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Review Article

The 10 facts in cirrhosis every Hepatology fellow should know

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Abstract: Where does ascites come from in cirrhosis? Why is there a cut off of 250 neutrophils for diagnosis of spontaneous bacterial peritonitis? Why does hypokalemia lead to hepatic encephalopathy? Why does spur cell anaemia occur in cirrhosis? These are simple issues that we see in a liver intensive unit and during care in a cirrhotic. The purpose of this brief, but reinforcing article targeting Fellows interested in or caring for a liver disease patient is to bring clarity to these every day, but important issues.
Keywords: Cirrhosis, Portal Hypertension, Ascites, HVPG, Hepatic Encephalopathy, Spur cells

INTRODUCTION

Cirrhotics form a major bulk of the patients seen daily in the outpatient department and also intensive care units. It becomes imperative that the physician caring for such patients be well versed with the minutest fact related to liver disease in such a way that resourceful management based on simple, but adequate knowledge prevail. One needs a clear understanding of the common manifestations in cirrhosis. The following ten facts form a part of what a herpetologist or a fellow caring for a liver disease patient witness daily.

1. FACT

In cirrhosis, the right lobe is commonly atrophied with relative hypertrophy of left lobe

REASON

The portal vein supplies liver with blood that contains nutritious supply derived from the intestines through superior mesenteric vein and hepatotropic / proliferative elements from spleen through the splenic vein. In a way, liver volume and growth is related to the distribution of blood from the spleno-portal system. Normally, there is uniform distribution of these substances through the portal vein to both lobes of liver. In what is known as 'laminar flow' in the portal system, it has been shown that, the flow in the superior mesenteric vein is directed mostly at the right lobe whereas the splenic vein empties homogeneously into both lobes. In laminar flow, the blood cells move in layers, one layer sliding over another, with different layers moving at different velocities. In cirrhosis and portal hypertension, distribution of blood from the splenic and superior mesenteric vein changes because of distortion of angio-architecture of liver, resulting in re-routing of more hepatotropic substances to the left lobe and less to the right lobe leading to atrophy of right lobe and hypertrophy of left lobe. Thus right lobe morphologic change is influenced by the redistribution of blood supply from the splenic vein in cirrhotics wherein a major fraction of splenic blood flow is supplied via the left portal vein leading to the left lobe hypertrophy and the right lobe hypertrophy. [Figure 1] [1–4].

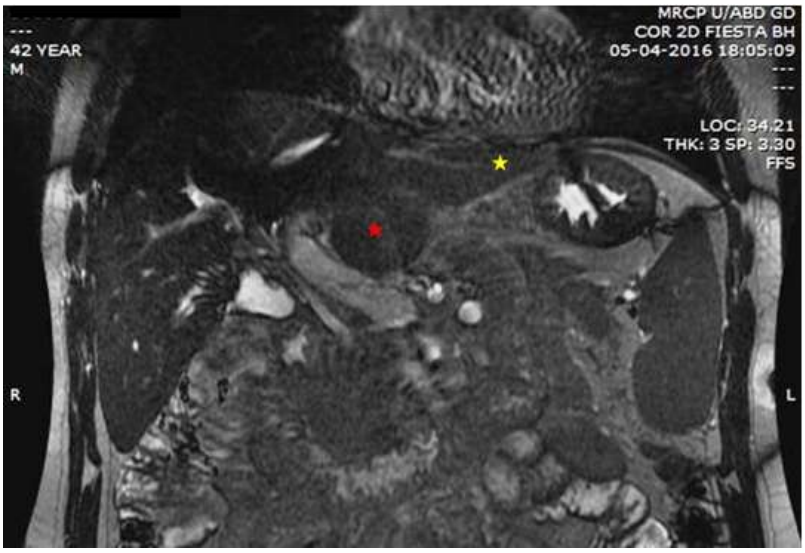

Fig 1: Magnetic resonance imaging of the abdomen showing left lobe hypertrophy (yellow star) and caudate hypertrophy (red star) with atrophy of the right lobe in a patient of alcoholic cirrhosis

