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Research Article

Hepatic Encephalopathy Masquerading as Delirium

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Abstract

Delirium in elderly is often an indicator of a host of more sinister underlying disease processes. Our case highlighted that liver cirrhosis in elderly may decompensate quickly with hepatic encephalopathy presenting as hypoactive delirium. Bleeding piles may signify variceal bleed due to portal hypertension. Hepatorenal syndrome followed rapidly with poor prognosis. There are many causes for delirium and correctly identifying the underlying cause(s) allows appropriate treatment to be initiated promptly.

Keywords: Delirium; Elderly; Hepatic Encephalopathy; Rectal Varices; Hepatorenal Syndrome

Background

As the world ages, there will be more elderly people living among us. The elderly utilizes healthcare services more than the younger patients. The elderly patients are prone to hospital acquired complications such as delirium, falls, incontinence, and infections which prolong their stay and cause increased mortality and morbidity. Based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), the criteria for diagnosing delirium include a new onset of disturbance in attention and awareness, with evidence of underlying organic cause(s) and the change in mental state is not due to a preexisting dementia (Table 1) [1]. A reliable way to diagnose delirium is by using the confusion assessment method (CAM) (Table 2) [2]. In the elderly, the prevalence of delirium ranges from 15 to 50% in the hospital setting [3-6]. Based on the psychomotor status of the patient, the delirious patients can either be hyperactive, hypoactive or mixed. Hypoactive delirium is often missed as the patient tends to be quiet and calm, and therefore carries higher morbidity and mortality risk [7-9]. The causes of delirium are diverse, ranging from single to multiple precipitating factors (Table 3) [3,10,11] and unless each one of them is addressed, the delirium episode may be protracted, and patient may not return to their baseline cognitive and physical functions [6,12]. In fact, delirium has not only been shown to expedite cognitive and functional decline in the long term, but it is also a predictor of mortality and a significant source of caregiver and financial stress [5,13,14].

DSM-5 criteria for delirium: Requires all the criteria to be met
○ Disturbance in attention and awareness
○ Disturbance develops acutely and tends to fluctuate in severity
○ At least one additional disturbance in cognition
○ Disturbances are not better explained by a preexisting dementia
○ Disturbances do not occur in the context of a severely reduced level of arousal or coma
○ Evidence of an underlying organic cause or causes

Table 1: DSM-5 Criteria for delirium (1).

Adapted from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. (fifth edition). DSM-5. 2013.

Confusion Assessment Method (CAM): Delirium requires features 1,2, and either 3 or 4	
Feature 1	Acute change in mental status with a fluctuating course
Feature 2	Inattention
Feature 3	Disorganized thinking
Feature 4	Altered level of consciousness

Table 2: Confusion Assessment Method (2)

Adapted from Inouye SK, Van Dyck CH, Alessi CA., *et al*. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990; 113:941-8.

Common causes of delirium: DELIRIUMSP	
Drugs	Anticholinergic, analgesia, neuroleptics, sedatives
Environment	Ears, eyes, unfamiliar places, unfamiliar persons may further confuse patients. Ensure spectacles and hearing aids to be on when patient is in the ward. Frequent orientation to time, place, person, is also a way to help patient familiarize himself.
Low O2 state	Myocardial infarction which can present silently in elderly, pulmonary embolism, stroke
Infection	Skin, soft tissue, prostate, ear infections often missed
Retention of urine or bowel	Ensure daily bowel movement, urination
Ictal	Non convulsive seizure may not be picked up especially in hypoactive delirium patient
Undernourished and under hydration	Elderly often are not meeting their caloric requirement and can easily became dehydrated
Metabolites	Electrolytes abnormalities including magnesium, phosphate and calcium
Subdural hematoma	For patient with recurrent fall even when he/she denies head injury
Pain	Pain from multiple causes

Table 3: Delirium mnemonics [3,10,11].

Adapted from Marcantonio ER. Delirium in hospitalized older adults. N Eng K Med 2017; 377: 1456-66.

