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Cervicofacial nontuberculous mycobacterial lymphadenitis in children

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ABSTRACT

INTRODUCTION: Nontuberculous mycobacteria are ubiquitous organisms readily isolated from natural waters, drinking water systems and soil. They form a continuous challenge to the human immune system which becomes apparent in patients with impaired immunity. However, most infections occur in seemingly healthy children. The clinical presentation consists of a unilateral, non-tender, persistent, cervical lymphadenopathy without systemic illness. Fistula formation may occur.

MATERIAL AND METHODS: Patients were included if one or more of the following were positive; 1) mycobacterial culture, 2) acid-fast microscopy, 3) polymerase chain reaction and/or 4) granulomatous inflammation.

RESULTS: On the basis of operative management, two distinct groups were established. Group 1 had an excision of all pathological tissue performed and Group 2 was treated with incision and drainage. There was a difference between the two groups in regard to the risk of developing a postoperative fistula. In Group 1, 50% developed a fistula compared with 91% in Group 2 (p = 0.06).

CONCLUSION: Surgical treatment is generally advocated as the treatment of choice. Antibiotic treatment is associated with adverse effects and avoidance of surgery does not justify the inferior results related to antibiotics. A watch-andwait strategy or antibiotic therapy may be considered when surgical excision carries a high risk of facial nerve injury. Although the lymph nodes may persist for months, spontaneous regression may occur and the children remain systemically well.

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Nontuberculous mycobacteria (NTM) are ubiquitous organisms that are readily isolated from natural waters, drinking water distribution systems and soil. A cardinal feature of mycobacterial cells is a hydrophobic outer membrane, which is a major determinant in biofilm formation, surface adherence, as well as in disinfectantand antibiotic resistance [1-3]. The conventional, and still widely accepted, dogma that NTM infections in humans are derived from birds has been studied, but a relation was not established and the source of the infection may be environmental [4]. NTM infections challenge the human immune system. This is becomes apparent in patients with impaired cell-mediated immunity (e.g. HIV infection or immunosuppressive drugs) who are at particular risk [1-5]. However, most NTM infections occur in seemingly healthy children, especially those aged 1-5 years [6]. There is no strong evidence that these children lack essential immunological protection, although a recent study suggests a weak relation between a certain genotype and susceptibility to NTM infection [7]. The predominance of cervical lymphadenitis suggests infection through the oral route and studies argue that direct exposure of oral mucosa to mycobacteria during eruption of teeth may be relevant to the aetiology [1, 8].

NTM infection of the head and neck was first described in the 1950s [5]. In developed countries the rate of tuberculosis has declined, while cervical lymphadenitis due to NTM has become more common [9, 10]. A prospective surveillance study reports an annual incidence rate of 0.77 NTM infections per 100,000 children per year (0-18 years). The highest incidence rate of 2.3 cases per 100,000 per year occurs among children 0-4 years of age [8].

The clinical presentation consists of a unilateral, non-tender, persistent, cervical lymphadenopathy without systemic illness. The lymph nodes may suppurate spontaneously and fistula formation can occur and may discharge for months, or even years. However, the condition is benign and ultimately all cases will be resolved irrespective of treatment [6, 8, 9, 11-15]. The most important differential diagnoses are streptococcaland staphylococcal infection, congenital cysts, cat scratch disease and malignant disease [9]. Hence, the challenge in the management of these children is to ensure the correct diagnosis and to limit the morbidity of the disease and balance this with the morbidity of treatment, which can be either surgery, antibiotics or a watch-and-wait strategy [6, 8, 12, 13, 16-18].

The present study aims to describe and analyse a population of children with cervicofacial lymphadenitis due to NTM and to review the literature with regard to recommendations on the management of NTM infections in children.

MATERIAL AND METHODS

The clinical files of children (age 0-15 years) diagnosed

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Dan Med J 2012;59(1):A4349 with culture-positive cervicofacial NTM lymphadenitis between 1996 and 2010 were reviewed retrospectively. All patients were examined at the Ear- Nose- and Throat Department at Viborg Regional Hospital, Denmark, and associated medical treatment was carried out by the Paediatric Department.