2. FACT

The caudate lobe is enlarged in cirrhosis and more so, in patients of Budd-Chiari Syndrome

REASON

The caudate lobe is enlarged up to 2 times normal, in patients with cirrhosis and more so in those with Budd Chiari Syndrome. Consistent with the 'laminar flow' theory, larger redistribution of nutritive elements, hormones and hepatotropic factors to the left hemi liver at the caudate level is one reason for caudate lobe hypertrophy. Most portal branches supplying the caudate lobe arise from left portal vein or from bifurcation of main portal vein. But anomalous supply can be seen from right portal vein or even posterior segmental branches. Caudate lobe also receives specific venous supply independent of portal vein and right gastric vein. Sometimes, para biliary venous system occasionally drains into the medial segment or caudate, as was shown by Coined. Thus anatomical differences and preferential supply in cirrhosis contributes to caudate lobe hypertrophy. [Figure 1]

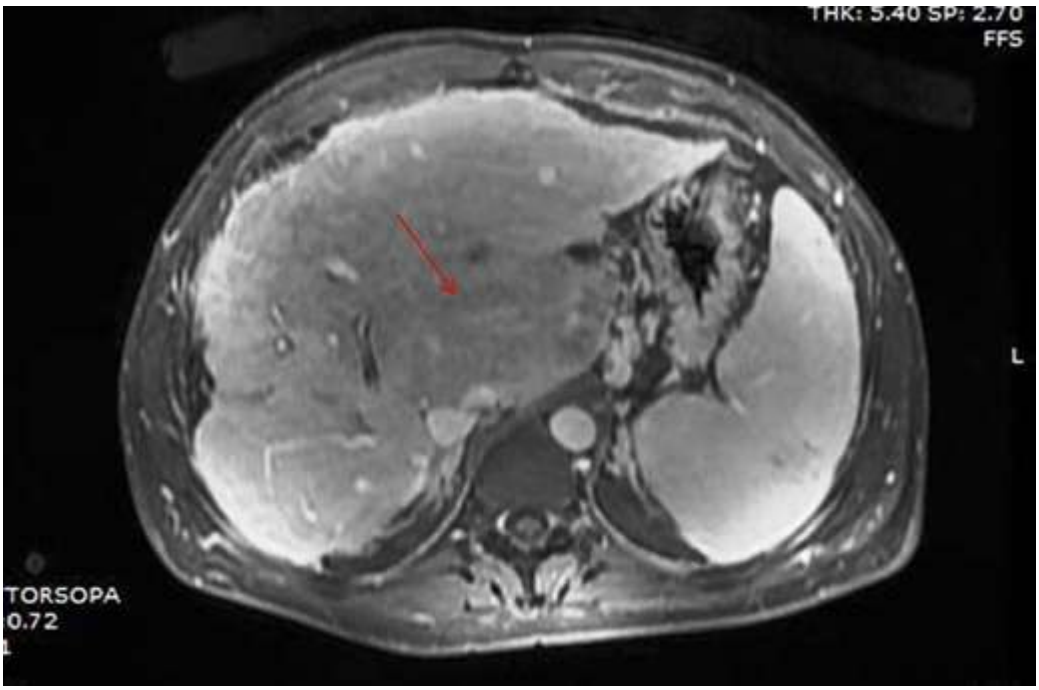

Fig 2: Magnetic resonance imaging of the upper abdomen showing massive caudate lobe hypertrophy (red arrow) in a patient of Budd Chiari syndrome

In Budd Chiari Syndrome, the caudate lobe hypertrophy [**Figure 2**] has a different pathophysiology. Hepatic veins are the only conduits of blood from the liver to the right heart through the inferior vena cava (IVC). The right hepatic vein drains directly into the IVC whereas the left and middle hepatic veins sometimes drain jointly in 60-85% patients. The caudate lobe is the only segment with direct venous drainage to the IVC. This is the reason why, in hepatic venous outflow tract obstruction, there is a higher degree of hypertrophy and perfusion changes of this segment [5–8].

3. FACT

Fatigue is the predominant symptom in primary biliary cholangitis so much that, patients with severe refractory fatigue impairing quality of life can be considered candidates for liver transplantation in the absence of other classical indications.

