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Lower nephron nephrosis

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LOWER NEPHRON NEPHROSIS

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The objective of this paper is to present an abstract of various aspects of lower nephron nephrosis. A survey of the disease was made with reference to many authorities and the following compilation of facts is intended to serve as a resume. The syndrome will be discussed in the light of historical background, etiology, physiological pathology, pathology, clinical features, and treatment.

A syndrome similar to what is now termed lower nephron nephrosis was first described by Pfieffer[23] in 1897. During the intervening years this was overlooked, and in 1917, Minami[19] again noted such a clinical syndrome. Minami studied the microscopic pathology of the kidney, but failed to note the tubulo-venus thromboses. In 1940, during the London Blitz, Bywaters[6] noted renal failure in severly wounded persons. He found this suppression of urine to be especially prevalent in persons who had been crushed under the debris of fallen buildings. Bywaters described the syndrome under the heading of "crush injury" and "ischemic muscle necrosis". In 1942 Dunn[11] and his co-workers first noted tubulo-venous thromboses when they described the renal lesions in two cases of the crush syndrome.

For reasons described in succeeding paragraphs,

the syndrome is now generally referred to as lower nephron nephrosis or the lower nephron syndrome.

The etiological factors in the lower nephron syndrome are variable. Lucke[16] list eleven, which include: 1) severe trauma to muscle; 2) non-traumatic ischemia; 3) burns; 4) transfusion with incompatible blood; 5) heat stroke; 6) black-water fever; 7) toxemias of pregnancy; 8) alkalosis; 9) utero-placental damage; 10) sulfonamide intoxication; and 11) poisoning with certain vegetable and chemical agents. Other conditions or agents that may cause lower nephron nephrosis are: hemolytic reactions during transurethral prostatic surgery[9], typhus fever, shock induced by anoxia, yellow fever, in severe nonspecific infections, hyperthermia, intravenous hemolysis of patient's erythrocytes after intravenous administration of hypotonic solutions, peri-arteritis nodosa, and paroxysmal nocturnal hemoglobinuria.

Lower nephron nephrosis which follows a crushing injury has been described by Bywaters and many other authors. Compression of a limb for only forty-five minutes has been shown to cause this syndrome. Usually, however, the syndrome appears after at least two hours compression of one or several limbs, or thorax or abdomen. The severity of the syndrome is generally proportional to the extent of the muscle lesions, but seems

independent of the duration of the compression beyond the critical limit of three hours.

Regardless of any of the foregoing factors which may be the primary cause of lower nephron nephrosis, the early oliguria and either a sudden or subsequent anuria is dependent on three precipitating precursors. These are tissue damage or blood destruction, or both, and the presence of shock at different times and of varying duration and degree. Furthermore, there seems to be agreement that when the process begins, the unfolding of the clinical, pathologic, and laboratory picture forms a common pattern which is essentially the same in most instances. This pattern varies only as to the degree and outcome.

The pathologic physiology in this syndrome seems to be: 1) clinical shock leading to a vasoconstrictive renal ischemia, which experimentally is principally neurogenic from painful stimulation and, in a smaller degree, humoral[3]; 2) oliguria and aciduria; with 3) ischemic damage to the tubules because of redistribution of renal blood flow from regions of higher to areas of lower vascular resistance[26]; and 4) addition of pigment deposition, either as the result of filtration of circulating pigment through the glomeruli or of the diapedesis of red blood cells through injured glomeruli into

slightly damaged tubules[8].

