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MAGNETIC RESONANCE IMAGING

Analysis of magnetic resonance imaging findings of children with neurologic complications after liver transplantation

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Abstract
Objective To analyze the magnetic resonance imaging findings in children diagnosed with neurologic complications after liver transplantation (LT).
Materials and methods A total of 39 patients diagnosed with neurologic complications following LT between 2010 and 2016. Neuroradiologic imaging was performed using cranial magnetic resonance imaging (MRI). Descriptive statistics regarding age, gender, type of complication, diagnostic and therapeutic modalities were calculated and presented as number and percentage.
Results Our series consisted of 18 girls and 21 boys. Cryptogenic hepatitis ($n = 13$, 32%), metabolic diseases (Wilson's disease, tyrosinemia and glycogen storage disease) ($n = 7$, 18%) and fulminant toxic hepatitis ($n = 4$, 11%) constitute the most frequent indications for LT. The indications for neuroradiological imaging were convulsion and alteration of mental status.
Conclusion These central nervous system complications may present in a variable spectrum and convulsions and altered mental state were the most frequent clinical pictures. Imaging studies were normal in approximately one-third of cases; the most frequent pathologic findings were diffuse cerebral edema, atrophy, and PRES. Clinical history, careful examination and integrated analysis of radiologic data as well as close collaboration and multidisciplinary approach are of utmost importance for establishing the diagnosis rapidly and accurately.

Keywords Liver · Transplantation · Neurologic · Complication · Children · Magnetic resonance imaging

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Introduction

Liver transplantation (LT) is the only curative treatment in patients with end-stage liver disease, and neurological complications can affect up to one-third of cases after the transplantation procedure [1, 2]. Central nervous system (CNS) complications constitute an important cause of morbidity and mortality in LT patients. The rates of morbidity and mortality due to CNS complications after LT are reported as high as 19 and 47% [3].

Neurologic complications may develop due to the transplantation itself, or a previously identified organ failure, or both conditions. Alteration of mental status, seizures, and focal motor deficits may occur, and these morbidities can be associated with several pathogenetic factors like poorly

functioning graft, intracranial hemorrhage, cerebral infarctions, infections, or immunosuppressive drug toxicity. The majority of these cases present within the first month after the LT [4]. Cerebral atrophy, stroke, meningitis, hemorrhage, cerebrovascular infarct, cerebral abscess, encephalopathy, central pontine myelinolysis, cognitive decline, tremor, peripheral neuropathy and sinus thrombosis are the most frequent neurologic complications reported in LT patients [5]. Both computerized tomography (CT) scans and magnetic resonance images (MRI) may be utilized for imaging in patients that develop CNS complications after LT [6]. Increased intensity of T1-weighted magnetic resonance images (MRI) may be seen in the globus pallidus of patients with hepatic failure owing to manganese accumulation. Findings on MRI may have clinical significance with relevant neurologic symptoms and signs. Increased awareness on the clinical and radiologic findings linked with possible CNS complications subsequent transplantation is important to establish the diagnosis and initiate the appropriate treatment without delay [5].

The range of indications for LT in pediatric patients is different from adults, and a different spectrum of complications is more likely in children. In the medical literature, there are scarce data on CNS complications in pediatric LT recipients [6–8]. The aim of the current study was to share our experience with CNS complications in pediatric LT patients with emphasis on the radiological findings derived from MRI.

Patients and methods

Study design

This retrospective study was carried out following the approval of local institutional review board. Adherence to principles announced in Declaration of Helsinki was provided. Between January 2010 and July 2016, three hundred children underwent LT in the Transplant Surgery Department of our Tertiary Care Center. Out of these 300 cases, the case records of 39 pediatric patients (18 girls, 21 boys) who developed acute neurologic signs and symptoms following the procedure were reviewed. Neuroradiologic imaging was performed using cranial MRI.

Basic descriptive data (age, sex), indications for LT, spectrum of CNS complications after LT, initial time of each complication, diagnosis, treatment and follow-up were recorded. Initially, all patients received tacrolimus for immunosuppression. However, posterior reversible encephalopathy syndrome (PRES) was detected in eight cases. In four of these patients, immunosuppression was discontinued, whereas cyclosporine A was given in four cases.