REASON

Fatigue is unrelated to severity of liver disease and unresponsive to ursodeoxycholic acid therapy in primary biliary cholangitis (PBC) and has complex pathogenesis. There are 2 types of fatigue – central and peripheral. Central component leads to cognitive impairment, depression, anxiety and sleep disturbances, while the latter consists of muscle dysfunction and exercise intolerance. In PBC, cholestasis, endotoxemia, unchecked progressive systemic inflammation and autoimmunity leads to dysautonomia that originate within the central nervous system (important areas included are basal ganglia, brainstem, reticular, limbic and higher cortical centers; with neurotransmitters including corticotropin releasing hormone, serotonin and noradrenaline) that result in central neurological effects along with peripheral neurovascular dysfunction, sympathetic over activity, impaired baroreflex sensitivity leading to poor peripheral muscle perfusion and improper lactic acid handling. These changes result in clinical manifestation of weakness, with poor muscle perfusion contributing more to fatigue and its progression [9 – 11].

4. FACT

Ascites is the commonest decompensation in cirrhosis occurring in approximately 60% of patients within 10 years of diagnosis. The development of ascites predicts a poor prognosis with 50% mortality within 3 years. What is the origin of excessive fluid in the peritoneal cavity in cirrhosis?

REASON

Ascites is defined as accumulation of > 25 mL of fluid in the peritoneal cavity. The cause of ascites in approximately 70% patients is cirrhosis and portal hypertension. Portal hypertension is defined when the hepatic venous pressure gradient (HVPG) is > 5 mm Hg (wedge hepatic pressure – free hepatic wedge pressure) with clinically significant portal hypertension occurring beyond 10 mm Hg. Some authors state that can ascites occur above an HVPG of 8 mm Hg in portal hypertension. Observations in studies conducted in the 1950's revealed that protein rich lymph can be forced from the plasma compartment of sinusoids in the liver and exit through two ways – weeping from the surface of the liver or through the hepatic lymphatic outflow. Starling in 1896 elevated hepatic venous pressures and observed that high protein, high volume fluid flow occurred from the hepatic lymphatics in association with the venous outflow. But when there was total occlusion of the venous outflow, then the protein rich fluid exuded across surface of liver. When this liver was encased in a plethysmograph filled with mineral oil, every exuded fluid droplet was visible as a growing pearl of tear on the surface of the liver. In experimental animal models, it was shown that the normal lymph outflow was around 0.04 to 0.06 mL/min per 100g of liver tissue. This was found to increase as much as 28% over a 24 hour period when the liver was cirrhotic. There is virtually no hydrostatic pressure gradient or colloid osmotic pressure gradient across the fenestrated endothelial cells in the liver. Also, the space of Disse (equivalent to the interstitial space) has free connections to the plasma space. Hence in cirrhosis, when sinusoidal pressure increases, the fluid moves from sinusoidal space of Disse to space of Mall, into hepatic lymphatics that open on to the surface of liver through Glisson's capsule through free channels. Excluding the lymphatic efflux by ligation of vessels in liver, all filtered fluid from the sinusoidal space can be quantified by measuring the hepatic surface exudates. Hence the major source of ascites in cirrhosis in conditions of sinusoidal hypertension is directly through the surface of liver through a rich lymphatic network with unclear connections to deeper sinusoidal lymphatic system [12 – 15].

5. FACT

Hepatic encephalopathy (HE) is spectrum of neuropsychiatric manifestations ranging from subclinical psychological derangements to frank hepatic coma, seen in patients of cirrhosis and portal hypertension. A broad division of HE into types include – A (seen with acute liver failure), B (seen with large port systemic shunts in absence of liver disease) and C, seen in patients of cirrhosis. Within type C, most patients either develop HE that is spontaneous or precipitated. Hypokalemia is a common cause of precipitated HE.