Case Report

Madam R was a 74 year old lady with background of hypertension, ischemic heart disease, chronic kidney disease (CKD) stage 4, atrial fibrillation, and Child's B liver cirrhosis due to primary biliary cholangitis (PBC). Her PBC was diagnosed 2 months before admission with the presence of antibody M2 62 (>15 is the upper limit of normal) and features of liver cirrhosis on ultrasound. She was on treatment with ursodeoxycholic acid, frusemide, spironolactone and propranolol for PBC. Prior to hospital admission, she was independent in her activities of daily living and ambulating at home with walking frame. She presented to General Surgery with lower gastrointestinal bleed which was attributed to hemorrhoids. Prior to this admission, she had several episodes of PR bleeding which were controlled by medical management. However, the patient continued to have recurrent per rectal bleeding causing multiple admissions. Subsequently, the patient became deconditioned physically due to prolonged bed rest and was noted to be more confused.

Geriatric medicine was consulted to address the functional decline and change in mental status. At the time of geriatric evaluation, patient was hemodynamically stable but was somnolent and inattentive. She also had alternating level of consciousness, which her family members determined to be not at her baseline.

Her blood pressure was 137/61 mmHg, heart rate 95 beats per minute, respiratory rate of 22 and oxygen saturation was at 99% on room air. Physical finding showed that she was fluid overloaded with mild dyspnea, elevated jugular venous pressure with reduced air entry on the bilateral lung bases suggestive of pleural effusion. Abdomen was distended with presence of shifting dullness and bilateral pitting lower limb oedema. No asterixis was elicited. Her intake output chart indicated that Madam R had not passed motion for several days and laxatives were held off in view of PR bleeding. No formal cognitive assessment or baseline was able to be obtained, as patient was drowsy and confused at the time of contact. She was on intravenous furosemide 60 mg twice a day, spironolactone, and propranolol.

Her liver function test showed albumin 32 g/L, total bilirubin of 19.7 µmol/L, AST 29 U/L, ALT 11 U/L, and ALP 106 U/L. Her Hb 9.5 g/dL, platelet 59 x 10^3/µL, white blood count 7.6 x 10^3/µL. Her PT 14.9 sec, aPTT 76.5 sec. Urea 15 mmol/L, sodium 141 mmol/L, bicarbonate 19 mmol/L, eGFR (CKD-EPI) 16 mL/min/1.73 m^2, potassium 4.9 mmol/L, and creatinine 245 µmol/L. Her ammonia level was 52 µmol/L (normal range 15-50 µmol/L). Her chest X-ray showed signs consistent with pulmonary congestions and pleural effusion.

Ultrasound abdomen showed heterogeneous and coarse echoes indicative of liver cirrhosis without any hepatic mass. Oesophago gastroduodenoscopy (OGD) showed a 3-4 cm hyperplastic polyp at the cardia and portal gastropathy at the fundus and body. Rigid sigmoidoscopy identified circumferential prolapsed hemorrhoids with largest sites at 4 and 7 o'clock position which were oozing. Hemorrhoidectomy was done but patient continued to have multiple episodes of PR bleeding during the stay. Over the course of several days, the patient's kidney and liver functions deteriorated. She became oliguric, with increasing drowsiness, confused and breathlessness. Oliguria was not responsive to higher doses of intravenous furosemide and albumin. She also developed hospital acquired pneumonia which was treated with intravenous piperacillin- tazobactam.

Her creatinine level increased more than 2.5 fold (101 µmol/L to 318 µmol/L) in less than one week, and subsequently became anuric and hypotensive. Review by gastroenterologist revealed that patient had developed hepatorenal syndrome. In view of her ischemic heart disease, terlipressin was not given. Patient was brought to intensive care unit and was initiated on IV norephinephrine and placed on continuous renal replacement therapy. However, patient continued to deteriorate, suffered a pulseless electrical activity collapse, and demised.

Discussion

From the general viewpoint, it was another ordinary elderly woman who presented with functional decline and hypoactive delirium. Along with her delirium, she had fluid overload and recurrent PR bleeding. The key diagnostic challenge was to decide if the liver disease played a part in precipitating the onset of delirium, caused the fluid overload state and if the bleeding haemorrhoids were what they seemed.

