INTRADERMAL SKIN TESTING IN THE LOIN PAIN HAEMATURIA SYNDROME

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Summary

Intradermal skin testing to standard recall antigens was performed in 10 subjects with the loin pain haematuria syndrome. Ten patients with other forms of glomerulonephritis and 10 normal subjects acted as age and sex matched control groups. In the loin pain haematuria syndrome severe localized skin erythema and swelling occurred within 12 hours to at least two of the five antigens, significantly greater reactions than in both control groups (p<0.01). Systemic complaints and lymphadenopathy occurred in eight patients with the loin pain haematuria syndrome but in none of the control groups (p<0.01). This suggests that the hyperimmune status of the loin pain haematuria syndrome, of type 3 hypersensitivity character, may play a role in the pathogenesis of the renal lesion.

Introduction

A rare syndrome of recurrent unilateral or bilateral severe loin pain with frank or microscopic haematuria has been described, which occurs predominantly in young women [1–3]. The diagnosis of the loin pain haematuria syndrome is made by exclusion of other causes of loin pain, and in many instances renal biopsy reveals granular deposition of C3 in the walls of the arterioles [4]. Although progression to renal failure rarely, if ever, occurs in this syndrome, the recurrent loin pain is frequently severe and disabling. The aetiology of the disorder is unknown and potent analgesics are often required to relieve the loin pain.

In our first two patients with this syndrome we observed severe accelerated reactions to intradermal tuberculin (1 in 10,000 dilution), the test having been performed because the clinical presentation of renal tuberculosis may closely mimic that of the loin pain haematuria syndrome [5]. After subsequent investigations had excluded tuberculous disease of the urinary tract, we embarked upon a controlled study which was designed to assess tuberculin and other skin reactions in patients with the loin pain haematuria syndrome.
Patients and Methods

Ten patients with the loin pain haematuria syndrome were studied (mean age 35±8 years, 5 male and 5 female). The age and sex matched control groups were 10 patients with glomerulonephritis without loin pain (mean age 31±6 years) and 10 normal subjects (30±3 years).

In the group with loin pain haematuria syndrome, two patients related the onset of symptoms to starting the oral contraceptive pill which was discontinued subsequent to the renal biopsy. The following investigations were normal in all loin pain haematuria syndrome patients: mid-stream urine cultures for pyogenic organisms and early morning urine cultures for M tuberculosis, plasma chemistry, plasma albumin, antinuclear factor, anti-DNA antibody, serum complement and immunoglobulins, chest X-ray, and intravenous pyelogram. In all patients renal biopsy showed no significant glomerular lesion on light microscopy but immunofluorescence revealed a consistent granular deposit of C3 in the media of the arterioles. There was no significant fluorescence in glomeruli or tubular basement membranes.

Ten patients with biopsy proven glomerulonephritis without loin pain comprised the first control group. Seven had proliferative glomerulonephritis of unknown aetiology (negative antistreptolysin O titre, negative antinuclear factor, normal anti-DNA antibody, normal serum complement and immunoglobulins) and three had mesangial IgA disease. All had normal plasma chemistry and normal serum albumin.

Ten normal subjects with negative urine analysis and normal renal function comprised the second control group.

Skin testing was done in a standard fashion [6] with 0.1ml intradermal injections each of five recall antigens: tuberculin purified protein derivative (1ml in 10,000 dilution), ‘Varidase’ (streptokinase 100 units/ml + streptodornase 25 units/ml; Lederle), mumps skin test antigen (undiluted, Eli-Lilly Company), 1% Candida albicans (BV Hal Allergenen Laboratorium, Haarlem, Netherlands), and trichophyton mixture (BV Hal). A control injection of 0.1ml buffered diluent solution (BV Hal) was also given. Three injections were given into each forearm.

Statistical analysis was by analysis of variance.