Imaging

A 1.5 MR scanner (Magnetom, Siemens, Erlangen, Germany) was utilized. Both contrast and non-contrast images were obtained using T2-weighted (TR/TE 3750/91) axial, sagittal, FLAIR (TR/TE 8000/109) axial, T1-weighted (TR/TE 427/8.7) axial views. Automated apparent diffusion coefficient (ADC) maps were constituted using diffusion-weighted images b: 1000 (TR/TE 3300/96) and b:0 (TR/TE 3750/91).

Before imaging, all patients received chloral hydrate (50 mg/kg, p.o) for sedation. All MRI scans were retrospectively reviewed by two radiologists who were aware of the clinical history of the patients. Inclusion criteria consisted of age ≤17 years and occurrence of neurologic complications. Every patient presenting with CNS complications underwent analyses for serum biochemistry panel, the level of the immunosuppressive agent, complete blood cell count and coagulation profile. Magnetic resonance images were performed when clinically indicated [6].

Diagnosis of CNS complication was established by pediatric neurologists with respect to history, neurological examination and neuroradiological studies including MRI and EEG. Clinical evaluation was made by clinicians from the pediatric intensive care unit as well as the gastroenterology and transplantation departments. Preoperative neurological examination and postoperative neuropsychological assessment were carried out routinely.

Statistical analysis

Descriptive statistics regarding age, gender, type of complication, diagnostic and therapeutic modalities were calculated and presented as number and percentage.

Results

Our series consisted of 18 girls and 21 boys with an average age of 95.7 ± 56.4 months (range 15–204). As it can be seen in Table 1, cryptogenic hepatitis ($n = 13$, 33.3%), metabolic diseases (Wilson's disease, tyrosinemia and glycogen storage disease) ($n = 7$, 17.4%) and fulminant toxic hepatitis ($n = 5$, 12.8%) constitute the most frequent indications for LT. The main indications for neuroradiological imaging were convulsion ($n = 11$, 28.2%), alteration of mental status ($n = 9$, 23%), headache ($n = 4$, 10.3%) and visual impairment ($n = 4$, 10.3%) (Table 2).

Magnetic resonance views were normal in twelve patients (26.7%). The most common abnormal imaging findings consisted of PRES ($n = 8$, 17.8%), diffuse

cerebral edema ($n = 6$, 13.3%), diffuse cerebral atrophy ($n = 6$, 13.3%) and arterial ischemic stroke ($n = 5$, 11.1%) (Table 3).

Figure 1 demonstrates MRI findings consistent with PRES in a 14-year-old patient transplanted due to cryptogenic hepatitis. Intracranial abscesses on both cerebral hemispheres were detected in an 11-year-old patient with Wilson's disease (Fig. 2) and histopathological examination confirmed invasive aspergillosis.

Discussion

The objective of the present study was to define the neuroradiologic findings detected in pediatric LT patients presenting with CNS complications. We suggest that MRI may provide useful data for establishing the diagnosis of CNS complication after LT procedure.

Liver transplantation is a dynamic field in modern medicine and can be a life-saving option for patients with the end-stage liver disease. It has been performed successfully in many centers since 1967 [9]. However, the clinical course after LT must be monitored closely since neurologic complications that may lead to mortality can occur. The incidence of CNS complications after LT ranges from 10 to 75% and this wide range may be linked with various inclusion criteria, the definition of CNS complications and observation period [10]. The incidence observed in the present study was within this spectrum (50/300, 16.7%).

In many publications, CNS complications have been classified based on symptomatology and also disease time course was not taken into account. Due to the time-based course of CNS complication after LT, the majority of complications (80%) occur within one month after transplantation [11]. In the present study, we included the complications detected within one month after LT. Currently, it is necessary to update the etiologic diversity and to identify the initial manifestation of CNS complications following LT [9]. This issue gains more importance in pediatric patients for whom the clinical picture may deteriorate abruptly, and morbidity and mortality may develop without very prominent clinical signs and symptoms.