Liver cirrhosis in the elderly can be due to many causes (Table 4) [15]. Among them, primary biliary cholangitis (PBC), which was previously known as primary biliary cirrhosis, is an autoimmune condition destroying the intralobular bile ducts. PBC presents very insidiously with anemia and fatigue. The diagnosis of PBC is confirmed when two of the three criteria are present: increase alkaline phosphatase level of at least 1.5 times the upper limit of normal, presence of anti-mitochondrial antibodies at a titre 1:40 or higher and histologic evidence of non-suppurative destructive cholangitis and destruction of intralobular bile ducts [16-18]. This condition is more prevalent in woman and is also known to cause portal hypertension early in the disease.

Common causes:	**Rare causes:**
• Alcoholic liver disease • Non- alcoholic fatty liver disease • Autoimmune hepatitis • Primary biliary cholangitis • Primary sclerosing cholangitis • Viral hepatitis – hepatitis B and C • Hepatocellular carcinoma	• Haemochromatosis • α-1 Antitrypsin deficiency • Wilson's disease

Table 4: Causes of liver cirrhosis in the elderly [15].

Adapted from Frith J, Jones D, Newton JL. Chronic liver disease in an ageing population. Age Ageing 2009; 38:11-8.

In an elderly patient with liver dysfunction from any cause, it is always pertinent to observe for the possible complications such as hepatic encephalopathy (HE). Liver function test alone may not be the best marker of decompensation. Upper gastrointestinal tract bleeding is often caused by oesophageal varices, portal gastropathy, or ulcers in the stomach or duodenum. Rectal varices in portal hypertension can occur as well although not very commonly thought of [19]. Other complications arising in a patient with liver cirrhosis include ascites, spontaneous bacterial peritonitis, hepatorenal syndrome (HRS), hepatopulmonary syndrome, coagulopathy and hepatic encephalopathy (HE) [15,20,21]. Elderly patients are generally poorer in their physiological reserve. Therefore, they decompensate within a shorter period and suffer multiple complications of liver cirrhosis, increasing their morbidity and mortality.

The key to assess an elderly patient's state of cognition often relies on the establishment of baseline cognition and behavior. For Madam R, conversations with her family members revealed that her state of confusion was new. At the time, the precipitating factors for her delirium included recurrent admissions with invasive procedures (OGD and colonoscopy), anemia, electrolytes derangement, fluid overloaded state and constipation. Upon further evaluation, taking into considerations ultrasound findings of cirrhosis and OGD finding of portal gastropathy, the unifying diagnosis to patient's condition was decompensated liver failure with hepatic encephalopathy. Her persistent PR bleeding may be contributed not only by hemorrhoids but likely the presence of rectal varices and coagulopathy from her elevated PT and thrombocytopenia. Her worsening ascites and oliguria was due to hepatorenal syndrome setting in.

The exact mechanism on the development of delirium in an elderly brain remains unknown [3,8,10]. However, the interplay between systemic inflammation, hypoxemia, and metabolic derangements have been shown to cause imbalances in neurotransmitters which disrupt synaptic communication in the brain and cause delirium [22]. The neurotransmitters with possible links with delirium include acetylcholine, dopamine, 5-hydroxytryptamine, norepinephrine, glutamate and gamma aminobutyric acid (GABA). Interestingly, gamma-aminobutyric acid has been shown to have increased activity in hepatic encephalopathy and itself is an inhibitory neurotransmitter [23,24]. The increased activity of this inhibitory mechanism may explain why hepatic encephalopathy often present as hypoactive delirium [22-24]. Advanced age (> 65 years), cognitive impairment, history of chronic or hepatic disease are recognized as non-modifiable risk factors to development of delirium which were all are present in the case of Madam R [11,22].

Hepatic encephalopathy occurs when liver decompensates and causes brain dysfunction [21]. This condition can present insidiously, and the clinical features are very similar to the description of delirium with psychomotor retardation, inattention, disorganized thoughts, and fluctuations in consciousness. Manifestations of HE ranges from minimal change in cognition to a comatose state. Currently, the West- Haven criteria is often use for staging HE severity (Table 5) which involves some subjectivity in assessing the patient [21,23,25]. Subtle changes in HE may be very difficult to pick up, especially in an elderly with hypoactive delirium and if the patient had no previous episode of HE. The patient may have decrease activity, slower action speed, listlessness, and withdrawal which may lead the physician to suspect more common causes of hypoactive delirium such as stroke, electrolyte imbalances, medications and infections [9,21].

