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Natural History of Lymphatic Malformation Progression in Children: A Retrospective Study

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Abstract

Background/Objectives: Lymphatic malformation (LM) is a challenging lifetime disorder that can significantly impact children's lives, and a key challenge in management is knowing when interventions might be appropriate. The purpose of this study was to determine (i) natural progression of complications associated with lymphatic malformations during childhood and adolescence, (ii) risk factors associated with complications, and (iii) whether early intervention decreases LM complication rates in adolescents or young adults.

Methods: Pediatric patients with LMs of soft tissue and integument were included in the study. Clinical records were reviewed for demographic data, progression, and interventions.

Results: The study comprised 293 pediatric patients (<20 years of age), including 157 females and 136 males. The delayed diagnosis of LM at an older age was associated with higher risk of complication ($p<0.0001$). The odds ratios of complications for patients between 5-10; 10-15; and 15-20 years of age *vs.* those between 0-5 years of age was 1.81 (95% confidence interval: 0.97-3.40); 0.83 (95% confidence interval: 0.38-1.82) and 2.08 (95% confidence interval: 0.71-6.11), respectively. In the multivariate analysis, the odds ratio of complications between patients with no treatment *vs.* those with treatment was statistically significant at 2.82 (95% confidence interval: 1.42-5.63).

Conclusions: In this study, we found a trend of increased complication rates in children over the age of 5 compared to early childhood between birth and 5 years of age. Delayed diagnosis at an older age therefore associates with significant risk of complication. This is also consistent with the finding that patients who did not receive treatment were nearly three times as likely to experience complications compared to patients who received an intervention before 20 years of age.

Keywords: Vascular malformation; Progression; Lymphangioma; Childhood; Adolescence

Abbreviations: CI: Confidence Interval; LM: Lymphatic Malformation; OR: Odds Ratio

Introduction

Lymphatic malformations (LMs) are congenital slow-flow vascular malformations that are composed of endothelial cell lined lymphatic cysts. LMs most commonly occur in the head and neck region and become clinically apparent by two years of age [1]. The typical clinical presentation is a soft, painless, slow-growing mass. These LMs may be initially asymptomatic, but complications, including recurrent infections, pain, acute swelling, hemorrhage, or obstruction of vital structures [1-3], can often occur as patients get older. Therefore, treatment may be required for relief of symptoms or aesthetic or functional impairment.

Recent literature has demonstrated a significant percentage of LMs have documented somatic *PIK3CA* mutations [4], resulting in uncontrolled local proliferation of dysfunctional lymphatic tissue [5,6]. The condition is progressive over lifetime due to persistent activation of the signaling pathways leading to cell proliferation and increased angiogenesis. The malformed lymphatic system often contains heterogeneous cystic spaces. Additional mutations such as those within the homeobox transcription factor Prox-1 may also affect early differentiation of lymphatic endothelial cells during lymphangiogenesis, therefore attributing to the malformation [7,8].

The purpose of this study is to determine (i) natural progression of LM indicated by complications during early childhood and adolescence, (ii) developmental and disease risk factors associated with disease complications, and (iii) role of early intervention in reducing complication rates among adolescents and young adults.

Methods

Institutional review board approval was obtained for the study. Retrospective chart review of the clinical database at Lucille Packard Children's Hospital of Stanford University was performed to identify all pediatric patients (20 years of age or younger) with LMs. Generalized lymphatic dysplasia, lymphedema, visceral lesions (e.g. liver or spleen), and combined malformations (e.g. venolymphatic malformations)

were excluded. Diagnoses of LMs were made based on clinical history, physical examination, as well as diagnostic radioimaging and histopathological evaluation. LMs are categorized by size of cystic space within, and divided into macrocystic, microcystic or mixed macrocystic and microcystic. Macrocystic LMs (previously termed cystic hygromas) have a majority of cystic spaces that are greater than 2 cm in diameter, whereas microcystic LMs have a majority of cystic spaces that are less than 2 cm in diameter. Mixed macro-and micro-cystic LMs have a combination of both in the same lesion [1].

