The association of Peyronie's disease with HLA B7 cross-reactive antigens

A case report of identical twins

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Previous reports in the literature suggest an association between Peyronie's disease and certain histocompatibility antigens. To the authors' knowledge, these are the first-reported cases of identical twins with Peyronie's disease. Each was initially treated with medical therapy. This failing, they then underwent successful plaque excision with dermal grafting to correct their marked penile curvature with restoration of sexual function. HLA typing was carried out on these twins as well as all available family members. Physical examination of the family members indicates that the twins' father has Peyronie's disease and the son of one of the twins has mild induration of the dorsum of the penis as well as a slight lateral deviation of the erect penis. A brother of the twins has some dorsal penile thickening but no penile deviation. Each of the twins, the symptomatic son, and the affected father were found to have the B7 cross-reactive antigen. These data suggest that a form of Peyronie's disease may be inherited. Further understanding of these histocompatibility antigens may allow greater understanding of the pathogenesis of this disorder in a subset of the population.

Index terms: HLA antigens•Penile induration


Peyronie's disease is characterized by fibrosis of the tunica albuginea, most often limited to the dorsum of the penis. Because of this plaque, the penis can become deformed and painful with erection. This plaque may be the result of an inflammatory process in the areolar tissue between the tunica albuginea and corpus cavernosum.

Although the specific stimulus leading to the inflammation has never been elucidated, venereal infections, trauma, gout, diabetes, arteriosclerosis, serotonin excess, adrenal abnormalities, and vitamin E deficiency have been implicated.

Associated with the penile plaque are both Dupuytren's contracture and fibrous degeneration of the auricular cartilage. An autoimmune reaction may be involved. This would imply that antibodies cross-react with tissue antigens resulting in inflammation. The cell-surface antigens may react by virtue of their molecular configuration or become altered in some way by infection or chemical stimulus.

Reports by Willscher as well as Nyberg and Bias have pointed out the association between Peyronie's disease and certain histocompatibility antigens. It has been suggested that, in certain patients, Peyronie's disease represents an inherited disorder. This can be likened to the theory held by many that other localized fibrosing disorders (i.e., Dupuytren's contracture) and those with systemic manifestations, such as retroperitoneal fibrosis, are genetically determined.

Case reports and family studies

This is, to our knowledge, the first case report of identical twins with Peyronie's disease. HLA typing of both patients and members of their immediate families was performed to
establish whether the disease segregated with a particular HLA haplotype or was associated with a particular HLA antigen.

**Patient 1.** This man presented at age 50 with an 18-month history of painful erection and penile curvature that did not allow vaginal penetration. Six months before urological consultation, he suffered a myocardial infarction and subsequently underwent coronary artery bypass surgery. Medications included only nifedipine and diazepam. He denied any history of penile trauma or urinary infection.

Physical examination disclosed a 3.5 x 1.5 cm plaque on the dorsum of the penis. Photographs documented severe dorsal curvature on erection (Fig. 1). For six months before seeking an opinion at our institution, he took potassium aminobenzoate and vitamin E without improvement. Because of pain and sexual frustration, the patient elected to undergo surgery.

**Patient 2.** Patient 1’s identical twin presented nine months later with a one-year history of penile complaints similar to his brother’s. His medical history was significant only for chronic prostatitis, which was inactive at the time of presentation. He had been taking vitamin E for the year before presentation.

Physical examination revealed a 4 x 3 cm plaque on the dorsum of his penis. Erection produced marked dorsal curvature and lateral torsion. Surgical correction was suggested and accepted.

Each patient underwent plaque excision and replacement with a dermal graft from the inguinal area. Postoperatively, both men had restored sexual function though with some shortening of the penis. It is of interest to note that patient 1 had scarring of his coronary saphenous graft necessitating repeat bypass surgery, and the sternal incision healed with keloid formation.

A careful family history was obtained from the two subjects. The pedigree is shown in Figure 2. The majority of all genetically related male family members were examined by one of the investigators (M.Z.). Because they were unavailable for physical examination, certain members were interviewed by telephone only.

Of those examined, the 83-year-old father of the index cases was noted to have a definite Peyronie’s plaque. Symptoms could be dated to somewhere in his late 50s. One brother of the patients, who was 43 years old, was noted to have a subtle dorsal thickening on examination but denied erectile curvature or pain. A similar, subtle dorsal induration was also noted in the 22-year-old son of one twin. He did report a lateral deviation on erection but had no pain or problems with vaginal penetration.

The 14 remaining males had no penile pain or deformity as confirmed by examination (5) or telephone interview (9). Neither our patients nor their relatives had Dupuytren’s contracture or any rheumatologic problems. Blood for HLA typing was taken from both patients and their nuclear families. Typing of the father and one brother was also done.

### Results

The results of HLA typing are noted in Fig. 2. Each of the twins and their affected father had an A24, B40 haplotype. The B40 antigen cross-reacts with other members of the B7 cross-reactive group. Cross-reactivity of antigens within an allelic series is common. The B7 cross-reactive group includes B7, B27, B40, BW22, and B13.

The A24, B40 haplotype was also found in both sons of one twin, one of whom was found to have a subtle penile induration on examination. The unaffected brother and both wives of the twins lacked antigens of the B7 cross-reactive group. The brother noted to have subtle dorsal thickening refused HLA typing.