Grade	Consciousness	Intellect and behavior	Neurological findings
0	Normal	Normal	Normal examinations; if impaired psychomotor testing, consider minimal hepatic encephalopathy
1	Mild lack of awareness	Shortened attention span	Impaired addition or subtraction, mild asterixis or tremor
2	Lethargic	Disorientated; inappropriate behavior	Obvious asterixis; slurred speech
3	Somnolent but arousable	Gross disorientation; bizarre behavior	Muscular rigidity and clonus; hyperreflexia
4	Coma	Coma	Decerebrate posturing

Table 5: West-Haven criteria for hepatic encephalopathy [21,23,25].

Adapted from Poh Z, Chang PE. A current review of the diagnostic and treatment strategies of hepatic encephalopathy. Int J Hepatol 2012; 2012: 480309.

Serum ammonia level is useful in diagnosing HE. In a normal person, ammonia is processed into urea by the liver, the kidney, skeletal muscle and the intestine. In the brain, ammonia is cleared by the astrocytes, which convert excess ammonia and glutamate into glutamine by enzyme glutamine synthetase [26]. Elevated ammonia level may cause neuroinhibition, disruption on the GABA and glutamine balance, swelling of astrocytes, resulting in increase in intracranial pressure and cerebral edema [27]. Presence of high ammonia alone is not helpful as indicator for prognosis or diagnosis of HE [21] but high serum ammonia is suspicious for presence of hepatic encephalopathy. Other tests to help with the diagnosis and grading of HE includes psychometric hepatic encephalopathy score test, neuropsychological testing, electroencephalogram, inhibitory control test and neuroimaging [21,25]. However, many elderly may not be able to complete these test as they may be limited by their background cognitive decline.

In Madam R, constipation precipitated her hepatic encephalopathy. Lactulose is often used as the first line treatment for HE. This laxative is broken down by gastrointestinal bacteria into short-chain fatty acids: lactic acid in the gut and acetic acid in the colon. This acidification converts ammonia into ammonium, which is more difficult to be absorbed into the blood stream. As an osmotic laxative, lactulose also cause increase frequency of bowel movement and help to remove ammonia from the body [27]. Therefore, lactulose should be prescribed regularly for patients with liver cirrhosis.

Madam R had a very difficult to control lower gastrointestinal bleeding. Initially, her recurrent PR bleeding was attributed to hemorrhoids. Despite hemorrhoidectomy, patient continued to have hematochezia. In patients with cirrhosis, there is usually underlying coagulopathy which will increase the risk of bleeding. Physicians often thought of oesophageal varices in patients with

portal hypertension. However, these patients may also have rectal varices. The incidence of rectal varices in cirrhotic patients with portal hypertension can vary from 38% to 92% [19]. In many cases it may be difficult to distinguish rectal varices from hemorrhoids as the view may be obscured during colonoscopy in the setting of massive bleeding. Maslekar., *et al.* described that rectal varices can extend from rectum to the anal canal, usually appearing tortuous, compressible and refill immediately after being released [19]. Varices do not prolapse into proctoscopy and may extend beyond 4 cm from the anal verge [20,28]. Madam R did have recurrent bleeding hemorrhoids. However, persistent bleeding despite hemorrhoidectomy increases the suspicion for presence of rectal varices at a higher location in the rectum. Treatment for rectal varices varies from endoscopic band ligation, sclerotherapy, embolization therapy, to a transjugular intrahepatic portosystemic shunt [29].

In addition to all the complications she had, Madam R also developed hepatorenal syndrome. A mostly fatal condition, HRS is very difficult to reverse once it sets in [30,31]. Classically, HRS was differentiated into two types (Table 6 and 7) [35-37], however, in practice, it may be difficult to distinguish a clear cut type in a patient with deteriorating liver and kidney function. Madam R met the diagnostic criteria for HRS, and she is type 2 HRS due to background CKD stage 4. The definitive treatment for HRS is liver transplant [31]. However, the older patients may be excluded from the option of transplant even though the long term outcomes may be similar between older and younger patients [32]. Most patients with HRS, regardless of age, are medically treated with terlipressin and albumin [33,34]. The underlying pathology of HRS is thought to be due to renal vasoconstriction as there is reduction in effective arterial blood volume caused by splanchnic arterial vasodilation from portal hypertension [33]. Terlipressin, a vasoconstrictor often used as a bridge before liver transplant, has been shown to increase cardiac output and renal blood flow by reducing splanchnic vasodilation. However, its use is contraindicated in patient with ischemic heart disease like Madam R [31] who was treated alternatively with intravenous norepinephrine and intravenous albumin as well as supported by renal replacement therapy. Nevertheless, she did not respond to dialysis nor medical treatment.

