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Some current concepts in therapy of acute glomerulonephritis with presentation of a case of unusual severity

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SOME CURRENT CONCEPTS IN THERAPY OF ACUTE GLOMERULONEPHRITIS WITH PRESENTATION OF A CASE OF UNUSUAL SEVERITY

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I. Introduction

Much has been written in past years concerning acute glomerulonephritis. Researchers have made great strides in understanding the etiology, pathology, and physiology of the disorder. There still remains, however, great gaps in our knowledge of, and ability to treat acute glomerulonephritis.

II. Epidemiology

Acute glomerulonephritis has been known for years to follow beta-hemolytic streptococcal infections.

It has been demonstrated that certain types of streptococci have nephritogenic properties. The majority of cases has the group 12 streptococcus as the offending agent, although other types have been noted in a few instances (1).

III. Immunology

It has been suggested that antibodies of the "extracellular antigens" of the streptococcus (ASO, ASK, and AH) confer little or no immunity on the patient with a streptococcal infection, but are useful chiefly as a signpost that infection has

occurred (2). The risk of development of acute nephritis does not appear to be greater for patients with a high antibody response than those with a low antibody response (3).

Penicillin treatment of streptococcal infections has been shown to suppress mean antibody rise, inhibiting response to type 12 infections by approximately 50 per cent (3). Before antibiotic therapy a lack of rise of antibody titer argued against a diagnosis of acute glomerulonephritis. One may note from the above that this contention no longer holds true.

It has been demonstrated that serum complement is nearly always low in acute glomerulonephritis. The low titers are not believed to be due to urinary loss (4).

IV. Clinical Aspects

(a) Onset

As mentioned earlier, the onset of acute glomerulonephritis is usually preceded by a pharyngitis with the group 12 beta-hemolytic streptococcus.

Jennings and Earle (5) reviewed 36 cases of acute glomerulonephritis and found that 24 were preceded by pharyngitis, 5 by tonsillitis, 1 by pneumonitis, 1 by cellulitis, 3 had no known

antecedent infection, one was unknown, and one by "flu". Seventeen of the cases presented with gross hematuria, 7 were detected by routine urinalysis, 11 by edema, and one with costovertebral angle tenderness.

The average number of days from the onset of the inciting infection to the onset of the symptoms was 17.2 days. The patients varied from ages 17-66 years. The mean age was 28.3 years. All cases were proven to be acute glomerulonephritis by biopsy.

(b) Acute glomerulonephritis over fifty years of age

Acute glomerulonephritis has been reported in patients over fifty years of age. In Jennings and Earles (5) series of 36 cases three of the patients were over 50 years of age. The oldest was 66.

Nelson and Robbins (6) work suggests that the incidence of acute glomerulonephritis in older age groups may be higher than previously suggested. In their study of 23 post-mortem cases of acute glomerulonephritis they found that 20 (87 per cent) of the deaths occurred in patients over 40 years of age, and that the average

age of necropsy of the acute group was 56.3 years.

(c) Mortality

In past years the mortality of acute glomerulonephritis was 5 to 10 per cent. The development of antibiotics, hypotensives, steroids, and mechanisms of dialysis have brought about a reduction in mortality in recent years. The death rate in acute glomerulonephritis is now believed to be in the range of 1-2 per cent (7).

V. Pathophysiology

(a) Cardiovascular Function

Historically, it was thought that the congestive phenomena in acute glomerulonephritis were due to a generalized increase in capillary permeability (2). This thesis was based on the unusual distribution of the edema and its high protein content. It was shown in 1943 (8) that the protein content of the edema fluid is not elevated but similar to that of other transudates.

Pathological and EKG studies have shown that myocarditis may be responsible for the "congestive heart failure" seen in acute glomerulonephritis.

Gore and Saphir (9) showed in their studies of 1947 that a serous type of myocarditis with interstitial edema existed in 10 per cent of cases

of acute glomerulonephritis coming to autopsy. They demonstrated microscopic changes in the myocardium consisting of small amounts of muscle necrosis and minimal amounts of inflammatory cell infiltration. EKG changes when present may be minor and nonspecific (2).

