Journal of Pediatric Surgery 59 (2024) 1611–1614

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.sciencedirect.com/journal/journal-of-pediatric-surgery

Review Article

Incidence and Risk Factors for Chyle Leaks After Neuroblastic Tumor Resection: A Systematic Review of Published Studies

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ARTICLE INFO

Article history:
Received 6 February 2024
Accepted 12 February 2024

Keywords:
Chyle leak
Chylous ascites
Neuroblastoma
Radical resection
Surgical oncology

ABSTRACT

Background: Chyle leakage/ascites after surgical resection of neuroblastic tumors may delay the start of chemotherapy and worsen prognosis. Previous studies have reported a highly variable incidence and risk factors remain largely unknown. This study aims to analyze the true incidence of chyle leaks and ascites and seeks to identify risk factors and optimal treatment strategies.
Methods: Medline/Embase databases were searched according to PRISMA guidelines. Literature reviews, case reports, and non-English papers were excluded. Data were extracted independently following paper selection by 2 authors.
Results: The final analysis yielded 15 studies with N = 1468 patients. Chylous ascites was recorded postoperatively in 171 patients (12%). Most patients experiencing chyle leaks were successfully treated conservatively with drainage, bowel rest, parenteral nutrition and octreotide with variable combinations of these treatment options. 7/171 (4%) patients required operative exploration to control troublesome persistent chyle leaks. In risk factor analysis, higher tumor stage was significantly associated with the risk of chyle leak ($P < 0.0001$) whereas no correlation was observed with adrenal vs non-adrenal tumor location, INRG risk groups and tumor laterality.
Conclusion: Chyle leakage after surgery for neuroblastic tumors is a common morbid complication occurring in some 12% of patients. Higher INSS tumor stage portends greater risk(s). Conservative therapy strategies appear successful in the majority of cases. To avert this complication meticulous mesenteric lymphatic ligation is recommended especially for those patients with higher tumor stage(s) requiring extensive radical surgery including retroperitoneal lymph node resection.
Level of Evidence: III.
Type of Study: Systematic review.

1. Introduction

Neuroblastoma is a malignant tumor of the sympathetic nervous system affecting 10.5/1 million children per year [1]. The most common tumor sites include the adrenal gland (48%), retroperitoneum (25%), and thorax (16%) [2]. Neuroblastoma is a heterogeneous disease; some tumors can regress or mature spontaneously while others display an aggressive, treatment-resistant phenotype. It has been estimated that neuroblastoma is responsible for 15% of all oncological deaths during childhood [3]. Tumor staging is based on patient age, metastatic pattern, and image-defined risk factors (IDRFs) with those locoregional disease without IDRFs classified as L1 and those with one or more IDRFs as L2 [4].

The role of surgery in the management of advanced stage neuroblastoma is controversial. Improved event-free survival is reported with ≥90% resection, however, overall survival is not significantly impacted [5,6]. Extensive surgery aimed at gross tumor resection with advanced staged disease is associated with high risk of intraoperative complications such as major vessel injury, nephrectomy, or even death [7]. Radical surgery for neuroblastoma has additionally been reported to be associated with troublesome postoperative diarrhea [8] and lymphatic/chylous leakage [9].

Abbreviations: INSS, International Neuroblastoma Staging System; IDRF, image-defined risk factor; INRG, International Neuroblastoma Risk Group.

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https://doi.org/10.1016/j.jpedsurg.2024.02.018

Detailed studies regarding postoperative chyle leaks, however, are sparse and widely variable incidence rate(s) (2%–40%) are reported [9,10]. Optimal therapeutic strategies to offset postoperative lymphatic leakage and identify its associated risk factors remain mainly unknown. Against this background of controversy, the aim of this systematic review study was therefore to define the true incidence of postoperative chyle leak after neuroblastic tumor resection, identify potential risk factors and seek ways to optimize effective treatment strategies.

