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Original Article

Comparison of brain magnetic resonance imaging findings before and after liver transplantation

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Abstract

Aim: The purpose was to compare the brain Magnetic Resonance Imaging (MRI) findings of the liver transplant recipients who had a neurological symptom, before and after liver transplantation.

Material and Methods: Patients were evaluated in the terms of age, gender, etiology of chronic liver disease and the clinical symptoms. The brain MRI findings before and after liver transplantation were compared.

Results: Thirty liver transplant patients with brain MRIs before and after liver transplantation were included. Hyper intensities on T1 weighted images which is compatible with manganese deposition in the basal ganglia was found from the first brain MRI of 18 patients. In thirteen of them the deposition was disappeared or decreased but in five of them the deposition persisted after transplantation. Hyper intensities on T2 weighted images which is compatible with copper deposition in the basal ganglia of four patients with Wilson's disease persisted after transplantation. Five patients who had normal brain MRI findings before transplantation had posterior reversible encephalopathy syndrome (PRES) after the transplantation. One patient had focal cerebritis, three patients had acute infarct and one patient had intraparenchymal hemorrhage after transplantation.

Conclusion: Most of the neurological symptoms during chronic liver disease are associated with the deposition of paramagnetic substances. After transplantation there could be regression in manganese deposition but the copper deposition stayed the same. Post-transplant PRES, central nervous system infections, infarct, and hemorrhage were not rare. Pre and post-transplant patients with neurological symptoms should be evaluated with brain MRI for rapid diagnosis and proper management.

Keywords: Liver Transplantation; Brain MRI; Manganese Deposition; Copper Deposition.

INTRODUCTION

Chronic liver disease comprises liver dysfunction which lasts longer than 6 months of a recent year and the symptoms secondary to this condition (1). Its most common cause is chronic hepatitis B infection (1). Behavioral changes, tremor, disorientation can be observed in 25% of the cirrhosis patients, and chronic hepatic encephalopathy characterized by hepatic coma can be found in more severe cases (1). Accumulation of toxic substances such as ammonium and manganese in the blood and brain, which are normally removed by liver, is considered to be involved in the etiology of chronic hepatic encephalopathy (2,3,4). In patients with hepatic encephalopathy, secondary to manganese accumulation, increased signal intensity in the bilateral basal ganglia are observed on T1-weighted images obtained using magnetic resonance imaging (MRI) (5). In hepatic encephalopathy, various degrees of brain edema and brain volume loss can also be seen (6). Liver transplantation is the only curative therapy of the end-stage chronic liver disease and acute liver failure (7). After liver transplantation, improvements in cases with increased signal intensity on T1-weighted images, brain edema, hepatic encephalopathy symptoms have been reported (5,7,8).

In Wilson's disease, an autosomal recessive disorder which is also a cause of chronic liver disease, secondary to the disorder of the copper metabolism, accumulation of copper in the eye, liver and brain is observed (9). Increased signal intensities in bilateral basal ganglia, thalami, and mesencephalon are observed on the T2-weighted images obtained via brain MRI. Movement disorders, dystonia, tremor, motor control disorder and rigidity can be observed

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(10,11). There have been cases with improved neurological findings after liver transplantation, but no difference was detected in the findings obtained using brain MRI (12,13).

After liver transplantation, neurological complications are detected in approximately one-third of the patients (14). Clinical spectrum varies from encephalopathy to focal neurological deficits. Due to the underlying metabolic, systemic diseases and immunosuppressive medication, diagnosis of neurological complications is difficult (15). Brain MRI is very important when evaluating the treatment response in the diagnosis of neurological complications (14). The most frequently observed neurological complications after transplantation are posterior reversible encephalopathy syndrome (PRES), infection, stroke and brain hemorrhage (14,15).

PRES is a neurological complication observed at the early stage after transplantation and characterized by symptoms such as headache, visual impairment and changes in consciousness. (14). In brain MRI, foci of hyper intense edema localized particularly in the bilateral cortical and sub cortical parietal and occipital lobes are observed on the T2-weighted images. In diffusion-weighted-imaging (DWI) most of the lesions show increased diffusion, 10-15% of the lesions can show decreased diffusion. Also hemorrhage could be added to 15% of the lesions (14). Brain MRI is the gold standard in the diagnosis and follow-up of PRES. Bacterial, viral and fungal encephalitis can be found secondary to immunosuppression, and brain MRI is the gold standard in its diagnosis (14).