REASON

Excretion of ammonia through urine accounts for the largest portion of net acid secretion and is an important aspect of acid-base homeostasis. Un-excreted ammonia is returned to circulation where it is

metabolized by liver to produce urea with consumption of bicarbonate (Rouelle in 1773 first isolated urea from urine and found that splitting yielded carbonic acid and ammonia; Hans Krebs and Henseleit in 1932 showed that ornithine, without self depletion, stimulated synthesis of urea from ammonia in incubated liver slices – The Krebs-Henseleit Cycle or Urea Cycle, the first metabolic cycle described in history). The proximal tubule of kidney is the most prolific portion in renal ammonia genesis, occurring as a result of cellular metabolism of glutamine to glutamic acid and ammonia within the mitochondria of the basolateral membrane by way of transporter SN1. Ammonia produced in the proximal tubule is then secreted into lumen by diffusion and by ammonium (NH_4^+) conversion transport via apical sodium/hydrogen (Na^+/H^+) exchanger. About 20% of ammonia also reached the renal venous blood via substitution of NH_4^+ for potassium (K^+) – a crucial role played by apical Na^+/K^+ co-transporter. In hypokalemia, there is increase in renal ammonia production due to increase in glutamine uptake into proximal tubule. As less potassium reaches the collecting tubules, more hydrogen ions are taken into the cells, leading to state of relative intracellular acidosis. Renal ammonia generation from glutamine and bicarbonate increases to balance this acid base change, leading to hyper ammonemia and clinically, HE in the patient. [16–18].

6. FACT

Spontaneous bacterial peritonitis (SBP) is a life threatening complication of end stage liver disease. The diagnosis of SBP requires an absolute neutrophil count of 250 cells or above on ascites examination.

REASON

Spontaneous bacterial peritonitis was first described in German and French literature in patients who had bacteraemia associated with peritonitis. Kerr et al and Conn in 1963 and 1964 respectively described infection of the ascites without associated contiguous sources in the abdomen. The latter study was the one in which the term SBP was coined. Multiple studies have thence discussed an ideal way to diagnose SBP faster, without the need to wait for cultures. It was also known that patients did develop infection of the ascites without cultures been positive. Studies on fluid pH, leukocyte count, lactate, protein and various combinations of fluid analytic parameters shed light on different ways to diagnose SBP and for a long time, a cut off value of 500 polymorphonuclear cells/ cm^3 of ascites was considered diagnostic of SBP. In the millennium year, Rimola et al laid guidelines on SBP diagnosis and management and recommended that SBP be diagnosed when the peritoneal fluid neutrophil counts are above 250 cells/ cm^3. This cut off value was taken because it was the most sensitive in diagnosis SBP as against the previous recommendation cut off of 500 cells/ cm^3, the latter being most specific. In patients with bloody ascetic tap (red blood cells > 10,000/mm^3) a correction factor of 1 neutrophil per 250 red blood cells has been recommended. This is because the maximum expected ratio of neutrophils to red blood cells normally present in peripheral blood is 1:250. [19, 20].

7. FACT

Acute variceal bleeding in patients of cirrhosis and portal hypertension has a morality reaching 28 to 30% at 6 weeks. Use of non-selective beta blockers have shown to decrease rates of re bleeding in such patients. A cirrhotic patient on beta blocker (propanolol) therapy since 6 months comes to the outpatient department. His blood pressure is 100/62 mm of Hg and heart rate is 54 beats per minute. He has a recent history of acute variceal bleeding and is confused because his hemodynamic targets (as described by his local physician) were well achieved and he still bled. He wants to change to carvedilol and stop propanolol.

