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A Study Of MR Imaging Of The Basal Ganglia And Serum Manganese Concentration In Cirrhotic Patients With Portosystemic Shunting

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Abstract

Manganese in normally removed by hepatobiliary route. In long term hepatic dysfunction with portosystemic shunting it accumulates in systemic circulation and may deposit in CNS particularly in the basal ganglia, resulting in permanent extrapyramidal manifestations and a unique form of parkinsonism characterized by early gait impairment, postural fine tremor, symmetric akinetic rigidity and sometimes associated with focal dystonia (Purkhard et al., 2003). In this study: 50 male cirrhotic patients, aged 28 –59 years, were selected from Internal Medicine department – Al Hussein university hospital, in addition to 20 age-matched healthy males as a control group. All subjects (patients & controls) were submitted to (1) Full clinical & laboratory examination including liver function tests and serum manganese estimation using atomic absorption technique. (2) Abdominal triphasic spiral CT scanning for evaluation of portosystemic collaterals and to assess the hepatic intensity and the splenic size (3) MR Imaging of the brain. We have concluded that: (i) The studied cirrhotic patients had a statistically higher serum manganese concentration than that of the controls. (ii) 24/50 patients (48%) showed variable degrees of basal ganglia hyperintensity on T_1- weighted MR images, associated with marked elevation of serum manganese levels (five to seven fold the normal level) and advanced grades of gastroesophageal varices on triphasic spiral CT scanning (iii) 26/50 patients (52%) showed normal intensity in the basal ganglia on T_1- weighted MR images with relatively Lower levels of serum manganese (two to four fold the normal level) and early grade of gastroesophageal varices on triphasic spiral CT scanning (iv) serum manganese concentration of cirrhotic patients with hyperintensity in the basal ganglia on T1 weighted MR imaging was statistically higher than that of cirrhotic patients with normal intensity – basal ganglia.

Introduction & Aim Of The Work:

Cirrhotic patients with hepatic insufficiency and portosystemic shunting may have neurological syndromes resulting from permanent central nervous system (CNS) changes mainly in the basal ganglia, less commonly in other CNS sites such as cerebellum, spinal cord and even cerebral cortex. Symptoms of these syndromes respond partially to treatment of hepatic encephalopathy and thought to be related to organic changes in CNS (Bernthal *et al*., 1987). The precise relationship between chronic liver disease and these syndromes is unknown. The clinical, neuroradiological and biochemical characteristics of such acquired hepatocerebral degeneration have not yet been fully determined (Burk hard, 2003), Hypermanganemia with deposition of manganese (Mn) in CNS may be implicated (Rose *et al*., 1999).

Lesion with high signal intensity on T1- weighted MR imaging are unusual and are associated with relatively few entities, including paramagnetic trace elements (particularly manganese) infiltration.

In this study, we aimed to demonstrate prospectively the prevalence of extrapyramidal symptoms in cirrhotic patients, determine their main neurological features and to establish the correlation of

biochemical findings (Serum manganese concentration) in such patients with their clinical features, neuroradiological findings and magnitude of portosystemic shunting (grading of gastrooesophageal varices).

Subjects, materials and Methods

Fifty male patients with liver cirrhosis, aged 28 – 59 years, were selected from Al Hussein university hospital-department of internal medicine, in addition to twenty age-matched healthy control males with normally ranged liver function tests. All subjects (patients and controls) were non-diabetic non-hypertensive and non-smoker with normal lipid profile. They all were submitted to the following:

1 - Full clinical assessment: (using Child pugh's score) with detailed neurological examination (Table 1 & 2).

Severity of cirrhosis is the sum of the severity scores for the variables shown in table 1.

2 – Laboratory tests:

(i) Evaluation of liver functions (using child pugl's score), including:

a) serum albumin estimation: by direct calorimetric method with bromocresol green (Doumas *et al*., 1971).

b) Total serum bilirubin by direct bilirubin reagent set (Martienk., 1966).

c) Prothrombin time / INR: using photemetric determination method (Dati *et al.*, 1966).

(ii) Estimation of serum manganese (Mn) concentration using flame atomic absorption technique (FAAS) – Perkin elmer 2380 apparatus – in which sera were deproteinized using 0.2 ml of 10% trichloro – acetic acid. This procedure permits direct determination of Manganese in the sera without matrix interferences. Sera were centrifuged and the metal determined in the filtrate then directly aspirated into the flame of the spectrophotometer. The absorbance was measured at a wavelength of 279.5nm. Calibration graph was linear for 1-4 μg/ml of Mn. Normal serum Mn ranges from 0.01 to 0.03 μg/ml according to such procedure (Cart A et al,. 2000).

