Rhinology, 34, 35–37, 1996

Young's syndrome: A further cause of chronic rhinosinusitis*

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SUMMARY

Three males – aged 32, 35, and 27 years – presented Young's syndrome: a combination of obstructive azoospermia and chronic sinopulmonary infection. The evaluation of nasal mucociliary transport using an isotopic technique revealed mucociliary stasis in one case and decreased clearance in the others (<2 mm/min). Ciliary ultrastructure was normal in two patients, while the other showed mucous hyperplasia and low ciliary density which made correct ciliary evaluation not possible. The clinical development of this syndrome is chronic, although less severe than in the other two syndromes that exhibit primary failure of mucociliary transport: cystic fibrosis and primary ciliary dyskinesia. Young's syndrome should be considered in the differential diagnosis of patients suffering from chronic rhinosinusitis, particularly with cystic fibrosis and primary ciliary dyskinesia syndrome.

Key words: chronic respiratory infection, primary mucociliary transport failure

INTRODUCTION

The association of recurrent nasosinusal and bronchopulmonary infections with azoospermia, commonly known as Young's syndrome, was first described in 1970 (Young, 1970). There has been little interest in this pathology to date, as reflected by the few publications found in the specialized literature over the past five years (Smallman et al., 1988; Smallman, 1989). However, the prevalence of Young's syndrome is considerably greater than that of the other two better known conditions, cystic fibrosis (CF) and primary ciliary dyskinesia syndrome (PCDS), that combine sinopulmonary infections and male infertility (Handelsman et al., 1984).

Azoospermia in patients with CF is due to malformations of the vasa deferentia and epididymis (Holsclaw et al., 1971). The secretion of abnormal mucus is the only cause of the mucociliary clearance dysfunction, which is in turn responsible for the recurrent respiratory infections that characterize this disease (Di Sant'Agnese and Davis, 1976; Rutland et al., 1981). In CF, both ciliary ultrastructure and *in vitro* functional analysis of beat frequency are normal (Rutland et al., 1981; Simel et al., 1984). In PCDS, the defective mucociliary clearance is caused by defects in the ciliary axoneme (Afzelius, 1976), although in some cases the ultrastructure is normal and the underlying defect is located at the molecular or enzymatic level (Gagnon et al., 1982; Armengot et al., 1994). Similar spermatic axoneme defects in turn account for male sterility. In the case of Young's syndrome, no cause has been found to fully explain either the chronic respiratory infections or azoospermia.

The present study investigates the clinical manifestations, mucociliary transport and ciliary ultrastructure in three patients with Young's syndrome. These alterations must be taken into account in otorhinolaryngology in the differential diagnosis of chronic rhinosinusitis, particularly with regard to PCDS and CF.

PATIENTS AND METHODS

Three males aged 32 (A), 35 (B), and 27 years (C) were referred by the Urology Unit, where they had been studied for infertility. All patients exhibited the same symptoms and signs, i.e. coughing and expectoration with mucopurulent rhinorrhoea, since infancy. As the only background characteristic of interest, the father of patient A presented chronic bronchitis of undetermined aetiology. Patients B and C suffered from repeated episodes of sinusitis, while patient A suffered from sporadic acute sinusitis.

A thoracic and maxillofacial high-resolution CT scan was performed, along with allergy tests, blood immunoglobulin, α-1-antitrypsin assays, semen analysis, and functional respiratory and sweat tests. All three patients underwent a testicle biopsy.