The aim of the study is to compare the findings of the brain MRI performed due to a neurological symptom prior to the liver transplantation and the findings of the brain MRI performed after the transplantation, and to reveal any changes that might occur after the transplantation.

MATERIAL and METHODS

This study was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of the university. Brain MRI findings of the patients who underwent living donor or cadaveric liver transplantation in our center from 1999 to 2017 were retrospectively reviewed. Thirty patients who underwent brain MRI before and after liver transplantation due to neurological symptoms were included in the study. In addition to demographic characteristics of the patients such as age and gender, underlying etiology of liver disease and clinical symptoms at the time of both of the MRIs was obtained using patient files and electronic medical records. MRI findings before and after transplantation were compared and analyzed and any new symptoms that emerge after the transplantation were recorded.

All of the brain MRIs was performed using 1.5 Tesla MRI devices (Avanto, Symphony, Siemens, Erlangen, Germany) with 16-channel head coil. MRI protocol comprises axial FLAIR (repetition time / echo time [TR/TE]: 8000/84 msec, section thickness: 5.5 mm, field of view [FOV]: 22 cm, matrix: 256 × 157, flip angle:150°, number of sections: 20); axial T1-weighted images (TR/TE: 410/9.2 msec, section thickness: 5.5 mm, FOV: 22 cm, matrix : 448 × 186, flip angle: 90°, number of sections: 20); axial T2-weighted images (TR/TE: 3630/103 msec, section thickness: 5.5 mm, FOV: 22 cm, matrix: 512 × 325, flip angle: 150°, number of sections: 20); coronal T2-weighted images (TR/TE: 3630/103 msec, section thickness: 5.5 mm, FOV: 22 cm, matrix: 512 × 302, flip angle: 150°, number of sections: 20); sagittal T2-weighted images (TR/TE: 3630/103 msec, section thickness: 5.5 mm, FOV: 22 cm, matrix: 512 × 358, flip angle: 150°, number of sections: 20). In addition to routine Brain MRI sequences in some cases DWI (TR/TE: 4000/105 msec, slice thickness: 5.5 mm, field of view (FOV): 23 cm, number of sections: 20, bandwidth: 964) with echo planar imaging at b values of 0, 500 and 1000 were obtained. Apparent diffusion coefficient (ADC) maps were created automatically. Axial Gradient Echo (GRE) (TR/TE:820/25 msec, slice thickness:5.5 mm, field of view (FOV): 23 cm, matrix size:256x320;ü, FA:20, bandwidth: 130, number of sections: 20) or axial SWI (TR/TE:50/40 msec, slice thickness:2.5 mm, field of view (FOV): 22 cm, matrix size:256x320, FA:15°, number of sections: 20), post-gadolinium-enhanced axial, sagittal T1-weighted images and coronal fat suppressed (FS) T1-weighted images (TR/TE:552/17ms, slice thickness: 5.5 mm, field of view (FOV): 22 cm, matrix size:384x192, bandwidth: 130, flip angle:90°, number of slices:20) also added to the standard protocol in some cases. A standard dose of gadobenate-dimeglumine (Multihance) 0.1 mmol or 0, 2 ml/kg was applied intravenously as a bolus. Sixty one brain MRIs of 30 patients (one patient has 3 brain MRIs) were reevaluated by a radiologist with 6 years of experience in neuroradiology.

RESULTS

A total of 30 patients, whose brain MRIs before and after liver transplantation was available, were included in the study. Of these patients, 12 were male and 18 were female, and the mean age was 33 (2-74 years). Indications for liver transplantation were variable, with the most common cause being chronic liver failure due to hepatitis. Demographic data of the patients, indications for the brain MRI before and after the transplantation, and brain MRI results are presented in Table 1. Indications for liver transplantation are given in Table 2.

Six patients have post contrast images, eight patients have DWI and six patients have GRE or SWI sequences before the liver transplantation. Whereas six patients have post contrast images, ten patients have DWI and ten patients have GRE or SWI sequences after the liver transplantation.

Prior to transplantation, the most common indications for brain MRI were hepatic encephalopathy (n=8), screening for metastasis (n=4), seizure (n=4), headache (n=3), dizziness (n=3), drowsiness (n=3), whereas after the transplantation, the most common indications for brain MRI were seizure (n=13), headache (n=7), and impaired consciousness (n=3). The mean duration between the first brain MRI and transplantation was 3 months (10 days-36

months), and the mean duration between transplantation and the second MRI was 24 months (1 day-15 years).