(3) Abdominal triphasic spiral CT scanning: to assess the degree of portal – systemic shunting, the caliber of portal vein, the size & density of the liver, the size of the spleen and the presence of ascites. Scanning was performed during the portal phase for revealing of portosystemic collaterals that can be detected by triphasic abdominal CT scanning as accurate as endoscopy; furthermore, it has the advantage over endoscopy in evaluating the liver, spleen and the entire portal circulation (Schozo H, 1999). The apparatus used was Somatom plus 4-simens. Iopamidol was the contrast medium used, CT section thickness was 5mm. According to (Sarin SK, 1992) gastrooespohageal varices were categorized into:

(A) Isolated Gastric varices: (IGV):

Gastric varices that occur independently of esophageal varices, subdivided into:

i – Type A-1 (early IGV): refer to varices that occur in the fundus of the stomach

ii- Type A-2 (advanced IGV): refer to varices anywhere in the stomach including the body, antrum, pylorus and duodenum.

(B) Gastroesophageal varices (GOV):

i – Type B-1 (early GBV): varices which extend for 2-5 cm below gastro-esophageal junction along the lesser curvature of the stomach

ii – Type B-2(advanced GOV): esophageal varices which extend below gastroesophageal Junction into the fundus of the stomach.

4 - MR imaging of the brain:

Imaging was carried out at Al Hussein University hospital, using 1.5 tesla system: simens vision apparatus with a standard head coil.

Routine MR imaging of the brain was performed which included T1 sagittal imaging as well as proton density weighted, T1 & T2 weighted axial imaging. Both imaging studies were performed with 256 x 512 matrix over a 22 – cm field of view with 5mm – thickness sections and one mm gap. The exact parameters of conventional sequence imaging were 500/15 (repetition time - TR-) msec /echo time (TE), 3000/30 and 80; with two signals acquired for the T1 weighted imaging and one signal acquired for the proton density – weighted and T2- weighted imaging.

Table 1:Child pugh's score: according to (Jalan and Hayes, 2000)

Variable	A	B	C
- Enceplalopalty	O	I/II	III/IV
- Ascites	Absent	Mild/moderate	Severe
- Total serum bilirubin (mg/dl)	< 34	2.4 – 3.5	< 2.8
- Serum albumin(gm/dl)	> 3.5	2.8 – 3.5	< 2.8
- Prothrombin time (INR)	< 1.3	1.3 – 1.5	> 1.5
- Score	≤ 6	9 – 7	≥ 10

Results:

Results obtained were statistically analysed and tabulated in table (2 - 7):

Table 2: Clinical & biochemical profiles of cirrhotic patients:

Variables	Child's classes		
	A (8/50)	B (14/50)	C (28/50)
Age (years):	36.4±4.8	48.6±5.7	54.5±6.3
Ascites: - No ascites. - mild/moderate. - marked.	 8 - -	 - 14 -	 - 12 16
Total serum bilirubin (mg/dl): - Range. - Mean.	 0.4-1.2 0.75 - 0.35	 1.4 - 2.9 2.08 – 0.32	 2.5 – 6.8 3.86 – 2.92
Serum ablumin (gm/dl): - Range. - Mean.	3.6 - 4.1 3.66 ±0.42	2.5 – 3.3 2.91 – 3.76	1.4 – 2.8 1.94 – 0.65
Prothrombin time (INR): - Range. - Mean.	 1.1 – 1.2 1.18 ± 0.05	 1.3 – 1.5 1.41 ± 0.95	 1.5 – 1.8 1.67 ± 0.15
Child's score: - Range. - Mean.	 5-6 5.5 ± 0.48	 7-9 8.2 ±6.6	 10-12 10.9 ± 0.88
Neurological sings:	+ Rigidity No tremor	++ Rigidity ± Postural tremor	+++ Rigidity ++ Postural tremor

Table 3:Comparison between control subjects and cirrhotic patients as regards serum manganese concentration:

Serum manganese (µg/ml)	Control subjects	Cirrhotic patients	t-value	P-value
- Range	0.01 – 0.035	0.071 - 0.199	9.135	<0.001
- Mean	0.021±0.039	0.141-0.039		H.sig.

Tabulated t value at 95% degree of freedom, significant difference: p value <0.05.

Table 4:Correlation between the grade of gastroesophageal varices and serum manganese concentration in cirrhotic patients:

Serum manganese: (µg/ml)	Patients with early grades varices: No.=26/50	Patients with advanced grades varices: No.=24/50	t-value	P-value
- Range.	0.071-0.121	0.149-0.199	5.21	<0.01
- Mean.	0.109±0.023	0.175±0.19		H.sig

Table 5: Correlation between MRI findings in the basal ganglia and serum manganese concentration in cirrhotic patients

Serum manganese (µg/ml)	Patients with normal intensity basal ganglia No.=26/50	Patients with hyper-intensity – basal ganglia No.=24/50	t-value	P-value
- Range.	0.071-0.121	0.149-0.199	5.1	<0.01 H.sig.
- Mean.	0.109±0.023	0.175±0.019		

