic transaminase, SGPT- as serum glutamic-pyruvic transaminase or ALT- alanine aminotransferase, ALP- alkaline phosphatase , GGT-Gamma-Glutamyl Transpeptidas

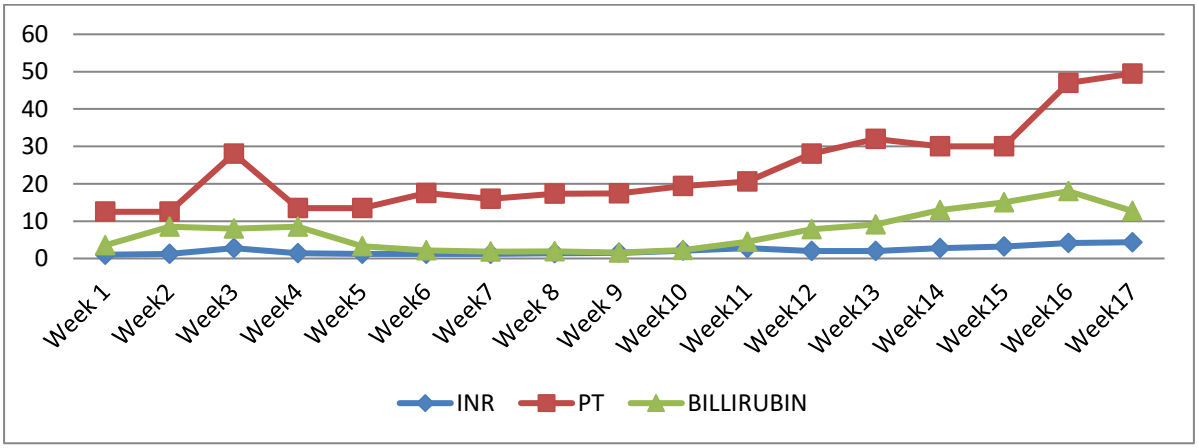

Figure1: graph showing values of INR, PT and Total billirubinfromweek 1 to week 17

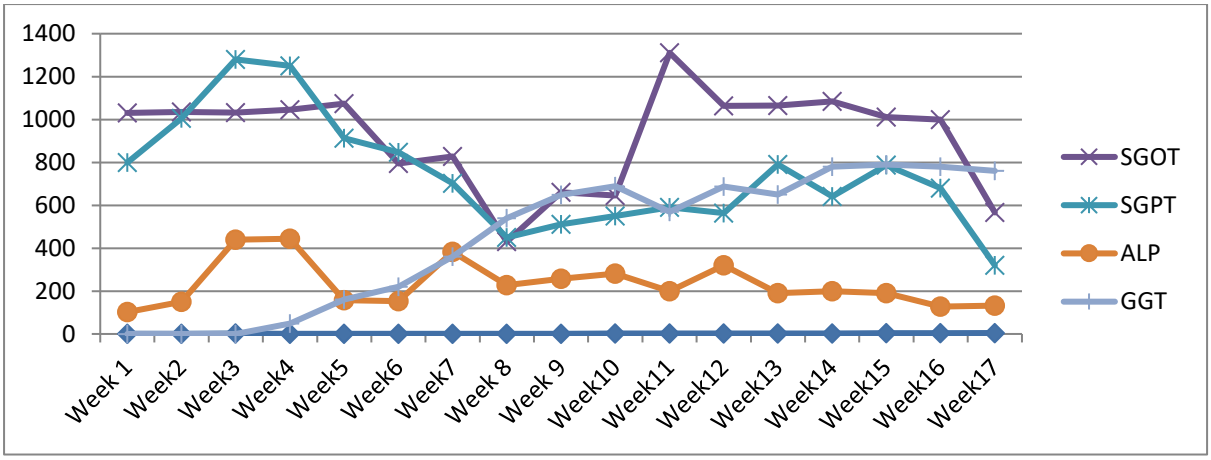

Figure2: graph showing progressive values of SGOT, SGPT, ALP and GGT from week 1 to week 17

	SGOT	SGPT	ALP
SGOT	1		
SGPT	.507*	1	
ALP	-.138	-.026	1

Table2 : Showing Pearson correlation among SGOT, SGPT, ALP at significant value of 0.05 level

	INR	PT	BILLi. .TOTAL
INR	1		
PT	0.950**	1	
BILLIRUBIN TOTAL	0.789**	0.844**	1

Table 3: Showing Pearson correlation among INR, PT, Billirubin direct significant value of 0.01 level.

Pearson correlation was calculated using SPPS for SGOT:SGPT (0.507*) which was found positively correlated and significant at 0.05 level while ALP:SGOT (-0.138) and ALP:SGPT (-0.026) that were negatively correlated to each other.

Pearson correlation was calculated for INR, PT(0.950**), Billirubin and INR (0.789**) and PT and billirubin total (0.844**) was found significantly positively correlated at significance level of 0.01 (table 3).

Also we have tried to analyse the significance of the INR levels as Dependent variable (DV) withbillirubin levels as independent variable (IV) using linear regression and following result were observed.

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	BILLI[b]	.	Enter

a. Dependent Variable: INR
b. All requested variables entered.

Table 4: Showing output of variables used to analyse regression analysis using SPSS calculating INR (dependent variable) using the Billirubin levels.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.789[a]	.622	.609	.59071

a. Predictors: (Constant), BILLI

Table 5: Showing the model summary of the linear regression using SPSS

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	16.081	1	16.081	46.084	.000[b]
	Residual	9.770	28	.349		
	Total	25.851	29			

a. Dependent Variable: INR
b. Predictors: (Constant), BILLI

Table 6: ANOVA showing the significant level of the model used.

From the tables of ANOVA and the Model summary we can say that the significance level of the model used for INR and the billirubin is highly significant with degree of freedom as F(1-28)=46.084, p=0.00.
The adjusted R square =0.6098*100

i.e 60.9% of the variance in INR levels can be explained by the billirubin levels of the patient.

Conclusion:

This case study revealed **sub acute liver failure** according to the**O' Grady system of classification.** This also emphasises the importance of getting the hepatitis B vaccination well at time so that body can develop the antibodies and can fight back even after getting infected. Also any kind of symptoms should not be ignored as the body signals the inner health of the body's vital organs and should consult a doctor immediately. Once the problem is detected we should prefer the specialist. Secondly the timely availability of the donor saved the life of the patient in this case, so organ donation should be promoted and should spread the awareness among the masses through various means so that more lives can be saved.

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