Chronic Sinopulmonary Disease in Chinese Patients with Obstructive Azoospermia

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The prevalence of chronic infections of the nasal sinuses and the lung (chronic sinopulmonary disease) was investigated in 33 Chinese patients with obstructive azoospermia who were compared with 32 patients with azoospermia due to failure of the germinal epithelium. Ten out of the group of 33 patients with obstructive azoospermia had congenital absence of the vas and/or epididymis and were excluded from that group. The patients with obstructive azoospermia had normal testis size, normal levels of serum FSH and LH, lower seminal fluid fructose, and a higher incidence of serum sperm agglutinating and immobilizing antibodies when compared with the group with damage to the germinal epithelium. The number of patients with symptoms of chronic sinopulmonary infections were similar in all groups. One patient with obstructive azoospermia had bronchiectasis. All other patients had normal chest x-ray studies. About 40% of the patients in all three groups had abnormal sinus X-rays. However, the nonsmoking patients with obstructive azoospermia had a statistically significant ($P < 0.05$) lower mid-expiratory flow rate than the nonsmoking patients with nonobstructive azoospermia. Only three additional patients with obstructive azoospermia had both abnormal sinus x-ray and a reduced mid-expiratory flow rate, suggestive of Young's syndrome. It was concluded that Young's syndrome (sinopulmonary infections associated with acquired obstructive azoospermia) is much less common in Chinese men (four out of 23, 17%) and their sinopulmonary problems are less severe than in Caucasians.

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In recent years, the association of male infertility and chronic infections of the nasal sinuses and the lung (chronic sinopulmonary disease), in particular bronchiectasis, has drawn the attention of clinicians. One of these, the immotile cilia syndrome (Eliasson et al, 1977; Afzelius, 1979), is characterized by the presence of immotile spermatozoa in the ejaculate and ultrastructural defects of the cilia and the axoneme. In cystic fibrosis, recurrent pulmonary infection is associated with abnormal sweat tests, abnormal pancreatic function and male infertility due to malformation of the vas and the epididymis (Kaplan et al, 1968; Taussig et al, 1972). Cystic fibrosis occurs predominantly in Caucasians. It is one-tenth less common in Negros and is very rare or nonexistent in Orientals (di Sant'Agnese, 1967; Shwachman, 1983). Young's syndrome is a combination of obstructive azoospermia and chronic sinopulmonary infections (Young, 1970; Hendry et al, 1978). The pattern of

infection is characterized by onset in childhood with amelioration in adulthood. The symptoms are usually very mild and much less severe than in cystic fibrosis or immotile cilia syndrome. Radiographic studies of the chest may show evidence of bronchiectasis and those of the paranasal sinuses usually reveal varying degrees of mucosal thickening, polyp, fluid levels or opacification of the sinuses (Neville et al, 1983). Infertility is due to obstruction of the epididymis by thick secretions. It has recently been shown that Young's syndrome is a common cause of obstructive azoospermia with a prevalence comparable to that of Klinefelter's syndrome (Handelsman et al, 1984). Since cystic fibrosis is extremely rare in Chinese, and has not been reported in the Chinese Hong Kong population, we studied a group of patients with azoospermia and attempted to define the prevalence and the clinical manifestations of Young's syndrome in Chinese men.

Materials and Methods

Subjects

Consecutive patients with azoospermia attending the Male Infertility Clinic of Queen Mary Hospital between 1984 and 1985 were studied. All the patients were Chinese. They were divided into three groups according to their history, physical examination, testicular volume, as determined by a Prader orchidometer, serum FSH levels, and, in cases of suspected obstructive azoospermia, testicular biopsy. Group I consisted of 32 patients with small testes (less than 12 ml) and elevated FSH levels (over 8 IU/l). They presumably had severe germinal epithelial damage. Groups II and III consisted of patients with normal testis size (over 12 ml), normal FSH (between 0.5 to 8 IU/l, the normal adult range of our laboratory) levels, and testicular biopsies showing evidence of normal spermatogenesis (i.e. obstructive azoospermia). Congenital absence of the vas was confirmed at surgery in 10 of these patients, who formed Group III. The rest of the patients had obstructive azoospermia of undetermined etiology, probably at the level of the epididymis (23, Group II). Three of the patients in Group I had undergone orchidopexy for cryptorchidism in childhood. None of the patients in Group II or III had previous surgery on the genitourinary system. As microsurgical techniques were not available at our center, epididymal biopsy and vaso-epididymal anastomosis were not feasible for ethical reasons. Informed consents were obtained from all patients for blood tests, semen analyses, respiratory function tests, and radiology of the chest and paranasal sinuses. Sweat tests were not performed because of the known absence of cystic fibrosis in the Chinese population (Shwachman, 1983).

