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Gallbladder abnormalities in children with metachromatic leukodystrophy



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ABSTRACT

Background: Metachromatic leukodystrophy (MLD) is a lysosomal storage disease that leads to neurological deterioration and visceral involvement, including sulphatide deposition in the gallbladder wall. Using our institution's extensive experience in treating MLD, we examined the incidence of gallbladder abnormalities in the largest cohort of children with MLD to date.

Methods: We conducted a retrospective review of all children with MLD, adrenoleukodystrophy (ALD), or Krabbe disease who underwent hematopoietic stem cell transplantation (HSCT) at our institution between 1994 and 2015. Baseline characteristics and unadjusted outcomes were compared using the Kruskal–Wallis test for continuous variables and Pearson χ^2 test for categorical variables, with significance defined as $P < 0.05$.

Results: In total, 87 children met study criteria: 29 children with MLD and 58 children with ALD or Krabbe disease. Children with MLD were more likely to demonstrate gallbladder abnormalities on imaging, both before HSCT (41.4% versus 5.2%, $P < 0.001$) and after HSCT (75.9% versus 41.4%, $P = 0.002$). Consequently, a larger proportion of children with MLD underwent surgical or interventional management of biliary disease (10.3% versus 3.4%, $P = 0.03$).

Conclusions: Children with MLD have a significantly greater incidence of gallbladder abnormalities than children with other lysosomal storage diseases. Biliary disease should be considered in children with MLD who develop abdominal pain, and cholecystectomy should be considered for persistent, symptomatic gallbladder abnormalities.

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Introduction

Many inherited lysosomal and peroxisomal storage diseases cause progressive neurological deterioration, organ failure, and death early in life.¹ In the past 25 y, nearly a thousand patients with metachromatic leukodystrophy (MLD) and other

inherited metabolic storage disorders, including mucopolysaccharidosis (MPS) type I (Hurler syndrome), other MPS, adrenoleukodystrophy (ALD), and globoid leukodystrophy (Krabbe disease), have received hematopoietic stem cell transplantation (HSCT), either from allogeneic matched or mismatched bone marrow or umbilical cord blood.^{2,3} In the

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last 15 y, unrelated umbilical cord blood transplantation has been the preferred type of HSCT for these diseases. If transplantation is performed early in the disease course, the survival of children approaches 80%-85% and quality of life is improved.^{4,5} This benefit is derived primarily from the replacement of missing enzyme produced by circulating donor cells as well as from engraftment of donor-derived glial cells in the brain.⁴

Children and adults undergoing HSCT have a high incidence of biliary abnormalities such as cholelithiasis and gallbladder sludge, presumably related to factors such as frequent transfusions, prolonged bowel rest, parenteral nutrition, and sepsis.^{6,7} For example, Safford *et al.* identified an increased incidence of cholelithiasis and cholecystitis in children undergoing HSCT compared to the general pediatric population.⁷ In children with MLD, the underlying disease further complicates biliary disease. MLD causes deposition of sulphatides in the gallbladder wall, leading to contraction and wall thickening. This can also cause hyperplastic polyps, papillomatosis, and metachromatic histochemical changes, which lead to acute biliary symptoms as well as an increased risk of gallbladder cancer.⁸⁻¹³

Currently, management of biliary abnormalities in children with MLD remains unclear because relevant evidence is limited to small case series or single reports. Over the past 2 decades, our institution has gained extensive experience treating children with MLD, and therefore, we examined the incidence and clinical management of gallbladder abnormalities in the largest cohort of MLD children to date.

Methods

Study design

This retrospective cohort study was approved by the Duke Medical Center Institutional Review Board. Using a prospectively maintained database, we identified all children with MLD, ALD, or Krabbe disease who underwent HSCT at our institution between 1994 and 2015. Patient characteristics, radiographic findings (ultrasound or computed tomography), and clinical outcomes were documented via chart review. Hyperbilirubinemia was defined as total bilirubin greater than twice the upper limit of normal. The primary clinical outcome of interest was need for cholecystectomy. We hypothesized that children with MLD have a higher prevalence of gallbladder abnormalities and subsequently require cholecystectomy more often than those with ALD or Krabbe disease.

Standard summary statistics were used to describe patient characteristics and outcomes as well as to screen for outliers. Patients then were stratified into two groups based on disease type: MLD *versus* ALD/Krabbe disease. Baseline characteristics and unadjusted outcomes were compared using the Kruskal-Wallis test for continuous variables and Pearson χ^2 test for categorical variables. A *P* value <0.05 was considered statistically significant. Statistical analysis was performed using R, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Literature review

We conducted a review of the medical literature to identify all reports of biliary abnormalities related to MLD and other storage diseases. We searched MEDLINE (National Library of Medicine, Bethesda, Maryland) for all journal articles and clinical reports published between January 1980 and December 2015 using the search terms “metachromatic leukodystrophy”, with associated terms of “biliary abnormalities”, “gallbladder polyps”, “cholelithiasis”, or “gallbladder”. We restricted the search to human subjects <18 y and reports in English.