It has been shown that the syndrome of dyspnea, peripheral edema, pulmonary congestion, cardiac enlargement and increased venous pressure can be produced by rapid infusion of ACTH and steroids (10,11).

In a study of 20 non-cardiac subjects all received ACTH or cortisone. Twelve received ACTH and 8 received cortisone (11). Essentially, the same result was produced by the two drugs. Three of the patients gained sixteen or more pounds of fluid, developed slight cardiac enlargement, and manifested in a mild form of congestive heart failure. The associated hemodynamic changes of elevation of pressures in the right heart and systemic arteries increases in "blood volume" were similar to those seen in congestive heart failure; however, unlike congestive heart failure, but like acute glomerulonephritis, cardiac output, and arteriovenous oxygen differences remained normal.

Typically in congestive heart failure caused by hypertension, or coronary artery disease, cardiac output is reduced, and circulation time is increased. As a consequence of inadequate delivery of blood to the tissues, the A - V oxygen difference is increased.

It has also been recognized that the "congestive failure" seen in acute glomerulonephritis does not respond to digitalis as does primary congestive failure. It was shown that a prompt, considerable, and continuing diuresis of water and sodium was induced by intravenously administered digoxin in congestive heart failure.

In contrast there was no increase in urine volume and a much smaller increase in sodium excretion following intravenous digoxin in patients with non-cardiac circulatory congestion.

This study also shows that response of arterial-mixed venous oxygen difference following intravenously administered digoxin was likewise different in the two types of circulatory congestion and as expected reflected the changes in cardiac output.

It would in summary appear that circulatory congestion in acute glomerulonephritis is primarily the result of sodium and water retention. There, of course, exists the possibility that underlying

heart disease contributes to the clinical picture in an occasional individual.

(b) Renal Function

Some disturbance of renal function occurs in the majority of patients with acute glomerulonephritis (12).

In general glomerular filtration rates are moderately to markedly depressed as shown by Bradley et al. (12). In another study (13) it was shown that in eleven of sixteen patients that glomerular filtration measured by mannitol or inulin clearance was significantly reduced. Correction of the clearance value by observed extractions yielded values for renal blood flow that were above or in excess of the normal range.

Even though there is a normal or increased renal plasma flow the A - V oxygen difference and the total oxygen consumption are reduced (14). In patients with acute and subacute glomerulonephritis the extraction of oxygen is increased in spite of increased renal blood flow (14).

It has been hypothesized that the marked and disproportionate reduction in glomerular filtration rate is most likely an important factor in causing water and salt retention (13). This is supported

by the finding that edematous patients usually have a significantly lower inulin clearance (13). It was shown (15), however, that salt and water diuresis during the recovery phase of acute glomerulonephritis may take place without a change in glomerular filtration rate. The same study shows that urea clearance is sometimes reduced out of proportion to the filtration rate in acute glomerulonephritis, and during recovery may increase without a change in glomerular filtration rate.

VI. Renal Histology

In recent years biopsy techniques and electron microscopy have made possible the demonstration of even the early histological changes occurring in acute glomerulonephritis (2).

The basic alteration in acute glomerulonephritis is inflammation of the intercapillary mesangium with inflammation progressing through the stages of exudation, cellular proliferation, and resolution (18). The initial accumulation of leukocytes in the capillary lumina with swelling and some proliferation of endothelial cells is rapidly followed by edema, exudation, and proliferation of moncytes in the intercapillary area (16). The intercapillary changes being mainly responsible for capillary ischemia.

In the later stages fibers may appear in the

mesangium, constituting transition to subacute glomerulonephritis (16). A rough correlation between the degree of glomerular damage and the degree of impairment of inulin clearance has been demonstrated (17). Renal biopsies carried out at varying intervals during recovery have been demonstrated and there has been shown to be a progressive restoration of normal glomerular architecture (18). As the active process declines glomerular swelling is decreased, capillaries reopen and Bowman's space enlarges (2). About one month after onset about half of the glomeruli are grossly hypercellular, but a few have already gained an essentially normal appearance (2). About two months later hypercellularity and slight swelling persist in a few glomeruli and these changes may be found for six months or more after the acute illness (2).

