

Original Article

Liver involvement of Langerhans' cell histiocytosis in children

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Abstract: Objective: Liver involvement is relatively frequent in children with Langerhans cell histiocytosis (LCH). Its features remain poorly defined. Methods: A retrospective study was carried out on 14 hepatic LCH children in our hospital. The Clinicopathological and radiological features of this disease was discussed. Results: The rate of liver involvement in children LCH patients is 51.9%. Majority of the patients were disseminated cases. Hepatomegaly was clinically confirmed in 11 cases (78.6%). Liver function dysfunction was seen in nine (64.3%) children. The association of multi-modal imaging significantly yielded more diagnostic information. There are some imaging characteristics of this disease, CT and MRI could help to assess the staging, extent of the hepatic lesions. We found that liver involvement had a significant impact on survival. Patients treated with systemic chemotherapy earlier from time of diagnosis had a relatively better outcome. Conclusions: The rate of liver involvement in children LCH patients maybe much higher than that of expected. We suggest that clinical and biological liver evaluation and abdominal imaging must be performed regularly onwards to screen every LCH children patient from the time of the initial diagnosis. Patient should be treated with systemic chemotherapy earlier.

Keywords: Langerhans cell histiocytosis (LCH), liver involvement, children, imaging, prognosis

Introduction

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X (which included eosinophilic granuloma, Letterer-Siwe disease and Hand-Schuller-Christian disease), is a rare disease typically occurs in children and adolescents, although it can develop in all age groups. Histopathologically, LCH is characterized by oligoclonal proliferation and migration of Langerhans cells [1], which are capable of infiltrating almost any tissue or organ. The etiology of LCH is unknown, though this proliferation is thought to reflect an immune response to an as yet unknown antigenic stimulant.

The disease is rare, with an annual incidence of approximately 2-5 per million per year and a peak incidence at 1-4 years of age [2]. It may manifest at any age, with males being affected more frequently than females [3]. The clinical presentation may be variable, with a clinical spectrum that ranges from a solitary bone lesion with a favorable natural history to a disseminated disease with multisystem involvement (such as liver, lung, bone, spleen, lymph

nodes, hypothalamus, pituitary gland, gastrointestinal tract). Liver involvement occurs mainly in multisystem cases and reported to be relatively rare and usually presents as a part of a disseminated process. However, its frequency is known to be high (from 19% to 60% of cases) and it bears a poor prognosis [4-6]. Among children with LCH (especially in children younger than 5 years old), liver involvement is relatively frequent, even though it is often overlooked. In fact, the liver involvement may be missed in apparently localized LCH or when it is the sole site of involvement [7]. Therefore, the diagnosis of Langerhan's cell histiocytosis (LCH) is often difficult and delayed [3].

Based on a retrospective data collection in our hospital over a time period of 10 years, we aimed to determine the clinicopathological and radiological features of liver LCH in this study.

Patients and methods

This was a retrospective cohort study of a subgroup of children with LCH enrolled in Xiangya hospital, Central South University. We searched

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Table 1. Characteristics of the children liver LCH

	All patients	LCH with liver involvement	LCH without liver involvement	P
<i>Number of patients</i>	31	14	17	
<i>Men/Women (sex ratio)</i>	19/8 (2.4)	9/5 (1.8)	10/3 (3.3)	0.68
<i>Age at diagnosis (years)</i>				
Median	64	45	85	0.03
Range	2-156	2-108	16-156	
<i>Clinical Signs/Site of localizations n (%)</i>				
Hepatomegaly	13 (41.9%)	13 (92.9)	0 (0%)	<0.01
Splenomegaly	6 (19.4)	6 (42.9%)	0 (0%)	<0.01
Fever	3 (9.7%)	3 (21.4%)	0 (0%)	<0.01
Jaundice	5 (16.1%)	5 (35.7%)	0 (0%)	<0.01
Bones	24 (77.4%)	7 (50%)	17 (100%)	<0.01
Lung	4 (12.9%)	4 (28.6%)	0 (0%)	<0.01
Skin	4 (12.9%)	4 (28.6%)	0 (0%)	<0.01
Lymph node	5 (16.1%)	5 (35.7%)	0 (0%)	<0.01
Central nervous system	3 (9.7%)	3 (21.4%)	0 (0%)	<0.01
Thymus	3 (9.7%)	2 (14.3%)	1 (5.8%)	0.57
Deceased	5 (16.1%)	4 (28.6%)	1 (5.8%)	0.15

