



## Head and neck mycobacterial infections in pediatric patients

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### ABSTRACT

**Objective:** Lymph nodal disease is one of the most common manifestations of head and neck tuberculosis and is particularly frequent in paediatric patients with an increasing incidence in the last decade. It may represent the manifestation of a systemic tuberculous disease or a clinical entity specific of the neck. Aim of this paper is to retrospectively analyse mycobacterial cervical adenopathies observed in two Paediatric European Centers between 1986 and 2004 and the outcomes of medical or surgical treatment.

**Methods:** 353 children were examined for mycobacterial cervical lymphadenopathies since January 1986 to December 2004. Demographic data about the sample are showed. The retrospective evaluation of the sample underlined distribution according to etiologic patterns, head and neck adenopathies localization. Previous or simultaneous medical or surgical treatment were analyzed. Statistical analysis with Chi Square test was performed.

**Results:** 281 (79.60%) cases showed a higher localization and 72 (20.40%) a lower localization. In relation to the etiological agent, 8 (2.27%) *Mycobacterium tuberculosis* (MTB) and 222 (62.89%) mycobacteria other than tuberculosis (MOTT) lymphadenopathies were observed in the upper localization as opposed to 21 (5.95%) MTB and 39 (11.05%) MOTT in the lower plane. Two (0.56%) were detected as upper lymph nodal tumefaction in the median line. In 86 (24.36%) cases at the MRI the so-called “iceberg effect” was noted. 163 (62.45%) patients underwent primary excisional biopsy whereas 74 (28.35%) underwent exeresis after other unsuccessful therapies, 9 underwent only drainage, and 15 drainage with subsequent antibiotic therapy. Number of relapses after surgery was 16 (6.13%).

**Conclusions:** A not homogeneous therapeutic approach to the mycobacterial cervical adenitis arises from literature and WHO guidelines does not give indications for the treatment of the cervical pattern.

A therapeutic strategy based on the etiology is mandatory. In case of MBT adenopathy the therapy of choice includes the association, in variable way, of different chemotherapeutic drugs; surgery is reserved to advanced cases. Conversely, in cases of MOTT adenopathy, surgery is the treatment of choice.

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### 1. Introduction

Tuberculosis (TB) is usually considered an infectious disease whose multiple etiologic agents are commonly classified into two

large groups: *Mycobacterium tuberculosis* (MTB) and mycobacteria other than tuberculosis (MOTT) also called atypical mycobacteria (AM). In children, the principal causative agents are AM in 92% of cases, while MTB is involved in the rest of cases [1]. It has been estimated that 65% to 80% of children under 12 years are infected by *Mycobacterium avium* complex; 10% to 20% by *Mycobacterium scrofulaceum*; and 10% by MT. On the other hand, in paediatric patients aged more than 12 years MT is the principal etiologic agent. Incidence and prevalence of pediatric tuberculosis

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worldwide has been estimated around 3.1 million children under 15 years of age [2]; the majority of cases occur in countries where the prevalence HIV/AIDS is high. TB occurs frequently among disadvantaged populations, such as malnourished individuals, and those living in crowded areas [3]. TB cases are once again frequent in low socio-economic urban areas and among different ethnic groups. A fair percentage (25%) is composed by immigrant children from endemic areas who, together with suckling and post-puberal teenagers, appear to be at a higher risk of infection [4]. It is important that pediatric otolaryngologists are aware of tubercular infection of head and neck with its different, varied and sometimes unusual presentations [5] not only in third world countries but also in industrialized areas. TB is an airborne disease, transmitted by Pfluge particles expelled by subjects sneezing, coughing, speaking or singing with pulmonary or laryngeal TB. The source of infection in cervical lymph nodes is controversial. The initial tubercular infection starts in the tonsillar crypts and hence diffuse to the cervical lymph glands.

Lymph nodal disease is one of the most common manifestations of extra-pulmonary tuberculosis and is particularly frequent in paediatric patients. TB involving cervical lymph nodes represents the 50% of extrapulmonary TB [6].