It is generally agreed[3,7,14,16] that renal cortical ischemia is the main mechanism of producing the clinical manifestations of oliguria or anuria in lower nephron nephrosis. In their studies of renal circulation Trueta[26] and his co-workers have found that the afferent vessel of the cortical glomerulus is of large caliber, while the efferent vessel is of small caliber. Conversly, in the juxtamedullary glomeruli the efferent vessels drain into small cortical capillaries. The relatively large efferent vessels of the juxtamedullary glomeruli drain into the vasa recta, which are straight medullary vessels of large caliber, and from there into the interlobular veins. The blood which has passed through the juxtamedullary glomeruli therefore does not supply the tubules. The importance of the large caliber of these efferent vessels of the juxtamedullary glomeruli becomes apparent when one considers the large amount of blood that must flow through these glomeruli when the medullary by-pass acts as the vascular functioning unit and thereby directs a large part of the cortical blood through the juxtamedullary glomeruli. As will be pointed out, when there is peripheral hypotension, the kidney vascular tree is markedly embarassed and thereby responds by vasoconstriction. In the presence of the renal

vasoconstriction, the blood flow through the kidney takes the course of least resistance and consequently there is renal cortical ischemia. The greater part of the renal blood flows through the low resistance juxtamedullary glomeruli rather than the high resistance cortical glomeruli. Trueta also demonstrated that parts of the loop of Henle which lie in the medullary ray receive blood most rich in oxygen, for the capillaries surrounding these parts of the tubule derive their blood supply directly from the efferent vessels of the cortical glomeruli. Conversely, the proximal and distal convoluted tubules, adjacent to the malpighian corpuscle, receive blood with a lower oxygen content, because the capillaries which surround these parts of the nephron are supplied with blood which has already circulated through the arterial side of the cortical intertubular capillary bed. It is apparent that in the event of a medullary by-pass far less blood than normal would go to the renal cortex. This dual circulation is regulated by a nervous control mechanism. By stimulation of a sensory nerve of an extremity, and also in shock, the cortical circulation is reduced to a minimum and nearly all the blood follows the medullary circulation and by-passes the cortical glomeruli and tubules. Thus, the arterial blood which reaches the kidneys then flows via the juxtamedullary

glomeruli and the vasa recta to the interlobular veins. Under these circumstances, the tubular network becomes ischemic and tubular necrosis may result. Also, the amount of oxygenated blood reaching the distal convoluted tubules would be less than normal. This, in part, is the reason that much of the damage is confined to the lower nephron.

Corcoran and Page[7] believe that renal ischemia causes oliguria and that this permits a precipitation of pigmented casts to occur in the presence of aciduria.

The gross appearance of the kidneys is not pathognomonic. They are usually swollen and show some increase in weight. There is no definite correlation between the weight of the kidneys and the duration of the disease, but there is a tendency for greater swelling as the survival period is prolonged[16]. The kidney is flaccid and the capsule strips with ease. The cut surface is wet and oozes a clear or slightly blood-tinged fluid. The cortex tends to bulge above the capsule. The cortex is widened and pale as compared to the purplish medulla. The medullary striations are often accentuated. In the inner zone of the cortex a fine line of blanching may be seen.

McManus[18] described the microscopic pathological changes which are seen in lower nephron nephrosis

under seven different catagories, the first five of which can be found by any usual fixation and stain, while the last two require special procedures and techniques. First, he noted that the glomeruli were normal. There were no adhesions or demonstrable disease of the capillary loops. Occasionally, Bowman's capsule may be slightly dilated and may contain a granular material which stains with eosin. Second, the tubular epithelium was flattened. This was true in the proximal as well as the distal convolutions. The "brush" border of the proximal convolutions was preserved and there was no marked fatty changes, except in the cells of the distal convoluted tubules. Third, there was absence of the normal colloid droplets in the proximal convoluted tubule epithelium (which suggests to him that the epithelium was functionally not intact). Fourth, there were casts in many levels of the tubules. These may include pigmented casts. The greatest concentration of these casts was found in the distal convoluted tubule and collecting tubules, and the least number was found in the proximal convoluted tubule. The interstitial tissue, when invaded by casts, may show acute, sub-acute, or chronic inflammatory reaction, often with giant cells around the casts. Fifth, there was tubulo-venous thromboses, which usually were not seen until three days after the accident, due to

herniation of the casts through the interstitial tissues into a thin-walled vein. Sixth, by special staining technique, McManus noted hyperplasia of granular cells of the renal arterioles. This was not related to the degree of hypertension and was not seen until two or three days after the accident. Seventh, by using the alkaline phosphotase method of Gomori, it was demonstrated that there was a diffuse loss of alkaline phosphotase from the proximal convoluted tubule. This, McManus states, "Is an excellent indication of damage to the tubules. The diffuseness of involvement and the fact that the proximal tubules are involved is against the terminology 'lower nephron nephrosis'."