the Xiangya hospital inpatient database during a 10-year period (October 2003 to July 2013) for patients younger than 14 years who had the terms “Langerhans cell histiocytosis” in their discharge diagnosis. Finally 27 patients fulfilled search criteria. One pathologist with an interest in gastrointestinal pathology reviewed all of the slides to confirm the histologic findings.

The diagnosis of LCH was established by histological examination, and liver involvement was diagnosed by the patient's physicians and verified by histological examination when necessary. liver involvement by one or more of the following: either abnormal liver architecture on microscopy, or otherwise unexplained liver enlargement, or abnormalities of the liver biochemistry, or abnormal images (using ultrasonography, CT-scan, magnetic resonance imaging (MRI), echoendoscopy, retrograde endoscopic cholangiography). Microscopic LCH criteria from biopsies: typical granulomatous lesions with positive reading of CD1a on the histiocyte membranes. All available biopsies were checked and validated by the coordinating pathologist (JFE).

Cholestasis was defined by the elevation of the following blood enzymes: gamma-glutamyl-transferase greater than 3 N and/or alkaline phosphatases greater than 1.5 N. The diagno-

sis of sclerosing cholangitis was made either on the microscopic patterns of periductal fibrosis with ductular reaction sometimes associated with inflammatory infiltrates on liver biopsy; or when specific images (irregular and tortuous main bile duct with a thickened wall) were obtained by echoendoscopy or retrograde endoscopic cholangiography; we also used the MRI images of abnormal periportal signal and biliary stenosis and dilatations [8].

All LCH patients routinely underwent radiographic skeletal survey, chest radiography and abdominal US. CT and MRI were performed according to the individual clinical indication, limited to the areas of histiocytic infiltration. All liver LCH patients were examined by abdominal ultrasonography and abdominal CT scan, some of them were also examined by abdominal MRI.

The data files were obtained from the medical files and from personal phone calls with the physicians, and obtained from outpatient clinical records and telephone interview with members of their present responsible physicians or their families. The patient's follow-up included repeated clinical examinations, biology testing and imaging. The response to the treatments was evaluated according to the course of the hepatomegaly as well as the liver biochemistry and imaging.

Table 2. Patterns observed by CT-scan in children liver LCH in 14 cases

Patterns	Number of patients
<i>Periportal hypoattenuation</i>	1
<i>Hepatomegaly + periportal hypoattenuation</i>	2
<i>Hepatomegaly + periportal hypoattenuation+ Hypodense nodules</i>	2
<i>Hepatomegaly + Splenomegaly + periportal hypoattenuation</i>	4
<i>Hepatomegaly + Splenomegaly + periportal hypoattenuation + Hypodense nodules</i>	2
<i>Cirrhosis + periportal hypoattenuation + Hypodense nodules</i>	2

The clinical records of the patients, histopathological data, imaging data, and survival data of liver LCH patients were analyzed retrospectively. Statistical analysis of survival was performed by the Kaplan-Meier method and the results examined using the log-rank test. A *P* value less than 0.05 was considered statistically significant. Statistics were calculated using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

From October 2003 to July 2013, 27 consecutive children diagnosed as LCH in our hospital. Among them, live involvement was discovered in 14 patients (51.9%). In 10 of 14 liver LCH patents (71.4%), the pattern of multiorgan involvement was diagnosed -i.e. three organs or more were involved; in the left 4 cases (28.6%) there were only two organs involved-2 cases with liver and skeleton and 2 cases with liver and skin localizations. Of the 27 LCH patients, 11 patients were multi pattern and 10 of them (90.9%, 10/11) with liver involvement.

