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Pediatric non-tuberculous mycobacterial cervicofacial adenitis: A systematic review

Dear Editor,

We read with interest the article by Zimmerman et al., who described the first systematic literature review and meta-analysis of non-tuberculous mycobacterial (NTM) cervicofacial lymphadenitis in children.[1] NTM cervicofacial adenitis is a well-described entity, typically affecting otherwise healthy children under 5 years of age.[2,3] The disease frequently arises from infection with NTM from the *Mycobacterium avium intracellulare* complex (MAC).[3]

Management of NTM cervicofacial adenitis is controversial. Successful outcomes have been demonstrated with either complete or incomplete surgical excision of involved nodes, as well as with either observation or antimycobacterial therapy.[4–7] Complicating treatment decisions is the risk of facial nerve damage, which has been reported as high as 20% for radical excision.[8] Non-excisional surgeries are associated with a lower risk of post-operative nerve damage, but also an increased rate of fistula formation.[2,9]

We recently completed a systematic literature review of otherwise healthy children with non-tuberculous mycobacterial lymphadenitis. Details of the methodology and an analysis of lymphadenitis outside the head and neck region from this review have been previously published.[10] We also isolated cases of head and neck lymphadenitis from this dataset, all of which were culture or PCR-confirmed. We believe this serves as an interesting corroboration of the findings of Zimmerman et al., and presents new data and analyses as well.

Briefly, a literature search was conducted in PubMed and Web of Knowledge on November 19th, 2014 as previously described.[10] Inclusion criteria required an age under 18 years with no mention of an immunosuppressive condition and demonstration of culture or polymerase-chain-reaction (PCR)-proven infection with NTM isolated from lymphatic tissue. For assessment of surgical outcomes in children undergoing more than one surgery, only the outcome from the first surgery was included in order to avoid a clustering bias which may occur with repetitive outcome measurements of the same subject over time. Excisional surgery was defined as complete removal of infected tissue, while non-excisional surgery was categorized as incomplete removal of infected tissue (e.g. curettage, partial resection).

A logistic regression model compared the outcomes of post-surgical sinus formation and a PPD size >10 mm against the species of NTM. A linear regression model analyzed the relationship between the dependent variable 'NTM species' and the continuous variable 'age'. A Chi-square test assessed for statistical significance between categorical variables.

Our original search produced 246 articles, of which 141 articles describing 2194 cases of NTM adenitis were found as previously described.[10] Of these, 134 articles contained clinically accessible information on 1915 cases of culture or PCR-confirmed NTM head and neck adenitis in children

published from 1956 to 2014. Detailed surgical data was available on 627 cases.

53.6% of patients with information on gender available were female, with a mean age of 3.6 years (range 4 months–15.0 years), similar to the findings of Zimmerman (52.0% female, mean age of 3.4 years) (Table 1). 96.6% of all lesions were unilateral, corresponding to the 98.0% reported by Zimmerman.

321 cases reported PPD results, with 57.6% listed as 'positive' or with a value ≥10 mm. 58 reports provided a specific PPD size (mean 10.3 mm, largest 35.0 mm). 22.4% of PPD's demonstrated 0 mm of induration, while 67.2% were ≥5 mm in size, 44.8% were ≥10 mm, 17.2% were ≥15 mm and 8.6% were ≥20 mm in size.

MAC was the most common isolate described, constituting 66.5% of all reported NTM. However, 18 different NTM species were identified, including three species (*Mycobacterium szulgi, Mycobacterium abscessus* and *Mycobacterium florentium*) not identified in the prior review (Table 2). Of note, 70.8% of *Mycobacterium scrofulaceum* infections were described prior to 1996. No species of NTM was linked to an excess risk of sinus formation or surgical failure (p-values 0.34 to 1.00), nor to a PPD reaction >10 mm (p-values 0.55 to 1.00). Use of a linear regression model failed to detect an association between infection with any NTM species and age ($p = 0.45$). PCR was used as a diagnostic modality in just 6.5% of all cases, but with 68.6% of all usage reported after 2006.

Excisional surgery was utilized in 52.0% of initial surgeries, with non-excisional approaches utilized in 48.0%. Fistula formation occurred 33.6% of the time following non-excisional surgery compared with 8.6% of the time after excisional surgeries ($p < 0.001$, Table 3). This corresponds

Table 1 Clinical and demographic features of 3866 children with non-tuberculous mycobacterial adenitis of the cervicofacial region.

Variable	Zimmerman et al. Number patients (%)	Dehority et al. Number patients (%)[a]
Gender		
Male	726 (42)	416 (46)
Female	1018 (58)	481 (54)
Unspecified	207	1018
Mean age	3.4 years	3.6 years
Location		
Submandibular/ submental	926 (48)	435 (23)
Cervical	609 (31)	798 (41)
Cervicofacial NOS or other	97 (5)[b]	577 (30)[c]
Facial	0	13 (1)
Preauricular or parotid	269 (14)	136 (7)
Not specified	144 (7)	0
Other[d]	19 (1)	0
>1 Location	131 (7)	44 (2)
Bilateral	35 (2)	18 (1)

[a] 1915 patients comprising 1959 separate locations (44 patients with multiple sites).
[b] Cervicofacial not otherwise specified or other location (buccal, retropharyngeal, infraclavicular, retroauricular, occipital).
[c] One occipital case; the remainder of cases are cervicofacial disease without further specification.
[d] Axillary, inguinal, limb, mediastinal.

Table 2 Species distribution of non-tuberculous mycobacteria isolated from 1915 pediatric patients with head and neck adenitis.

Species	Number	Percentage
MAC[a]	1274	66.50%
M. haemophilum	181	9.40%
NTMNOS[b]	162	8.40%
M. malmoense	94	4.90%
M. scrofulaceum	47	2.40%
M. fortuitum	27	1.40%
M. kansasii	28	1.40%
Runyon II[c]	26	1.30%
M. lentiflaveum	24	1.20%
M. chelonae	10	0.50%
M. interjectum	9	0.46%
Runyon I[d]	8	0.40%
Runyon III[e]	6	0.31%
M. bohemicum	3	0.15%
M. simiae	3	0.15%
M. fortuitum-chelonae complex	2	0.10%
M. xenopi	2	0.10%
M. celatum	2	0.10%
M. florentium	2	0.10%
M. gordonae	2	0.10%
M. abscessus	1	0.05%
M. marinum	1	0.05%
M. szulgi	1	0.05%

[a] *Mycobacterium avium intracellulare* complex.
[b] Non-tuberculous mycobacteria not otherwise specified.
[c] Slow-growing scotochromogens (e.g. *M. scrofulaceum, M. gordonae, M. szulgai*).[11]
[d] Slow-growing photochromogens (e.g. *M. kansassi, M. marinum*).[11]
[e] Slow-growing nonchromogens (e.g. MAC, *M. xenopi, M. terrae*).[11]

Table 3 Surgical outcomes following the initial surgery for 627 cases of non-tuberculous mycobacterial adenitis of the head and neck region in children.

Surgical outcome	Excisional surgery ($N = 326$)	Non-excisional surgery ($N = 301$)
Sinus formation	28 (8.6%)	101 (33.6%)
Required further surgery	20 (6.1%)	98 (32.6%)
Facial nerve damage[a]	38 (15.8%)	0 (0%)
Accessory nerve damage[a]	1 (0.4%)	0 (0%)

[a] Among 241 patients with available data on nerve integrity.