Table 6: Correlation between MRI findings in the basal ganglia and clinical features:

Clinical data	Patients with normal intensity basal ganglia No.=26/50	Patients with hyper-intensity – basal ganglia No.=24/50	t-value	P-value
Child's score:				
- Range.	5 – 8	9.0 – 11	7.72	<0.01
- Mean.	6.4±0.82	10.33±0.94		H.sig.
Neurological Signs	+ Rigidity ± postural fine tremor	+++ Rigidity +postural fine tremor		

Table 7:Distribution of cirrhotic patients with different grades of gastroesophagial varices in relation to the intensity of the basal ganglia on MRI

Clinical data	Patients with normal intensity basal ganglia No.=26/50	Patients with hyper-intensity – basal ganglia No.=24/50
Early grades varices Type A – 1 Type B – 1	 5 21	
Advanced grade varices Type A – 2 Type B – 2		 2 22

[a]

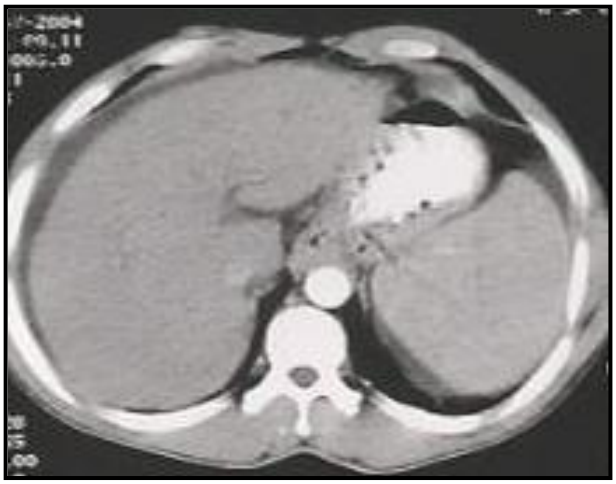
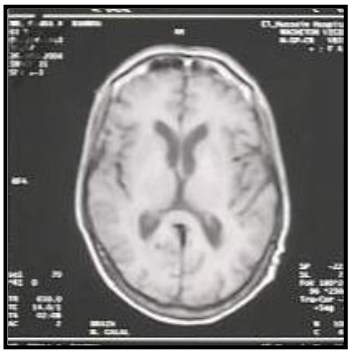


Fig (1-a): Axial CT scan shows small esophageal varices (Gastroesophageal varices type 1).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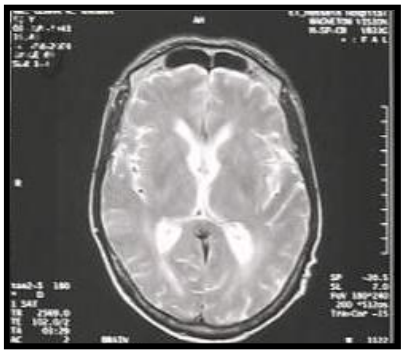
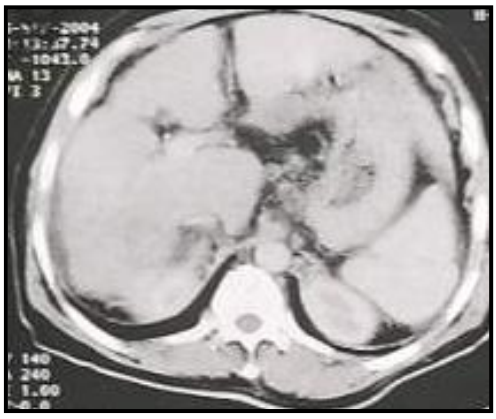
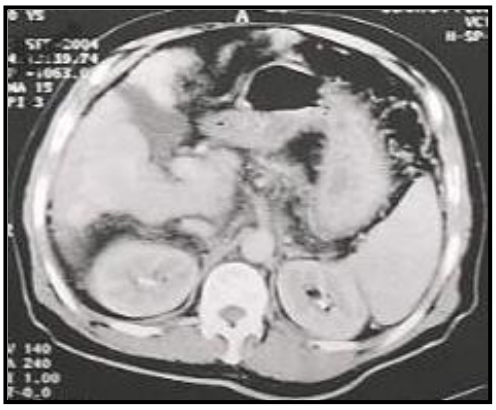

[c]

Fig (1-b,c): Serial MRI scan axial T_1 & T_2 – weighted images show normal signal intensity of globus pallidus.