The clinical records of the patients, histopathological data, and survival data of UGC patients were analyzed retrospectively. The clinical characteristics of these 14 liver LCH patients are presented in **Table 1**.

A liver biopsy was done in 4 cases (28.6%). The microscopy patterns are varied: 1 case shows Steatosis only; 2 case show Periductal fibrosis, ductular reaction and inflammatory infiltrate; the left 1 case shows systematized peri-centrolobular steatosis, inflammatory infiltrate. However, in all the four cases, the immunostaining (antigen CD1a and protein S100) were positive. Electron microscopy study was done in 1 case simultaneously, and the result shows the presence of cells with Birbeck granules as expected.

The liver involvement was initially discovered by various means: abnormal liver biochemistry (*n*

= 3), otherwise unexplained liver enlargement (*n* = 2) or both (*n* = 2); in some cases, imaging by CT-scan done as routine examination (*n* = 1), or done for other reasons like chest imaging showed incident liver abnormalities (*n* = 6). Biochemistry tests indicated that cholestasis was present in 9 cases (64.3%), absent in 5 cases (35.7%) when diagnosed; the transaminases were raised in 6 cases (42.9%) and normal in eight cases (57.1%) during the initial episode. However, cholestasis and/or elevated transaminases were finally detected in all patients in subsequent episodes. Hepatomegaly was clinically confirmed in 11 cases (78.6%) when diagnosed, among whom the liver size was finally clinically normal in 3 of patients (21.4%) after therapy. Of 14 liver LCH patients, diagnosis of cirrhosis was determined in 2 cases.

All patients (100%) underwent multiple imaging studies: ultrasonography (US) and CT-scan in 11 cases, US and CT and MRI in 3 cases. The association of different images significantly yielded more diagnostic information in 6 cases (discovering the periportal lesions at CT and/or MRI after negative US examination).

Generally, US of the liver showed hepatomegaly, periportal hypoechogenicity, with or without multiple hypoechoic nodules within the liver parenchyma, some of which had a target-like appearance.

The various imaging patterns observed by CT-scan have been summarized in **Table 2**. Examples of CT-scan images of LCH in the liver are shown in **Figures 1, 2**.

MRI was performed in 3 patients only. Axial T1-weighted images (WIs) showed hepatomegaly and lesions with intermediate to low signal intensity around the portal branches (**Figure 3B**). On T2-WIs, periportal lesions appeared to have moderate to high signal intensity (**Figure 3A-D**). The periportal lesions enhanced after

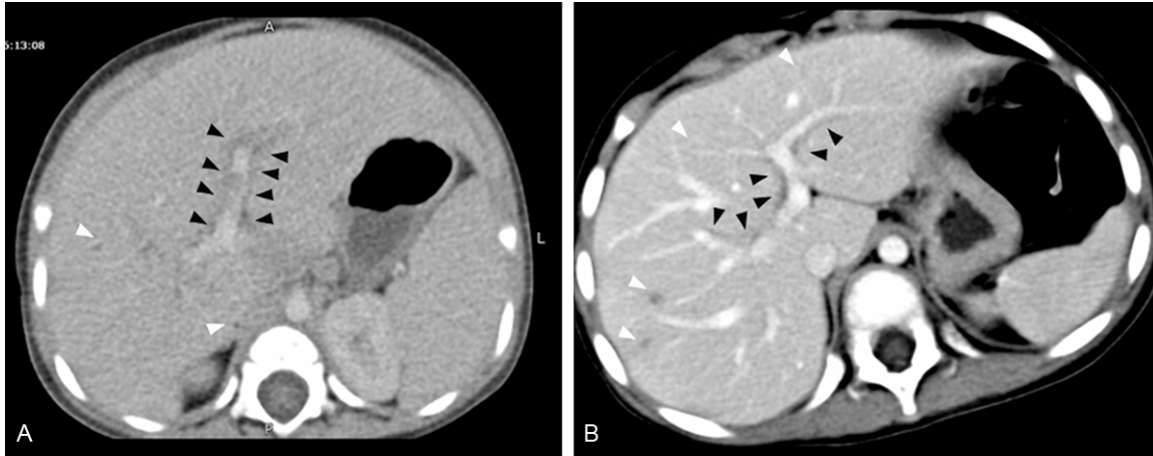


Figure 1. CT-scan of the liver in 2 hepatic LCH cases: periportal hypo-densities (black arrow) and low density nodules in liver parenchyma (white arrow) reflecting the proliferative and granulomatous phases.