REASON

In 1981, Lebrec and co-workers for the first time, showed the value of utilizing non selective beta blockers (NSBB) in prevention of acute variceal bleeding in patients who had one episode of bleeding. In their study, they targeted a reduction in heart rate by 25% from baseline using propanolol and showed that 25% of patients on NSBB bled as against 50% receiving placebo. All trials thereafter, concentrating on use of NSBB in variceal bleeding has always targeted heart rate reduction by at least 25%. In clinical practice, patients are advised to take NSBB until they achieve heart rate not less than 55 beats per minute and blood pressure of not less than 90/60 mm Hg. These are not targets really. The ideal target for reduction, to prevent a variceal bleed in patients of portal hypertension is hepatic venous pressure gradient (HVPG, **Figure 3**). An HVPG $\geq$ 6 mm Hg is portal hypertension, $\geq$ 10 mm of Hg is clinically significant portal hypertension and $\geq$ 12 mm of Hg carries the highest risk of bleeding from varices. The benefit of reduction in variceal bleeding has been proven in patients who have good hemodynamic response to NSBB – a decrease in HVPG > 20% baseline or to values below 12 mm Hg on continued therapy or in whom, there is a decrease in HVPG to > 10% of baseline 20 minutes after an intravenous infusion of NSBB (propanolol). However, HVPG measurement cannot be performed routinely and is not available at many centres and heart rate does not correlate with reduction in HVPG and hence all patients are advised to titrate the dosing of NSBB to maximal tolerable doses – which means, the blood pressure and heart rate targets are to ensure that patients do not develop untoward hemodynamic complications of overdone NSBB therapy and are in no way related to targets for HVPG reduction. Patients with portal hypertension have a hyper dynamic circulatory state

with increased cardiac output, splanchnic blood inflow and reduced peripheral vascular resistance with relative central hypovulemia, expanded plasma volume and increased intra-hepatic resistance because of angio-architectural changes due to cirrhosis. Propanolol acts on the β1 and β2 receptors and decreases cardiac output and splanchnic vasoconstriction respectively, resulting in reduction of portal pressure and variceal flow due to direct effect on increase in porto-collateral resistance. Carvedilol is a potent NSBB (milligram for milligram, 2 to 4 times >propanolol) with mild antagonistic action at α-1 adrenergic receptors and additive anti-oxidant activity. Apart from its action at β1 and 2 receptors, through its α-1 receptor blocking action, it also decreases hepatic vascular tone and intrahepatic resistance (by enhancing nitric oxide release), resulting in further decrease in portal pressures. But excessive vasodilating effect of carvedilol can worsen arterial hypotension and sodium retention in advanced cirrhotics in whom possibly, propanolol could be a better agent [20 – 23].

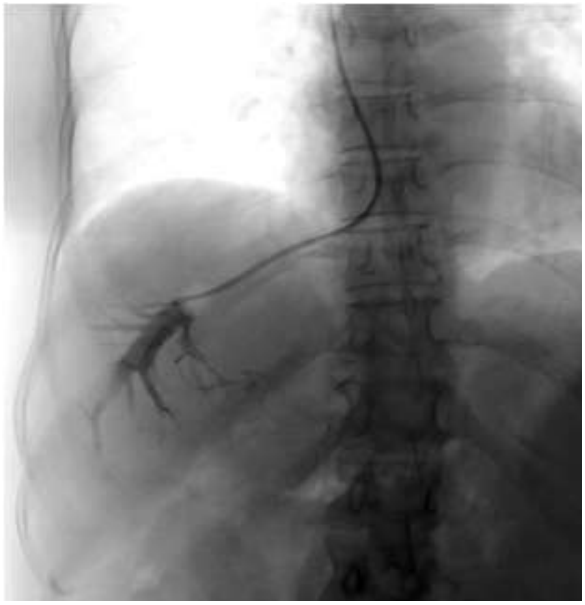

Fig 3: Dynamic fluoroscopy imaging during transjugular liver biopsy showing hepatic venous catheterization, balloon occlusion and hepatic venous pressure measurement

8. FACT

A patient of decompensated alcoholic cirrhosis presents to the emergency department of a peripheral hospital with 2 day history of loose stools and pain abdomen. The medical officer on call prescribed oral antibiotics and probiotic with oral rehydration solution and sends the patient home. Twelve hours later, the patient develops irritability, agitation and confusion and is rushed to a specialized centre in an ambulance. The junior doctor on call notifies the registrar in gastroenterology who advices a bedside ascites evaluation and IV antibiotics with albumin. The junior doctor sees that the patient's INR report done 2 days back was 3.5. He orders 4 units of FFP transfusion prior to a diagnostic bedside paracentesis. During transfusion, the patient develops respiratory embarrassment and fluid overload after which he is intubated and put on mechanical ventilation.