After LT, we observed that PRES was diagnosed with MRI. PRES is a common complication characterized by a headache, seizures, visual impairment and altered mental status. Its etiology is not understood completely, but it may be linked to a breakdown in cerebral autoregulation that leads to leakage of the fluid into the interstitium [12, 13]. It may occur due to immunosuppressive drug toxicity, and typical radiologic changes involve edema in white matter with symmetrical hyperintense signals in the posterior hemispheres on T2 weighted images [5]. Anti-rejection treatment with tacrolimus and cyclosporin A has been accused of PRES in transplantation [14]. In the present study, cessation of tacrolimus resulted in resolution of the clinical picture of PRES in eight patients. Notably, initiation of cyclosporine A instead of tacrolimus in four patients did not hinder recovery of PRES. Ghosh et al. reported that the most common form of early neurologic complications (within three months after LT) was seizures [1]. The etiology was attributed to PRES which was linked with

Table 1 Indications for liver transplantation in our pediatric population

Indication	Number (%)
Cryptogenic hepatitis	13 (33.3)
Fulminant toxic hepatitis	5 (12.8)
Wilson's disease	5 (12.2)
Biliary atresia	3 (7.7)
Fulminant hepatitis A	3 (7.7)
Hepatoblastoma	2 (5.1)
Carole syndrome	2 (5.1)
Biliary cirrhosis	1 (2.6)
Chronic portal vein thrombosis	1 (2.6)
Autoimmune hepatitis	1 (2.6)
Tyrosinemia	1 (2.6)
Hepatocellular carcinoma	1 (2.6)
Glycogen storage disease	1 (2.6)

Table 2 Indications for neuroradiologic imaging

Indication	Number (%)
Convulsion	11 (28.2)
Alteration of mental status	9 (23)
Tremor	6 (15.4)
Visual impairment	5 (12.8)
Headache	4 (10.3)
Fever	2 (5.1)
Cardiopulmonary arrest	2 (5.1)

Table 3 Findings derived from magnetic resonance images ($n = 45$)

Finding	Number (%)
Normal	12 (26.7)
Posterior reversible encephalopathy	8 (17.8)
Diffuse cerebral edema	6 (13.3)
Diffuse cerebral atrophy	6 (13.3)
Arterial ischemic stroke	5 (11.1)
Hyperintensity in basal ganglia	4 (8.9)
Changes reflecting chronic infarct	1 (2.2)
Intracranial fungal abscesses	1 (2.2)
Intraparenchymal hemorrhage	1 (2.2)
Hemorrhagic infarct	1 (2.2)