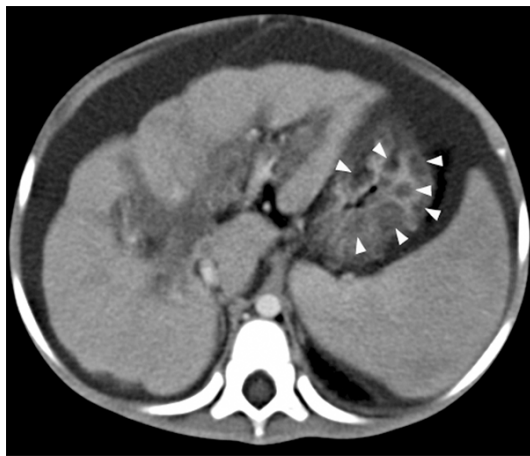


Figure 2. CT-scan of a hepatic LCH case: hypodense nodules centered by hepatic vessels, periductular fibrosis and micronodular biliary cirrhosis. White arrow indicates stomach involvement.

injection of Gd-DTPA (0.1 mmol/kg; Magnevist, Schering, Germany; **Figure 3C**).

Altogether, the liver involvement pattern was suggestive of early injury with hepatomegaly and slight periportal lesions in 4 cases (28.6%), hepatic nodules in 8 case (57.1%) and suggestive of late injury with obvious cirrhosis and sclerosing cholangitis in 2 cases (14.3%). Biochemistry abnormalities present in 9 cases (64.3%) at the time of diagnosis, including cholestasis in 4 case, cholestasis with raised liver enzymes in 5 cases.

All LCH patients with liver involvement underwent systemic chemotherapy except 5 patients whose legal guardian (the parents) refused.

The treatment strategies used in these 9 cases was vinblastine-prednisone-Etoposide association, which was recommended by the Histiocyte Society.

The median follow-up was 20 months from the beginning of LCH (range 1 to 40 months), and 18 months from the treatment start (range 1 to 37 months).

For 9 cases who received chemotherapy, the outcome varied. Four cases (44.4%) presented with amelioration and finally normalization of the liver biochemistry, and regression of the hepatic lesion and hepato-splenomegaly in different degree (**Figure 4**). The outcome of liver LCH patients was poor in five cases (55.6%) with worsening of the associated abnormalities: such as abnormal liver function, neurological worsening and bone marrow involvement. Two patients (22.2%) died, which was due to multiple organ failure secondary to worsening liver dysfunction.

Five cases refused to underwent chemotherapy. Three of them died due to liver failure. The left two cases have been observed for more than 25 months, and mildly liver insufficiency began to emerge in several months after diagnosed by liver LCH and got worse gradually in resent months. Overall, patients treated at an early stage (before severe liver insufficiency/cholestasis, or obvious cirrhosis) had a relatively better outcome than those diagnosed and treated relatively late or refused to accept chemotherapy.