Nasal mucociliary transport was evaluated in the three patients on two occasions, spaced 6 months apart. The Tc-99m-labelled

* Received for publication November 2, 1994; accepted April 24, 1995

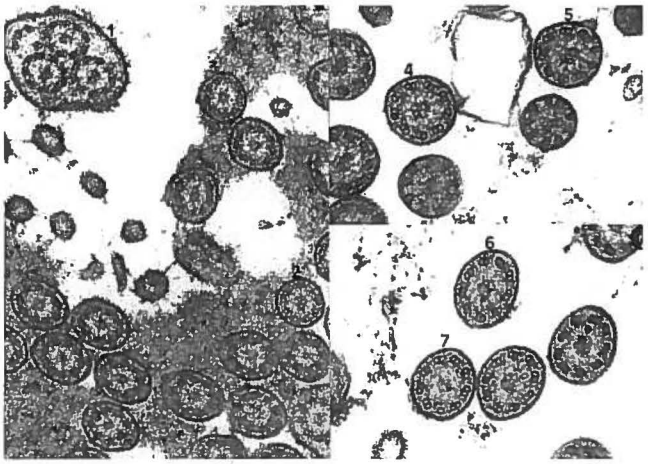

Figure 1. Electron micrographs of cross-sectioned cilia from a patient with Young's syndrome. In *A* (×75,000) can be seen a compound cilium (1), a cilium with absent central pair (2), and a normal cilium (3). In *B* (×100,000) cilia with alterations of the peripheral microtubules (5) are observed along normal cilia (4). In *C* (×100,000) cilia with absent central pairs (7) are observed together with normal cilia (6).

serum albumin technique (Armengot et al., 1989) was used as follows: 0.01 ml of Tc-99m-labelled albumin macroaggregates (25 μCi) was placed on the posterior side of the lower turbinate. Eighty per cent of the macroaggregates were 60–80 μm in diameter, and none exceeded 100 μm. The amount deposited was less than 3.5 mg. The study was carried out at room temperature (25°C), at a relative humidity of 65%. The test lasted 18 min, after which the nasal cavity was aspirated to eliminate the isotope. The studies were carried out at least five weeks after any acute overinfection that could affect the epithelium.

Tissue samples were collected for the study of ciliary ultrastructure by curettage of the lower turbinate under topical anaesthesia with 2% lidocaine. The biopsies were fixed by immersion for 1 h in 2.5% glutaraldehyde in 0.03 M phosphate buffer, followed by washing for 30 min in the same buffer and post-fixation in 1% osmium tetroxide for 1 h. The specimens were then dehydrated in a graded acetone series and embedded in Epon. Semithin sections were cut and stained with toluidine blue; these were in turn used to select the most representative areas for the preparation of ultrathin sections. The latter were stained with uranyl acetate and lead citrate and examined with a Seol Roo B transmission electron microscope (60 kV). Not less than 60 transverse and 5 longitudinal sections were photographed for quantification of the ciliary axoneme.

RESULTS

In all three patients functional respiratory testing revealed slight obstruction, while the chest CT-scan showed voluminous bilateral bronchiectasis. The maxillofacial CT-scan revealed partial occupation of all the paranasal sinuses by a soft-tissue density substance in all patients. Patient A, moreover, exhibited aplasia of the frontal sinuses, and hypoplasia of the maxillary sinuses. The sweat test showed sodium and chloride concentrations to be below 40 mM in all cases. Normal α-1-antitrypsin and total as well as IgG-subclass immunoglobulin levels (assayed by kinetic nephelometry) were recorded. The allergy tests were normal in all patients. Semen analysis revealed azoospermia. The testicle biopsies showed spermiogenesis to be normal. All patients were diagnosed to have obstructive azoospermia.

Patient B presented a nasal mucociliary transport velocity of 1.3 mm/min at the first evaluation, which decreased to <1 mm/min. In the second study, six months later, clearance proved abnormally slow. In patient A testing revealed mucociliary stasis on both occasions, while in patient C nasal mucociliary transport velocity was 1.3 mm/min in both studies.

Ciliary ultrastructure was normal in patient B, while in patient A repeated biopsies showed mucosal hyperplastic changes and a low ciliary density that made evaluation of ciliary ultrastructure impossible. In patient C ciliary ultrastructure was normal. However, at least 20% of the cilia showed non-specific alterations in the form of compound cilia and numerical anomalies in the central and peripheral microtubules (Figure 1).

