Original Research Article

Treatment Outcome in Children with Nontuberculous Mycobacterial Lymphadenitis: A Retrospective Follow-up Study

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Abstract

Introduction: Information on the long-term treatment outcome following nontuberculous mycobacterial (NTM) lymphadenitis is very limited. We performed a study to (a) compare cure rates following different initial treatment courses, (b) describe subsequent treatment courses and their outcomes, and (c) determine the occurrence of late sequelae in immunocompetent children with NTM lymphadenitis. **Materials and Methods:** In 2011, we conducted a retrospective follow-up study in 71 parents whose children had been hospitalized with NTM disease 2002–2005. A telephone survey was performed using a standardized questionnaire to collect information on the therapeutic management and treatment outcome. **Results:** Of 61 children with NTM lymphadenitis, 33 (54%) children were cured after the initial treatment. We found no significant difference in cure rates following surgical intervention only (45%, 13/29 children) and a combination of surgical intervention and chemotherapy (61%, 19/31 children). In 7 out of 11 children, the cure rate following complete lymph node excision was 64%. Subsequent courses of treatment including repeated surgical intervention, combination therapy, chemotherapy only, and wait-and-see strategy in children where initial therapy failed resulted in the cure of all 61 children. In four children (7%), recurrences were observed up to 5 years later. **Conclusions:** Our study showed that recurrent NTM lymphadenitis might be observed several years after initial resolution of disease. The cure rate following complete lymph node excision was lower than reported in other studies. Subsequent treatment courses were necessary in half of the children. Physicians and parents need to be aware that NTM lymphadenitis in children requires careful choice of intervention and active follow-up.

Keywords: Antimycobacterial drugs, ethambutol, Germany, immunocompromised patients, nontuberculous mycobacterial lymphadenitis, rifamycin

Introduction

Nontuberculous mycobacteria (NTM) are widely spread in the environment (e.g., in soil and water) and can cause diseases in humans, particularly in young children and immunocompromised patients.[1,2] The clinical presentations of NTM infections include pulmonary, lymphatic, skin and soft tissue, and disseminated disease. In immunocompetent children, the predominant clinical presentation is cervical lymphadenitis, mainly caused by *Mycobacterium avium* complex.[3]

According to international and national guidance documents, the therapy of choice for NTM lymphadenitis in children is the complete excision of all affected lymph nodes regardless of the NTM species causing lymphadenitis.[3-5] If surgical intervention poses a risk, for example, in cases where lymph nodes are located close to facial nerves or blood vessels, chemotherapy with a combination of three antimycobacterial drugs presents an alternative albeit less effective.[3-6] It is recommended that chemotherapy includes a macrolide (e.g., clarithromycin or azithromycin), rifamycin (e.g., rifampicin or rifabutin), and ethambutol.[3-5] According to German guidelines, the duration of chemotherapy should be 6–12 months.[5] However, it is unknown how those recommended measures are implemented in Germany.

Access this article online

Quick Response Code:

Website: www.ijmyco.org

DOI: 10.4103/2212-5531.201898

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How to cite this article: Reuss A, Drzymala S, Hauer B, von Kries R, Haas W. Treatment outcome in children with nontuberculous mycobacterial lymphadenitis: A retrospective follow-up study. Int J Mycobacteriol 2017;6:76-82.

Recommendations for treatment of NTM lymphadenitis are based on studies that compared NTM cure rates following different types of therapy.[6-17] The majority of these studies reported a better outcome after complete surgical excision of affected lymph nodes than after other surgical procedures or after a combination of surgical intervention and chemotherapy. These findings were also highlighted in a systematic literature review and meta-analysis of the treatment of NTM cervicofacial lymphadenitis.[18] Specific time points after which treatment outcomes were determined are usually short (6 months or 12 months).[6,19,20]

Disease caused by NTM is not notifiable in Germany. Overall, information on the long-term outcome after treatment of childhood NTM lymphadenitis is scarce.[16,21] Consequently, little is known about the course of disease, the clinical management, and the treatment outcome in children with NTM lymphadenitis in Germany.[22-24]

We, therefore, performed a retrospective follow-up study to (1) compare cure rates following different initial treatment courses, (2) describe subsequent treatment courses and their outcomes, and (3) determine the occurrence of late sequelae in immunocompetent children with NTM lymphadenitis.