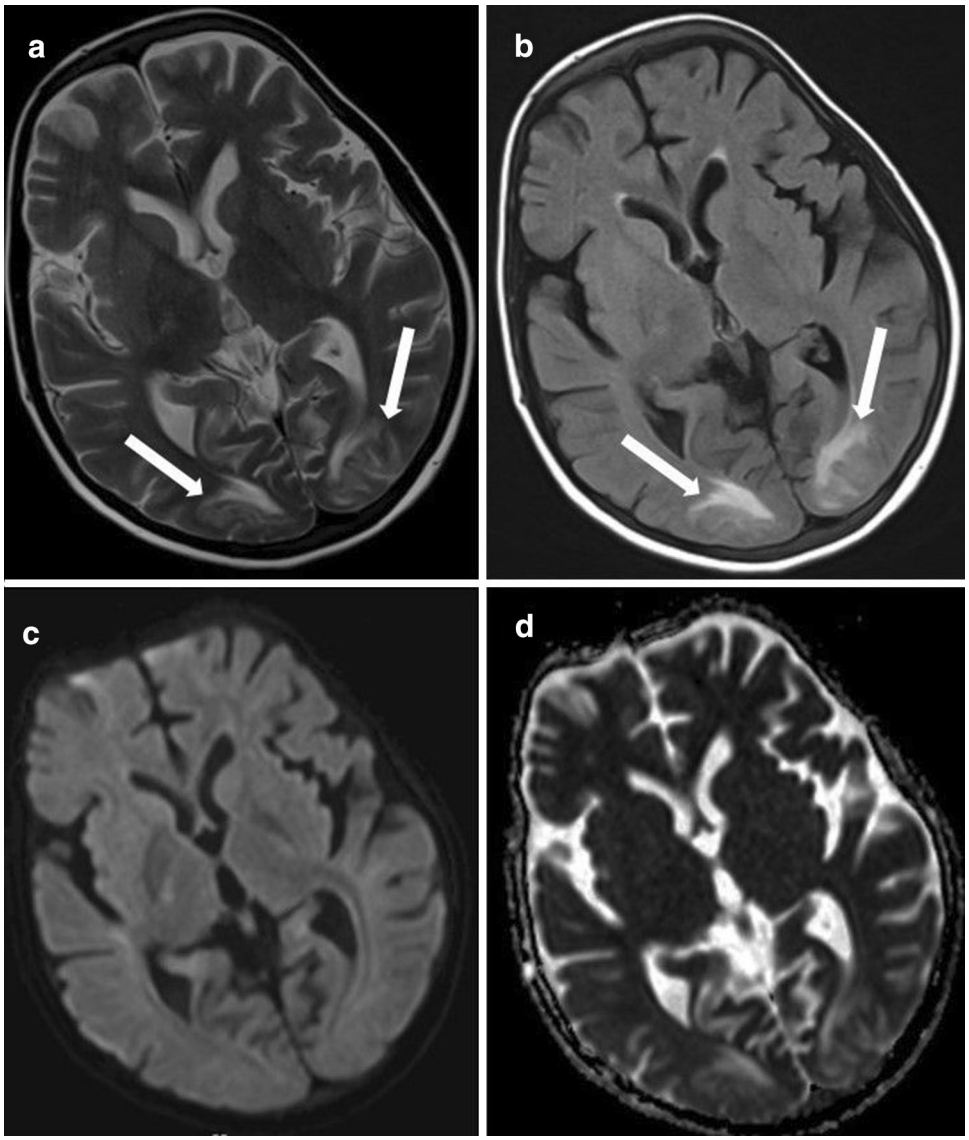

Fig. 1 The 14-year-old patient with cryptogenic hepatitis had convulsions on 12th day after the procedure. Cranial MRI views indicate symmetrical hyperintensity without restriction of diffusion in occipital lobes bilaterally at T2-weighted and FLAIR images. *Arrows* show these findings which are consistent with PRES

tacrolimus toxicity, intracerebral hemorrhage, and electrolyte disturbances.

Predisposing factors for CNS complications after LT include impaired host defense, glucose intolerance, hyperlipidemia, leukopenia and hypertension. Neurologic complications that necessitate neuroradiologic imaging were reported in 15.9% of LT patients [5]. Similar to these data, the rate of CNS complications was 16.7% in our pediatric LT population. In our series, neuroradiologic imaging was performed in all cases. After LT, 24.1% of patients exhibited cranial MRI findings linked with LT and 65.5% of LT patients displayed cranial MRI findings secondary to chronic liver disease [5].

Our results have shown that MRI images were reported as normal in 23.1% of cases. Selection of the appropriate mode of imaging as well as the increased awareness on the significance of radiologic findings is crucial for setting diagnosis timely and starting the appropriate treatment without delay. This study demonstrated that diverse etiologies and various patterns of cranial CT and MRI findings might accompany CNS complications after LT in the pediatric population. Careful assessment of the initial manifestation and symptom may be useful for prediction of the etiologic diagnosis [1, 9].

The main restrictions of the current study include retrospective design, relatively small sample size and data limited to the experience of a single center. Furthermore, technical limitations linked with equipment and operator must be remembered during interpretation of our results.