### Discussion

The HLA complex, the major human histocompatibility complex, is a group of closely linked genes that code for a variety of cell-surface antigens involved in the immune response. Many HLA antigens have been shown to be associated with a number of diseases. Certain of these diseases are known to be determined by a gene or genes linked to an HLA complex, as in congenital adrenal hyperplasia.

Other diseases are associated with certain HLA antigens, such as HLA B27 and the rheumatoid arthritides. In the case of a linked disease, association with a particular factor (i.e., linkage disequilibrium) is well recognized.

Because of prior reports discussing the association with the histocompatibility antigen of the B7 cross-reactive group, specific attention was paid to the B locus, the site along chromosome number 6 where the gene is situated. The gene encodes for a protein. In our patients and their family, particular attention was paid to the cell-surface-antigen protein termed HLA B7.

In 1979, Willscher et al. reported a relationship between Peyronie’s disease and histocom-
patibility antigens of the B7 cross-reacting complex. Recognizing that other diseases with localized fibrosis were associated with HLA B27, he had tissue typed in eight patients with idiopathic Peyronie's disease. Seven of these possessed an antigen of the B7 cross-reacting group. None of the three patients with fibrosis secondary to penile trauma expressed a similar phenotype.

A more recent analysis of three family groups by Nyberg and Bias suggested familial transmission of the disorder as an autosomal dominant trait. They noted that 90% of affected individuals had genotypes within the B7 cross-reacting group. In addition, a 78% occurrence of Dupuytren's contracture in this series was seen, as opposed to the 10% frequency of Dupuytren's contracture seen in reported sporadic cases of Peyronie's disease. Nyberg and Bias postulated a possible pleiotropic effect of the gene in these families, intimating that these patients represent only a subgroup of patients with Peyronie's disease.

Leffel, in 1982, found no significant association between HLA type and Peyronie's disease in 28 unrelated patients and their families. There were, however, three patients with both Peyronie's disease and Dupuytren's contracture. Two of the three patients had a B7 cross-reacting antigen.

There are, then, three separate studies (including our own) that suggest an association between HLA B7 cross-reacting group and Peyronie's disease. A familial aspect to this disorder is noted in two of these reports. It must be taken into account that 50% of the population carries at least one allele of the B7 cross-reacting group. Therefore, it is difficult to state with absolute certainty that there is a significant relationship between the B7 group and Peyronie's disease. Nevertheless, the concept of a genetically transmissible and HLA-associated disease generates interesting theories regarding the pathogenesis of Peyronie's disease. It may suggest that a specific molecular configuration in the host cell surface plays an important role in the disease process.

According to one theory, autoantibodies that cross-react between the HLA antigens and an infectious agent can mediate the inflammatory response and subsequent fibrosis. Second, it can be proposed that HLA antigens serve as receptors for an infectious agent or chemical, inciting the disease, perhaps by becoming an immunologic target. Third, the HLA system may not provide the antigen site but may be linked with
the genes responsible for the immune response.²

**Conclusion**

We have identified the first-reported case of twins with Peyronie's disease. The presence of the disorder in other family members as well as HLA B7 cross-reacting antigens in some of the members may be more than coincidental. Although the clinical impact is not totally clear, there would seem to be some relevance to male offspring and siblings of affected men.

That an HLA haplotype was shared among three known affected kin and possibly a fourth suggests a possible genetic component. Previous studies suggest that certain forms of Peyronie's disease have a genetic component and are associated with the B7 cross-reacting group. There may be a need for certain environmental factors to instigate the inflammatory response. If this is so, identifying such an agent might enable specific therapeutic manipulation. Whether this theory could be extended to other fibrosing disorders of greater clinical importance⁸ (i.e., retroperitoneal fibrosis) is yet to be determined, but it could help us understand these problems.

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**Commentaries**

_Drogo K. Montague, M.D., Department of Urology, The Cleveland Clinic Foundation, comments:_

Peyronie's disease occurs in middle-aged men, usually without warning, and causes anxiety as they observe curvature and foreshortening of their erections. If the resulting erectile deformity is severe, coitus may be impossible. Little is known about the cause of this disorder. This report, the first of Peyronie's disease in identical twins, suggests an association between HLA B7 cross-reactive group and Peyronie's disease as well as a possible genetic component for this disorder.

_Allen H. Mackenzie, M.D., Department of Rheumatic and Immunologic Disease, The Cleveland Clinic Foundation, comments:_

The development of fibrosis is poorly understood. Fibrosis is one common response to tissue disruption through wounding and is a common mode of healing from diverse inflammatory processes. Tissue culture studies of fibroblasts have begun to delineate some of the many influences that govern proliferation and secretion. There is already a long and growing list of stimulators to proliferation and to secretion of collagen, but it is not yet clear which ones dominate the process.

The possibility that Peyronie's disease may be a manifestation of a more generalized fibrosing diathesis has long been of interest, though infrequently reported. Peyronie's camptophallus may be associated with Dupuytren's contracture and with strange knuckle pads, or thickenings of skin, over the proximal interphalangeal and metacarpophalangeal knuckles. Furthermore, these features may be associated with nodular plantar fasciitis. Such patients provide an intriguing and tantalizing glimpse of fibrosis in action. The patients reported on here, however, appear to have none of these other findings. There is probably a weak association between these diverse fibrotic problems and a generalized alteration in the biology of tissue, which may be under some HLA B7 control, an association that will require confirmation.

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**References**