In the neck the posterior, the anterior and supraclavicular cervical regions are usually involved. The submandibular, submental, axillary, and inguinal lymph nodes are less frequently affected. The involved lymph nodes are typically firm, non-tender, and painless, with non-erythematous overlying skin. They are initially non-fluctuant: lymph node suppuration and spontaneous drainage may occur after caseation and necrosis development [7,8]. Fever, weight loss, fatigue, and malaise are usually absent or minimal. Lymph node involvement typically occurs between six to nine months following the initial infection.

Diagnosis is not always simple and sometimes only a “plausible” diagnosis of mycobacterial lymphadenopathy is formulated, based on positive skin reactivity tests, a highly suggestive clinical course and histological findings with acid-alcohol resistant bacteria with impossibility of isolating the microorganism. Actually, mainly thanks to PCR, the identifications of bacteria is almost always possible. Furthermore, differential diagnosis of cervical swelling in paediatric patients is extremely demanding as this comprises several conditions which cannot be easily distinguished [9]. It emerges that no diagnostic-therapeutical gold standard has been set as far as mycobacterial cervical lymphadenopathy is concerned. Several therapies are attempted, each of them with valid application criteria and presenting contraindications.

Aim of this paper is to retrospectively analyse mycobacterial cervical adenopathies observed in two Paediatric European Centers between 1986 and 2004. Of these cases, treatment modalities and outcome have been evaluated over time.

## 2. Materials and methods

At the Paediatric Surgery Unit of the Department of Paediatrics, Obstetrics and Reproductive Medicine of the University of Siena (Italy) and the Paediatric Surgery Unit of the Maternal-Paediatric Department of the Hospital University Vall d’Hebron in Barcelona (Spain) between January 1986 and December 2004, 353 children were examined for mycobacterial cervical lymphadenopathies. Inclusion criteria in the study were “incontrovertible” isolation and identification of mycobacteria in the cervical lesion, or at least evidence of acid alcohol resistant bacteria in the involved tissues.

Patients were 142 males (40.22%) and 211 females (59.78%), age ranging between 1 month and 16 years. All subjects were examined at 10 to 14 months from the cervical onset. Two hundred forty three patients (68.83%) were already undergone a wide spectrum antibiotic therapy for at least 2 weeks with no clinical improvement.

**Table 1**

Distribution according to sex and other previous or simultaneous therapy

N = 353	142 M (40.22%) 211 F (59.78%)
- 243 (68.83%)	previous wide spectrum antibiotic therapy
- 17 (4.81%)	chemotherapy for malignancies
- 5 (1.4%)	immunosuppressive therapy

**Table 2**

Distribution according to treatment

Group A: 311 primary surgery (88.1%)	218 excisional biopsy 69 drainage and exeresis 24 drainage
Group B: 42 specific antibiotic treatment (11.9%)	

Out of 353 children in the study, 3 (0.84%) were undergone liver transplantation and 2 (0.56%) kidney transplantation: in both of them anti-rejection immunosuppressive therapy was being administered; 17 (4.81%) were contemporarily undergoing chemotherapy for different malignancies. Of them only 2 (0.56%) had completed chemotherapy 6 weeks and 5 months prior, respectively; 2 (0.56%) were HIV positive and 8 (2.27%) showed active AIDS, 2 of these patients had been previously diagnosed with abdominal mycobacterial lymphonodal infection (Table 1).

All patients underwent clinical evaluation and tubercoline reactivity skin tests, ultrasonography and neck Magnetic Resonance Imaging (MRI).

A subclassification of the patients was made regarding the localization (above or below the plane of the hyoid bone) and the etiologic agent. The subjects were also subdivided into two groups on the basis of treatment received: group A 311 (88.10%) patients submitted to primary surgery, 218 (61.76%) of them had primary excisional biopsy, 24 (6.80%) drainage, 69 (19.55%) drainage followed by excisional biopsy; and group B 42 (11.9%) patients submitted to specific antibiotic therapy prior to surgery, based on the results of skin reactivity tests (Table 2).

