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Adenoids of patients with mucopolysaccharidoses demonstrate typical alterations

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ABSTRACT

Objective: Tonsillar hypertrophy caused by the progressive accumulation of partially degraded glycosaminoglycans (GAGs) within the cells is a typical symptom in patients with mucopolysaccharidoses (MPS). We studied the tissue of adenoids and tonsils of patients suffering from MPS with special regard to characteristic morphological features serving as possible markers for diagnosis.
Methods: Adenoids of 87 patients and tonsils of 4 patients with MPS (2 patients with MPS I, 7 MPS II, 5 MPS IV and 10 MPS VI and 63 controls) and controls were examined. Examinations were repeated in a blinded manner by two pathologists.
Results: The key feature observed was a subepithelial "clearing" on scanning magnification, induced by perivascular accumulation of histiocytoid cell forms. Similar agglomerates could sometimes be found at the base of lymphoid follicles.

In the blinded assessment a specificity of 92% (100% for adenoids) and a sensitivity of 100% were achieved. The inter-observer-consistency was 92% (100% for adenoids). In tonsillectomy specimens marked subepithelilal fibrosis can lead to a false-negative evaluation.
Conclusions: Qualified histological examination could be an option for early diagnosis of MPS.

1. Introduction

Mucopolysaccharidoses (MPS) are a group of relatively rare, inborn errors of metabolism caused by a deficiency of specific lysosomal enzymes that affect glycosaminoglycan (GAG) degradation. The accumulation of GAG in various organs and tissues of patients affected by MPS results in a series of signs and symptoms which make up a multisystemic clinical picture. To date, eleven enzyme defects that cause seven different types of MPS have been identified [1]. All are inherited in a recessive manner: MPS II (Hunter syndrome) being X-linked, whereas the other types are autosomal. Due to the ubiquitous nature of GAGs in the body this deposition can occur in many tissue types and may interfere with cellular function. Patients with MPS suffer from alterations of the skeleton, the heart and the lung. Patients with the severe forms of MPS often demonstrate a neurocognitive decline. Ear Nose Throat (ENT) manifestations include facial dysmorphism, upper airway obstructive disease, nasal obstruction, rhinorrhea, wide nares, flat nasal bridge, wide mouth with downturned angles, macroglossia, and thickened lips. Later gingival hyperplasia and gapped teeth are seen. Comprehensive oral examinations reveal hypoplastic condyles, malposition of unerupted teeth, large dental follicles, and anterior open bite in most of the patients [2]. Otitis media, conductive and sensorineural hearing loss are also common. Adenotonsillar hypertrophy is almost universal in this group of patients due to the deposition of GAGs.

All these symptoms are not apparent at birth, but they develop gradually, for most patients in early childhood. Typically diagnosis may be several years after the onset of signs and symptoms [3]. Until now for MPS I, II and VI enzyme replacement therapy (ERT) is available. As the effect of an ERT is the better the earlier the treatment starts, the time of diagnosis is crucial [1].

As nearly a half of the patients undergo adenoidectomy or tonsillectomy prior to diagnosis [4] the histological examination of the tissue could lead to an earlier diagnosis.

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We studied the tissue of adenoids and tonsils of patients suffering MPS with special regard to characteristic morphological features which could serve as a marker for the early diagnosis independent from the distinct form of MPS.

2. Materials and methods

In this study 177 children underwent surgery at the Department for Otolaryngology of the Mainz Medical Centre after being diagnosed with MPS. They were between 1 and 13 years old (mean: 5.5 years) when surgery was conducted. In general and also valid for this study, a test of enzyme activity levels is required for a definitive diagnosis of MPS. The enzymatic assessment was done, based on suspicious clinical symptoms of MPS. From this cohort histological specimen from adenoids could be re-evaluated in 2 out of 38 patients with MPS I, 7 out of 47 patients with MPS II, 5 out of 42 patients with MPS IV and 10 out of 50 patients with MPS VI. Additionally, histologic specimens of tonsils of 4 patients with MPS were included. Adenoid tissue of 63 non-MPS patients served as control.

All hematoxylin–eosin stained slides of the patients' specimens were evaluated for typical alterations as described by Fujitani et al. [5] and Nayak et al. [6].

For unbiased evaluation an independent examiner selected 87 adenoid specimens (24 with MPS) and 8 tonsillar specimens (4 with MPS) in a blinded manner to two pathologists for independent characterization of changes in the lymphatic tissue. The two pathologists were asked to evaluate specimens from patients with upper respiratory tract infection and did not know about the diagnosis of MPS when receiving specimens for histological analysis. Specificity and sensitivity were calculated for adenoids and tonsils.

