

Association between atopy and cryptorchidism

To the Editor:

Epidemiologic studies have shown an increasing prevalence of both atopic diseases and disorders of male sexual differentiation such as cryptorchidism (testicular maldescent: 1 or both testes do not lie in the scrotum by the age of 1 year). Physiologic testicular descent during embryogenesis is testosterone-dependent. Cryptorchidism is known to be the major risk factor for testicular cancer. Interestingly, testicular cancer has been shown to be associated with atopy,¹ and serum levels of testosterone have been reported to be decreased in male patients with atopic eczema.²

To further elucidate associations between atopy and testicular disorders, we prospectively examined 908 consecutive male patients aged 19 to 62 years attending our andrologic outpatient department because of unfulfilled desire for children. All patients were examined by experienced dermatologists, allergologists, and andrologists and completed a standardized questionnaire including basic allergologic and andrologic information. Ejaculates of all patients were analyzed for standard semen parameters according to the World Health Organization, and serum levels of sex hormones were measured. Specific serum IgE antibodies (allergens: dust mite, cat, birch pollen, mugwort pollen, mixed grass pollen, cladospodium, milk, egg) were determined by using a system testing for multiple allergens (S-Phadiatop; Pharmacia & Upjohn, Uppsala, Sweden).

Diagnosis of atopic eczema was made according to the criteria of Hanifin and Rajka. Patients who reported a physician's diagnosis of asthma, recurrent spastic bronchitis, or recurrent asthmatic bronchitis as well as a history of asthmatic symptoms and the use of antiasthmatic medication were classified as having asthma. Classification as having allergic rhinoconjunctivitis was based on typical symptoms during the pollen season and a physician's diagnosis of hay fever.

Atopic diseases show a strong variability in clinical parameters and disease course. Therefore, in recent years, a new disease classification of allergic and nonallergic subtypes of atopic diseases has been established.³ On the basis of these considerations we have analyzed associations between andrologic disorders and allergic sensitization and atopic diseases separately. Therefore the patients were divided into subgroups following clinical or immunologic parameters: (1) clinically apparent atopy (atopic dermatitis or allergic asthma or allergic rhinoconjunctivitis with or without specific IgE), (2) clinically apparent atopy with concomitant sensitization (detectable specific IgE antibodies), and (3) allergic sensitization (detectable specific IgE antibodies). Nineteen percent of all patients manifested at least 1 atopic disease (1), 16.2%

showed an atopic disease with concomitant sensitization (2), and 34.3% exhibited detectable specific IgE (3). Comparison of atopic and nonatopic individuals showed no significant differences of sex hormone levels and ejaculate parameters (Mann-Whitney *U* test). However, the mean testicular volumes were slightly lower in patients with any of the 3 definitions of atopy (Mann-Whitney *U* test; Table I). In addition, the prevalence of cryptorchidism was significantly higher in sensitized patients or patients with clinically apparent atopy and concomitant sensitization (χ^2 test; Table II). In logistic regression models, after adjustment for age and smoking, clinically apparent atopy with concomitant sensitization (group 2) was significantly related to both cryptorchidism and low testicular volume (left and right, <35 mL vs >35 mL; Table III).

These observations indicate an association between atopy and disturbed testicular development and may give some explanation for the observed association of atopy with testicular cancer.¹

Testicular descent is critically dependent on normal action of androgens and a certain androgen:estrogen ratio during embryogenesis. Genetic factors and disturbed hormonal balance—for example, by endogenous hormonal abnormalities or exposure to environmental xenoestrogens during pregnancy—have been suggested to be main risk factors for cryptorchidism.⁴ Estrogens also play an important role in immune modulation and contribute to the approximately 2-fold to 10-fold higher incidence of inflammatory diseases seen in females of all mammalian species, whereas androgens exert suppressive effects on both humoral and cellular immune responses and seem to represent natural anti-inflammatory hormones.⁵ Because the influence of environmental and lifestyle factors on the expression of atopy seems to be most important during gestation and early childhood, it may be hypothesized that next to genetic factors, environmental influences during pregnancy, like disturbance of the hormonal balance, might contribute to the development of both atopy and testicular disorders.