Surgically removed lymph nodes underwent Ziehl-Neelsen staining, and histopathologic examination.

In 103 cases (29.18%) the surgery was followed by medical antitubercular therapy, usually when skin results were unequivocal and a “cross reactivity” was observed or when a clinical negative neck was only achieved by a “safety” pharmacological support.

Results were compared by means of Square chi test with a significance at  $p \leq 0.05$ .

## 3. Results

281 cases (79.60%) showed a higher localization of adenopathies (above the hyoid bone) and 72 (20.40%) a lower localization. In relation to the aetiological agent 8 (2.27%) MTB lymph adenopathies and 222 MOTT (62.89%) were observed in the upper localization as opposed to 21 MTB (5.95%) and 39 MOTT (11.05%) in the lower plane. Two cases were detected (0.56%) of upper lymph nodal tumefaction in the median line which placed a differential diagnostic doubt with a cysts of the thyroglossal duct.

In 86 cases (24.36%) at the MRI the so-called “iceberg effect” was noted: the lesions appeared small upon palpation and enough mobile on the surface but during the surgery they revealed a 5–6 times larger volume than expected and firm adherence to the deep neck structures. All the cases in the study with no exception, showed at least the presence of acid-alcohol fast bacilli in the cervical lesion. However, in the noticeable percentage of 17.84% (63 children) the bacillus could not be isolated and positively identified.

Out of 290 identified cases, 23 (7.93%) were affected by MTB and 6 (2.06%) by *M. bovis*. Of these, 19 underwent antibiotic therapy

**Table 3**

Distribution according to etiologic agents

Mycobacteria other than tuberculosis (MOTT)	261
<i>Mycobacterium tuberculosis</i> (MBT)	29
Not otherwise specified (NOS)	63

with 12 recovery and 7 relapses treated subsequently with surgery. Ten pediatric patients underwent surgery as first option: in 6 cases a drainage was associated to antibiotic therapy with no relapse, in the other 4 cases affected by large and fistulized neck lesions a successful complete surgical excision was performed.

In 261 cases (90%) an unequivocal diagnosis of MOTT infection was expressed and respectively in 163 cases (62.45%) an intracellular *M. avium* was detected, in 39 cases (14.94%) a *M. scrofulaceum*, in 19 cases (7.27%) a *M. fortuitum*, in 36 cases (13.79%) a *M. kansasii*, in 2 cases (0.76%) a *M. xenopi*, in 1 case (0.38%) a *M. genavensis* and finally in 1 case (0.38%) a *M. simiae* (Table 3).

No patient with MOTT cervical adenopathy recovered with exclusive antibiotic therapy. One hundred sixty three patients (62.45%) underwent primary excisional biopsy, whereas 74 (28.35%) underwent exeresis after other unsuccessful therapies, 9 underwent only drainage, and 15 drainage with subsequent antibiotic therapy: of these respectively 8 and 12 pediatric patients relapsed and were treated subsequently with a complete exeresis. The number of relapses after surgery was 16 (6.13%).

The statistical analysis of data shows that in cases of MOTT cervical adenopathies, the efficacy of surgery is higher than that of pharmacological therapy ( $p < 0.01$ ) and that among different surgical options exeresis is more effective than the drainage alone ( $p < 0.01$ ).

On the contrary, in lymph nodal infection due to MTB, antibiotic therapy is as effective as surgery in case of small and non fistulized lesions ( $p < 0.01$ ). Conversely, in large, collimated lesions, or in lesions with skin fistulae, surgery is always required ( $p < 0.01$ ) since the healing rate is exceedingly higher. In this case as well, the efficacy of complete exeresis proved to be higher than that of drainage ( $p < 0.05$ ).

#### 4. Discussion

Mycobacterial lymphadenopathies are scarcely invasive and easily identifiable; however a differential diagnosis from MOTT and MTB should be made, mainly because the treatment of both is thoroughly different [10].

Clinical presentation of MOTT lymphadenopathies often overlaps with that of MBT, though these generally evolve with a less severe pattern. The most frequently affected subjects are children under 5 years of age, showing an adenopathy of the upper cervical nodes resistant to a 10–15 days large spectrum antibiotic treatment.