While manganese accumulation at the basal ganglia was observed in 18 patients before the transplantation, manganese accumulation improved in 11 patients (61%) and decreased in 2 patients (11%) after the transplantation. In 5 patients (28%), manganese accumulation persisted (Figure 1).

Table 1. Age, gender, indications for brain MRI and findings of the patients

Age	Gender	Preoperative indications for MRI	Preoperative MRI findings	Postoperative indications for MRI	Postoperative MRI findings
53	Male	Hepatic encephalopathy	Accumulation of manganese and copper	Headache	Manganese accumulation disappeared, Copper accumulation persists
5	Female	Structural abnormality	Delayed myelination	Hypotonia	PRES
20	Male	Hepatic encephalopathy	Accumulation of manganese Osmotic demyelination	Control	Decrease in manganese accumulation Osmotic demyelination disappeared
55	Female	Metastasis?	Accumulation of manganese	Headache	Manganese accumulation disappeared
62	Female	Metastasis?	Accumulation of manganese, ischemic gliosis	Headache	Manganese accumulation disappeared Ischemic gliosis persists
15	Female	Hepatic encephalopathy	Normal	Seizure	PRES
35	Female	Headache	Accumulation of manganese and copper	Dizziness	Manganese accumulation disappeared Copper accumulation persists
68	Male	Numbness at the corner of the mouth	Accumulation of manganese	Falling	Manganese accumulation disappeared, atrophy
67	Male	Metastasis?	Normal	Headache	Atrophy, ischemic gliosis
21	Male	Headache	Accumulation of manganese	Cognitive impairment	Decreased manganese accumulation
55	Male	Metastasis?	Atrophy	Cognitive impairment	Acute infarction, atrophy
26	Male	Drowsiness	Accumulation of manganese	Seizure	Manganese accumulation disappeared, atrophy
21	Female	Hepatic encephalopathy	Normal	Seizure, fever	Cerebritis
4	Male	Seizure	PRES	Control	Sequela
33	Female	Drowsiness	Minimal atrophy, accumulation of manganese	Headache	Atrophy, manganese accumulation persists
39	Female	Tremor	Minimal atrophy, accumulation of manganese	Headache	Atrophy, manganese accumulation disappeared
37	Male	Seizure	Accumulation of manganese, PRES	Seizure	PRES disappeared, manganese accumulation disappeared
55	Male	Seizure	Accumulation of manganese	Loss of vision	Acute infarction, manganese accumulation persists
74	Male	Hepatic encephalopathy	Atrophy	Seizure	Atrophy
25	Male	Dizziness	Accumulation of manganese and copper	Seizure	Manganese accumulation disappeared, copper accumulation persists, ischemic gliosis
16	Male	Headache	Accumulation of manganese	Seizure	Manganese accumulation persists, intraparenchymal hemorrhage
27	Male	Dizziness	Accumulation of copper	Seizure	PRES, copper accumulation persists
44	Female	Hepatic encephalopathy	Accumulation of manganese	Cognitive impairment	Manganese accumulation disappeared
23	Female	Seizure	Accumulation of manganese	Seizure	Manganese accumulation disappeared
22	Male	Hepatic encephalopathy	Normal	Seizure	PRES
3	Male	Structural abnormality?	Normal	Seizure	Normal
20	Male	Numbness in the arm	Accumulation of manganese, chronic infarction, ischemic gliosis	Seizure	PRES, Manganese accumulation persists, chronic infarction, ischemic gliosis persists
2	Female	Structural abnormality?	T2 hyper intensities compatible with urea cycle disorders	Seizure	Acute infarction, T2 hyper intensities compatible with urea cycle disorders
54	Female	Hepatic encephalopathy	Accumulation of manganese, minimal atrophy, ischemic gliosis	Falling	Manganese accumulation persists, minimal atrophy, ischemic gliosis
9	Male	Drowsiness	Normal	Headache	Lacunar infarctions, ischemic gliosis