The outcome variable in this study was the development of LM complications, defined as either (i) enlargement of the lesion at a rate greater than growth of the patient or (ii) onset/worsening of signs and symptoms including pain, acute swelling, infection, hemorrhage and functional impairment [1,9]. These criteria were used in previous studies to document worsening of LMs and other vascular anomalies, such as arteriovenous malformations. To assess natural LM complication risk, 5-year intervals from birth to age 20 were stratified and compared. Because the Body Mass Indices (BMI) are lowest during the first five years of life and reach a nadir at an average age of 5, these 5-year intervals were selected to better characterize disease progression with incremental changes of BMI up to 20 years of age [10]. Each group over the age of 5 was compared to the baseline age group (0-5 years), in order to evaluate age-related disease progression of complications. Potential risk factors evaluated in this study were age, sex, LM subtype (macrocystic, microcystic, mixed), location, and lesion size. Location was categorized as head/neck, upper extremities, lower extremities, chest, trunk, back, or multiple sites. The correlation between risk factors and complications was analyzed using binary logistic regression modeling in a univariate and multivariate fashion. All tests were two-tailed and $p<0.05$ were considered significant. Additionally, analyses of the effects of intervention on complication rates were completed using age as both 5-year discrete interval age groups and as a continuous variable. Interventions included for analysis were surgical, medical, or both. Statistical analysis was performed using the SAS software package (version 9.4; SAS Institute, Inc, Cary, NC).

Results

The study comprised of 293 pediatric patients (<20 years of age) with a near equal gender distribution: 157 females (53.5%) and 136 males (46.4%). Lesions were noted at a mean age of 2.12 years (median 0.17 years).Macrocystic LMs (44.7%) occurred more often than microcystic (20.1%) and mixed lesions (35.2%). LMs most often involved the head/neck (59.7%), then lower extremities (15.0%), chest (13.3%), upper extremities (12.3%), trunk (4.1%), and back (3.1%) (Table 1). Most patients had a single lesion involving one specific anatomic site, but there were a small number of patients with multifocal involvement (6.5%). Complications included swelling (43.7%), pain (17.4%), infection (13.3%), and hemorrhage (8.5%).

Demographics	
Age group (yrs)	**Number of patients (%)**
0-5	215 (73.4)
5-10	42 (14.3)
10-15	21 (7.1)
15-20	15 (5.1)
Sex	
Male	153 (52.2)
Female	140 (47.8)
Characteristics	
Location	Number of patients (%)
Head/neck	175 (59.7)
Lower extremities	44 (15.0)
Chest	39 (13.3)
Upper extremities	36 (12.3)
Trunk	12 (4.1)
Back	9 (3.1)
Channel Type	
Macrocystic	131 (44.7)
Microcystic	59 (20.1)
Mixed/Combined	103 (35.2)

Table 1: LM demographics and characteristics – out of 293 pediatric patients, head and neck LMs and macrocystic LMs were the most common.

Progression of complications

In this analysis, there was a slight increased risk of complications for the 5-10 years old (OR 1.81, 95% CI: 0.97-3.40, p=0.06) and 15-20 years old (OR 2.08, 95% CI: 0.75-6.11, p=0.19) when compared to 0-5 years old, but these results were not statistically significant (Table 2). Mean age for the development of an LM complication was 8.77 years (median 4.89 years).

Risk factors associated with complications

Of the analyzed risk factors, diagnosis of LM at an older age was associated with a higher risk of complications with an odds ratio of 1.20 (95% CI: 1.10-1.31, p<0.0001); for this analysis, age of onset was treated as a continuous variable to provide a more precise assessment. Other risk factors, including sex, channel type, anatomic location of LM, and more diffuse LM involvement of more than one anatomic region were not associated with progression risk (Table 2). Among the various anatomic locations analyzed, head and neck LMs had a slightly higher risk of complications, such as need for tracheostomy tube, but the incidence of complications was statistically insignificant compared to that of other locations (odds ratio 1.71, 95% CI: 0.69-4.20, p=0.25).