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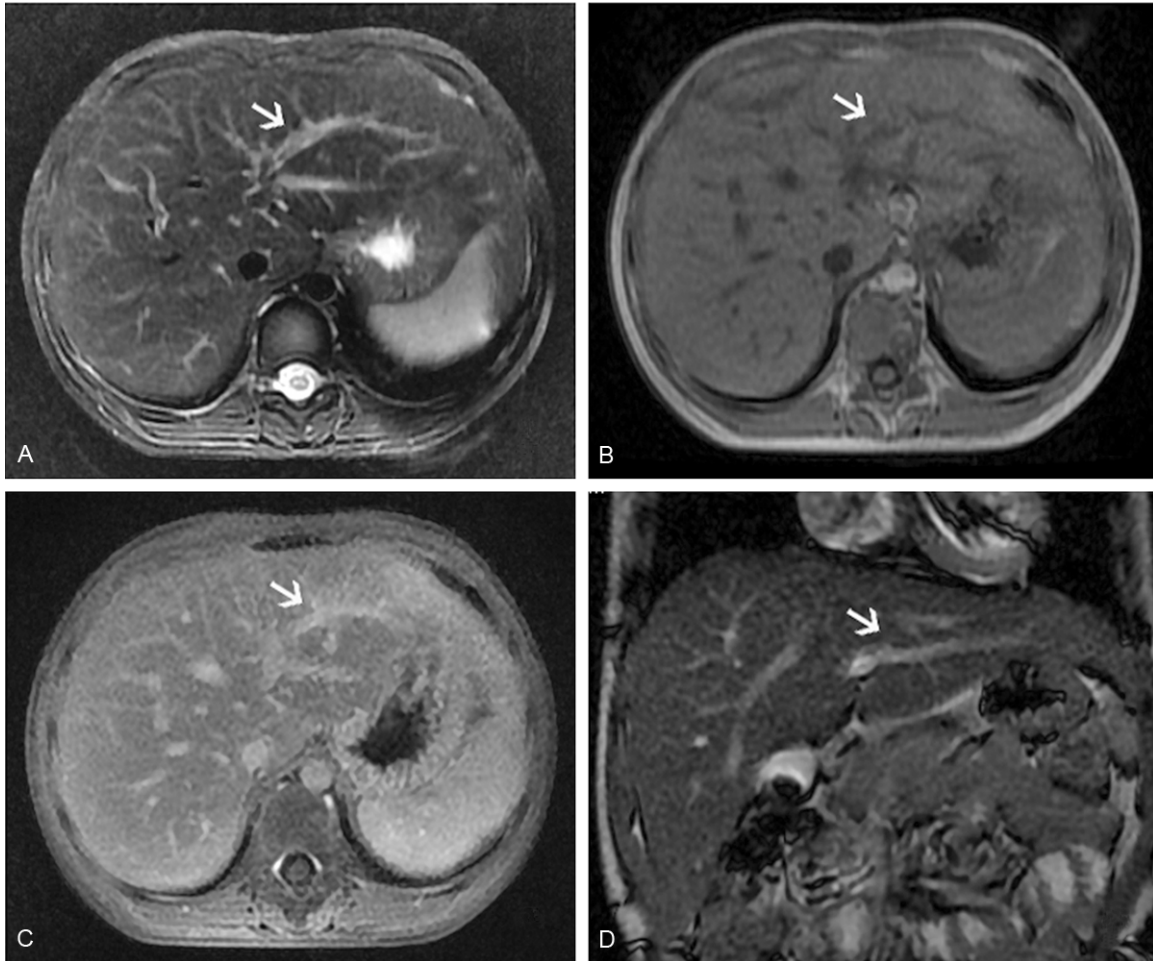


Figure 3. MRI images of the liver in a hepatic LCH case: A and D. Axial and Coronal T2-W image of the liver shows diffuse periportal high signal intensity. B. Axial T1-W image shows periportal low signal intensity surrounding the portal veins. C. Contrast-enhanced T1-Weighted image with fat suppression shows periportal enhancement.