Materials and Methods

Study design

In a previous prospective nationwide study ("NTM hospital study"), we collected data on immunocompetent children younger than 15 years who were hospitalized with initial manifestation of NTM disease between October 2002 and September 2005. The methods and results of the study are described elsewhere.[24] In brief, 102 children with NTM disease were identified, including 99 children (97%) with NTM lymphadenitis. Seventy-one of the 102 parents (70%) gave their consent to be contacted for a follow-up study about the course of NTM disease in their children. Seven years (range, 5–8.5 years) after the first hospitalization of their children, a letter was sent to these 71 parents. In this letter, the parents were informed of a telephone survey to obtain information on the long-term outcome of their children's NTM disease. Telephone interviews with the parents were performed between March 2011 and April 2011 using a standardized questionnaire. Information on the children's demographic and clinical characteristics, initial and subsequent treatment courses, treatment outcomes, and on observed complications, side effects, and late sequelae was collected.

Study population

The study population consisted of immunocompetent children younger than 15 years with the initial manifestation of NTM disease who were admitted to a hospital between October 2002 and September 2005. NTM infection had to be laboratory confirmed by culture or polymerase chain reaction and additional characteristic mycobacterial histology. Children with NTM disease other than lymphadenitis were excluded from the analyses.

Definitions

Cases were considered cured if there was no disease activity (i.e., swelling of lymph nodes, fistula, or abscess) following the completion of a treatment course. In analogy to the World Health Organization's definition of a tuberculosis relapse case, recurrence was defined as reappearance of NTM lymphadenitis 6 months or later following the completion of a treatment course. Chemotherapy was defined as antimycobacterial chemotherapy with drugs known to be effective against NTM such as clarithromycin, rifampicin, rifabutin, and ethambutol for at least 1 month.

Statistical analyses

The demographic and clinical case characteristics are described by absolute and relative frequencies. The Chi-square test or Fisher's exact test was applied to assess differences in cure rates following different treatment approaches. All reported *P* values are two-sided and $P < 0.05$ is considered statistically significant. Calculations and statistical analyses were performed using STATA (version 12; StataCorp LP, College Station, TX, USA).

Ethical approval

The study was approved by the Ethics Committee of Charité, Berlin, Germany.

Ethics, consent, and permissions

All 63 parents gave their consent to participate in the telephone interview and the study.

Results

Study population

In total, 63 of 71 parents (89%) who gave their consent to be contacted for a follow-up study about the course of NTM disease in their children were successfully contacted by letter [Figure 1]. The contact details for eight parents were no

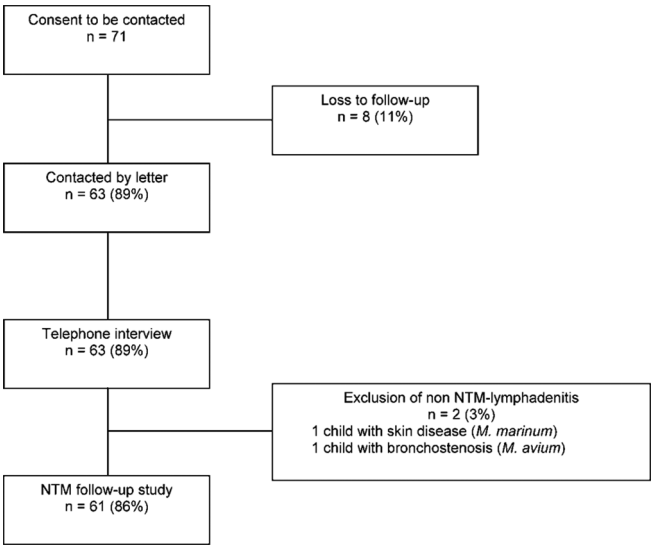

Figure 1: Study population. NTM follow-up study in children with NTM lymphadenitis. NTM: Nontuberculous mycobacteria.

longer valid, and therefore, they were lost to follow-up. All 63 parents agreed to participate in the telephone interview, resulting in a response rate of 86%. Two children were excluded from the NTM follow-up study because they had NTM disease other than lymphadenitis. The median age at the day of the telephone survey was 10 years (range, 7–13 years). The study was carried out after a median of 7 years after the children's first hospitalization.