2. Methods

2.1. Identification and selection of studies

According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [11], a comprehensive search of the published literature in Medline and Embase database(s) was performed. The search was made using terms 'neuroblastoma' or 'neuroblastic tumo(u)r' in combination with one of the following as keywords: 'chyle (leak)' or 'chylous (leak)' or 'ascites'. All articles published up to January 31, 2023, were included in the review.

2.2. Inclusion and exclusion criteria

This study included all original articles reporting on incidence of postoperative chyle leak/ascites after surgical resection of neuroblastic tumors. Non-English papers, and case reports (<3 patients) were first excluded with title and abstract screening. Studies reporting duplicate data were also excluded (Fig. 1).

2.3. Data extraction and analysis

Identified papers were independently reviewed by both authors, and final selection was approved by the senior author (PDL). The extracted data included International Neuroblastoma Staging System (INSS) tumor stage [12], tumor laterality and localization as well as incidence, duration, and treatments required for postoperative chylous leakage. International Neuroblastoma Risk Group (INRG) [2], MYCN status, presence IDRFs, and survival were also included where available. Our primary outcome assessed were notably

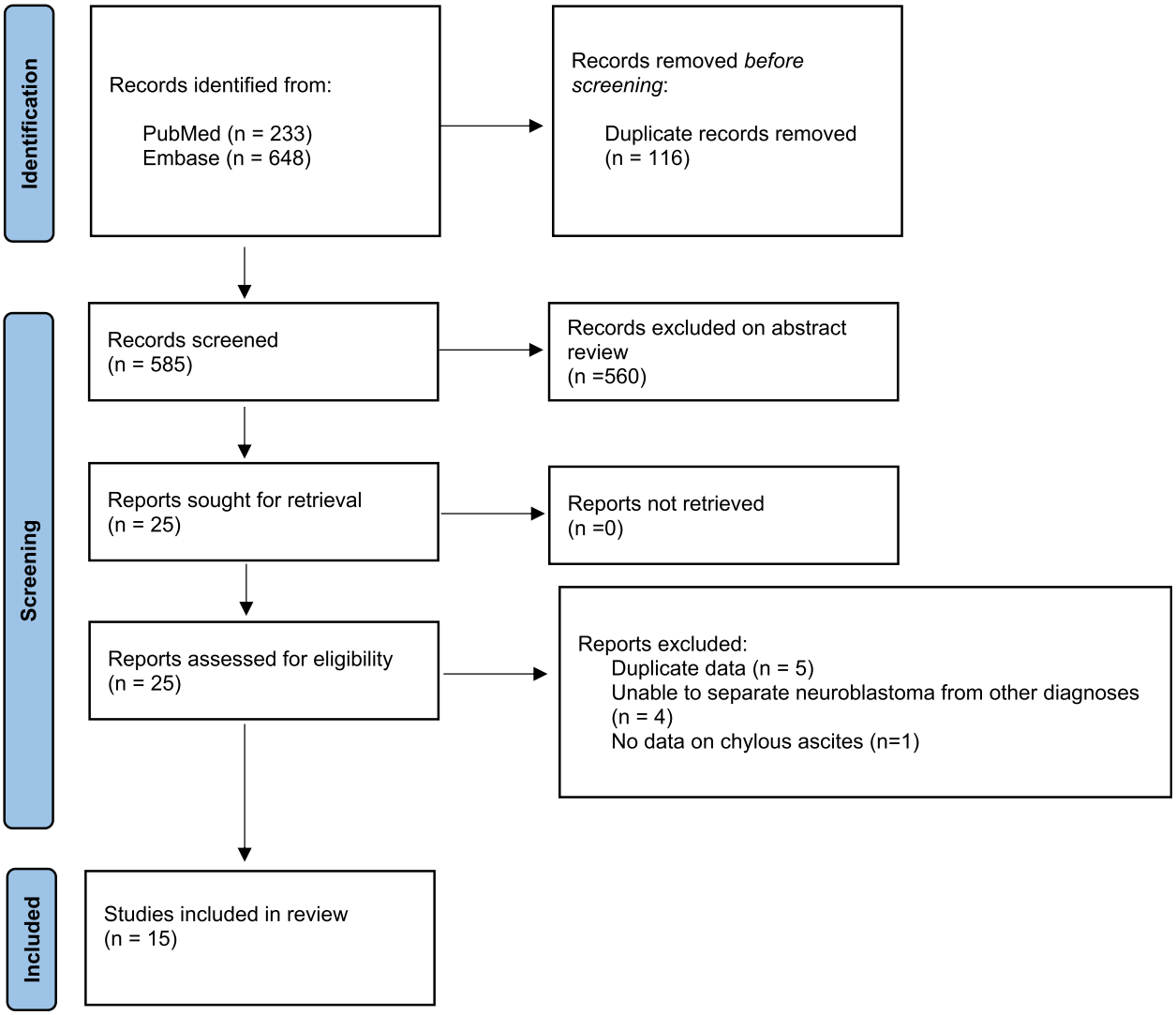

Fig. 1. PRISMA study selection flow diagram.

postoperative chylous ascites/leaks. Secondary outcomes were duration of ascites/leaks and treatment thereafter required for it.

2.4. Statistical analysis

Chi-Square and Fisher's exact tests were utilized to analyze categorical variables. A significance level of $p \leq 0.05$ (two-tailed) was set. Analyses were performed using JMP Pro, version 17.0.0 for Windows (SAS Institute Inc., Cary, NC, USA).

3. Results

The original search through different databases identified 881 articles. A total of 585 studies were evaluated in screening of titles and abstracts after duplicates were excluded. Twenty-five papers met the inclusion criteria and were retrieved for full text review. After full text review, 15 papers with N = 1468 patients met the eligibility criteria and were included for final review (Fig. 1). The published studies covered the time period(s) 1998–2022 [9,10,13–25].