The fact that in this condition the glomeruli are intact is of fundamental importance. The tubular lesion is purely epithelial in character and, as in all epithelial lesions, a complete recovery without scar formation is possible when sufficient time is available. The necrotic tubules regenerate and a completely normal kidney results. As soon as the glomeruli are involved, complete regeneration is much less probable, because scar formation and fibrous degeneration of the glomeruli will result. It has been demonstrated that regeneration of the necrotic tubules starts after an average of ten days. It follows that in the majority of patients with

acute anuria, the purpose of treatment consists in extending the survival period of the patient to ten or fourteen days.(24)

Following a crushing injury, an extremity may show scanty visible alterations but the circulation usually is re-established rapidly. A characteristic erythema appears after the patient has been put to bed and warmed. Vesicles may appear at the place of compression. The skin may be red and warm, or white and cold. Very hard muscle masses may be palpable. Autopsy reveals edematous infiltration of the subcutaneous tissues and muscles. Muscles which show ischemic necrosis are homogeneous, dry on section, of increased consistency yet highly friable, and well characterized delimitation between necrotic and healthy muscle.

The liver may show minute areas of necrosis in the paracentral or intermediary portions of the acini. After five days the liver shows many mitoses of the parenchymal cells.(21)

Regardless of the etiological or pathogenic factors, the constant finding in these patients is a marked oliguria or anuria due to severe renal failure. Another constant finding is a lowering of blood pressure to shock levels early in the course of the syndrome. The peripheral hypotension is reflected to an even

greater degree in the renal circulation. The latter may be reduced to one-tenth or one-twentieth its usual flow.

The main clinical feature of lower nephron nephrosis is oliguria, which often proceeds to anuria. The earliest clinical finding, however, is shock. This shock is not often found in the patient's history, but Lucke believed that this may easily be overlooked because it may manifest itself so early in the disease process. This fact has also caused some speculation as to the possibility that renal vasoconstriction may not always be accompanied by peripheral vasoconstriction. Thus, part of the clinical picture of the shock syndrome may not be so apparent(16). Following the period of shock there is an early but moderate increase in blood pressure. Generally speaking, Lucke has found that during the first day of the disease process the patient's blood pressure is at shock levels. The second day it gradually returns to normal and the third day the blood pressure rises to approximately 150/90. Thereafter, it is 150/90 or higher. It must be remembered, however, that the blood pressure at different times during the disease process varies greatly with the patient's usual blood pressure.

During the first day or two the patient is quite well. He may complain of a lack of urination, but

in the usual case it is not until the second or third twenty-four hour period following the injury that there is a marked oliguria. This oliguria of 500.0 cc. or less may ra idly progress to acute renal insufficiency and thence, to complete anuria. In one case reported by Bywaters, the urinary output on the second day was 650.0 cc. On the third day it was 205.0 cc. as obtained by catheter. After a delay ranging between 20 and 46 hours from the onset, the urine turns highly acid (pH of 4.8 - 5.6) and red, with an abundant red or brownish-red deposit. It contains albumin, creatine, pigment in solution, and abundant pigmented detritus in the sediment, while erythrocytes are usually absent(21). The benzidine reaction will be positive, at least in the sediment. The pigment in the urine and urinary sediment when examined spectroscopically is proved to be myoglobin(28). This pigment is usually absent after the first 72 hours. The urine that is excreted throughout the course of the disease is of low specific gravity, tending to become fixed at 1.010.