Results

In the past 21 y at our institution, 87 children underwent HSCT for MLD, ALD, or Krabbe disease: 29 with MLD and 58 with ALD or Krabbe (Table 1). Children with MLD were more likely to demonstrate gallbladder abnormalities on imaging, both before HSCT (41.4% *versus* 5.2%, *P* < 0.001) and after HSCT (75.9% *versus* 41.4%, *P* = 0.002). The most common gallbladder abnormality was sludge, which was seen in nearly half (49.4%) of the whole cohort (Fig. 1). Children with MLD were more likely to have gallbladder contraction (37.9% *versus* 6.9%, *P* < 0.001) and larger common bile duct diameter (2.7 *versus* 1.8 mm, *P* = 0.002). Consequently, children with MLD were also more likely to receive surgical or interventional management of biliary disease. Three of 29 MLD patients underwent laparoscopic cholecystectomy, whereas two of 58 patients in the comparison group underwent either open cholecystectomy or percutaneous cholecystostomy (10.3% *versus* 3.4%, *P* = 0.03).

Our literature review identified an additional 26 children with MLD reported to have gallbladder abnormalities (Table 2). The most common radiographic or pathologic findings were wall thickening (14 cases, 53.8%) and polyposis or papillomatosis (14 cases, 53.8%) (Fig. 2). Eleven of the 26 patients (42.3%) underwent either surgical or interventional management of the gallbladder.

Discussion

To date, our study describes the largest cohort of children with MLD and associated biliary abnormalities. We found that children with MLD were more likely to have biliary abnormalities on imaging and undergo cholecystectomy compared to those with other lysosomal storage diseases. At our institution, cholecystectomy was typically performed in children with MLD who demonstrated radiographic abnormalities and clinical symptoms such as abdominal pain or jaundice.

Similar to our cohort, common biliary findings in the 26 MLD children described in prior literature were wall thickening and polyps or papillomas. Nearly half of the reported cases resulted in cholecystectomy, >10.3% of children with MLD undergoing interventional or surgical biliary management in our study. This difference likely represents selection

Table 1 – Clinical characteristics, biliary findings, and gallbladder management of children who were treated with HSCT for MLD, ALD, or Krabbe disease.

Variable	MLD (n = 29)	ALD/Krabbe (n = 58)	P value
Age at HSCT (y)	5 (2-7)	2 (0-8)	0.04
Type of HSCT			0.30
Unrelated UCBT	82.8% (24)	93.0% (53)	
Related UCBT	3.4% (1)	1.8% (1)	
Unrelated BMT	3.4% (1)	0.0% (0)	
Related BMT	10.3% (3)	5.3% (3)	
Symptoms			
Abdominal pain	17.2% (5)	3.4% (2)	0.04
Hyperbilirubinemia	3.4% (1)	15.5% (9)	0.16
Imaging			
Number of CT obtained, per Patient	1 (1-2)	1 (0-1)	0.03
Number of US obtained, per Patient	2 (1-4)	1 (0-2)	0.002
Gallbladder abnormality on imaging			
Before HSCT	41.4% (12)	5.2% (3)	<0.001
After HSCT	75.9% (22)	41.4% (24)	0.003
Gallbladder abnormalities			
Contraction	37.9% (11)	6.9% (4)	<0.001
Wall thickening	51.7% (15)	29.3% (17)	0.06
Polyposis	13.8% (4)	3.4% (2)	0.09
Cholelithiasis	10.3% (3)	6.9% (4)	0.68
Sludge	58.6% (17)	44.8% (26)	0.26
Pericholecystic fluid	3.4% (1)	6.9% (4)	0.66
Average CBD size (mm)	2.7 (2.0-4.1)	1.8 (1.0-2.2)	0.002
Surgical management			0.03
None	89.7% (26)	96.6% (56)	
Laparoscopic cholecystectomy	10.3% (3)	0.0% (0)	
Open cholecystectomy	0.0% (0)	1.7% (1)	
Percutaneous cholecystostomy	0.0% (0)	1.7% (1)	

UCBT = umbilical cord blood transplant; BMT = bone marrow transplant; CT = computed tomography; US = ultrasound; CBD = common bile duct.

Data are represented as median (interquartile range) or percentage (number).

bias: authors are apt to publish cases with outstanding clinical presentations and interesting management. But similar to our practice, cholecystectomy was typically performed when clinical symptoms such as abdominal pain or mass, hemobilia, or infection coincided with radiographic evidence of biliary abnormalities. Asymptomatic cases were more likely to be observed, in both the published literature and our own experience.

Based on the results of our study and previous literature, gallbladder pathology should be a consideration in the



Fig. 1 – Longitudinal image of the gallbladder in this 6-y-old girl with MLD reveals mildly increased wall thickness (arrow) and complete filling of the gallbladder with sludge (*).

evaluation of child with MLD who presents with abdominal pain. If a child with MLD presents with abdominal pain or other biliary symptoms, ultrasound or computed tomography should be pursued. In the presence of gallbladder disease on imaging, intervention with either cholecystectomy (laparoscopic or open) or percutaneous drainage via cholecystostomy is indicated. Or, if an asymptomatic child is incidentally found to have biliary abnormalities on imaging, then nonoperative management and subsequent radiographic monitoring are appropriate.

