ARE \( \beta \)-HAEMOLYTIC STREPTOCOCCI INVOLVED IN THE PATHOGENESIS OF MESANGIAL IgA-NEPHROPATHY?

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Summary

In retrospect we have found that 38 of 187 patients who fulfilled the criteria of mesangial IgA-nephropathy had possible acute glomerulonephritis at the onset of their disease. We have therefore studied anti-streptococcal antibodies (ASO and ADNAseB) prospectively. Forty-three per cent of the patients had ADNAseB >800 units. Thirty-one per cent of the patients studied more than once had a fourfold or greater change in their ADNAseB titre. Thirty-three per cent of the patients had different groups of \( \beta \)-haemolytic streptococci isolated from their throats. This indicates a possible role of \( \beta \)-haemolytic streptococci in the pathogenesis of some cases of mesangial IgA-nephropathy.

Introduction

The connection between many cases of acute glomerulonephritis and \( \beta \)-haemolytic streptococci (\( \beta \)-HS) group A is well established. In acute post-streptococcal glomeronephritis (APSGN) there is a latent period of about 10 days between the onset of infection and the manifestations of glomerulonephritis. The short-term prognosis is regarded as good, children seem to have a particularly good prognosis [1]. However in adults the long-term prognosis is probably worse [2].

In 1968 Berger and Hinglais [3] reported a group of patients with persistent or recurrent haematuria. By immunofluorescence microscopy they found IgA and C3, but also other immunoglobulins, with chiefly mesangial localisation. Many of these patients have episodes of macroscopic haematuria in association with upper respiratory tract infections or gastroenteritis. In contrast to APSGN these patients have no latent period between the infection and the episodes of macroscopic haematuria.

This disease has already been called by many different names but we prefer mesangial IgA-nephropathy (MesIgAN) because of lack of inflammation in most biopsy specimens. Glomerulonephritis is thought to appear after deposition
of either circulating soluble immunocomplexes in the glomeruli or fixation of antibodies on pre-existing antigens in the glomeruli. These antigens can be endogenous or exogenous.

In APSGN Lange [4] has in early biopsies seen streptococcal antigens which later appear to be covered by antibodies. In MesIgAN the infections preceding the haematuria are thought to be non-specific. Tomino [5] has eluted IgA from some renal biopsies and then recombined it with the same mesangium it was eluted from. This could indicate that there exists specific binding sites in the glomeruli of these patients. There was a cross-reaction with the mesangium of other patients with IgAN. The cross-reactions were however not 100 per cent, and it could be caused by different antigenic sites perhaps of exogenous origin.

Materials

Of all renal biopsies in Stockholm between 1974–1983, 187 fulfilled our criteria for mesangial IgA-nephropathy. These were: IgA should be the main immunoglobulin with predominantly mesangial localisation. Patients with evident systemic disease were excluded. Male to female ratio was 2:1. The mean age at onset of symptoms was 26 years.

In the prospective study we have estimated the apparent onset of renal disease and the clinical symptoms at the onset.

Serum creatinine, immunoglobulins, complement-factors (C₃, C₄), autoantibodies, anti-streptococcal antibodies (ASO, ADNaseB) and anti-viral antibodies were taken every six to 12 months. Endogenous creatinine-clearance, 24 hour urinary protein excretion, clearances of albumin and IgG are also estimated at every visit. Bacterial cultures from the tonsils are taken every visit.

Fresh urinary sediment was examined by the physician (HB or SR). Every 18–24 months a Cr-EDTA-clearance was performed. The patients were informed to contact us if they have macroscopic haematuria or infection, these ‘acute’ patients were investigated also after one week and after one month.

Results

The apparent onset of disease was as follows: 73 patients had recurrent macroscopic haematuria in connection with upper respiratory tract or gastrointestinal infection, 46 had asymptomatic haematuria and/or proteinuria, and 38 patients had in their history signs of classical acute glomerulonephritis with a latent period. Two patients presented with nephrotic syndrome and one patient was found because of malignant hypertension. In 27 patients we had not enough information to be able to clearly define the onset of the disease.

We have investigated 92 patients prospectively. ASO titres were ≥400 units in five of them, ADNaseB titres were ≥800 units in 40 patients (43%). These patients had the following titres, 800 units in 22, 1,600 units in 13, 3,200 units in two and ≥6,400 units in three. All these tests were taken at a routine visit without any signs of infection.