DISCUSSION

Young's syndrome should be considered in the diagnosis of chronic rhinosinusitis. When this condition is associated with male infertility, differential diagnosis must be established with primary ciliary dyskinesia syndrome and cystic fibrosis (Table 1). Azoospermia is common to both CF and Young's syndrome, although sweat sodium and chloride concentrations of less than 40 mM, adult age, the absence of digestive symptoms and signs, and non-severe respiratory alterations discard CF (Goodchild and Dodge, 1985; Verra et al., 1991; Boucher, 1994; Boat and Boucher, 1994). In PCDS the sperms in the spermogram have a normal apppearance, but are immotile (Afzelius, 1976).

Table 1. Differential diagnosis of the syndromes with primary mucociliary transport failure (PCDS: primary ciliary dyskinesia syndrome; CF: cystic fibrosis; YS: Young's syndrome).

	PCDS	CF	YS
sinopulmonary infection	yes	yes	yes
ciliary ultrastructure	abnormal*	normal	normal
sweat test	negative	positive	negative
spermiogram	immotile sperms	obstructive azoospermia	obstructive azoospermia
pancreatic function	normal	abnormal	normal
vasa deferentia and epididymis	normal	malformed	obstructed by thick secretion

* Cases exist with normal ciliary axonemes, but probably with defects at molecular or enzymatic level.

The mucociliary clearance defect is responsible for the chronic rhinosinusal and bronchial infections observed in patients with Young's syndrome (Handelsman et al., 1984; Wilton et al., 1991; De Jongh et al., 1992). However, the ciliary beat frequency is normal (Wilton et al., 1991; De Jongh et al., 1992). Abnormal variations in the secretions seem to be responsible for the alterations in mucociliary activity, both in the upper airways and epididymis (Greenston et al., 1988). The mechanisms that

produce such abnormal variations remain unclear, however (De Jongh et al., 1992). The viscoelastic properties of the mucus in these patients are common to those of other hypersecretory chronic defects of the airways (Lopez-Vidriero et al., 1986). Different mucolytic agents such as ambroxol, bromexin, *N*-acetylcysteine and carbocysteine are unable to improve the mucociliary clearance (Currie et al., 1988).

The ultrastructure of the respiratory cilia in Young's syndrome is considered to be normal by most authors (Hendry et al., 1978; Wilton et al., 1991; De Jongh et al., 1992). The ciliary defects occasionally encountered (as in patient C) are characteristic of acquired ciliary pathology and secondary to chronic infection (Afzelius et al., 1983). Patient A showed mucous hyperplasia and low ciliary density secondary to chronic infection. Other authors have reported similar findings (Finnstron et al., 1983).

Our patients did not require surgical management of the sinusitis, and they did not suffer frequent hospitalizations because of the respiratory pathology. In effect, sinopulmonary infection in Young's syndrome is characterized by an early onset, with a relative improvement in adulthood - as a result of which it is less severe than in either CF or PCDS (Handelsman et al., 1984).

Circumstantial evidence suggests that Young's syndrome may be a complication of mercury intoxication in childhood (Hendry et al., 1990, 1993). In none of our cases was this possible, as calomel has been banned in this country since 1960. The early onset of the disease and the widespread effects observed in the nasal fossae, sinuses, lungs and genital tract suggest a genetic origin (Handelsman et al., 1984; Hirch et al., 1993). In this sense, CF, PCDS and Young's syndrome possess similar clinical manifestations as a consequence of a congenital defect of the mucociliary system. A number of authors (Umeki, 1988) have proposed the term "primary mucociliary transport failure" as a jointed denomination.

In conclusion, chronic rhinosinusal infections of prolonged development, when accompanied by lower airways infections and male infertility, are probably attributable to a primary mucociliary transport failure. Such failure, along with a normal sweat test and the presence of obstructive azoospermia, typifies Young's syndrome.

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