VII. Prophylaxis of Acute Glomerulonephritis

Mass prophylaxis with benzathine penicillin aborted, within two weeks, an epidemic of nephritis which had developed apparently caused by a beta-hemolytic group A streptococcus, with strongly nephritogenic properties (19). Acute glomerulonephritis is therefore a preventable disease.

It would seem logical that since acute glomerulo-

nephritis can exist in an epidemic form, and since it is a preventable disease, that not only the patient should be treated, but his immediate contacts as well.

It has been indicated that as little as 600,000 units of benzathine penicillin administered in a single injection may be enough to prevent an attack (19).

VIII. Treatment

The main therapy in acute glomerulonephritis is the treatment of its complications which threaten life, such as hyperkalemia, hypertensive encephalopathy and pulmonary edema (20). In cases with severe oliguria or frank anuria the life of the patient can be prolonged to provide optimal opportunity for healing of the lesion (20). No therapeutic measure has been found to modify either the glomerular inflammatory process in the glomeruli or to influence the rapidity or probability of healing (20).

(a) Treatment of Edema and Congestion

Digitalis has been shown to be a little value in treating the edema and congestion associated with acute glomerulonephritis (11). Acute glomerulonephritis is characterized by accumulation of ex-

cessive amounts of salt and water in patients with normal hearts (21). It appears logical that the best method in the prevention of the edema and congestion would be the restriction of sodium and fluid intake.

Diuretics have been employed in an attempt to mobilize edema fluid in acute glomerulonephritis.

Chlorthiazide is suggested to be the agent of choice since it is a good naturetic and little evidence of nephro-toxicity has been seen (20).

(b) Hypertension and Encephalopathy

Hydralazine has been shown to be efficacious in the therapy of hypertension associated with acute glomerulonephritis even though it has been shown to cause a temporary depression in renal function (22). A study has shown that temporary reductions in increased blood pressure were produced by parenteral and oral apresoline in 5 of 7 children with acute nephritis (23). The effect of the drug on two of the patients with hypertension and chronic renal disease was shown to be far less impressive (23).

Reserpine has also been shown to be efficacious in the treatment of hypertension with acute glomerulonephritis (24). In a study of eight patients seven obtained a significant reduction in blood

pressure (24) and excessive hypotension was found to be rare.

Another study showed that reserpine given prior to or simultaneously with hydralazine enhances and prolongs the response of hydralazine (29). This same study showed that if the drugs were used in the proper dosage in combination that they were free from side effects and minimally altered renal function. It would appear from the findings that apresoline and reserpine administered in combination are better than either drug used alone.

Veratrum preparations have been shown to produce a hypotensive effect by generalized vasodilitation, the renal bed sharing in this generalized vasodilitation (26). This results in an initial decrease in renal blood flow followed by a quick return to normal or above normal values (26).

Goldman has shown that a lesser amount of urine is produced during the period of hemodynamic adjustment to the lower pressure (27).

It has been shown that intravenous magnesium sulfate is of some value in treating the convulsions due to hypertensive encephalopathy seen in acute glomerulonephritis (28). If an initial slow intravenous injection of 500 cc. of 2 per cent magnesium sulfate fails to control convulsions

they will almost surely be controlled by a second dosage (28). It is known that after two injections, serum magnesium may become so high that its depressant effects may become manifest (28). Magnesium sulfate in recent years has fallen out of use in therapy of acute glomerulonephritis with the introduction of the newer anti-hypertensives.

Sedatives are regarded as adequate adjuncts to the therapy of the convulsions along with other anticonvulsants such as diphenylhydantoin (20).

(c) Protein Restriction

Protein restriction has long been employed in the treatment of acute glomerulonephritis in the hope of decreasing the work of the kidneys by decreasing nitrogen loss (20).