Sinopulmonary Function

The patients were administered a questionnaire on nasal-sinopulmonary symptoms by the same two physicians. Emphasis was placed on recurrent symptoms of cough and sputum, pneumonia, sinusitis, and otitis media. Questions on the annual consumption of antimicrobial agents, history of surgical drainage of the nasal sinus, and family history of bronchiectasis and sinusitis also were asked. Chest roentgenograms were taken for all patients, and x-rays of paranasal sinuses were done whenever possible. These x-rays were assessed by radiologists without knowledge of the clinical status of the patient. Respiratory function tests, including forced expiratory volume in one second, forced vital capacity, mid-expiratory flow, peak expiratory flow, lung volumes and single-breath transfer factor for carbon monoxide were done using a computerized rolling seal spirometer system (Gould 5000 IV, U.S.A.).

Laboratory Analyses

Semen analyses were performed using the standard methods described by the World Health Organization (WHO, 1980). After an abstinence period of 2 to 5 days, at least two seminal fluid samples were collected by each patient. Serum samples were obtained from all patients for sperm antibody studies and hormone levels at their initial visit before any medical treatment or surgical procedure. Serum sperm agglutinating and immobilizing antibodies were measured by established techniques (Kibrick et al, 1952; Isojima et al, 1968). Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone (T) were measured with radioimmunoassay kits provided by the WHO Matched Assay Reagents Programme.

Analysis

Results were assessed using analysis of variance followed by the Student's *t*-test, or chi-square test as appropriate.

Results

Clinical Data and Gonadal Function

The clinical characteristics of the three groups of patients are shown in Table 1. All patients provided at least two seminal fluid samples to confirm persistent azoospermia. In the group of patients with germinal epithelial damage (Group I), the mean testicular volume was smaller while the semen volume, seminal fluid fructose, and serum FSH and LH levels were significantly higher than in the other two groups. However, the seminal fluid fructose level was much below the lower limit of the normal range (3 mmol/l) in the group of patients with congenital absence of vas (Group III), consistent with the associated abnormality or absence of the seminal vesicles. None of the patients in Group I or III had significant levels of serum sperm agglutinating or immobilizing antibodies. In Group II patients with obstructive azoospermia, 33.0% (7) had positive sperm agglutinating

TABLE 1. Clinical Characteristics of the Three Groups of Patients with Azoospermia

Group	Normal range	Azoospermia due to germinal epithelial damage I	Obstructive azoospermia II	Congenital absence of vas III
No. of subjects		32	23	10
Age (years)		31.0 ± 4.1*	33.8 ± 4.5	32.6 ± 3.3
Height (cm)		167.6 ± 5.6	166.3 ± 5.5	165.3 ± 5.3
Weight (kg)		62.3 ± 8.6	62.1 ± 12.1	60.6 ± 8.5
Testicular volume				
right (ml)	> 12	8.4 ± 4.2†	16.8 ± 3.5	16.9 ± 4.2
left (ml)	> 12	8.7 ± 4.3†	16.2 ± 3.4	16.8 ± 4.1
Semen volume (ml)	2-5	2.9 ± 1.4‡	1.7 ± 1.4	0.9 ± 0.5
Semen fructose (mmol/l)	3-25	7.6 ± 2.8†	3.8 ± 3.4§	0.9 ± 1.2
Serum hormone concentrations				
FSH (IU/l)	0.5-8	19.7 ± 12.0†	3.6 ± 2.2	2.7 ± 0.6
LH (IU/l)	0.5-5	7.5 ± 6.3†	2.5 ± 0.9	2.8 ± 0.8
Testosterone (nmol/l)	10-40	18.3 ± 6.1	20.7 ± 6.1	20.5 ± 4.9
Serum sperm antibodies				
Agglutinating (titer > 1:8)	-	-	7 (33%)	-
Immobilizing (titer > 1:2)	-	-	1 (0.5%)	-

*Mean ± SD.
† = $P < 0.0001$ when compared with groups II and III.
‡ = $P < 0.005$ when compared with groups II and III.
§ = $P < 0.05$ when compared with group III.

antibodies (the titer was over 1:32 in five patients) and 0.5% had sperm immobilizing antibodies.