Of the 61 children included in the study, two-thirds were female [Table 1]. The majority of the children (97%) were younger than 5 years at the time of initial hospitalization. The predominant localization of NTM lymphadenitis was cervical and/or parotid (58 children, 95%), and the majority of the children had unilateral lymphadenitis (54 children, 93%). Bacteriological investigation at the time of initial hospitalization had mainly revealed *M. avium* complex, but uncommon species such as *Mycobacterium heidelbergense* and *Mycobacterium celatum* were also identified. No other family members had experienced NTM disease.

Table 1: Demographic, clinical, and microbiological characteristics of children younger than 15 years with nontuberculous mycobacterial lymphadenitis at the time of initial hospitalization (*n*=61)

Characteristic (*n*=61 unless otherwise specified)	Number of cases
Sex	
Female	40 (66)
Male	21 (34)
Age at time of initial diagnosis (years)	
<5	59 (97)
5-9	2 (3)
10-14	0
Lymphadenitis	
Cervical only	47 (77)
Cervical plus parotid	8 (13)
Parotid only	3 (5)
Preauricular	1
Inguinal	1
Submandibular	1
Femoral	1
Unilateral disease (*n*=58)	54 (93)
Symptoms (*n*=55)	
Fever (temperature >38.5°C)	11 (20)
Pain	21 (38)
Fistula	0
BCG vaccination (*n*=55)	1
Species	
Mycobacterium avium	46 (75)
Mycobacterium kansasii	3 (5)
Mycobacterium malmoense	3 (5)
Mycobacterium intracellulare	2 (3)
Mycobacterium celatum	2 (3)
Mycobacterium heidelbergense	1
Mycobacterium chelonae	1
>1 species	3 (5)

Data are presented as *n* or *n* (%). BCG: *Bacillus* Calmette-Guerin

Initial treatments and outcomes

After the first course of treatment, 33 of 61 children (54%) were cured. Initially, 29 of 61 children (48%) underwent surgical intervention only, 31 children (51%) received a combination of surgical intervention and chemotherapy, and in 1 child, the wait-and-see approach was taken 1% [Table 2]. The cure rate was 45% (13 of 29 children) following surgical intervention only compared to 61% (19 of 31 children) following a combination treatment ($P = 0.2$). One child with a conservative wait-and-see policy for treatment had disease resolution.

A complete excision of lymph nodes was reported for 23 of 61 children (38%) including 11 children with surgical intervention only and 12 children with a combination treatment. There was no difference between the cure rate following complete excision of lymph nodes only (7 of 11 children, 64%) and the cure rate following a combination of complete excision of lymph nodes and chemotherapy (8 of 12 children, 67%), $P = 1.0$.

Likewise, in the group with incompletely excised lymph nodes (24 children), there was no difference between the cure rate following incomplete excision of lymph nodes only (5 of 12 children, 42%) and the cure rate following a combination of incomplete excision of lymph nodes and chemotherapy (8 of 12 children, 67%), $P = 0.4$.

Thirty-one of 61 children (51%) were treated with chemotherapy in addition to surgical intervention for the initial course of treatment. Details on the treatment regimen were available for 23 (72%) children. One child (4%) received monotherapy, 7 children (30%) received a combination of two drugs, and 15 children (65%) received a combination of three drugs [Table 3]. Of those children treated with three drugs, the majority received clarithromycin, rifampicin, and prothionamide or rifabutin for 6–8 months. Four (17%) children were treated in line with national recommendations with a combination of clarithromycin, ethambutol, and rifampicin or rifabutin. Treatment durations were 6 months, 12 months, and 18 months.

Subsequent treatments, outcomes, and recurrence

More than one course of treatment was required for resolution of NTM lymphadenitis in half of the 61 children. Those courses of treatment included surgical intervention only, a combination of surgical approach and chemotherapy, chemotherapy only, and the wait-and-see approach with a varying order [Figure 2]. Figure 2 shows initial treatment courses and subsequent treatment courses in those children where the previous treatmen t failed. Up to four courses of treatment were required to achieve cure in all 61 children.