Table 2. Our patients' indications for liver transplantation

Indication	Number
Wilson's	7
Chronic Hepatitis+HCC*	5
Hepatitis	4
Citrullinemia	1
Histiocytosis	1
Oxalosis	1
Hypercholesterolemia	1
Cystinosis	1
Alagille Syndrome	1
Cryptogenic cirrhosis	1
Primary biliary cirrhosis	1
Tyrosinemia	1
Biliary atresia	1
Agammaglobulinemia	1
Urea cycle disorder	1
Methylmalonic acidemia	1
Progressive familial intrahepatic cholestasis	1

*HCC: Hepatocellular carcinoma

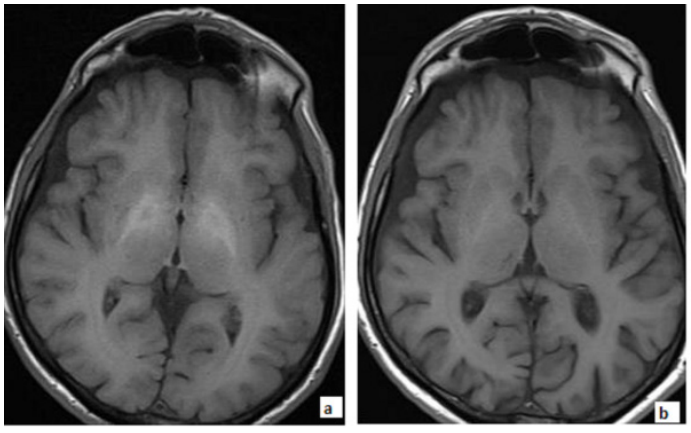

Figure 1. Hyperintense foci compatible with manganese accumulation at the basal ganglia (Figure 1a) that can be seen on the axial T1-weighted brain MR image of 64-year-old male patient who underwent liver transplantation due to chronic hepatitis B infection seems to have disappeared on the post-transplant brain MRI (Figure 1b).

Accumulation of copper, which was found in 4 of the 7 patients diagnosed with Wilson's disease, was observed in all patients after the transplantation (Figure 2).

Results of the brain MRI performed before transplantation was normal in 5 patients, whereas later on, these patients developed drug toxicity-related PRES (Figure 3). PRES secondary to the accompanying hypertension was observed in 2 patients before transplantation, and sequel symptoms were detected after transplantation. Osmotic demyelination was found in one patient before transplantation, whereas the results of control brain MRI after transplantation were normal. Brain MRI results were normal in one patient before transplantation, whereas focal cerebritis was observed later on, and in the 3rd MRI of this patient, it was found that cerebritis findings improved (Figure 4).

In three patients, acute infarction, and in one patient, intraparenchymal hemorrhage was observed after transplantation. In five patients, cerebral atrophy, ischemic gliotic changes, and lacunar infarctions that had not been found in the preoperative tests were observed. In 7 patients with preoperative cerebral atrophy and ischemic gliotic changes, symptoms persisted after the transplantation. In one patient with urea cycle disorder, T2 hyper intensities observed on preoperative brain MRI persisted after transplantation and were found compatible with the urea cycle disorder.