Chylous ascites was documented postoperatively in 171 patients (11.6%). There was no correlation in the incidence of chyle leak and adrenal vs non-adrenal tumor site location, INRG risk groups and tumor laterality. Higher INSS tumor stage was though significantly associated with risk of chyle leak ($P < 0.0001$, Table 1). Also, L2 tumors with one or more IDFRs were more likely to have chylous ascites (11 in 141) than L1 tumors (2 in 105) – [$p = 0.04$]. A single study reported that chylous ascites did not impact patient survival but correlated with the number of resected lymph nodes [9]. Another further study observed a higher risk (%) of lymphatic leaks with MYCN amplification and abdominal vs thoracic tumor site. An inverse correlation with survival and lymphatic leak was also reported [10].

The vast majority of patients (96%) experiencing postoperative chyle leaks were successfully treated conservatively with drainage, bowel rest, total parenteral nutrition and octreotide with variable combinations of these treatment options. The reported mean duration of chyle leak ranged from 12 to 60 days. Only seven (4.1%) patients required surgical exploration to control the chyle leaks. A significant reduction in the incidence of lymphatic leakage (15.6% → 0%) was reported by one study group following the routine deployment of mesenteric lymphatic ligation at time of primary tumor resection [18].

4. Discussion

This systematic review study demonstrates that surgical resection of neuroblastic tumors is often associated with postoperative chyle leakage affecting approximately 12% of all index cases. Higher INSS tumor stage is a significant risk factor for this complication which appears to be self-limiting in most cases. Surgical interventions were required in 4% of patients with troublesome persistent postoperative lymphatic leaks.

Table 1
Incidence of lymphatic leakage after neuroblastoma resection.