Although this study is the largest to date examining biliary abnormalities in children with MLD, we recognize that this study harbors limitations such as small cohort size and variability in radiographic findings. In regard to the latter limitation, as we collected imaging data from the ultrasound and CT reports, we cannot account for potentially different interpretations of the imaging studies by individual radiologists. In addition, our study does not provide evidence for the role of prophylactic cholecystectomy in children with MLD found to have gallbladder polyps, which is an important clinical issue. Owing to their malignant potential, gallbladder polyps in children with MLD may need to be managed differently than cholelithiasis or wall thickening.¹¹ Although our institutional experience cannot speak for use of cholecystectomy in the setting of asymptomatic gallbladder polyps, we do support cholecystectomy in children with MLD who are found to have gallbladder abnormalities in the setting of relevant clinical symptoms.

In conclusion, gallbladder abnormalities are an important part of the differential diagnosis for a child with MLD who presents with abdominal pain. Improved survival after hematopoietic stem cell transplantation in children

Table 2 – Literature review of prior reports of children with MLD who had biliary abnormalities.

Year	Author	Age (years)	Clinical Presentation	Biliary Abnormalities	Management
1983	Heier ¹⁴	2	N/A	Wall thickening Contraction	N/A
		2	N/A	Wall thickening Contraction	N/A
		2	N/A	Wall thickening	N/A
		11	N/A	Wall irregularity	N/A
		15	N/A	Nonfunctional GB	N/A
		16	Hemobilia	Wall thickening Contraction Polyposis/papillomatosis	Cholecystectomy
1984	Warfel ¹³	2	Asymptomatic	Polyposis/papillomatosis	N/A
1985	Burgess ⁹	9	N/A	Polyposis/papillomatosis	N/A
1989	Clarke ¹⁵	16	Cholecystitis	N/A	Cholecystectomy
1989	Tesluk ¹²	N/A	Abdominal mass	Polyposis/papillomatosis	Cholecystectomy
1993	Ries ¹⁶	2	Asymptomatic	Wall thickening	Observation
		4	Chronic hemorrhagic pancreatitis	Polyposis/papillomatosis	Cholecystectomy, partial pancreatectomy with pancreatico-jejunostomy
1995	Fock ¹⁷	6	Asymptomatic	Polyposis/papillomatosis	Observation
1996	Kim ¹⁸	2	Asymptomatic	Wall thickening	Observation
		2	Asymptomatic	Wall thickening	Observation
		2	Asymptomatic	Wall thickening Sludge	Observation
		4	Asymptomatic	Wall thickening Polyposis/papillomatosis	Observation
1997	Oak ¹⁹	2	Painless mass	Wall thickening Polyposis/papillomatosis	Observation
1998	Simanovsky ¹¹	18	Gastric outlet obstruction	Enlarged GB with polyps, later GB adenocarcinoma	Bile aspiration
		21	Asymptomatic	Wall thickening Gallstones	Observation
2000	Vettoretto ²⁰	17	Hemobilia	Polyposis/papillomatosis	Open cholecystectomy
2009	Garavelli ²¹	5	Hemobilia, fever	Polyposis/papillomatosis	Cholecystectomy
2011	Rodriguez-Waitkus ¹⁰	9	Abdominal pain, fever, diarrhea	Wall thickening Pericholecystic fluid Polyposis/papillomatosis	Open cholecystectomy
2013	Agarwal ⁸	2	Abnormal LFTs	Polyposis/papillomatosis Low grade dysplasia	Cholecystectomy
2015	Wanner ²²	4	Abdominal pain, hematemesis, pancreatitis	Wall thickening Polyposis/papillomatosis Intra- and extra-hepatic biliary dilatation	Cholecystectomy
2015	McFadden ²³	4	Abdominal pain	Wall thickening Polyposis/papillomatosis	Laparoscopic cholecystectomy

GB = gallbladder.

with inherited lysosomal storage diseases has brought attention to the management of peritransplant and long-term issues that may be related to the underlying disease, exposure to high-dose chemotherapy, or other complications of the transplantation process. Our study shows that, compared to other lysosomal storage diseases,

children with MLD are more likely to have with biliary abnormalities on radiographic studies and consequent need for cholecystectomy. Surgeons should consider cholecystectomy if gallbladder abnormalities are detected in association with abdominal symptoms in a child with metachromatic leukodystrophy.



Fig. 2 – Longitudinal image of the gallbladder in a 14-y-old boy with MLD shows a distended gallbladder with wall thickening (arrow) and two polyps (arrow heads) at the gallbladder fundus. (Color version of figure is available online.)

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Disclosure

The authors have no conflicts of interest to declare.

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