REASON

Spontaneous bacterial peritonitis occurs in 10 to 30% of decompensated cirrhotics admitted to the hospital. It commonly presents as new onset change in mental status, pain abdomen or fever. In some patients, diarrhea or ileus can be a heralding symptom. The diagnosis of 'acute infectious enteritis' should not be used in advanced liver disease and a very strong suspicion and evaluation for SBP must be undertaken in the presence of these clinical features. The diagnosis of SBP requires a bed side paracentesis and should be performed anytime in cases of suspicion. Paracentesis is safe and even in the presence of coagulation failure identified in the presence of grossly deranged traditional parameters like platelet counts and prothrombin time/INR – there is chance of 1 in every 1000 procedures being complication with a hemorrhagic event. Even in the presence of obvious disseminated intravascular coagulation (which was considered one of the absolute contraindications to paracentesis), a cautious fluid tap is worth the risk, especially in patients with multi drug resistant infections or fungal infections of ascites. There is no data to support prophylactic use of fresh frozen plasma or platelet concentrate prior to paracentesis. In procedures like liver biopsy, the American Association for Study of Liver Diseases recommend targeting fibrinogen (>120 g/dL) and platelet counts (more than 50,000/mm^3, the basic level at which adequate thrombin generation is maintained). Excessive transfusion triggers portal hypertensive bleeding. Zimmon and Kessler in 1974 demonstrated

linear correlation between portal pressure and blood volume in cirrhotics. Every 100 mL blood volume expansion in short periods, resulted in a mean increase of portal pressure by 1.4 cm of H_2O equivalent to 1.03 mm Hg. Gianni, Stravitz and Caldwell showed that correction of INR to acceptable value of 1.5 from higher values using large volume plasma transfusions resulted in highly augmented portal pressures deleterious for the cirrhotic (Table 1) [24, 25].

Table 1: INR target of 1.5 and transfusion related portal pressure increase

INR	Volume of fresh frozen plasma transfused (L) to target INR = 1.5	Expected portal pressure increase (mm of Hg)
2.0	1.5	15.5
3.0	2.0	20.6
4.0	2.5	25.8

Modified from: Gianni *et al.;* Hepatology, 2014; 60: 1442

9. FACT

A 38 year old decompensated alcohol related cirrhotic, abstinent since 4 months, presents with severe breathlessness and weakness since one week. He is unable to climb one flight of stairs. A local practitioner orders an echocardiography and complete blood counts. The former shows mild diastolic dysfunction and the latter showed hemoglobin of 4.3 g/dL in the absence of overt bleeds. He is transfused 3 units of packed red cells and transferred to a liver intensive unit where he undergoes an upper and lower gastrointestinal endoscopy which reveals grade 2 esophageal varices without red color signs, stigmata of recent bleed and with mild portal hypertensive gastropathy. Further laboratory investigations reveal haemoglobin of 6 g/dL; total bilirubin 12.5 mg/dL with direct fraction 4.8 mg/dL, INR 5.68, transferrin saturation of 96.6%, corrected retic counts 3.4 %, lactate dehydrogenase level 888 IU/L and presence of 12% spur cells on peripheral smear. The attending registrar prognosticates the family and calls for an expedited living donor liver transplant evaluation.