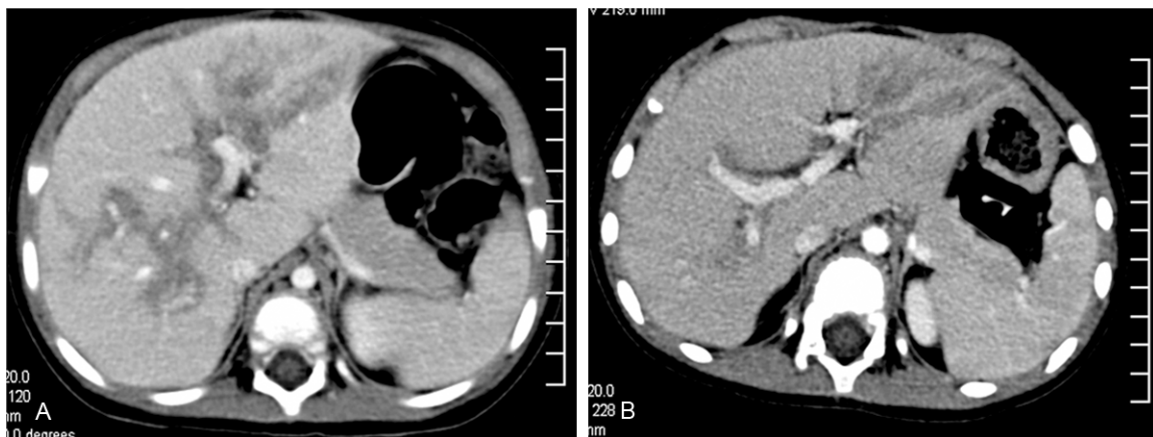


Figure 4. CT-scan of a hepatic LCH case received chemotherapy. A. At the time of diagnoses; B. 1 year after chemotherapy.

The actuarial survival of the liver-involved LCH patients was short (median = 45 months) as

opposed to non-live involvement LCH patients (median = 85 months) (**Figure 5**). There were

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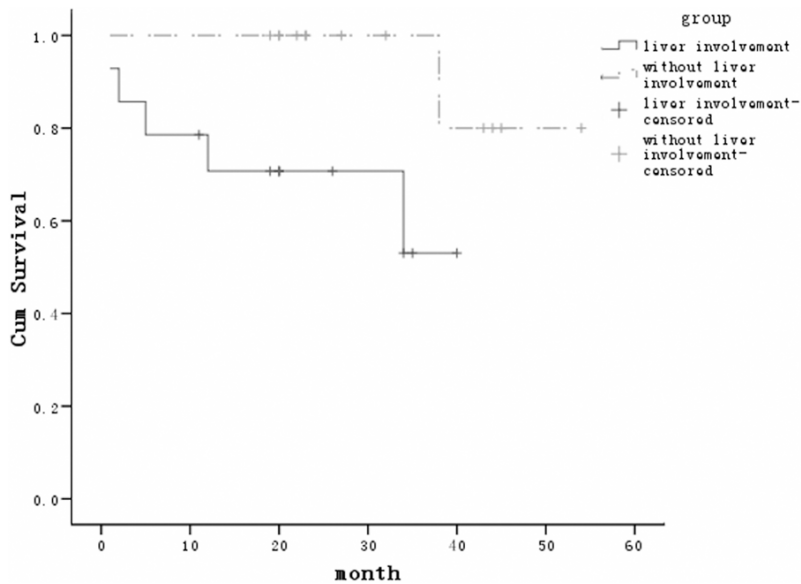


Figure 5. Kaplan-Meier curve for LCH children with (n = 14) or without (n = 13) liver involvement.

five and 1 dead cases respectively in the two groups during follow-up.

Discussion

The definite diagnosis of LCH is based on cytology or histology in combination with immunohistochemical tests for CD1a and S100 protein expression. However, little is yet known about the etiology and pathogenesis of LCH [9]. Usually, the natural history of liver LCH fits into two stages: early infiltration by histiocytes and late sclerosis of the biliary tree [10]. The clinical presentation may be variable, and the course of the disease may show extreme case-to-case variation. The clinical course and outcome depending on the patient's age, the distribution and extension of the lesions, and the degree of organ dysfunction present at the time of initial diagnosis [6, 11]. Therefore, it is very difficult to make a precise diagnosis of this disease early. Clinical diagnosis largely depends on a high degree of suspicion, as most patients who have liver involvement have disease at other sites [3]. It must be looked for not only in multi-organ LCH where it is common, but also in localized LCH forms and it can even be the first manifestation of LCH.