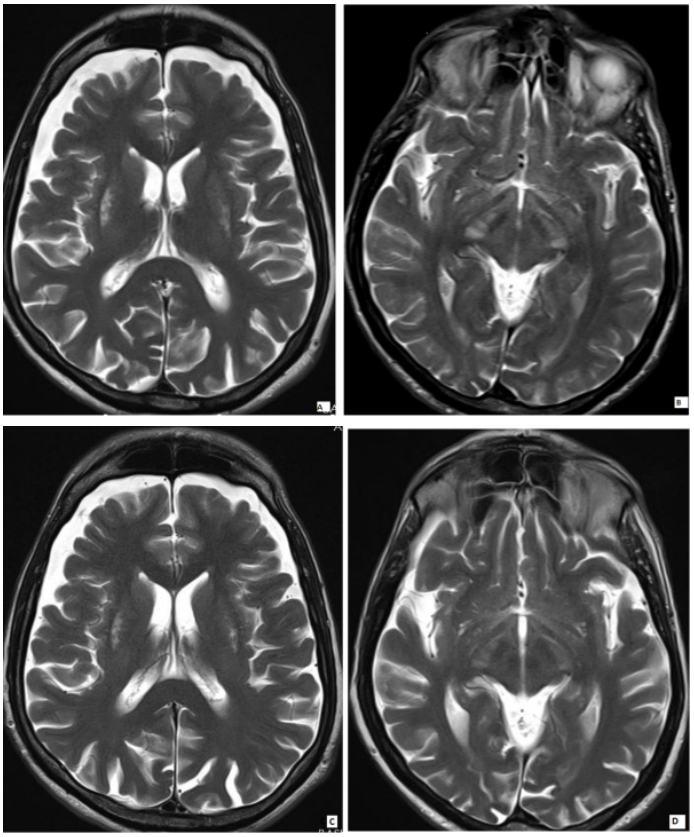

Figure 2. Hyperintense foci compatible with copper accumulation at the basal ganglia (Figure 2a) and midbrain (Figure2b) that can be seen on the axial T2-weighted brain MR image of 53-year-old male patient who underwent liver transplantation due to Wilson's cirrhosis. No changes in the findings are detected on post-transplant brain MRI (Figure 2c and Figure 2d).

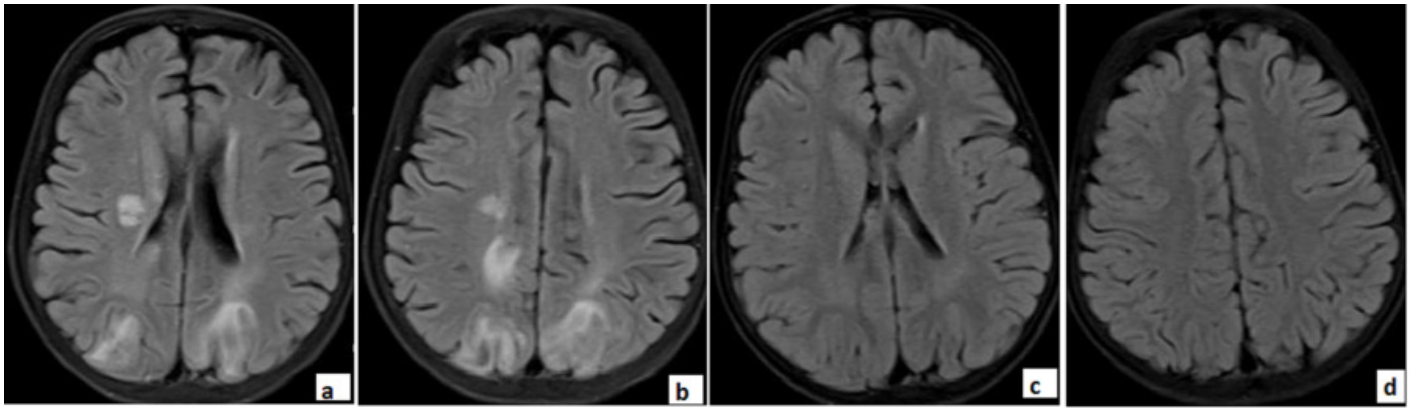

Figure 3. In the 15-year-old female patient who underwent liver transplantation due to oxalosis, the hyperintense foci, which on the axial FLAIR image can be observed in Figure 3a and 3b, at the bilateral parietooccipital cortical, subcortical white matter, right parietal periventricular white matter in the brain MRI performed after transplantation, and which are compatible with PRES seems to have disappeared on the control brain MRI (Figure 3c, 3d).