Experiments as early as 1939 have shown that the life of rats with artificially induced acute glomerulonephritis may be prolonged by dietary restrictions (29). In these studies rats tended to recover promptly from the induced nephritis on a low protein - high carbohydrate diet. Nephritic rats maintained on a medium protein diet almost invariably became chronic and nearly half of the animals died during ten and one-half months of observation. No rats on a high protein - low

carbohydrate diet recovered from the acute renal injury; all developed chronic progressive nephritis and many died of renal failure after several months. This finding has not been borne out on experiments with human subjects where the dietary protein has not been shown to influence the progress in acute glomerulonephritis (30).

(d) Tonsillectomy

Tonsillectomy was employed for many years in an attempt to improve the prognosis of acute glomerulonephritis as early as 1939 it was shown that tonsillectomy does not prevent nephritis but may predispose to it, and that tonsillectomy does not cure nephritis or prevent it from progressing to the chronic stage, and that tonsillectomy may lead to nephritis (31).

(e) Bed Rest

It has been generally felt that bed rest is indicated during the early and active phases of acute glomerulonephritis, however, a study of 62 patients with acute glomerulonephritis which were divided into two groups were studied by Addis red blood cell counts (32).

There was shown to be little if any adverse effect on healing in acute glomerulonephritis by

early ambulation. Statistically, different findings were not noted between those ambulated early and those ambulated late.

(f) Steroids

Research with cortisone in acute glomerulonephritis was instituted as early as 1950 (33). The initial study of a single case showed that the number of formed elements in the urine did not decrease with cortisone therapy; and that a transitory increase in these elements suggested that the hormone had a deleterious effect. Inulin clearance rose on cortisone therapy and returned to control levels after withdrawal of therapy. Para-aminohippurate clearance, renal blood flow, and low initially showed progressive improvement throughout the course, suggesting a possible favorable influence on the disease process.

Other studies (34) in the same year failed to demonstrate conclusive evidence on a small series of patients treated with ACTH and cortisone that they exert any beneficial effect on the overall course of acute glomerulonephritis. One study in 1953 revealed that ACTH in moderate doses may be of some value in acute glomerulonephritis with persistent hematuria; but could not be recommended

as routine treatment because of spontaneous treatment occurring in the majority of patients (35). Extensive research throughout the past several years has failed to reveal that ACTH or adrenocortical steroids favorably alter the prognosis of acute glomerulonephritis (20).

(g) Hemodialysis

Much use has been made of exchange resins, peritoneal dialysis, and the artificial kidney in the treatment of electrolyte imbalances associated with acute glomerulonephritis. It has previously been suggested that these and other measures serve only to prolong the patient's life to allow the patient's kidneys extra time to undergo any possible healing.

Recently the artificial kidney has been widely used and popularized. The artificial kidney was first suggested in 1912 (36). In 1953, Inouye and Engleberg of the United States, constructed a relatively cheap and effective artificial kidney (37). Similar machines with modifications remain in use today.

IX. Presentation of a Case

(a) History and Physical

History -- The patient is a 17 year old white male who was admitted at a Omaha hospital on January 20.

He had apparently been in good health until December 19 of the previous year when he developed a severe sore throat, which was treated with penicillin with apparent recovery. On January 6, the patient vomited and shortly thereafter developed periorbital edema and dark urine. Shortly thereafter, his local physician found that he had albuminuria. The patient was hospitalized on January 10, at his local hospital outstate and for 48 hours was reported to have virtual anuria. Thereafter, he had some output, felt improved, was able to take fluid and food by mouth. Severe nausea and vomiting developed on January 16, and urinary output was again reduced. The patient was given intravenous fluids and steroids. Because of continued oliguria the patient was referred to an Omaha hospital for the possibility of dialysis on the artificial kidney. There was no previous history of significant renal disease, hypertension, albuminuria, or other serious illnesses.

Physical examination on admission revealed a red-headed, pale, freckled, while male of the stated age who was nauseated and lethargic. Blood pressure was 146 systolic and 94 diastolic. The ocular fundi revealed some arteriolar narrowing with edema of the retina but no adenopathy. There was no edema of the face, lids, or back. The lung fields were clear and no lymph nodes were felt. The tonsils were present but did not appear to be severely infected. The heart was not palpably enlarged. The apical impulse was prominent and the pulmonary second sound was greater than the aortic. There was an ejection type pulmonary systolic murmur. The abdomen and the rest of the physical examination were regarded as negative.