Symptoms of Sinopulmonary Infections (Table 2)

Only one patient in the group with obstructive azoospermia (Group II) had both bronchiectasis and chronic sinusitis. Two men had chest symptoms alone and three had nasal symptoms alone. Chest symptoms were those of mild, recurrent lower respiratory tract infection. There was no difference in the number of patients with recurrent chest infections among the three groups. None had features of chronic bronchitis. All four patients with chest symptoms in Group I were smokers, whereas only one patient with chest symptoms smoked in Group II. Therefore, excluding the smokers from all the groups, there appeared to be more nonsmokers with chest symptoms in Group II (two out of 13) than in group I (zero out of 18) ($P < 0.05$, Table 2). Chronic nasal symptoms such as nasal blockade or discharge were, however, more frequent in the group with obstructive azoospermia (17%). None of the patients with nasal symptoms in Group II were classified atopic by skin prick test for common allergens and none had previous sinus surgery. They were not excessively exposed to respiratory irritants as compared with the other groups. Analysis of symptoms therefore showed only one patient with typical Young's syndrome (the patient with bronchiectasis requiring a right lower lobectomy 5 years ago).

X-ray of Chest and Paranasal Sinuses (Table 2)

All patients had chest x-rays. Only one patient with obstructive azoospermia had x-ray evidence of a previous lobectomy for bronchiectasis. Other abnormalities such as peribronchial thickening and cystic areas were not seen. X-rays of the paranasal sinuses were available for 11 out of 32 (33%) patients from

TABLE 2. Number of Patients with Sinopulmonary Symptoms and Abnormal X-ray Findings

Symptoms	Group I (N = 32)	II (N = 23)	III (N = 10)
Chest symptoms			
whole group	4 (13%)	3 (13%)	1 (10%)
nonsmokers	0/18 (0%)	2/13 (15%)*	1/8 (12%)
Nasal symptoms	1 (3%)	4 (17%)*	1 (10%)
Abnormal chest x-ray	- (0%)	1 (4%)	- (0%)
Abnormal sinus x-ray	5/11 (45%)	9/19 (47%)	1/3 (33%)

*$P < 0.05$ when compared with group I.

Group I, 19 out of 23 (83%) from Group II, and three out of 10 (30%) from Group III. All the patients with nasal/sinus symptoms were sent for x-ray of the paranasal sinuses. The rest of the patients had paranasal sinus x-rays whenever consent was obtained. The patients with nonobstructive azoospermia appeared to have abnormal sinuses by x-ray as often as patients with obstructive azoospermia.

Respiratory Function Tests (Table 3)

There was no difference in lung volume and carbon monoxide transfer factor among the three groups. Spirometry was also normal with the exception of a lower mid-expiratory flow, that is, the average flow during exhalation of the middle 50% of vital capacity, in the group of nonsmokers with obstructive azoospermia. Airflow obstruction, however, was mild, as it was not associated with a significant increase in residual volume. About 44% of subjects in Group I, 44% in Group II and 20% in Group III were smokers and were excluded from analysis as the changes in airflow were mild and could be related to tobacco smoking.

Only three patients with obstructive azoospermia (Group II) had both abnormal sinus x-rays and lower mid-expiratory flow, whereas none from the nonobstructive azoospermia group had both abnormalities.

TABLE 3. Respiratory Function Tests in Nonsmokers, Expressed as Percentage Predicted of Normal Values

Lung Function	Group I	Group II	Group III
	N = 18	N = 13	N = 8
Forced expiratory volume in 1 second (FEV1, l)	113 ± 9	109 ± 16	120 ± 13
Forced vital capacity (FVC, l)	105 ± 10	107 ± 10	109 ± 14
Forced expiratory flow durating exhalation of 25 to 75% of the vital capacity (FEF 25–75%, l/sec)	96 ± 22	78 ± 28*	101 ± 17
Peak expiratory flow rate (PFR, l/sec)	97 ± 11	97 ± 18	110 ± 16
Residual volume (RV, l)	118 ± 30	123 ± 29	106 ± 10
Total lung capacity (TLC, l)	107 ± 9	108 ± 19	110 ± 10
Diffusion capacity for carbon monoxide (DLCO/VA, l/min/mmHg)	102 ± 15	103 ± 12	100 ± 14

*$P < 0.05$ when compared with Group I.

These three patients probably had mild Young's syndrome. Therefore, from the clinical symptoms, x-ray findings and lung function tests, only four patients out of the 23 with obstructive azoospermia had Young's syndrome, for a prevalence rate of 17%.