REASON

Spur cell anaemia has been well described in advanced liver disease and is defined when there is presence of ≥ 5% spur cells (5 to 10 irregularly spaced spiculations on surface of red cells) on peripheral smear evaluation. Spur cell anaemia, an acquired haemolytic anaemia is commonly seen in alcoholic cirrhosis, but can also be seen with other etiologies also. The presence of severe transfusion dependent anaemia, high unconjugated bilirubin, reticulocyte counts, and high INR, high MELD scores in a cirrhotic without overt bleeds must point towards spur cell anaemia and a baseline peripheral smear is always warranted in advanced cirrhotics. The mechanisms of spurring in severe liver disease are thought to be related to increase in free cholesterol in blood due to increased levels of lecithin-cholesterol-acyltransferase. This causes excess free cholesterol within the red cell membrane leading to lipid metabolism dysregulation and membrane fluidity defects, distortion of membrane architecture and impaired deformability. High INR is not uncommon in patients with severe spur cell anaemia. Determination of prothrombin time and INR is based on addition of thromboplastin (phospholipid protein extract) to citrated plasma. In spur cell anaemia, as described above, there is increase in total cholesterol and free cholesterol to phospholipid ration in the deformed red cell membrane. Prothrombin testing in spur cell patient, in the presence of elevated serum cholesterol could lead to altered phospholipid components of thromboplastic reagents. Spur cell anaemia is associated with severe secondary iron overload state, which leads to rapid progression of chronic liver disease. In vivo studies have shown that Chromium tagged spur cells have a half survival of 8 days where as freshly transfused red cells, in the presence of spur cells had a half survival of 6 days which clinically translates to transfusion dependency, which needs to be done to maintain a haemoglobin not more than 6 to 7 g/dL. The presence of spur cell anaemia is associated with a very high mortality at 3 months, independent of liver severity scores and these patients should be given priority for liver transplantation as per many recent studies published in literature [26–28].

10. FACT

A known patient of decompensated cirrhosis on evaluation in the outpatient department for a routine check up was found to have slurred speech and symmetrical bilateral tremors of both hands. The attending resident doctor documents this finding as ‘negative myoclonus’ in his notes and refers the patient to the emergency room, where the primary attending resident notices the patient has grade 2 hepatic encephalopathy and documents the movement disorder as ‘asterixis’. During the academic rounds, the final year senior registrar describes his finding as ‘mini-asterixis’.

REASON

Myoclonus is a sudden, brief, involuntary muscle jerk caused either by an abrupt muscle contraction (positive myoclonus) or by sudden cessation of ongoing muscular activity (negative myoclonus). Negative myoclonus is classified clinically or

etiologically. The former includes – asterixis, physiologic, postural lapses and epileptic; whereas the latter consist of asterixis seen with metabolic derangements, asterixis associated with focal neurological deficits (unilateral) and asterixis of epilepsy. In simple terms, asterixis is a type of myoclonus, sometimes used synonymously. Asterixis is derived from the Greek word – 'a' meaning, 'not' and 'sterixis' meaning 'fixed position', first described by Adams and Foley in 1949. Classical asterixis of hepatic encephalopathy is bilateral, flapping tremor, with frequency of 3 to 5 Hz – a momentary lapse of sustained posture. Asterixis can affect commonly the wrists, Meta carpo phalengeal joints, tongue, upper arms, and hip joints and in the most severe state, can present as drop attacks or falls in affected patients, without loss of consciousness. With arms held in extension and wrist dorsi-flexed, transient loss of extensor tone results in flexion at wrists or fingers in patients of hepatic encephalopathy. In the lower limbs, slight abduction and flexion at the hip and knee results in abduction movements at the joints when the adductor tone is lost intermittently. Mini asterixis is described when asterixis occurs at a higher rate (6 to 12 Hz) in some patients but does not change the prognosis or the clinical management. Some authors also describe the 'dynamic component' of the involuntary movement as mini asterixis and the 'pauses' as negative myoclonus. Clinically asterixis is graded as 0 – no flapping motions; 1 – rare flapping motion, one to two per second; 2 – occasional irregular flaps, three to four per 30 seconds; 3 – frequent flaps, five to thirty per 30 seconds and 4 – almost continuous flapping motions > 30 per 30 seconds. The pathophysiologic reasons behind asterixis are manifold – episodic dysfunction within neural circuits controlling maintenance of sustained/tonic muscle contraction due to a neuro chemical or hormonal imbalance and associated abnormal activity in the parietal and mid brain motor field areas in metabolic derangements or structural disease are been proposed. Unilateral asterixis is seen with lesions of the thalamus, bilateral asterixis is also seen with phenytoin or ceftazidime (in the presence of renal dysfunction) use. In some rare instances, such as anoxic encephalopathy, positive and negative myoclonus is seen to co-exist (Lance Adams Syndrome). Pseudo-asterixis also presents with similar clinical signs, but patient awareness of the abnormal movement exists, unlike true asterixis [29–32].

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