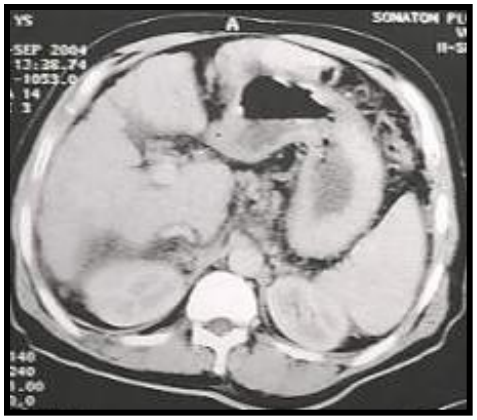
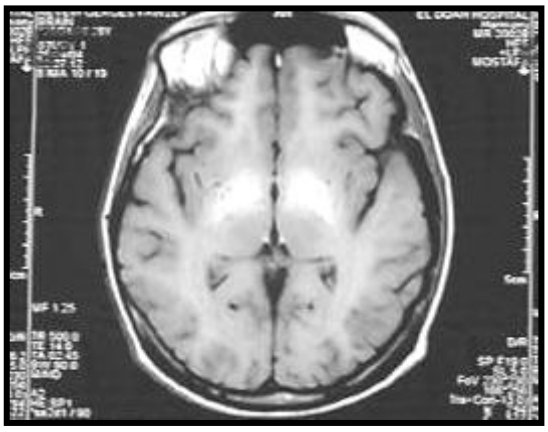


Fig (2-a): Serial films of contrast enhanced axial CT scan shows large gastric varices, which are connected with esophageal varices (Gastroeso-phageal varices type 2).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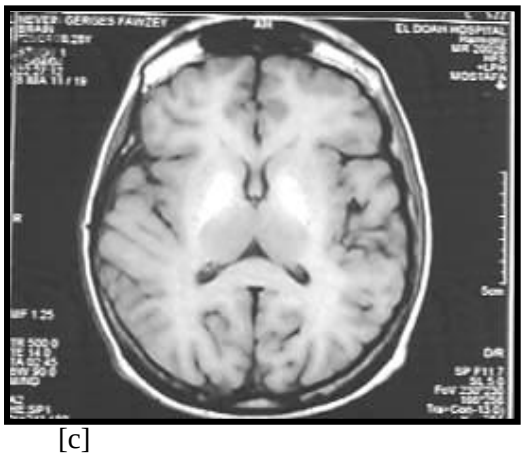
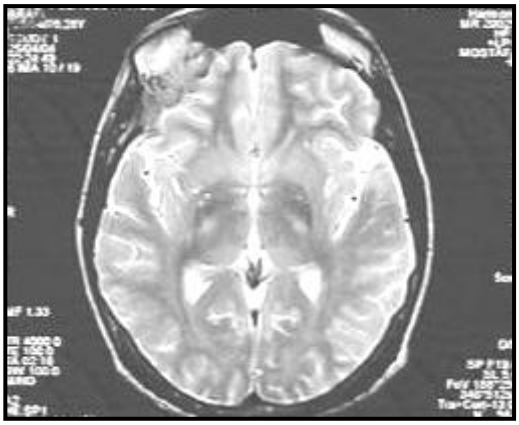
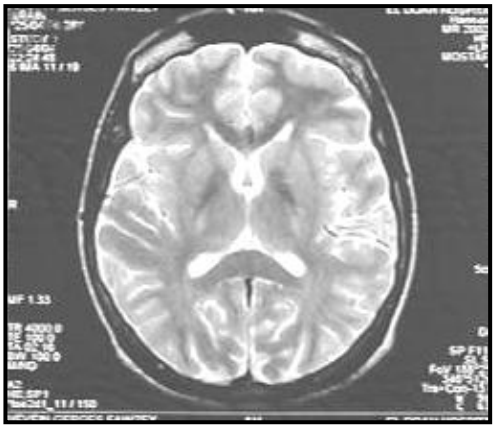

[c]

Fig (2-b,c): serial MRI scan axial T_1- weighted images show increased signal intensity of globus pallidus.





[d] [e]

Fig (2-d,e) serial MRI scan of axial T_2-weighted images corresponding to (Fig 2-b,c) show no alteration in signal intensity of globus pallidus .