To conclude, CNS complications are common in children after LT. These complications may present in a variable spectrum and convulsions and altered mental state were the most frequent clinical pictures in our series. Even though imaging studies were normal in approximately

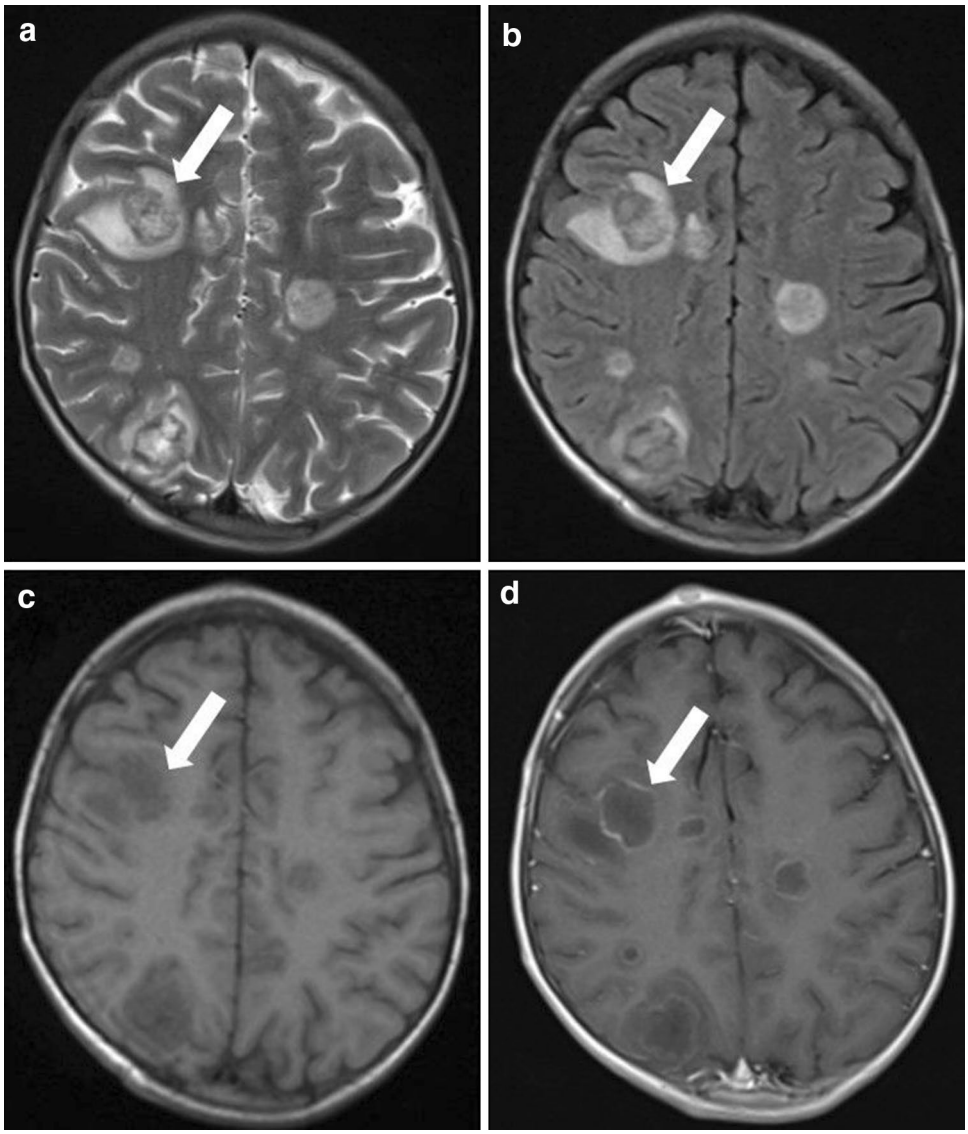

Fig. 2 Multiple abscesses were detected in cranial MRI of a 11-year-old Wilson's disease patient. The patient suffered from fever on 7th day after LT and lesions characterized with peripheral contrast and edema were evident (*arrows*). Histopathological examination was consistent with invasive aspergillus infection

one-third of cases, most frequent pathologic findings were cerebral edema, atrophy, and PRES. Clinical history, careful examination and integrated analysis of radiologic data as well as close collaboration and multidisciplinary approach are of utmost importance for establishing the diagnosis rapidly and accurately.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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