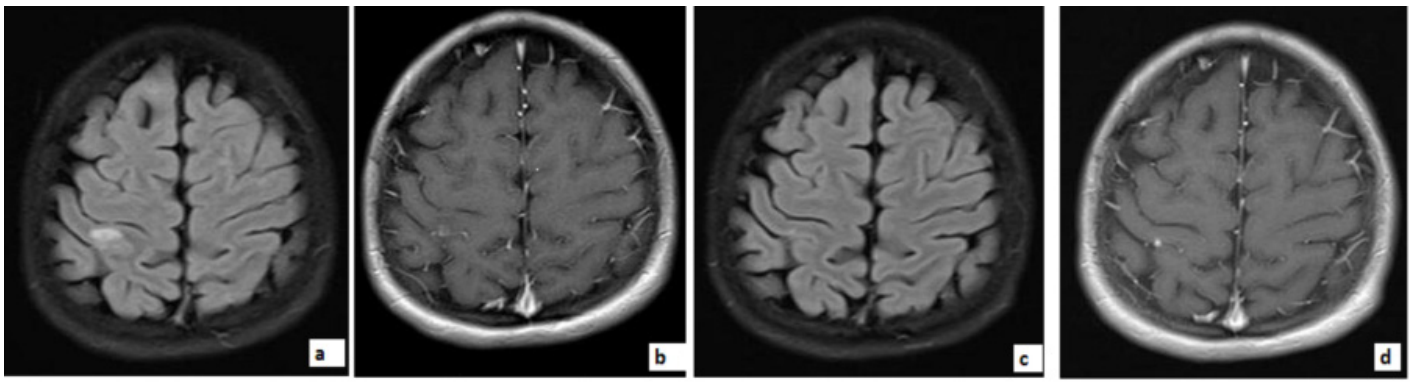

Figure 4. Area of hyperintense edema (Figure 4a) on the axial FLAIR image and contrast enhancement on the post-contrast T1-weighted axial image (Figure 4b) in post-transplant brain MRI, were found compatible with focal cerebritis in the 21-year-old female patient who underwent liver transplantation due to hypercholesterolemia. In the control brain MRI of the patient after the treatment findings were improved (Figure 4c, 4d).

DISCUSSION

Prior to liver transplantation, neurological symptoms such as changes in consciousness, cognitive disorders, involuntary movements secondary to chronic liver failure-related hepatic encephalopathy can be observed (1). Accumulation of toxic substances such as manganese and ammonia in the blood and brain, which are removed by the liver, is considered to play a role in the development of hepatic encephalopathy (1,5). There are studies in the literature demonstrating that increased signal intensities at the basal ganglia observed on the T1-weighted brain MR images are compatible with the increase in the manganese amount in basal ganglia (16,17). In our study, increased signal intensities compatible with the accumulation of manganese in the basal ganglia have been identified in the brain MRIs of 18 patients with symptoms of hepatic encephalopathy. While neurological symptoms of these patients improved after liver transplantation, in the control brain MRIs, it was found that the increase in the signal intensities observed on the T1-weighted images disappeared in 11 patients and decreased in 2 patients. In five patients, no changes were detected in the increased signal intensities. In these five patients liver function tests such as alanine transaminase (ALT), aspartate aminotransferase (AST) were increased, and serum albumin levels were decreased. Our findings suggest that the accumulation of manganese in the brain decreases after liver functions are restored after the transplantation. Persistent hyper intensities in these five patients could be explained by the post-transplant liver failure. Long et al. have found that increased signal intensities improved, which was compatible with the accumulation of manganese in the basal ganglia (1).

In our study, increased signal intensity was detected on the T2-weighted images of the bilateral basal ganglia, thalami, and mesencephalon, compatible with the accumulation of copper in the brains of 4 patients who underwent MRI because of the neurological symptoms prior to liver transplantation due to Wilson's cirrhosis. In the brain MRIs of patients whose neurological symptoms improved after transplantation, no difference was detected in terms of signal intensities, which had been compatible with the accumulation of copper. In the case presentation of Stracciari et al., it was reported that the neurological symptoms of the patients who underwent liver transplantation due to Wilson's disease improved after the transplantation, but no difference was detected in their brain MRI findings (13). Zhong et al studied brain MRI

findings and clinical findings of 76 patients with Wilson's disease (18). They found out that thalamic lesions could be associated with longer disease duration. On DWIs and SWI sequences there was hypo intensities in the basal ganglia and midbrain of some cases.

Another finding observed on T2-weighted brain MR images of the patients with chronic liver disease is the atrophy and increased signal intensities that are periventricular located and milimetric in diameter due to microvascular disease. In our study, in 7 patients, atrophy and increased signal intensities compatible with the microvascular disease observed before the transplantation persisted after the transplantation. After liver transplantation, no improvement in terms of atrophy was detected in the brain MRIs of these patients. In 5 patients, after the transplantation, atrophy, ischemic gliotic changes and lacunar infarctions, which were not observed in the pre-operative MRIs, were detected. In 4 patients, foci of chronic infarction which were not observed in the pre-operative MRIs were detected in the post-transplant brain MRIs. In the study by Martinez et al., brain MRIs of 22 patients before and after the transplantation were analyzed and compared with the healthy controls. Before the transplantation, atrophy and increased signal intensities on the T2-weighted brain MR images were detected, and after the transplantation, it was found that the atrophy was not alleviated and increased signal intensities on T2-weighted images progressed (19). Our results are consistent with this prior study.