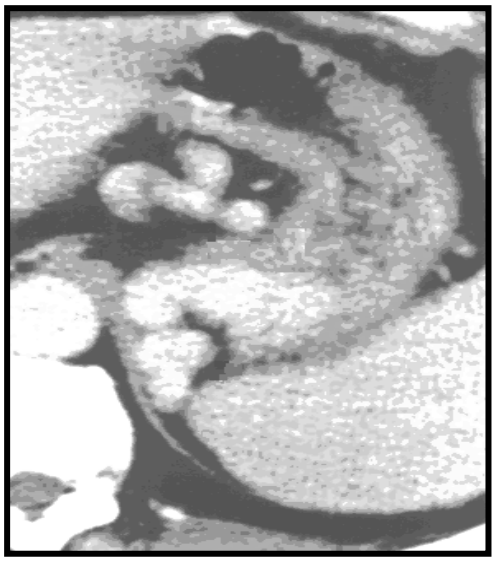
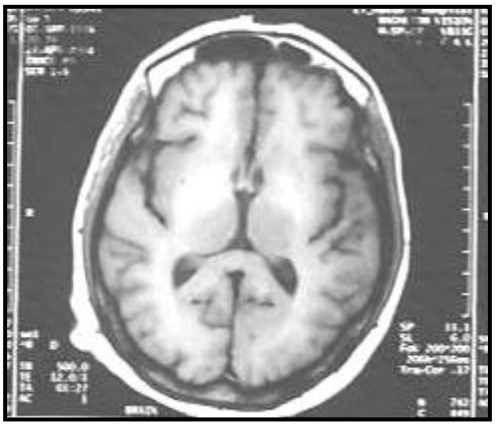
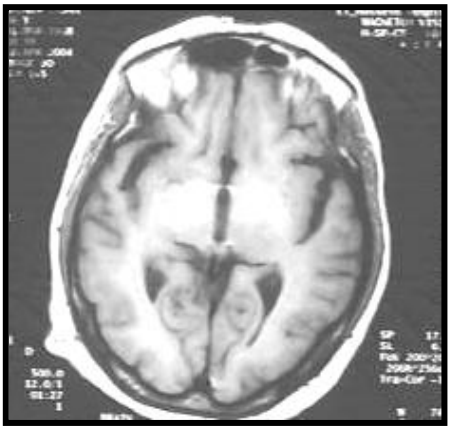


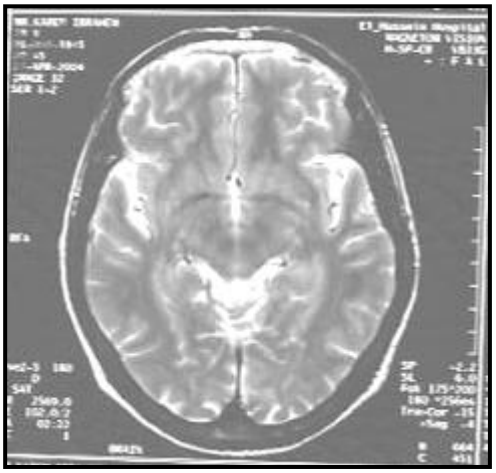
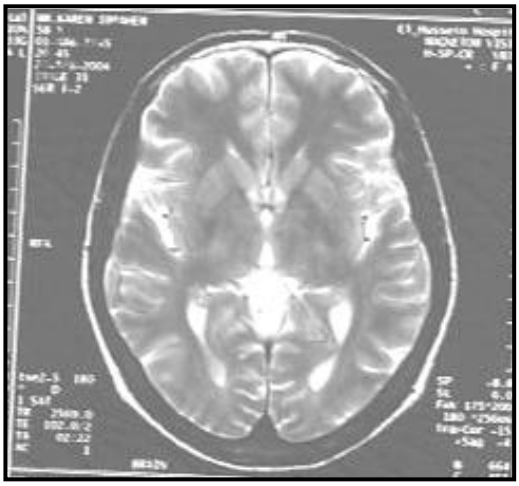
Fig (3-a): contrast enhanced axial CT scan shows large gastric varices extending from the fundus to the body of the stomach (isolated gastric varices-type 2).





[b] [c]

Fig (3-b,c) serial MRI scan axial T1-weighted MR images reveal increased signal intensity of glolus pallidus.

[d] [e]

Fig (3-d,e): serial MRI scan axial T2- weighted MR images corresponding to (Fig 3-b,c) show no alteration in signal intensity of globus pallidus.