Patients often develop nausea, vomiting, weakness, malaise, and sometimes pain in the abdomen or back. The severity of these symptoms may frequently divert the attention from what at the moment seems to be a minor consideration, i.e., the progressive oliguria,

so that it may be difficult to date the onset of the renal insufficiency. Therefore, it is important to keep the syndrome in mind when the preceeding symptoms present themselves in patients with an antecedent history involving known etiological factors of the lower nephron syndrome. As the renal shutdown becomes more marked, the non-protein nitrogen elements steadily mount, and acidosis becomes chemically apparent. The blood non-protein nitrogen levels seem to bear little correlation to the outcome. "Lower values (of nonprotein nitrogen) are more often encountered in fatal cases than in patients who ultimately recover."[25] As the renal insufficiency becomes more complete, the potassium and phosphate values of the blood increases as the alkali reserve decreases. During this period the carbon dioxide combining power is gradually decreasing. In some cases, there is a decrease in blood chloride levels. The hypochloremia, per se, has little renal effect, but the oft concommitant dehydration is a factor. Hyponatremia, on the other hand, produces a diminished blood volume[13]. Edema is a variable feature. When present, the edema is usually of the lungs or the lower extremities, but there is seldom edema of the face. In the last two or three days of life, uremia is a common finding. As uremia developes, vomiting tends to become an even more prominent feature of the

clinical picture. Shortly before death, patients show slight mental depression, become apprehensive and anxious, rales develop in the chest, the pulse weakens, the systolic blood pressure falls to a low level, and the patient dies[5].

Once the cardinal signs of the syndrome, e.g., oliguria, excretion of heme pigment, azotemia, and hypertension, have appeared, the mortality is probably in the neighborhood of 90 per cent[16]. In most fatal cases, the death occured three to ten days following the onset of the disease.

The early treatment of lower nephron nephrosis is to remove the precipitating factor and combat the threatened or actual shock. The shock is easily corrected by whole blood or plasma given intravenously. Other shock therapy measures such as the "shock position" (in the absence of head injuries), keeping the patient warm, relieving pain, and prompt fulfillment of any specific measures indicated should be performed immediately. If the treatment for shock is delayed or is inadequate the renal damage soon progresses to the degree that it cannot be controlled and the disease must run its inevitable course ending in death or recovery[22].

The treatment of acute anuria due to lower nephron nephrosis should be limited to: 1) replacement

of water lost during anuria, and 2) correction of the changes of the electrolytes of the blood which accompanies the uremia.

In the presence of anuria, no fluid is eliminated from the body save that by insensible loss, vomiting, and defecation. The insensible loss is variously judged as being from 500.0 cc. to 1000.0 cc. per day. It is necessary to replace this insensible loss in order to maintain the correct blood electrolyte values and to prevent dehydration. However, it is necessary to keep in mind that some of the functional areas of the kidneys are blocked with casts and debris from tissue destruction, and, it is therefore unwise to attempt diuresis by forcing fluids or attempting to "flush" the anuric kidneys. Excessive fluid, either oral or intravenous, must be avoided or pulmonary edema and death will result(17). In addition, it is well to keep the formation of the ketone bodies at a minimum and thereby reduce the tendency toward acidosis. A low protein diet helps to keep urea formation and potassium liberation at a minimum. One author states that no protein whatsoever should be given because the nitrogenous metabolites, such as urea, uric acid, and creatinine, cannot be eliminated(24). It has been shown that many patients who die before diuresis begins die of cardiac standstill due to hyperpotassiumemia.

Borst has suggested a diet of 800.0 cc. of fruit juice with sugar and, in addition, a mixture of 200.0 gm. of butter and 200.0 gm. of sugar. This diet, however, is very unpalatable and causes nausea and vomiting in many anuric patients.

Several authors have presented cases in which patients suffering from lower nephron nephrosis have been treated conservatively with recovery. It has been shown[12] that man can live anuric for a period of ten or eleven days without the use of artificial methods to remove urea and other toxic products from the blood. Fowler and Hunt state that diuresis usually occurs spontaneously by the eleventh or twelfth day of the disease.