	Chyle leak, N (%)	No chyle leak, N (%)	P value
Stage I-II	9 (10.3)	78 (89.7)	<0.0001
Stage III-IV	122 (32.1)	258 (67.9)	
Adrenal tumor	71 (25.6)	206 (74.4)	0.52
Non-adrenal tumor	48 (23.1)	160 (76.9)	
Right-sided tumor	27 (23.3)	89 (76.7)	0.12
Left-sided tumor	15 (14.9)	86 (85.1)	
Low risk	3 (12.5)	21 (87.5)	0.64
Intermediate risk	27 (21.4)	44 (78.6)	
High risk	27 (18.8)	117 (81.3)	
Total	171 (11.6)	1297 (88.4)	

The incidence of postoperative chylous leak from eligible published studies varied from 0.8 to 40% averaging some 11.6% cases. The highest incidence (40%) was reported by a German group who routinely left at least one abdominal or thoracic drain in situ after neuroblastic tumor resection [10]. Although the study authors defined high output (>300 mL/day) or over 7 days duration of drainage of lymphatic leakage, we speculate that the practice of routine drainage may have potentially increased the number of patients with chyle leaks in their series as compared to other published reports. Other studies by contrast may have missed perhaps i.e., under-reported those operative cases with minor asymptomatic, self-limiting lymphatic leak(s).

Neuroblastic tumors are often located retroperitoneally in close proximity to chylous lymphatic channels which likely predisposes such patients undergoing gross tumor resection to risk(s) of chyle fistulae. Also, higher INSS tumor stages (III & IV) and mandate more extensive radical surgery than in those patients harboring localized stage I & II tumors. Similarly, L2 tumors require more extensive surgery than L1 tumors. It is logical therefore that higher tumor stage and the presence of IDRFs will correlate with a higher risk (%) of postoperative lymphatic leakage, as we document in the current study. These risks can, however, be mitigated and offset by meticulous intraoperative mesenteric lymphatic ligation. The technique described by Chui et al. [18] involved consuming high-fat diet on the day before surgery to enhance operative identification of chylous fistulae and ligating any leaks with figure of eight polypropylene 5-0 sutures. A high-fat diet makes lymphatic channels creamy white in color whereas when patients are fed a normal diet chyle is often light yellow or a colorless fluid almost indistinguishable from peritoneal fluid.

Conservative treatment of postoperative chyle leaks appears though to be successful in most patients with only some 4% of index neuroblastoma cases with chylous leak requiring surgical lymphatic ligation to control refractory leaks. Most study groups report treating chylous leaks with percutaneous drainage and bowel rest, total parenteral nutrition, somatostatin, and/or octreotide in variable combinations of these treatment options. The mean duration of lymphatic leaks varied from 12 to 60 days and the majority of the published studies we identified advocated conservative therapy management even with a longer leak duration.

The impact of postoperative lymph leaks on overall patient survival remains unclear as only two of the 15 published studies reported survival data for those with and without chyle leaks. Froeba-Pohl et al. reported worse 5-year overall survival in patients with stage III & IV neuroblastoma and postoperative chylous leak as compared to those with no leak [10]. By contrast, Qureshi et al. observed no correlation between postoperative chyle leaks and survival in any INSS tumor stage or INRG risk category groups [9]. Persistent postoperative chyle leak can postpone or delay adjuvant chemotherapy and therefore may potentially impact survival. Further well-designed prospective studies are clearly required to address and answer these issues.

To the best of our knowledge, this is the first comprehensive systematic review study seeking to address this topic. We fully acknowledge that there are certain inherent limitations to this type of study due to varied methods of data reporting from all the eligible published studies, especially those lacking full information on detailed individual patient data, neuroblastoma tumor staging, and survival.

In conclusion, chyle leakage after surgery for neuroblastic tumors is a common troublesome post operative complication occurring in some 12% of patients. Higher INSS tumor stage(s)

mandating more extensive radical surgery increases the risks (%). Meticulous mesenteric lymphatic ligation at time of primary tumor resection should be considered and is recommended to offset risks (%) of postoperative lymphatic leak.

Funding statement

Dr Raitio reports having received research grants from Päivikki and Sakari Sohlberg Foundation. Funder had no role in the current study.

Disclosure statement

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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