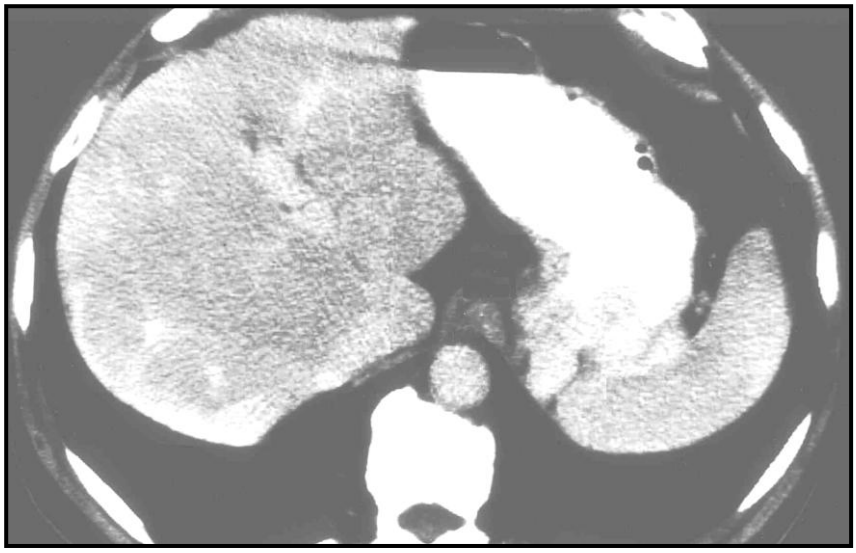
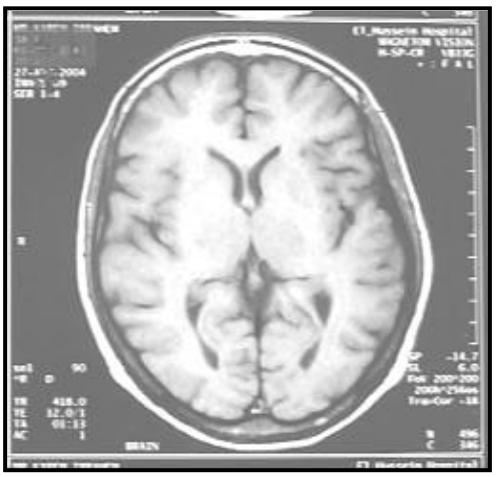
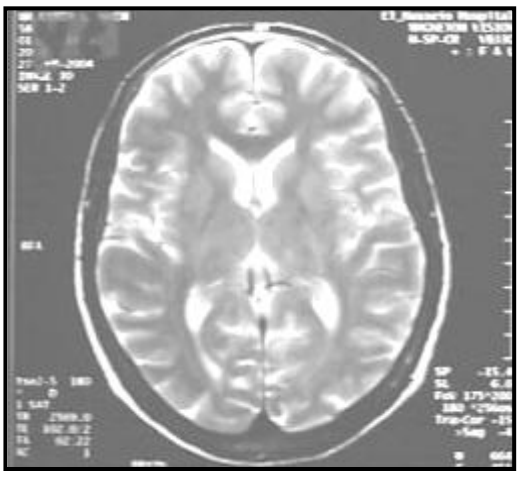


Fig (4-a): contrast enhanced axial CT scan shows gastric varices on the posteromedial border of the fundus (isolated gastric varices - type 1)

[b] [c]

Fig (4-b,c): Axial T1 & T2- weighted MR images reveal no changes in signal intensity of globus pallidus.

Discussion:

Cirrhotic patients with portosystemic shunting and hepatic insufficiency may have neuropsychiatiric syndromes as a result of acquired hepatocerebral degeneration mainly affecting the basal ganglia whose clinical features is permanent and entirely different from that of acute hepatic encephalopathy (Bernthal *et al*., 1987), these changes are thought to be due to deposition of paramagentic trace elements, particularly manganese (Mn), which is accumulated in the systemic circulation of cirrhotic patients with portosystemic shunting. Manganese is normally removed by hepatobiliary rout; in such patients it is deposited in CNS particularly the basal ganglia (mostly in globus pallidus, to a less extent in putamen and subthalamic nuclei) resulting in extrapyramidal manifestations and a unique form of parkinsonism characterized by early gait impairment, postural tremor, symmetric akinetic rigidity and sometimes associated with focal dystonia (Purkchard *et al*., 2003).

This study showed a significant difference between controls and cirrhotic patients as regards serum manganese concentration, being higher in cirrhotic patient (table 3); this goes with what was published by (Cordoba J *et al*., 2002) that hypermanganemia is a universal finding in cirrhotic patients with no evidence of overt hepatic encephalopathy which may be associated with pallidal hyperintensity on T_1- weighted MR images. This report is consistent with our findings that all studied cirrhotic patients had elevated serum manganese levels, 48% of them showed hyper intensity in the basal ganglia on T_1-weighted MR imaging and a relatively higher serum manganese levels compared to those with normal intensity-basal ganglia (52%) (Table 5).

On the other hand, there was a significant correlation between the grade of gastroesophageal varices and serum manganese concentration (Table 4); advanced grades of varices -grade A-2 & B-2- (Fig: 2-a & 3-a) were associated with significantly higher concentrations of serum manganese than early grades of varices -grade A-1 & B-1 (Fig: 1-a & 4-a), this finding goes with what was reported by (cordoba *et al*., 2002) that the magnitude of pallidal hyperintensity induced by manganese deposition in cirrhotic patients was correlated to the degree of portosystemic shunting rather than the grade of hepatic encephalopathy; this is also consistent with what was published by (Mizoguchi *et al*., 2001) that children with congenital portosystemic venous shunts showed elevation of serum manganese and magnetic response imaging changes in the basal ganglia, avoidance of excessive manganese intake is recommended for such children. Regarding to chelation therapy of manganese toxicity (using Ca Na_2 EDTA); it may improve neurological symptoms in those patients, but this is more evident for acute rather than chronic manganese toxicity (Matthew *et al*., 1988).