Patients were included if clinical findings were consistent with NTM infection and if their diagnosis was confirmed by one or more of the following: 1) positive mycobacterial culture of material obtained from the affected lymph nodes, 2) positive acid-fast microscopy, 3) positive real-time polymerase chain reaction (PCR) performed on lymph node aspirates or surgically obtained tissue biopsies, and 4) histopathological findings compatible with NTM infection, i.e. chronic granulomatous inflammation. In this study, the diagnosis was considered highly probable when histopathology results were compatible with NTM and definitive in case of growth, positive staining and/or positive PCR.

Information on age, gender, ethnic origin, duration of symptoms, clinical presentation, objective findings and types of diagnostic procedures was documented.

TABLE :

Clinical characteristics of 23 patients with nontuberculous mycobacterial infection.

	Group 1: excision (n = 12)	Group 2: incision (n = 11)	Total (n = 23)
Age, mean (range), years	3 (1-7)	3 (1-5)	3 (1-7)
Male:female, n	7:5	3:8	10:13
Danish:foreign, n	12:0	10:1	22:1
Duration of nodal mass, mean (range), months	2 (0.5-4)	1 (0.25-4)	1.25 (0.25-4)
Objective findings, n			
Discoloration	4	7	11
Palpatory tenderness	3	3	6
Fever	0	1	1
Skin perforation	0	1	1
General symptoms	0	0	0
Fistulas			
Formation, n	6	10	16
Duration of secretion, mean (range), months	6 (2-14)	4.5 (2-13)	4.5 (2-14)
Postoperative			
Antibiotics, n	3	10	13
Macrolides, n	2	9	11
Macrolides + myambutol/rifampicin, n	1	1	2
Duration, mean (range), months	8 (4-9)	3 (1-6)	3.5 (1-9)
Diagnostics, n			
PCR-positive (13 patients were tested)	0 (5 were tested)	3 (8 were tested)	3
Culture positive	12	11	23
Micoscopi	8	8	16
Histopathology	12	11	23
Species, n (%)			
Mycobacterium avium	12	9	21 (91)
Others (M. malmoense, M. heidelbergense)	0	2	2
PCR = polymerase chain reaction.			

Treatment, surgical and/or medical, was also noted. Finally, the specific mycobacterial specimen was registered (**Table 1**).

Statistics

Categorical variables were described by frequency distributions and the groups were compared by Fisher's exact test. Continuous variables were described by mean and range, and groups were compared with Wilcoxon's rank sum test. Stata version 10 was used for the statistical analysis. A two-sided p value of less than 0.05 was considered statistically significant.

Trial registration: not relevant.

RESULTS

In Table 1, details of the 23 patients are listed. The ages ranged from 1-7 years, with a mean age of three years. The male-to-female ratio was 10:13 (43%:57%). All were systemically well without fever and presented with a unilateral and in most cases non-tender nodal mass in the head and neck region. In some, the overlying skin showed a reddish or violaceous discoloration. All children underwent surgery and the mean duration of the period from presentation of the nodal mass to initial surgical treatment was 1.25 months. The diagnostic procedures registered showed that all patients had a positive culture (100%). In all cases the histopathology showed granulomatous inflammation (100%). The microscopy was positive for acid-fast bacilli in 16 cases (73%). Specimens were sent for PCR in 12 patients (55%) and the result was positive in three (25%). Mycobacterium avium-intracellulare was cultured in 91% of cases.

On the basis of initial operative management, two distinct groups were established. In Group 1, twelve patients (52%) had an excision of all pathological tissue performed. In Group 2, eleven patients (48%) had incision and drainage performed as the only surgical intervention. There was no significant difference between the two groups with regard to average age (p = 0.50), gender (p = 0.21) or duration of the nodal mass from presentation (p = 0.12).

However, as regards the risk of developing a postoperative fistula, there was a difference between the two groups. In Group 1 (excision), six patients (50%) developed a fistula as compared with ten patients (91%) in Group 2 (incision and drainage). The patients in Group 2 had a somewhat higher risk of this complication than the patients in Group 1 (p = 0.06). Overall, the mean secretion period was 4.5 months (range 2-14 months). Although the two groups differed with regard to the risk of developing a fistula, once the fistula was present there was no significant difference in the mean duration of the secretion period between the two groups (p = 0.66). In Group 1, a patient postoperatively developed partial paralysis of the marginal branch of the facial nerve, but this resolved spontaneously after a month. Otherwise, there were no complications to surgery. In another case in Group 2, the primary incision was followed up by a later second surgical procedure performed when the inflammatory response was reduced and total excision had become possible.