After liver transplantation, neurological symptoms such as mental disturbance, seizure, focal motor deficit are found in almost one-third of the patients (20). The most common neurological complications can be listed as infection, PRES, stroke, hemorrhage and post-transplant malignancies (14,15).

In our study, PRES was detected in 5 patients after liver transplantation. PRES is a rare neurological complication associated with the use of calcineurin inhibitors such as tacrolimus and cyclosporine A. Its symptoms vary from headache, visual impairment, focal neurological deficit, seizure, changes in mental status, to coma (20). Hemorrhage can accompany these symptoms in 15% of the PRES cases (14,21). Hemorrhage can be seen as subdural, intraparenchymal, subarachnoid forms. In order to find out hemorrhage SWI sequence should be added to routine brain MRI protocol of patients suspected PRES. Hemorrhagic areas are seen hypo intense on SWI sequence (21). Vasogenic edema foci characterized by increased signal intensities, which involve cortex and subcortical white matter at the bilateral parietal and occipital lobes, are observed on the T2-weighted images. Typical findings of PRES are hypo intense areas on DWI and hyper intense areas on ADC maps compatible with increased diffusion. In 10-15% of cases diffusion restriction revealing cytotoxic edema could be seen as hyper intense areas on DWI and hypo intense areas on ADC maps (14,21). Involvement of frontal lobe, basal ganglion, and thalamus can also be observed. MRI is the gold standard in the diagnosis of PRES. DWI and Susceptibility-weighted-imaging (SWI) sequences should also be added to brain MRI protocol. In our study, the clinical symptom in patients was seizure, whereas brain MRI demonstrated vasogenic edema foci with increased signal intensity on the T2-weighted images, which do not show restricted diffusion and are located at bilateral cerebral and cerebellar hemispheres and more pronounced occipitally.

After liver transplantation, another neurological complication due to immunosuppression is the infections of the central nervous system. Meningitis, cerebritis, abscesses due to bacterial, viral and parasitic agents can be observed (14). Dural enhancement in post contrast series is seen in meningitis. Cerebritis is the earlier manifestation of cerebral infection before brain abscess. It's seen as iso intense-hypo intense areas on T1 weighted images and hyper intense areas on T2 weighted and FLAIR images. On post contrast series minimal –moderate enhancement is seen. On DWI restricted diffusion is seen (22). In our study one patient with normal brain MRI findings before the transplantation had seizure and fever after transplantation. In the post-transplant brain MRI increased signal intensity was found on the T2-weighted images at the right frontal lobe and contrast uptake was detected in the post contrast series which was compatible with cerebritis. On DWI there was not marked diffusion restriction. In the 3rd brain MRI of the patient, findings were improved significantly.

Stroke is among the neurological complications that can be observed after liver transplantation. In our study, three patients, who had symptoms of cognitive impairment, visual impairment and seizure after transplantation had acute infarction foci characterized with increased signal intensity on the T2-weighted images and restricted diffusion on DWI in the post-transplant brain MRIs.

In our study, in the brain MRI performed due to seizure after transplantation of a patient who had a normal brain MRI prior to transplantation, intraparenchymal hematoma at cerebellar hemisphere was detected.

The current study has some limitations. First it's designed retrospectively which makes harder to find out the clinical symptoms and brain MRI indications of the patients. Also we did not have standard brain MRI protocol for patients with chronic liver disease and patients with liver transplantation and we did not have DWI, SWI sequences in all of the patients.

CONCLUSION

Neurological symptoms can be observed during the course of chronic liver disease, and the majority of these are related to substance accumulation. After transplantation, particularly due to the restoration of manganese metabolism, decrease in manganese accumulation is observed. Although neurological symptoms improve in patients who undergo liver transplantation due to Wilson's disease, no changes in the findings compatible

with copper accumulation are detected in the MRI. Neurological symptoms can also be observed after liver transplantation. PRES that can develop due to drug toxicity, infections of the central nervous system secondary to immunosuppression, stroke, hemorrhage, post-transplant malignancies are not uncommon. Patients with neurological symptoms both prior to and after transplantation must immediately undergo MRI examination for rapid diagnosis and appropriate treatment. We also think that DWI and SWI sequences should be added to conventional brain MRI sequences to show the neurological complications of the patients with either chronic liver disease or liver transplantation.

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