Four of 61 children (7%) experienced a recurrence of NTM lymphadenitis. These children initially underwent a combination therapy (3 children) and a wait-and-see strategy (1 child) and were cured according to our definition (and thus their subsequent

Table 2: Cure rates of nontuberculous mycobacterial lymphadenitis in children younger than 15 years following the initial course of treatment (*n*=61)

Initial treatment	Cure rate, % (number of cured cases/number of cases)	95% CI
Total	54 (33/61)	41-67
Surgical treatment only	45 (13/29)	26-64
Complete excision of lymph nodes	64 (7/11)	31-89
Incomplete excision of lymph nodes	42 (5/12)	15-72
Incision/puncture of lymph nodes	33 (1/3)	1-91
Other procedures[a]	0 (0/3)	NA
Combination of surgical intervention and chemotherapy	61 (19/31)	42-78
Complete excision of lymph nodes	67 (8/12)	35-90
Incomplete excision of lymph nodes	67 (8/12)	35-90
Incision/puncture of lymph nodes	25 (1/4)	1-81
Other surgical procedures[a]	67 (2/3)	9-99
Wait-and-see policy	100 (1/1)	NA

[a]Including curettage of lymph nodes, excision of abscess, and excision of salivary gland. NA: Not applicable, CI: Confidence interval

Table 3: Chemotherapy in children younger than 15 years with nontuberculous mycobacterial lymphadenitis (*n*=23)

Number of drugs	Name of drugs	Number of cases	Median duration, months (range)
Monotherapy	Rifabutin	1	12
Combination of 2 drugs	Clarithromycin and rifampicin	4	10 (6-18)
	Clarithromycin and rifabutin	1	5
	Clarithromycin and prothionamide	1	6
	Rifampicin and ethambutol	1	6
Combination of 3 drugs	Clarithromycin, rifampicin, and prothionamide	5	9 (1.5-18)
	Clarithromycin, rifampicin, and ethambutol	3	12 (6-18)
	Clarithromycin, rifampicin, and rifabutin	3	6
	Clarithromycin, azithromycin, and rifabutin	1	12
	Clarithromycin, rifabutin, and ethambutol	1	9
	Clarithromycin, rifabutin, and prothionamide	1	6
	Rifampicin, isoniazid, and other unknown drug	1	6

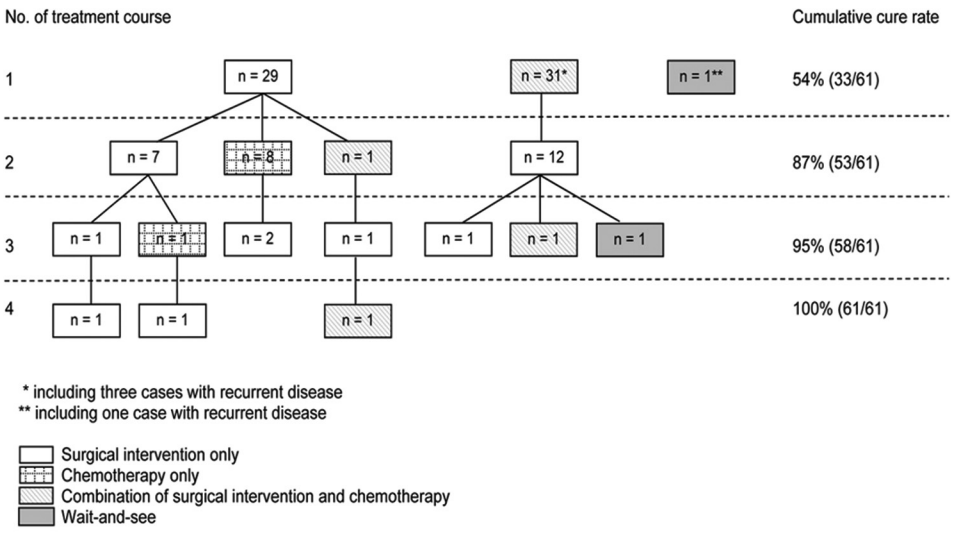

Figure 2: Sequence of treatment courses of NTM lymphadenitis in children younger than 15 years (*n* = 61). NTM: nontuberculous mycobacteria.

treatment courses are not shown in Figure 2). Six months or more after the completion of the initial course of treatment, disease activity had been observed again in those children. All four children were cured after a second treatment course [Table 4].