(b) Management and Hospital Course

Initial laboratory data on the admission date of January 20, revealed 4+ albuminuria with a urinary specific gravity of 1.026 and an osmolarity of 316 milliosmoles/liter. The urine contained numerous coarse and finely granular casts and numerous hyaline casts with 3-4 rbc's and 5-10 wbc's per high power field. The BUN was 160 mg. per cent. Complete blood count revealed no anemia but a leukocytosis of 17,900. The serum sodium was

125 mEq/L, serum potassium 7.1 mEq/liter, serum chloride 90.5 mEq/liter, and carbon dioxide content 21.5 mEq/liter. Total serum osmolality was 341 milliosmoles/liter. Total serum cholesterol was 260 mg per cent. Total serum protein was 4.5 gm with 2.4 gm of albumin and 2.1 gm of globulin. The LE test was negative. The urinary sodium concentration was 2.9 mEq/liter. The serum calcium was 7.4 mg per cent and serum inorganic phosphorous 8 mg per cent. Initial chest X-ray was normal. The initial ASO titer was within normal limits. The patient was scheduled for hemodialysis on the following day.

On January 21, the first hemodialysis was carried out for a 6 hour period, and was well tolerated by the patient.

The patient's weight dropped from 154 pounds to 145 pounds. The BUN fell from 200 mg per cent to 82 mg per cent and serum potassium fell to normal limits. The patient was maintained on parenteral alimentation during his initial hospital course. The patient tolerated the dialysis well but potassium accumulated rapidly.

Because of rapid chemical deterioration and continued oliguria, the patient was subjected to

a second hemodialysis on January 25, by this time severe epistaxis had developed. The second hemodialysis was well tolerated and the BUN fell from 160 to 80 mg per cent and serum potassium from 7.2 to 5.2 mEq/liter. The final BUN shortly after the second hemodialysis was 54 mg per cent. Following this, fluid was replaced parenterally in the form 25 per cent glucose through indwelling femoral cannulas in amounts of 5-700 cc/day above the measured loss. (The patient remained oliguric throughout his entire hospital course. The greatest single 24 hour urine volume was 285 cc and for 5 days between the 25th and 30th of January the patient had no urinary output whatsoever.)

The use of cation exchange resin in the form of Kayexalate by enema was employed to some extent. On January 28, it was noted that serum potassium was markedly elevated and the EKG showed evidences of potassium intoxication. The patient was treated for a 24 hour period with ion exchange resin and infusion of sodium, potassium, and bicarbonate. Hemodialysis was repeated on January 29. At this time anemia due to the disease, nosebleeds, and hemodilution became a problem. There was good chemical correction. Following this there was

no potassium intoxication since the ion exchange resin was administered orally.

On January 30, retrograde cystoscopy, ureteral catherizations and pyelograms were done. These failed to demonstrate post-renal pelvic obstruction or disease. The patient's general condition was regarded as satisfactory. The BUN was 85 mg per cent, the hemoglobin was 6.9 gm and the rbc was 2.68 million. Serum sodium was 117 mEq/liter and the serum potassium was 5.5 mEq/liter.

On January 31, the patient was started on injectable prednisolone in doses of 60 mg/day. Bleeding again became a problem in the form of epistaxis and bleeding from the rectum.

The patient's clinical condition continued to deteriorate. On February 2, the BUN had risen to 144 mg per cent. The patient required a fourth hemodialysis on the following day. There was again a good chemical correction. There were spikes of fever following this procedure but no localized focus of infection could be found. There was again chemical deterioration and on February 7, a fifth and final hemodialysis was carried out. The BUN rose rapidly; following this dialysis rose rapidly. On February 8, the patient complained of chest pains

and further fever spiking was noted. Blood cultures were drawn at this time.

On February 10, a loud pericardial friction rub was audible. The patient was noted to be edematous and hyponatremic at this time. Staphylococci were isolated from some furuncles on the thighs. Tetracycline therapy was initiated. By February 11, a loud pericardial friction rub was audible and the BUN had risen to 134 mg per cent. On February 12 the patient was noted to have severe bradycardia with a series of recurrent convulsions, dilated pupils, and a very loud pericardial friction rub. The electrocardiogram showed atrial fibrillation with a marked bradycardia and complete AV block with a nodal pacemaker or high ventricular pacemaker.