Mizuta et al., 2002, reported that hyperintensity in the basal ganglia on MR imaging of children with congenital portosystemic venous shunts disappeared after obliteration of such shunts with normalization of their serum manganese concentrations.

Regarding to the correlation between serum manganese concentration and the magnitude of basal ganglia intensity in cirrhotic patients studied in this study, although all of them had serum manganese levels above the normal range, not all of them showed basal ganglia hyperintensity. Patients with hyperintensity in the basal ganglia had relatively and significantly higher levels of serum manganese than those with normal intensity – basal ganglia on T_1- weighted MR imaging (Table 5). This finding goes with what was published by Cordoba *et al*., 2002. That typical pallidal hyperintensity on T_1- weighted MR images of patients with cirrhotic liver disease appeared to be secondary to accumulation of manganese in the basal ganglia.

Vymazal *et al*., 1996 reported that hypermanganemia induced MR1 changes in

the brain (Mainly in the basal ganglia) of cirrhotic patients were invisible on T_2-weighted MR study because T_2 is much shorter than T_1 specially in the globus pallidus.

Maeda *et al*., 1997 published that while causes of basal ganglia- hyperintensity on MR imaging are though to be due to deposition of paramagnetic trace elements (Manganese, Copper, Zinc, Iron and Calcium) the question was which of these elements is implicated in cirrhotic patients? To answer this question they underwent autopsy of four patients who had chronic cirrhotic liver disease for histopathological study and measurement of the concentration of these trace elements in their basal ganglia. Three patients out of them (75%) had high manganese concentrations five to ten fold the normal value; concentrations were higher in globus pallidus than putamen. Copper concentrations were also high in those patients but not as high as manganese, its concentrations were only about 50% more than normal. Other elements concentrations (Calcium, Iron and Zinc) were all normal. Prior to autopsy the three patients who had high concentrations of manganese and copper in the basal ganglia on autopsy showed hyperintensity in the basal ganglia on T_1-weighted MR imaging; while the fourth patient who had normal concentration of such elements showed no abnormal intensity in the basal ganglia on T_1-weighted MR imaging. Hyper intensity in the basal ganglia on T_1- weighted MR imaging was associated with normal intensity or rarely hyperintensity - basal ganglia on T_2- weighted MR imaging, but the relatively low copper concentrations in the basal ganglia of most of cirrhotic patients on autopsy compared to markedly higher manganese concentrations; may attribute the hyper intensity in the basal ganglia on T_1- MR imaging to be mainly induced by manganese deposition rather than copper deposition.

This report is consistent with our obtained results which showed that 24 out of 50 cirrhotic patients showed hyperintensity in the basal ganglia on T_1- weighted MR imaging (Fig. 2- b,c & Fig. 3- b,c) with serum manganese concentrations five to almost seven fold the normal range in comparison to 26 out of 50 patients with normal intensity-basal ganglia (Fig. 1-b,c & Fig. 4 - b, c) who had serum manganese concentrations ranging from two to four fold the normal level. (Table 5).

From (table: 4, 5) we can interpret a significant correlation between the grade of gastroesophogeal varices (which reflect the degree of portosystemic venous shunting) and the signal intensity in the basal ganglia on T_1- weighted MR imaging, as basal ganglia – hyperintensity was only noticed in the same patients with high grade varices and severe portosystemic shunting (Table 7).

There was a significant correlation between the clinical features and the intensity in the basal ganglia on T_1-weighted MR imaging; Child's; score was significantly higher in cirrhotic patients with hyperintensity in the basal ganglia than that in those with normal intensity - basal ganglia. (Table: 6).

Regarding to neurological manifestations; while patients with normal intensity-basal ganglia showed only mild degree of symmetric rigidity with or without postural fine tremor; those with hyperintensity basal ganglia showed marked symmetric rigidity associated with postural fine tremor.

From the above mentioned discussion, hypermanganemia is thought to be implicated in hepatocerebral degeneration which takes place in the basal ganglia, with its subsequent extrapyramidal features in cirrhotic patients who show evident portosystemic shunting.

Recommendation:

Estimation of manganese concentration in the cerebrospinal fluid as well as in the serum of cirrhotic patient is recommended to acertain its role in hepatocerebral degeneration in those patients.

Cirrhotic patients with portosystemic shunting and high serum manganese should avoid excessive manganese intake. Manganese chelating agent (Ca Na_2 EDTA) may be of help in lowering serum manga-

nese concentration and improving life style in such patients, particularly those with normal intensity-basal ganglia and high serum manganese.

MR imaging of the brain, particularly the basal ganglia is recommend for neuroradiological evaluation of cirrhotic patients with portosystemic shunting.