Discussion

In a recent report by Handelsman et al (1984), attention was drawn to the frequent occurrence of Young's syndrome, a combination of obstructive azoospermia and chronic sinopulmonary infections in infertile men. They identified 29 men with this syndrome. During the same period, 43 patients with obstructive azoospermia were seen. In other reports (Hendry et al, 1978; Neville et al, 1983), about 50 to 60% of patients with obstructive azoospermia had evidence of sinusitis, bronchitis or bronchiectasis. To examine the prevalence of chronic sinopulmonary diseases in Chinese patients with obstructive azoospermia, we studied a total of 65 consecutive patients with azoospermia.

The group of patients with severe germinal epithelial damage, as evidenced by the presence of bilateral small testes and grossly elevated FSH levels (Group I), served as controls for sinopulmonary disease. The patients with congenital absence of the vas or seminal vesicles (Group III) were excluded from the group with obstructive azoospermia. The group of patients with obstructive azoospermia (Group II) had normal testis volume, normal serum FSH, testicular biopsy showing normal spermatogenesis and the presence on scrotal exploration of the vas deferens and epididymis. Although the level of seminal fluid fructose in Group II was significantly lower than in Group I (germinal epithelial damage), only five patients had fructose levels below the normal range. In the group of patients with congenital absence of the vas (Group III), however, all 10 subjects had seminal fructose levels well below the normal range. Serum sperm agglutinating antibodies were present in seven patients from Group II (in five, the titer was over 1:32). In one of these subjects, serum sperm immobilizing antibodies were also detected. It is well known that over 50% of subjects develop high circulating titers of sperm antibodies after vasectomy. Occlusion of the reproductive tract by infection, trauma, or other causes may compromise the blood testis barrier and lead to formation of sperm autoantibodies (Jones, 1980). The prevalence of sperm antibodies in patients with obstructive azoospermia is not well documented. A previous report suggests that the occurrence of circulating sperm antibodies is not increased in

Young's syndrome (Handelsman et al, 1984). The only patient with bronchiectasis and obstructive azoospermia (Young's syndrome) in this study had a low titer of sperm agglutinating antibodies (1:8) and negative sperm immobilizing antibodies.

In our group of 23 patients with obstructive azoospermia (Group II), only one patient had clinical bronchiectasis and chronic sinusitis. Three additional patients had both abnormal mid-expiratory flow and x-ray of nasal sinuses. Assuming these four patients had Young's syndrome, they would represent a prevalence rate of 17% (four out of 23) among patients with obstructive azoospermia, which was much lower than the 50 to 60% reported from previous studies in Caucasians (Hendry et al, 1978; Neville et al, 1983; Handelsman et al, 1984).

All our patients except one had very mild and insignificant symptoms of recurrent chest infection. Chronic nasal symptoms were more frequent. This is in contrast to the histories of recurrent cough and sputum production occurring frequently in early childhood that have been reported previously in Young's syndrome (Hendry et al, 1978; Neville et al, 1983; Handelsman et al, 1984). In a recent series, 19 of 29 patients had radiologic evidence of bronchiectasis and 41% had abnormal chest x-ray (Handelsman et al, 1984), whereas only one of our patients had abnormal chest x-ray due to a previous lobectomy for bronchiectasis. Abnormal sinus x-rays were reported in over 90% of patients with Young's syndrome, which were abnormal in all four of our patients with this disease.

Detailed respiratory function tests performed on all of our patients showed that as a group the patients with obstructive azoospermia had normal lung volumes and gas transfer but a lower airflow during the exhalation of the middle 50% of vital capacity compared with the other groups. This is suggestive of airflow obstruction at low lung volumes, possibly associated with obliterative bronchiolitis resulting from repeated respiratory infections. It is not likely to be caused by smoking since smokers were excluded from the analysis of lung function. The airflow obstruction was mild as there was no increase in residual volume. Three of the patients with obstructive azoospermia had airflow obstruction at low lung volumes and all three had abnormal x-rays of the sinuses. Mild increases in residual volume and decreases in peak expiratory flow rate had been previously reported for patients with Young's syndrome (Handelsman et al, 1984).

We conclude that the prevalence of Young's syndrome is less common and appears to be less severe among the Chinese in Hong Kong than in Caucasian subjects. It is worth noting that cystic fibrosis, another condition where bronchiectasis is associated with malformation of the epididymis, is also nonexistent in the Chinese population.

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