Convulsions were treated with sodium phenobarbital and intravenous sodium amytal, and the patient received oxygen and supportive therapy. At 11:00 AM on February 12, the blood pressure was unobtainable. The femoral pulses were gradually diminuating and the respirations were rare and shallow. The patient was pronounced dead at 11:10 AM on February 12.

Final laboratory data revealed a BUN of 158 mg per cent, a serum inorganic phosphorous of

10.8 mg per cent, serum sodium 112 mEq/liter, and a serum potassium of 6.1 mEq/liter.

(c) Autopsy Findings

Autopsy revealed an acute diffuse glomerulonephritis. The immediate cause of death was believed to be a septic infarct of the anterior wall of the left ventricle and interventricular septum, due to a bacterial embolus in the anterior-descending branch of the left coronary artery.

Other septic infarcts were noted in the kidneys, and the lung. Culture of the kidney revealed a para-colon species, culture of a surgical incision in the left inguinal area yielded coagulase positive Staphylococcus aureus.

(d) Discussion

Here we see the classic history in acute glomerulonephritis. The patient suffers a sore throat and eighteen days later presents with edema, nausea, vomiting, and hematuria.

The history is vague concerning the early part of the illness. It is known, however, that during the ten days of hospitalization outstate that the patient became virtually anuric for two days and had persistent albuminuria (4+) the remainder of the initial hospitalization. Steroids failed to

result in improvement and fourteen days after the onset of symptoms the patient was already uremic and showed signs of hypertension. There was persistent and progressive renal failure in spite of repeated corrections of electrolyte imbalances by use of exchange resins and the artificial kidney. Steriods and protein restriction failed to be of avail. Potassium accumulated rapidly in spite of repeated dialyses until the patient was able to take exchange resins orally after which accumulation of potassium failed to be a further problem. The patient tolerated five dialyses within a period of eighteen days quite well. Signs of infection further indicated a poor prognosis following the final dialysis. A friction rub, bradycardia, convulsions, complete A-V block, and continued oliguria five days after the final dialysis signaled the terminal phase of the disease.

The immediate cause of death at the time of autopsy was believed to be a septic infarct of the anterior wall of the left ventricle and interventricular septum due to a bacterial embolus in the anterior descending branch of the left coronary artery. Histologic examination of the kidneys proved the diagnosis of acute glomerulonephritis.

The case is admittedly of unusual severity. The mortality (as previously mentioned) is believed to be only in the range of 1-2 per cent. This patient received extensive therapy yet the prognosis was shown to be unalterable.

X. Summary

Acute glomerulonephritis usually follows infection with a group 12 beta-hemolytic streptococcus. The initiating infection usually occurs in the form of a pharyngitis. Symptoms usually occur within two to three weeks of the streptococcal infection. The mean age of patients suffering from acute glomerulonephritis is in the third decade of life. Mortality is now believed to be in the range of 1-2 per cent. Cardiovascular failure may be seen in acute glomerulonephritis and is not necessarily altered by digitalis. Renal function tests generally show reduced values.

Acute glomerulonephritis is shown to be preventable if mass prophylaxis is employed. It is emphasized that no present therapeutic measure has been shown to modify either the glomerular inflammatory process in the glomeruli or to influence the rapidity or probability of healing. Various methods

of treatment are presented.

An extremely severe case of acute glomerulonephritis intractable to radical forms of therapy is presented. Autopsy findings are revealed as well as a discussion of the case.

XI. Conclusions

Present therapy of the basic disease process in acute glomerulonephritis is in a very primitive state. The present therapeutic measures evolve about the life threatening complications of the disease.

No single therapeutic measure or combination of therapeutic measures can alter the course of acute glomerulonephritis. They only provide an increased amount of life in severe cases of acute glomerulonephritis in the hope that the renal lesions will have optimal time to undergo any possible beneficial changes.

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