3. Results

Histological examinations of the adenoids revealed a subepithelial "clearing" on scanning magnification as a key feature. This was induced by perivascular accumulation of foamy macrophages. Similar agglomerates could sometimes be found at the base of the lymphoid follicle. Fig. 1 displays a 100-fold magnification. At the surface the regular respiratory epithelium is visible. Subepithelial histiocytoid cell forms are aggregated leading to a characteristic lucency of the tissue. More centrally lymphoid stroma with activated capillaries can be found. Fig. 2 demonstrates a 200-fold magnification, while Fig. 3 a 400-fold magnification of the adenoids of a patient with MPS. The specimen of the tonsils revealed aggregates of histoid cell forms, too (Fig. 4).

In the blinded assessment (Table 1) a specificity of 92% (100% for adenoids) and a sensitivity of 100% were achieved. The inter-observer-consistency was 92% (100% for adenoids) (Table 2). Tonsillectomy specimens contain an innate pitfall, as marked subepithelial fibrosis can lead to a false-negative evaluation.

4. Discussion

In patients with rare diseases often the diagnosis is made late. Children with MPS are born without typical symptoms and develop a variety of symptoms over time. Data on surgical interventions from the Hunter Outcome Survey (HOS), an observational database of patients with MPS II, suggested that most patients with MPS II will experience at least one operation in their lifetime, often before the later diagnosis. According to Mendelsohn et al. [4], 45.1% of the patients with MPS II undergo tympanostomy, 41.6% adenoidectomy and 29.4% tonsillectomy prior to diagnosis.

The treatment concept includes symptom-based treatment and for the more frequent forms of MPs an enzyme replacement therapy. Enzyme replacement therapy replaces the missing enzyme exogenously, through regular intravenous infusions. Additionally bone marrow transplantation has proven beneficial especially for patients with the severe forms of MPS I, if it is done early. Optimal therapy for children with an MPS disorder should involve both disease-specific treatments and symptom-based nonspecific treatments. For several endpoints it has been shown that enzyme replacement therapy can reduce the severity of the disease [7]. Early disease-specific treatment before the development of irreversible damage (i.e., fibrosis of heart valves) should result in an improved outcome no matter what type of treatment.

Upper airway obstruction is a frequent symptom in patients with MPS [8]. In a study using computed tomography patients with MPS had significantly smaller retropalatal and retroglossal spaces compared to healthy controls although one-third of the patients had an adenoidectomy or tonsillectomy before. The placement of ventilating tubes (51.4%), adenoidectomy (49.5%) and tonsillectomy (35.5%) are among the most commonly performed operations in patients with MPS, often prior to diagnosis [4].

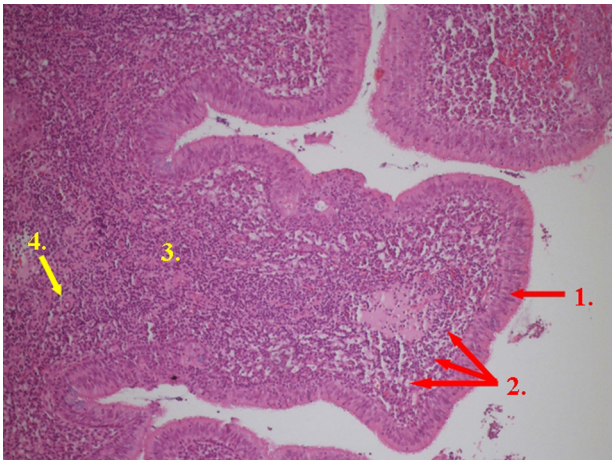

Fig. 1. Adenoids of a patient with MPS in 100-fold magnification. At the surface the regular respiratory epithelium is visible (1). Subepithelial clustering of histiocytoid cell forms (2) leads to a characteristic lucency of the area. Beneath, lymphoid stroma (3) with activated capillaries (4) is visible.

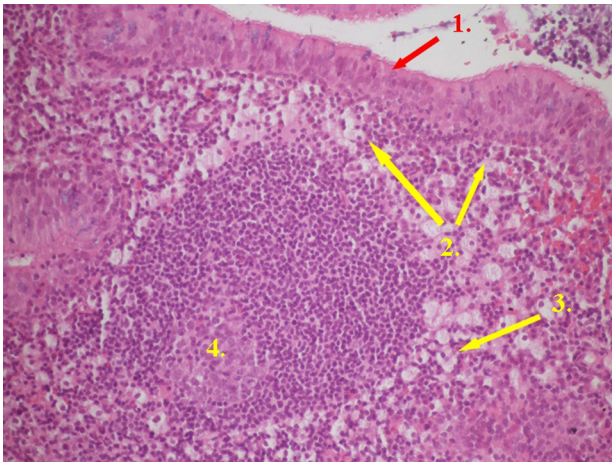

Fig. 2. Adenoids of a patient with MPS in 200-fold magnification. At the specimen surface regular respiratory epithelium (1). Beneath the epithelium and around lymphoid follicles (3) aggregates of histiocytoid cell forms (2) lead to a characteristic lucency of these areas. A well-demarcated germinal center is visible (4).