Although the rate of liver involvement is much lower than that in most other organs in LCH patients, it is relatively common in disseminat-

ed LCH (representing 40% to 60% of the cases), as confirmed by our study [12]. According to published papers and our results, the rate of liver involvement in children LCH patents (45.2%) maybe much higher than that of expected in LCH patients, especially in multiorgan involvement pattern (90.9%). In a review of 348 cases, the French Langerhans' Cell Histiocytosis Study Group found liver involvement in 10.1% of patients during the initial episode, rising to 14.4% in subsequent episodes [13]. The latest monocentric pediatric study [5] reported

a 15.6% rate of liver involvement among 217 cases. Braier et al. report an 18% incidence of liver involvement in patients with multisystem LCH [14]. In this study, 45.2% of the patients (14/27) were diagnosed as liver involvement, and almost all of the multi-pattern LCH patients (10/11) with liver involvement, both of which were much higher than that of others' reports mentioned above. Therefore, Liver involvement is probably more common than previously recognized. It is vital important to aware the possibility of liver involvement once the diagnosis of LCH was established in children.

Liver involvement in Children LCH typically presents with hepatomegaly, abnormal liver enzymes, or jaundice, associated with multiorgan involvement. As mentioned above, the majority of our patients have hepatomegaly with liver dysfunction. Hepatomegaly is a key sign of liver involvement and, along with other hepatic signs and symptoms, indicates the need for further investigations [1, 3, 15]. Generally, hepatomegaly was due to the direct infiltration of LCH [1, 10, 16]. This progression of damage may continue despite the regression of the LCH, and after an initial injury the fibrotic disease process can be self-perpetuating even without the presence of Langerhans cells [7]. Although the hepatomegaly usually regresses and is not predictive of the more severe liver involvement, children with hepato-

megaly is younger and has a higher overall mortality. In this study, most of the liver LCH patients (especially all the multi-pattern patients) have hepatomegaly, and the extent obtain partial remission in some patients after effective chemotherapy. It should to note that the enlarged liver size become normal gradually in 3 liver LCH patients with chemotherapy. Unfortunately, hepatomegaly in children is a common and nonspecific clinical finding, it may also be due to Kupffer cell hypertrophy and hyperplasia secondary to a generalized immune reaction or by enlarged portal lymph nodes causing obstruction. Moreover, it is important to bear in mind that hepatomegaly and steatosis may occur as adverse effects of systemic chemotherapy for Langerhans cell histiocytosis.

Liver involvement in LCH drastically changes a patient's prognosis and treatment. It is associated with a high mortality rate in patients with LCH [17]. Liver belongs to the risk organs and responds often to the chemotherapy/bone marrow grafting strategy [4, 6, 18, 19]. With liver involvement, the 3-year survival rate is 51.8% as compared to 96.7% in patients without [13], and the estimated relative risk of death is approximately threefold greater for patients with liver involvement than in those without. This was confirmed by our data that the actuarial survival of the liver-involved LCH patients was much shorter (median = 45 mons) than that of non-live involvement LCH patients (median = 85 months). Several poor prognostic factors for survival in liver LCH patients have been reported: hepatic involvement, age less than 1 year, and incomplete response to treatment [3, 13, 20]. There has not yet been a generally accepted prognostic factor or a completely satisfactory clinical classification. However, it seems that pituitary involvement is a protective factor for survival. Elevated Lactate dehydrogenase (LDH) (>2 N) was detected in the early course of the disease in the four dead cases, while it was detected only in one of the others'. It raised the possibility that elevated LDH maybe a candidate poor prognostic factor in children hepatic LCH. However, there is no published literature can confirm this to date. Further investigation will be necessary to answer this question.