In 48 patients the ADNaseB titres were tested more than once. A four-fold or greater change was seen in 15 of these patients (9 had a decrease and 6 had an increase).
Throat cultures were also taken routinely. β-HS were found in cultures of 33 patients (35%). Gr A was seen in only one patient, Gr C (17), Gr G (7), Gr B (5), Gr F (2) and three strains of β-HS were not possible to group. Two of the patients had two different strains at the same time.

We have so far seen 10 patients with acute macroscopic haematuria. Six of these had ADNaseB >800 units at their acute visit. Four acute patients had positive cultures of β-HS: Gr A (1), Gr C (2), Gr G (1). Two patients had an increase of their ADNaseB-titre. One patient rose from 100 units to 3,200 units in a month, no β-HS were found. The other rose from 200 units to 2,600 units, this patient had β-HS Gr C isolated from his throat at the acute visit.

Discussion

In our study 38 patients had an onset of their disease very like that of acute post-infectious glomerulonephritis. In fact eight of them also had evidence of infection with β-HS preceding their nephritis. Clarkson [6] also reported 10 per cent of patients with an onset of acute nephritic type.

In infections with β-HS Gr A with pharyngitis the ASO is regarded as the best index of infection, whereas the ADNase-titre is more a reflection of skin infection with β-HS. Our patients had a high percentage of ADNase-titres >800 units and few positive cultures of β-HS Gr A. Gr C β-HS are serologically very similar to Gr A β-HS and can sometimes produce DNaseB. We have not so far investigated if these strains we have isolated are able to produce DNaseB.

There is a possibility that the raised titres of ADNaseB is only due to a polyclonal activation of β-lymphocytes. However we have not seen any rise in antibody titres against streptococcal or viral antigens.

Our conclusion is that there is some indication of a possible pathogenetic role of β-HS in MesIgAN, which are worthy of further studies. Especially in patients with acute bouts of macroscopic haematuria there is a possibility of isolating streptococcal antigens from immunocomplexes either circulating or fixed in the mesangium.

References

1 Cameron JS. In Kincaid-Smith P, Mathew TH, Becker EL, eds. Glomerulonephritis: Morphology, Natural History and Treatment. New York: John Wiley and Sons. 1973: 63
3 Berger J, Hinglais N. J Urol Nephrol 1968; 74: 694
Open Discussion

RITZ (Heidelberg) Dr Rekola as you correctly pointed out there are two different explanations for the findings, an anamnestic response the other a true pathogenetic role. You discounted the first possibility on the basis that you failed to find changes in titres other than DNA-ase. However, there has been a report at the International Society of Nephrologists meeting in Los Angeles by a Japanese group* who found changes in anti-influenza virus titres in such patients clearly implicating that they are hyper-responders to a variety of immunological stimuli. I would be somewhat hesitant to discount this possibility on the basis of your findings.

REKOLA That is quite correct.

BROWING (Glasgow) Have you looked at the kidneys of any of these patients to see whether there are streptococcal antigens within the glomerulus?

REKOLA No. Because most of the biopsies in these patients were 10 years ago. We are now investigating with the bacteriologists to see if we could after some sort of elution, identify some antigens in the kidneys.

EGIDO (Spain) Have you any idea of the class of immunoglobulin elicited against the antigens of the streptococcus?

REKOLA No, we have not investigated it yet. About half of our patients have a rise in their IgA titres and you can see at the actual bouts there is a still higher rise which disappears in a few months.

EGIDO (Spain) In my opinion this may reflect only a non-specific effect related to immunological disturbances of IgA. We have a large number of these patients with antibodies against dextran and diet antigens.

REKOLA It is quite possible. There is one other possibility, it is known that viral infections can also activate latent streptococcal infection elsewhere in the body?

SCHENA (Chairman) Have you compared your data in IgA nephropathy with a group of patients with acute glomerulonephritis? What is the difference in the presence of high titre of these antibodies in patients with acute glomerulonephritis and patients with IgA nephropathy?

REKOLA The problem is we have mostly adult patients in our clinic and acute glomerulonephritis is much more common in children. Perhaps it will be possible to co-operate with a paediatric clinic.

DAVISON (Chairman) Can I ask about your fairly high incidence of streptococci isolated from the throat. Were these always at the time of macroscopic haematuria?

REKOLA No, the cultures were obtained when the patients were asymptomatic.

DAVISON Have you any control patients?

REKOLA Not yet.

DAVISON Therefore you do not know whether there is a large number of people in the general population with these streptococci?

REKOLA No. There is one problem in that previously the laboratory did not report streptococci of group C because they thought they were not pathogenetic. Now they have started but nobody in Sweden knows the frequency of these streptococci in the throat.