Postoperative long-term antibiotic treatment was given to 57% of all patients. The proportion of cases treated with long-term postoperative antibiotics was significantly higher in Group 2 where patients had initially received incision and drainage (10 (91%)) than in Group 1 where patients had initially been excised (3 (25%)) (p = 0.003). However, the mean duration of treatment was significantly longer in Group 1 (eight months) than in Group 2 (three months) (p = 0.03). Two patients received multi-drug therapy (macrolides in combination with ethambutol and rifampin), one patient from each group. A lack of improvement on initial treatment was characteristic for both these cases.

DISCUSSION

This study examined a population of 23 children with culture-proven NTM cervical lymphadenitis. We found that the surgical approach influenced postoperative healing. We observed a tendency to a higher frequency of fistula formation in patients treated with incision and drainage than with excision alone. A total of 50% of those who had an excision performed at their initial operation healed without fistula as compared with only 9% of those who had incision and drainage performed. In the present study, the reason for restraining from excision was, in some cases, difficult dissection due to severe inflammatory reactions or close proximity to major nerves.

In line with our results, a retrospective study of 57 children by Flint et al showed that the specific surgical approach is of great importance for subsequent healing and that there is a significantly higher healing rate after excision than after incision and drainage. A total of 80% of those who had an excision performed at their initial operation healed versus only 21% of those who received incision and drainage [16].

Several large retrospective studies have demonstrated that surgical excision of infected lymph nodes outperforms antibiotic therapy with cure rates varying from 81% to 95% [6, 11, 14]. Further support is provided for this approach by a recent well-conducted trial by Lindeboom et al in which 100 children were randomised for surgical excision or a minimum of 12 weeks of antibiotics. Surgery was clearly more effective than antibiotic therapy with cure rates of 96% and 66%, respect-



that of patients treated with antibiotics [13]. A large proportion of the patients included in the present study received supplementary postoperative treatment with antibiotics (55%), even though the general belief is that antibiotics are not indicated as the susceptibility patterns of most NTMs are unfavourable [11, 12, 19]. Some studies have, however, shown fairly good responses to antibiotic therapy alone [6, 11, 14]. The literature argues that if antibiotics are indicated, the best opportunity for treatment success is the first treatment effort. If antibiotic treatment for more rapid cure is the goal, it is preferable to initiate aggressive treatment rather than to initiate tentative therapy and raise the level of aggressiveness over time. Protection against the emergence of macrolide-resistant NTM isolates is crucial. It is therefore recommended that macrolide treatment does not stand alone; it should be co-administered with adequate companion drugs to prevent the emergence of resistant strains. Thus, regimens typically consist of a macrolide in combination with rifampin or ethambutol [2, 19]. An argument against the benefit of antibiotic therapy is that the resolution of disease during antibiotics therapy may represent the natural history of the infection rather than an effect of medication.

Surgical treatment is generally advocated as the treatment of choice, but this may be biased if the study includes only the more severe cases, which is probably also the case in the present study. It is important to

Unilateral, non-tender, cervical lymphadenopathy with violaceous discoloration.

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bear in mind that surgery is not without complications. Especially in the submandibular and parotid region, surgery holds a risk of damage to the facial nerve and, furthermore, surgery will always result in a scar [14].

Harris et al suggest that the morbidity of both the disease and its treatment can be reduced by selecting patients into various treatment arms with "watch-and-wait" management as an option for deep lymph nodes. This no-intervention strategy was associated with less morbidity than antibiotic treatment. Despite the possible disadvantage of a longer duration before resolution, it may have the benefits of avoiding surgical sequelae and adverse reactions to antibiotics [8, 14]. There is no placebo-controlled trials of treatment with observation alone, but a follow-up study by Zeharia et al described the observational approach in 92 children with NTM disease and concluded that although lymph nodes may persist for months, the children remain systemically well and morbidity from the mass remains low [20].

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