Side effects

Among those children treated with chemotherapy, severe side effects such as hepatotoxic reactions were not reported. The majority of reported side effects were temporary and included

Table 4: Recurrence of nontuberculous mycobacterial lymphadenitis in children younger than 15 years ($n=4$)

Case number	1st treatment course	Time between recurrence and completion of 1st treatment course	2nd treatment course
1	Partition/puncture of lymph node Combination of 2 unknown drugs for 6 months	6 months	Complete excision of lymph nodes
2	Wait-and-see	1.5 year	Clarithromycin and rifampicin for 14 months
3	Incomplete excision of lymph nodes Clarithromycin, rifampicin, and ethambutol for 6 months	3 years	Excision of fistula Clarithromycin, rifampicin, and ethambutol for 6 months
4	Complete excision of lymph nodes Rifabutin for 12 months	5 years	Clarithromycin, rifampicin, and ethambutol for 10 months

systemic symptoms (fatigue, nausea, headache, and fever) in 12 children (39%) and gastrointestinal symptoms (abdominal pain, diarrhea, vomiting, and obstipation) in 13 children (42%). Furthermore, permanent tooth coloration (4 children [13%], all treated with clarithromycin) was observed. In two children, chemotherapy was discontinued for other reasons than side effects. In one child, the initial dosage of rifabutin (115 mg/d in a 47-kg child) was reduced because of side effects.

The interviewed parents reported complications in 15 of 60 children treated with surgery (25%). Eleven children experienced a facial nerve dysfunction (18%) that was temporal in six children (10%) and permanent in five children (8%), including two children with slight improvement. In four children (7%), a secondary wound infection occurred.

Discussion

We performed a long-term follow-up study on the management of NTM lymphadenitis in children younger than 15 years in Germany. Half of the 61 children in the study initially underwent surgical intervention only. Cure rates following surgical intervention only and a combination of surgical intervention and chemotherapy did not differ significantly (45% vs. 61%, $P = 0.2$). Recurrence of NTM lymphadenitis was observed in 7% of children (4 of 61 children) up to 5 years later following different types of therapy.

Overall, we found that treatment of NTM lymphadenitis in children was highly variable and not in accordance with international and national guidance documents.[3,5] The recommended standard treatment, a complete excision of affected lymph nodes, was performed only in 11 children (18%). Three parents remembered that the lymph nodes of affected children were only partially removed because of their proximity to nervus facialis or arteria carotis. Two of these three children additionally received antimycobacterial chemotherapy. No systematic information was available (such as surgical reports), so it remains unclear whether these cases represent exceptions. However, the high number of incomplete lymph node excisions and extensive use of antimycobacterial drugs in our study population may not completely be explained by similar anatomical preconditions. Furthermore, the antimycobacterial drugs and drug combinations administered as well as the reported treatment duration were highly variable. Only four children were treated with antimycobacterial drugs in line with recommendations. A possible explanation for the observed treatment regimens may be that treating physicians were not aware of existing guidance documents. The national recommendations by the German Central Committee Against Tuberculosis (DZK) and the German Respiratory Society were developed recently, and awareness and information may improve over time.[4] The distribution and implementation of the national treatment recommendations for NTM disease can contribute to high-quality care of affected children. Information from observational studies on how guidelines for treatment of NTM lymphadenitis are followed is scarce. In a 3-year prospective nationwide surveillance study in Australia where excisional biopsy without chemotherapy is recommended, 66 of 68 children (97%) with NTM lymphadenitis had surgery and 17 children (25%) had medical treatment.[7,25] A 2-year prospective surveillance study in the Netherlands showed that 17 (28%) of 61 children with suspected NTM infection underwent complete surgical excision.[26]