So far, no explanation for the association between testicular maldescent and atopy can be presented. A variety of studies provide evidence for the essential role of the peptide hormone relaxin and other, similar members of the insulin-like protein family like the insulin-like factor (RLF) in the development of the male reproductive tract.⁶⁻⁸ RLF synthesized by Leydig cells in the fetal testis has been suggested to be responsible for the second phase of the testicular descent.⁶ In adults, relaxin is continuously secreted by the prostate and has been suggested to influence sperm motility.⁷ The primary source in women is the corpus luteum of the cycle and pregnancy. Minor amounts of the hormone are also produced by decidua and placenta and the mammary glands.^{6,7} The maximum concentrations can be measured during the first trimester

TABLE I. Atopy and testicular volume

	n	Testicular volume (left and right), mL	P*
Atopic disease† (1)	172	35.6	.043‡
No atopic disease	731	37.4	
Allergic sensitization§ (3)	311	36.6	.031‡
No sensitization	597	37.3	
Atopic disease and allergic sensitization (2)	146	35.9	.028‡
Control¶	757	37.3	

*Mann-Whitney U test.

†Diagnosis of atopic dermatitis, asthma, or allergic rhinitis.

‡P < .05.

§Presence of specific IgE.

||Diagnosis of atopic dermatitis, asthma, or allergic rhinitis, and presence of specific IgE.

¶Defined as (a) absence of atopic disease and specific IgE (n = 570),

(b) presence of atopic disease and absence of specific IgE (n = 26), or

(c) absence of atopic disease and presence of specific IgE (n = 161).

TABLE II. Atopy and cryptorchidism

	Prevalence of normal testicular descent	Prevalence of cryptorchidism	P*
Atopic disease† (1)	86.0% (n = 148)	14.0% (n = 24)	.103
No atopic disease	90.3% (n = 660)	9.7% (n = 71)	
Allergic sensitization‡ (3)	86.5% (n = 269)	13.5% (n = 42)	.047§
No sensitization	90.8% (n = 542)	9.2% (n = 55)	
Atopic disease and allergic sensitization (2)	84.2% (n = 123)	15.8% (n = 23)	.024§
Control¶	90.5% (n = 685)	9.5% (n = 72)	

* χ^2 Test.

†Diagnosis of atopic dermatitis, asthma, or allergic rhinitis.

‡Presence of specific IgE.

§P < .05.

||Diagnosis of atopic dermatitis, asthma, or allergic rhinitis, and presence of specific IgE.

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(b) presence of atopic disease and absence of specific IgE (n = 26), or (c)

absence of atopic disease and presence of specific IgE (n = 161).

of pregnancy, with a decline in the following months.⁶ To date, it is still unclear whether there is placental transfer of relaxin. In recent years, it has been shown that relaxin and RLF are secreted by various other tissues and that relaxin is a multifunctional hormone not involved in reproduction only.⁷ Interestingly, relaxin has also been shown to inhibit mast cell action, downregulate basophil action, stimulate the production of nitric oxide, and antagonize antigen-induced asthma.^{6,9,10}

Therefore, one possible hypothesis to explain the association between testicular maldescent and atopy may focus on decreased maternal ovarian production or impaired fetal testicular expression of relaxin or other hormones.

Causes of both cryptorchidism and atopic diseases are multiple and still largely unknown. However, the results of the current study indicate an association between atopy and testicular disorders, implying shared genetic or

TABLE III. Logistic regression models showed a significantly higher prevalence of cryptorchidism and low testicular volume (<35 mL) in patients with atopic diseases with specific IgE (adjusted odds ratios and 95% CIs)

	Cryptorchidism	Testicular volume (left and right) > 35 mL
Atopic disease* (1)	1.43 (0.87-2.37)	0.72 (0.52-1.00)
Allergic sensitization† (3)	1.50 (0.97-2.30)	0.85 (0.65-1.12)
Atopic disease and allergic sensitization‡ (2)	1.68 (1.00-2.80)§	0.70 (0.50-1.00)§

*Diagnosis of atopic dermatitis, asthma, or allergic rhinitis.

†Presence of specific IgE.

‡Diagnosis of atopic dermatitis, asthma, or allergic rhinitis, and presence of specific IgE.

§P < .05.

environmental factors. Our findings may stimulate further research to elucidate early pathogenetic events and environmental influences critical for both diseases.

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