Conclusion

Recognition of delirium in an elderly patient needs to be done in a timely matter, especially in the case of hypoactive delirium as patients are apathetic and poorly communicative. In fact, some consider mental state examination should be the 6th vital sign, in order not to miss diagnosis of delirium, as the features fluctuate.

Hepatorenal syndrome diagnostic criteria:
• Cirrhosis with ascites. • Serum creatinine >1.5 mg/dL (>133 umol/L). • No improvement of serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin. • Absence of shock. • No current or recent treatment with nephrotoxic drugs. • Absence of parenchymal kidney disease: absence of proteinuria (>500 mg/day), microhematuria, normal findings on renal ultrasound.
Type 1 hepatorenal syndrome:
• Sudden impairment of kidney function in patients with cirrhosis and ascites. • 100% increase in serum creatinine to a value >2.5 mg/dL (221 umol/L) in less than 2 weeks.
Type 2 hepatorenal syndrome:
• Chronic impairment of kidney function in patient with cirrhosis and ascites. • Persistent increase in serum creatinine >1.5 mg/dL (133 umol/L).
Adapted from Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996; 23:164-176.
Current diagnostic criteria
International Club of Ascites criteria (also known as acute kidney injury-hepatorenal syndrome (AKI-HRS)): • Cirrhosis with ascites. • AKI diagnosis according to ICA-AKI criteria. • No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kilogram of body weight. • Absence of shock. • No current or recent use of nephrotoxic drugs. • No signs of structural kidney injury: absence of proteinuria (> 500 mg/d), microhematuria, normal findings on renal ultrasound.
AKI in cirrhosis definition:
• increase in sCr ≥ 0.3 mg/dL (≥26.5 μmol/L) within 48 hours, or • increase in sCr ≥ 50% from a known baseline, or • presumed to have occurred within 7 days.
Adapted from Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015; 62: 968-974.

Table 6: Hepatorenal syndrome definition and criteria [35-37].

AKI, acute kidney injury; ICA, international club of ascites; SCr, serum creatinine; AKIN, Acute Kidney Injury

AKI stages	
AKI 1 • AKI 1A • AKI 1B	Increase in sCr ≥0.3 mg/dL (26.5 5 µmol/L) or an increase in sCr≥ 1.5-2 fold from baseline. SCr at diagnosis <1.5 mg/dL. SCr at diagnosis ≥ 1.5 mg/dL.
AKI 2	Increase in sCr >2 -3 fold from baseline.
AKI 3	Increase in sCr >3 from the baseline or sCr ≥ 4.0 mg/dL (353.6 µmol/L) with an acute increase ≥ 0.3 mg/dL (26.5 µmol/L) or initiation of renal replacement therapy.

Table 7: Stages of AKI in cirrhosis according to ICA-AKI based on AKIN criteria [36,37].

AKI, acute kidney injury; ICA, international club of ascites; SCr, serum creatinine; AKIN, Acute Kidney Injury Network. Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int 2012;2(Suppl 1):1-138.

This case illustrated the complexity of liver cirrhosis in elderly where decompensation manifested as hepatic encephalopathy and masqueraded as delirium, rectal varices, and hepatorenal syndrome. Hepatic encephalopathy is very similar to delirium but unless one realizes the cause is decompensating liver failure, one may not address the underlying problem. Similarly, lower gastrointestinal bleed which may seemingly be due to a benign cause such as hemorrhoids may in fact be more complex in cirrhosis as patient may have underlying coagulopathy and rectal varices. Many elderly patients have background of chronic kidney disease, and as the liver decompensates, these patients may develop hepatorenal syndrome, of which is very difficult to treat and may result in their further deterioration and death.

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