When LCH affects other organs, the disease may regress without treatment, but when the liver is affected, treatment is aggressive due to

the progressive irreversible damage of cholestasis [10]. The treatment of hepatic LCH consists of systemic chemotherapy, and the primary objectives for treatment are the control of symptoms and limitation of long term disability, which can be common in extensive disease. However, because the pathophysiology of Langerhans cell histiocytosis is only poorly understood, treatment approaches remain empirical, and the response to treatment is seldom predictable [3, 17]. Resolution of hepatic lesions and improvement of hepatic function after chemotherapy have been documented, as verified in this study. In 9 patients underwent systemic chemotherapy, CT showed restoration of the live size and reduction in the number and size of the hepatic lesions in different degree. However, the ideal treatment of liver LCH remains to be found, and in advanced cases transplantation is the sole option. Even so, patients who accepted chemotherapy in this study indeed obtain a relatively better prognosis than those refused. Therefore, administrating treatment early appears to significantly improve the prognosis of liver LCH, and it is essential to be able to make an accurate diagnosis as soon as possible.

Various imaging findings of the liver have been described in children and adults with LCH, and the severity and pattern of the abnormality at the onset of the disease, as well as monitoring of regression of tissue infiltration, can be precisely monitored by the specific imaging modalities currently available, and diagnostic imaging is able to visualize areas of LCH infiltration which may be missed on biopsy [3]. However, the diagnostic imaging findings in pediatric LCH are diverse and challenging. Initial imaging is directed at determining extent of disease. Further imaging is performed to identify other organ involvement, the treatment of which will alter prognosis. The radiological manifestations using different imaging modalities are rarely pathognomonic on their own. Nevertheless, familiarity with the imaging findings, especially in children with systemic disease, may be essential for early diagnosis. In the hepatic LCH children, the differing radiological findings are highly dependent on age and clinical presentation. The difference in density, delineation, and contrast enhancement of the lesions in comparison with previously reported imaging features might be due to a different histological stage of LCH lesions. The liver lesions are predominantly periportal and radio-

logical findings reflect the underlying histopathologic process, which comprises four phases of progression, proliferative, granulomatous, xanthomatous and fibrous [3]. Hepatomegaly and the different stages can be well depicted on US, CT and MRI. We recommend that physicians consider CT and MRI screening for liver involvement in patients with newly diagnosed LCH, as periportal involvement may be present with little or no liver function abnormality present. Moreover, the association of different images significantly yielded more diagnostic information. In this study, the periportal lesions which were missed in US examination were finally discovered by CT and/or MRI in 6 cases.

The natural history of liver LCH fits into two stages: early infiltration by histiocytes and late sclerosis of the liver. During the proliferative and granulomatous phases, the infiltration of Langerhans cells and other inflammatory cells causes periportal proliferative and granulomatous lesions, which appears as bandlike or nodular areas of relative hypoechogenicity at US, hypoattenuation at CT, and moderate to high signal intensity at T2-weighted MR imaging (T2WI). Associated periportal contrast enhancement is thought to reflect portal triaditis [3]. Besides these typical findings, hepatic parenchymal nodules of varying attenuation have also been described on CT. CT may show hypodense nodular lesions with ring enhancement simulating metastasis or granuloma, just as showed in this study. The fibrous stage is characterized by progression to periductal fibrosis and micronodular biliary cirrhosis which results from sclerosing cholangitis. Dilation and beading of the biliary ducts, consistent with sclerosing cholangitis, can be seen with conventional cholangiography and MR cholangiopancreatography [3, 8]. It should be noted that progression may occur despite treatment.

In summary, the rate of liver involvement in Children liver LCH appears to be much relatively frequent (roughly three fourth of all LCH patients and almost all of the multi pattern patients) but under diagnosed. We suggest that regular clinical and biological liver evaluation and multimodal images must be performed regularly onwards to screen every LCH children patient from the time of the initial diagnosis and during the follow-up. All liver LCH patients are recommended to receive chemotherapy early once the diagnosis was made. Awareness

of the variety of ways that the disease can manifest itself and the wide spectrum of possible organ involvement is vital for pediatricians and radiologists who encounter this disease.

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Disclosure of conflict of interest

None.

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