In our study, the case numbers were too small to prove a statistical difference in treatment outcomes stratified by different treatment approaches. The cure rate of 64% following complete excision of lymph nodes appears to be lower than in other studies.[6,7] In the surveillance study in Australia, complete surgical excision of affected lymph nodes resulted in a cure rate of 94% and was higher compared to antimycobacterial chemotherapy or combined surgical intervention and antimycobacterial chemotherapy (odds ratio, 9.48; 95% confidence interval, 2.00–44.97; $P = 0.001$).[7] After having performed a randomized controlled trial, Lindeboom *et al*.[6] reported cure rates of 96% following complete surgical excision and 66% following chemotherapy with clarithromycin and rifabutin 6 months after treatment initiation in 100 children with cervicofacial lymphadenitis. A combination of surgical intervention and antimycobacterial chemotherapy for treatment was not investigated in this study. In addition, after 1 year, the esthetic outcome in children with surgical intervention only was found to be superior compared to children who received antimycobacterial chemotherapy only.[27] However, in contrast to our study, all surgical interventions were performed by an experienced oral and maxillofacial surgeon, potentially leading to an optimal treatment outcome.

In general, comparison of treatment outcomes in childhood NTM lymphadenitis between different studies is difficult because standardized definitions are lacking. The development and use of international standardized treatment outcome categories (similar to tuberculosis) would clearly facilitate comparability between future studies.[28]

In our study population, 25% of children experienced complications after surgical procedures including wound infections in 4 children (7%) and facial nerve dysfunction in 11 children (18%). Previous studies reported similar rates of wound infection from 9% to 12% and rates of nerve dysfunction from 9% to 14%,[6,20] with higher complication rates in children with difficult-to-treat lesions.[29] The observed side effects of chemotherapy included temporary systemic and gastrointestinal symptoms. In four children, all treated with clarithromycin, permanent tooth coloration was reported. These are well-known side effects.

To the best of our knowledge, this is the first study to investigate the management and long-term treatment outcome in children with NTM lymphadenitis. We identified recurrence of NTM lymphadenitis retrospectively in 7% (4 children), 6 months to 5 years after the completion of the initial course of treatment. Previous studies reported recurrence rates of 2% in children following complete excision of lymph nodes after 6 months and in 29% of children with surgical and antibiotic therapy after 12 months.[6,20] Although NTM disease is not a severe or even life-threatening condition in immunocompetent children, it does represent a high burden for the affected children and families. This has become evident in light of the fact that in half of the children, several treatment courses were needed. Similar findings have also been reported by another study in Germany.[30] The high response rate of 86% reflects the high motivation of parents to contribute to research about NTM lymphadenitis after their children suffered from the disease.

Our study also has limitations. In our telephone survey, we addressed the children's parents and not the medical doctors in charge. There may be a general potential recall bias with regard to symptoms and side effects of chemotherapy although most parents kept notes about the course of disease in their children and the treatment. In addition, details of surgical procedures might not have been well known or understood by laypersons. Potentially, a relevant number of cases with incomplete lymph node excision for which parents reported complete lymph node excision may be a reason that we observed inferior resolution of disease in our study. Furthermore, the highly variable drug treatment regimens made it difficult to compare cure rates and the frequency of observed side effects, both between the several chemotherapeutic regimens and between the three different treatment approaches.

Overall, follow-up information from only 60% of children who were enrolled in the NTM hospital study from 2002 to 2005 was available. Comparison of the follow-up children and all children of the NTM hospital study revealed no difference regarding age, clinical presentation, and NTM species, but a higher proportion of cases in the follow-up children were female. We cannot rule out that cure rates might be different in those children whose parents did not participate in the follow-up study because determinants of treatment success are not well established.

Conclusions

Our study showed that NTM lymphadenitis in children might recur several years after initial resolution of disease. Furthermore, treatment of NTM lymphadenitis in children was not consistently following existing recommendations laid out by national guidance documents. The cure rate of childhood NTM lymphadenitis after complete excision of lymph nodes appears to be lower in Germany than in other countries albeit with small case numbers. Further studies with a higher number of participants are necessary to look into this finding. Subsequent treatment courses were necessary for half of the children, and there was a risk of developing recurrent disease after years. Physicians and parents need to be aware that NTM lymphadenitis in children requires careful choice of intervention and active follow-up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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