Results

In all patients with loin pain haematuria syndrome, severe localized skin erythema and swelling occurred within 12 hours to at least two of the five recall antigens (Table I). The reactions persisted for at least 48 hours and severe tuberculin hypersensitivity was the most common finding. Only one patient had a history of juvenile pulmonary tuberculosis. The responses were significantly greater (p<0.01) in patients with loin pain haematuria syndrome than in both glomerulonephritis and normal control subjects. Eight patients with loin pain haematuria syndrome developed associated lymphadenopathy and systemic complaints (fever, chills, rhinitis, or wheezing) which required prednisolone
| Skin test reagent | LOIN PAIN HAEMATURIA SYNDROME | | GLOMERULONEPHRITIS | | NORMAL SUBJECTS |
|-------------------|-------------------------------|------------------|-------------------|------------------|
|                   | Patient Number | | Patient Number | | Subject Number |
|                   | 1  2  3  4  5  6  7  8  9  10 | | 1  2  3  4  5  6  7  8  9  10 | | 1  2  3  4  5  6  7  8  9  10 |
| Tuberculin        | +++  +  +++  0  +++  +++  ++  0  +++  +++ | | +  +  0  0  0  +  0  0  +  0 | | 0  0  0  0  0  0  0  +  0  + |
| Varidase          | +++  +++  +++  ++  ++  0  ++  ++  ++  + | | 0  +++  0  0  +  0  +  +  +  + | | 0  0  +  0  +  0  0  0  +  + |
| Candida           | +  +++  0  +  +  +  +++  0  +  + | | +  +++  +++  +  0  0  0  +  0  + | | +  +  +  +  +  +  +  +  +  + 0 |
| Mumps             | +  +  0  ++  +  0  +  ++  0  +++ | | +  0  0  0  +  0  +  0  +  0  + | | 0  +  +  +  +  +  +  +  +  + 0 |
| Trichophyton      | 0  0  0  +  0  0  0  0  0  +  0 | | 0  0  0  0  0  0  0  0  0  0 0 | | 0  +  0  0  0  0  0  +  0  0 |
| Control agent     | 0  0  0  0  0  0  0  0  0  0 0 | | 0  0  0  0  0  0  0  0  0  0 0 | | 0  0  0  0  0  0  0  0  0  0 0 |

0 = <5 mm erythema
++ = 5–20 mm erythema and/or induration
+++ = >20 mm erythema and/or induration
++++ = >20 mm erythema and/or induration with lymphadenopathy
therapy. In contrast no patient in each of the control groups developed either lymphadenopathy or systemic symptoms (p<0.01).

In one patient with loin pain haematuria syndrome a skin biopsy was taken from the edge of one of the typical antigen reactions at 24 hours. There was histological evidence of an active inflammatory reaction comprising a perivascular, largely lymphocytic, infiltrate in upper, mid and lower dermis, with additional rather more specific features in the form of polymorphonuclear emigration and fragmentation. This latter element was most noticeable in papillary dermis and was associated with oedema and collagen fragmentation. Eosinophils were not a notable feature. The appearances were those of a small vessel vasculitis consistent with a type 3 hypersensitivity reaction.

Discussion

In this series of patients with the loin pain haematuria syndrome the onset of skin reactions within 12 hours of intradermal injection of antigen implies a local type 3 hypersensitivity reaction. The findings in a skin biopsy of a typical antigen reaction showed appearances of a small vessel vasculitis consistent with this type of response. While the aetiology and pathogenesis of the loin pain haematuria syndrome remain unknown it is of interest that several types of antigen induced an exaggerated type 3 hypersensitivity response. Although this form of hyperimmunity may play a role in the genesis of the renal arteriolar lesion, there is no evidence that circulating complexes are involved. On the other hand, even minute quantities of immunoglobulin may cause the deposition of large amounts of C₃ in arterioles. Further studies are required to determine the range of triggering antigens capable of inducing this state of hypersensitivity in this syndrome. Among those which were used in this study, tuberculin and streptococcal antigens (Varidase) provoked the most severe skin reactions.

References

1 Little PJ, Sloper JS, Wardener HE. Q J Med 1967; 36: 253