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دراسة فى صور الرنين المغنطيسى للنوى القاعدية بالدماغ وتركيز عنصر المنجنيز فى أمصال مرض التليف الكبدى المصحوب بالتحول الوريدى البابى – الجهازى

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فى الظروف الطبيعية يتم التخلص من المنجنيز الزائد بالدم عن طريق إفراز الكبد له فى العصارة الصفراوية. أما فى حالات تليف الكبد المصحوب بالتحول الوريدى البابى - الجهازى وفشل وظائف الكبد، فيزيد تركيز المنجنيز فى الدم ويترسب فى الجهاز العصبى وخاصة فى النوى القاعدية للدماغ مما ينتج عنه العلامات المرضية الدالة على اعتلال الجهاز العصبى اللاهرمى متمثلاً فى نوع خاص من الشلل الرعاش يتميز بارتعاش وضعى دقيق وتصلب بالعضلات متماثل فى الجانبين الأيسر والأيمن وخلل فى أسلوب المشى وقد يصاحبه عسر الحركة البؤرى.
وقد تم فحص خمسين مريضاً مصابين بالتليف الكبدى تراوحت أعمارهم من 28 – 59 عاماً تم اختيارهم من قسم الأمراض الباطنة بمستشفى الحسين الجامعى بالإضافة إلى عشرين من الأشخاص الأصحاء الذكور ممن توافقت أعمارهم مع أعمار المرضى اختيروا كمجموعة ضابطة. وقد خضع جميع الأشخاص (مرضى وأصحاء) للآتى:-
1 – الفحص الإكلينيكى والمعملى الذى شمل وظائف الكبد وقياس تركيز المنجنيز فى أمصال المرضى والمجموعة الضابطة.
2 – المسح الحلزونى المقطعى ثلاثى المراحل للبطن لتقييم التحولات الوريدية البابية الجهازية فى مجموعة المرضى ولتقييم حالة الكبد والطحال لديهم بدقة.
3 – تصوير المخ بالرنين المغنطيسى.
وأسفر البحث عن النتائج الآتية:-
1 - تركيز المنجنيز فى أمصال المرضى كان أعلى بدرجة ذات دلالة إحصائية منه فى أمصال المجموعة الضابطة من الأشخاص الأصحاء.
2 - 48% من المرضى أظهروا صوراً ذات حدة زائدة (بدرجات متفاوته) للنوى القاعدية للدماغ عند التصوير بالرنين المغنطيسى لهم. وهؤلاء المرضى تميزوا بارتفاع شديد فى تركيز المنجنيز فى أمصالهم تراوح بين خمسة وسبعة أضعاف التركيز الطبيعى وبوجود دوالى متقدمة بالمعدة والمرئ عند إجراء المسح المقطعى الحلزونى ثلاثى المراحل لهم.
3 - 52% من المرضى أظهروا صور ذات حدة طبيعية للنوى القاعدية للدماغ عند التصوير بالرنين المغنطيسى لهم. وهؤلاء المرضى تميزوا بارتفاع أقل نسبياً فى تركيز المنجنيز فى أمصالهم تراوح بين ضعفى وأربعة أضعاف التركيز الطبيعى؛ وبوجود دوالى مبكرة بالمعدة والمرئ عند إجراء المسح المقطعى الحلزونى ثلاثى المراحل لهم.

4 - كان تركيز المنجنيز فى أمصال المرضى الذين أظهروا صوراً ذات حدة زائدة بالنوى القاعدية للدماغ أعلى بدرجة ذات دلالة إحصائية منه فى أمصال المرضى الذين أظهروا صوراً ذات حدة طبيعية بالنوى القاعدية للدماغ.

ويوصى البحث بالآتى:

1 - ضرورة قياس تركيز المنجنيز فى كل من المصل والسائل المخى الشوكى لمرضى التليف الكبدى ممن أظهروا علامات عصبية لا هرمية مع التصوير بالرنين المغنطيسى للنوى القاعدية بالمخ لديهم للتأكد من دور المنجنيز فى إحداث التفسخ الكبدى المخى لتلك النوى.

2 - كما يوصى البحث بضرورة التصوير المغنطيسى للمخ بالنسبة لمرضى التليف الكبدى ممن أظهروا ارتفاعاً فى مستوى المنجنيز فى أمصالهم لدراسة تغلغل العناصر البارامغنطيسية – وخاصة عنصر المنجنيز – بدقة فى خلاياه ولا سيما فى خلايا النوى القاعدية للدماغ وربطه بمستوى المنجنيز فى الدم لهؤلاء المرضى.

3 - ضرورة تجنب مرضى التليف الكبدى لتناول المزيد من المنجنيز، كما يوصى باستعمالهم للعقاقير الكلابية لعنصر المنجنيز قبل ظهور صور ذات حدة زائدة للنوى القاعدية للدماغ بالرنين المغناطيسى مما قد يؤخر حدوث التفسخ المخى الكبدى فى النوى القاعدية للدماغ ويحسن من نمط الحياة لهؤلاء المرضى.