Intervention

LM patients often receive combined therapeutic interventions at various ages. The majority patients in this study received surgical interventions, including excision (n=170, average age of intervention was 14.93 years old), debulking (n=10, 7.36 years old), and sclerotherapy (n=85, 6.37 years old at 1st treatment). Limited number of patients were treated with off-label medical treatments including

sildenafil (n=13, 4.96 years old) and sirolimus (n=5, 8.11 years old). In the multivariate analysis, the odds of disease progression in patients without treatment compared to those with treatment is significantly greater at each age-matched group, with an odds ratio of 2.82 (95% CI: 1.42-5.63, p=0.0032) (Table 2).

Risk factor	Odds Ratio (95% confidence interval)	P-value [a]
Age group (years)		
5-10 *vs.* 0-5	1.81 (0.97-3.40)	0.06
10-15 *vs.* 0-5	0.83 (0.38-1.82)	0.65
15-20 *vs.* 0-5	2.08 (0.71-6.11)	0.19
Age at diagnosis		
Older *vs.* Younger [b]	1.20 (1.10-1.31)	<0.0001
Sex		
F *vs.* M	0.81 (0.49-1.35)	0.42
Channel type		
Macro *vs.* Micro	1.23 (0.60-2.50)	0.65
Location		
Multiple *vs.* Solitary	0.63 (0.15-2.65)	0.53
Treatment		
No *vs.* Yes	2.82 (1.42-5.63)	0.0032

Table 2: Risk factors associated with LM complications before 20 years of age–early diagnosis and treatment reduces risk of LM associated complications ([a] p-values<0.05 are statistically significant; [b] Age of onset was treated as a continuous variable in this analysis to provide a more precise assessment).

Discussion

Lymphatic malformations are dynamic lesions; they enlarge intermittently and progress gradually in both size and risk of complications over time. The underlying mechanism of LM progression remains to be elucidated, although recent genetic studies have begun to uncover the pro-growth signals driven by the activated mTOR pathway. Current evidence in LM patients demonstrates high rates of *PIK3CA* mutations [4], which may activate downstream pro-angiogenesis signaling. Previous studies have also suggested that the rapid proliferation and disorganization of the lymphatic system could be attributed to additional triggers such as sex hormones and repeated infections due to poor fluid drainage; the potential role of sex hormones was highlighted by a greater progression rate of LMs in adolescence (11-18 years) compared to in childhood (0-7 years) in a retrospective study [1,11].

The results of this study suggest pubertal hormones may not account for all of the risks in disease progression and complications. Our data was stratified into smaller groups in 5-year intervals (5-10, 10-15, and 15-20) to better compare LM growth with BMI increase. We evaluated disease progression by comparing lesion growth and complication rate to that of the youngest group (0-5 years of age), when BMI is the lowest. After the age of 5, the BMI steadily increases until about age 20 [12]. In this study, the higher BMI age group of adolescents and young adults ages 15-20 also had a two-fold increase in disease progression (OR 2.08, p=0.19), although not statistically significant. There was a similar increase in the group of 5-10 years (OR 1.81, p=0.06), as the BMI rises after 5 years of age.These results suggest that in addition to sex hormones, growth hormone (GH) increases also parallel LM progression and may play a role in disease pathogenesis.