After 3–4 weeks, the swelling considerably grows with redness of the skin and an extremely disagreeable appearance. If a MTB infection is mistakenly diagnosed, as it frequently happens, antibiotics will fail with consequent further enlargement and fluctuation of the lesion up to fistulization [11].

In our case series patients, diagnosis of MOTT adenopathy was made in 75.9% of cases in children from 0 to 6 years of age; in 17.9% of a cases ranging between 6 and 12 years and in 6.2% of cases ranging between 12 and 16 years. An inverted incidence is usually recorded in patients with MTB adenopathy.

The diagnostic path includes intra-dermal reactions [12]. These skin tests performed in all our patients for the detection of MTB and in 277 patients for the detection of MOTT, have shown highly effective and reliable and were confirmed by the isolation of the corresponding *Mycobacterium* in 73.9% of cases. Their application allowed a rational treatment even while waiting for the microbiological

logical results which usually take 8–12 weeks to be obtained, even if the diagnostic gold standard is still the culture of mycobacteria.

The subject's immunological reactivity is very important in case of mycobacterial lymphadenopathy: the severity of mycobacterial lymphadenitis in HIV positive patients is extensively described in the literature [13,14].

Our data clearly show that in children with primary immunodepression of any kind, or undergoing chemotherapy or being administered post-transplantation immunosuppressive therapies, lesions always rapidly grow and rapidly spread. The histopathological pattern is also typical in subjects with immunodeficiency; in none of these patient either collimation or caseous granulomas were observed. For this reason, a prompt therapeutic or surgical approach is mandatory as well as an evaluation of the immunological pattern. As concerns therapeutic strategy, the analysis of the collected data clearly show a difference between a MOTT infection and one caused by "typical" bacteria. In MBT lymphadenopathies, medical management proved effective with a more than acceptable success rate, though surgery is still mandatory in case of fistulized lesions [15]. Excisional biopsy may be immediately necessary in cases of bulky and advanced lesions as antibiotics have a limited efficacy in metabolically inert and scarcely vascularized lesions. An elective surgery should be postponed in patients with suspected active TB. In any case, major surgical procedures as selective neck dissection should be avoided [16].

On the contrary, antibiotics are ineffective in MOTT lesions and cannot even induce a regression of very limited and initial patterns. In a relevant percentage of cases, while waiting for the efficacy of drugs to be assessed, lesions may deteriorate and the following intervention may become complicated [17]. In our case series, the success rate was much higher with a primary surgical approach (92.3%) and the surgery of choice was a complete exeresis. When this is not applicable, surgical drainage can be performed and area courettage, although these treatments are still affected by an extremely high recurrence rate (up to 75%). On the contrary, post-exeresis recurrence rate is very low (6.1%).

A special reference has to be made to evaluate the aesthetic outcome over time following surgery. Out of 353 cases examined, only 4 patients developed keloid or pathological scar, all following very bulky and very skin infiltrating lesions. All the 4 cases showed a successful scar removal.

#### 5. Conclusions

Cervical adenopathies in children represent a major challenge to the Paediatrician and Paediatric Otorhinolaryngologist. The diagnostic chances in the neck are several and the difference must be highlighted between congenital and acquired tumoral and infectious masses. A review of the Literature shows a globally non homogeneous therapeutic approach to the mycobacterial cervical adenitis [18]. The WHO indicates guidelines to control childhood tuberculosis for the prevention of TB, but does not give indications for the treatment of the cervical pattern [19].

In our opinion, the most rational approach is to define a therapeutic strategy based on the etiology. In case of MBT adenopathy the therapy of choice includes the association in variable way of a different chemotherapeutic drugs and surgery in advanced cases (fistulae or relapses). Conversely, in cases of MOTT adenopathy, the surgery is the treatment of choice. In these case, the radicality of surgery is closely related to prognosis, whereas either administration or not of chemotherapeutic drugs does not seem to be determinant to recovery.

#### Conflict of interest

None declared.

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