Growth hormone is produced steadily during childhood, doubles in production during puberty [13], and is known to promote lymphangiogenesis [14]. Recently, a study of LM tissue found an overexpression of GH receptors (65%) compared to the control tissue (25.8%), which suggests that GH may play a role in LM pathophysiology and influencing disease progression [15]. This finding is consistent with our observation that patients experienced enlargement of LMs during growth spurts. Interestingly, the sex hormone receptors were not found to be elevated in the same study [13]. The combined effects of sex hormone and GH may culminate in overall disease progression, as sex hormones are known to increase GH signaling and production [16,17], vascular endothelial growth factor (VEGF) production, and endothelial proliferation [15,18]. Although more literature has focused on the role of sex hormones in LM development, the results of this observational study suggests the possible role of GH in the pathogenesis of LM, and prospective studies may be indicated.

Regardless of the underlying mechanism of LM development, the most important finding of our study is that patients may benefit from early surgical or medical interventions. Our study demonstrates that patients who received no treatment were nearly three-fold more likely to experience progression compared to patients with any intervention (OR 2.82, p=0.0032) after 5 years of age; this finding was consistent at all age-matched groups. Therefore, like with many progressive diseases, early intervention in children with LM may be considered to mitigate disease progression later in life. Owing to concerns of treatment-associated risks, it is common practice to postpone interventions until patients, especially children, experience significant morbidity from their LM. Our institution also typically initiated treatment of LM in children when families reported worsening symptoms, complications, or loss of function. Thus, our results may carry some intrinsic selection bias, as patients receiving early treatments were likely to be children with more severe disease. The true risk of progression without treatment could be greater than 2.82, should we compare two groups with similar disease severities that were randomized for treatments.

Although spontaneous regression occurs in 12.5-15.0%, the natural course of LMs is progressive and frequently followed by regrowth post-treatment [19,20]. In this study, the most common interventions were surgical excision and sclerotherapy, but differences in efficacy between interventions were not assessed. Optimal interventions for different subtypes of LM and appropriate management algorithms remain to be investigated. Although surgical excision or debulking have been the mainstay of therapy for LMs, complications including scarring, skin ulceration, nerve damage, and recurrence have been reported. There is growing evidence suggesting possible benefit of combinational treatment using disease-modifying medications such as sildenafil and/or mTOR inhibitors in conjunction with surgeries. It is common that interventions are often considered or even reserved for those patients who are symptomatic or with functional impairment. This is the first large scale retrospective study showing that early diagnosis and proactive treatment during early stages of disease is associated with less growth and fewer complications later in life, and therefore

more favorable clinical outcomes. Patients who received sclerotherapy and embolization started their treatments before the mean age of complication development (8.77 years). The risks and benefits of the medical and surgical interventions should nonetheless be evaluated carefully on an individual basis in young children. The complexity and the heterogeneity of the disorder demand a multidisciplinary approach.

Limitations of this study include potential confounding factors due to the retrospective design and lack of standardized longitudinal clinical data collection, such as regular measurements of growth and sex hormones to help further support the role of these hormones in disease pathogenesis. Another limitation is the subjective grading system based on clinical examination rather than a more objective system, such as quantified imaging studies with assessment of interval change in size of the malformation.

Conclusion

This is the first study that has demonstrated the benefits of interventions during early childhood for LM. Compared to age-matched groups, those who received treatments during early stages of disease have fewer complications and reduced disease burden. In addition, while earlier studies showed the role of sex hormones in LM [1], the results of our current study suggest a possible role of growth hormone in the natural progression of LM and warrant further prospective studies to help guide surveillance of disease progression. Thus, a proactive approach to management of children with complicated LM should be considered upon careful clinical evaluation and could be a major shift in the management paradigm of LM. Future prospective studies will be able to better delineate the role of growth hormone as well as other pathologic triggers and optimal management of LMs in children.

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Viraat Patel: Dr. Patel designed the study, carried out the initial analysis, drafted the initial manuscript, and approved the final manuscript as submitted. Joanna H. Tu: Ms. Tu carried out additional analyses, assisted in drafting the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. Joyce M. Teng: Dr. Teng conceptualized the study, designed the data collection instrument, critically reviewed the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest

All authors have no conflicts of interest to disclose. All authors have no financial relationships relevant to this article to disclose. No funding was secured for this study.

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