When the blood potassium level is rising, some authors have advised intestinal lavage[15]. This is accomplished by passing a Miller-Abbott tube through the nose and past the pylorous a distance of two to five feet. A Levine tube is then inserted into the stomach and the lavage fluid is passed through the Levine tube into the stomach. The fluids then pass into the intestines, during which course diffusible substances of high concentration in the blood pass into the fluid. Suction is maintained on the Miller-Abbott tube, and the fluids are removed from the intestine as they reach the tip of the tube. These authors used a lavage solution containing

sodium chloride (6 gm./L.), sodium bicarbonate (3 gm./L.), calcium chloride and magnesium chloride in concentrations (0.1 gm./L.) similar to plasma, and glucose (20 gm./L.) in concentration sufficient to supply the caloric requirements of the body as well as possible. The solution was introduced through the Levine tube at a rate of 10 liters/24 hours. The authors felt that intestinal lavage is an effective method for extrarenal clearance of urea and potassium.

Peritoneal lavage has been used in the treatment of lower nephron nephrosis. The logic in using this method of therapy is much the same as that for intestinal lavage, which has previously been discussed. In a case reported by Weinstock and Nitshe[27] a mushroom catheter was inserted into the abdomen, and sutured tightly in place. A Y tube was connected to the end of the catheter for the entrance and exit of irrigating fluid. The basic lavage fluid was 1000.0 cc. of Hartmann's solution made hypertonic with one per cent glucose, to which was added one-tenth gram of streptomycin, 20,000 units of penicillin, and 10.0 mg. heparin. Two thousand cubic centimeters of this fluid was allowed to run into the peritoneal cavity over a two hour period. After permitting the fluid to remain in the abdominal cavity for one-half hour the drainage tube was opened and the fluid allowed to drain

out. This procedure was repeated until 16,000 cc. of aliquot had bathed the peritoneum. Under this therapy the non-protein nitrogen rose no higher and on one occasion the fluid, following the lavage, contained 78.0 mg. per cent non-protein nitrogen. These authors feel that peritoneal lavage, as they described the procedure, is an effective method of combating impending uremia.

Dausett[10], in reporting forty-four cases of lower nephron nephrosis treated by repeated replacement transfusions, found that by using a replacement blood volume of two times the total blood volume, it was possible to decrease the urea-nitrogen by one-third of its initial value. The essential factor in the treatment of an anuric patient by replacement transfusions consists in calculating the quantity of blood needed to balance the ureogenesis of urea nitrogen, thus keeping the urea nitrogen at a level not immediately dangerous to life. Dausett feels that the urea nitrogen should be allowed to reach 125.0 mg. per cent before replacement transfusion is attempted. He further points out that when diuresis does begin, the urine often has a low urea nitrogen concentration, and replacement therapy should not be stopped until the kidneys can manage to carry on proper excretory function. An average of three or four replacement transfusions are necessary to obtain recovery, but

in this series, there was a variance of from one to eight. An important factor is possible by means of replacement transfusion which is lacking in other methods of treatment. That is, replacement transfusion therapy is able to remove nondialyzable poisons often linked with proteins and those nondialyzable pigments.

In medical centers where it is available the artificial kidney has been used in the treatment of lower nephron nephrosis. By using this device external dialysis is possible and the proper pH and osmolar concentration of the blood is possible(20). As the artificial kidney becomes available in more hospitals it promises to be of great benefit in tiding patients over until re-epithelialization of the kidneys has occured and diuresis begins.

Renal capsulectomy has also been attempted in the treatment of the anuria of lower nephron nephrosis(27). When one reviews the gross pathology of the kidney in lower nephron nephrosis this seems like a logical way to attempt an early diuresis, but the results have been very discouraging(4).

Abernathy et al(1) report three cases of lower nephron nephrosis which were treated with intravenous procaine. It was felt that procaine probably caused a transient blocking of the sympathetic nerves, perhaps with direct action on renal functions. This is a

promising aid in the treatment of the lower nephron syndrome but more study is necessary before its efficacy can be evaluated.

SUMMARY

The syndrome of lower nephron nephrosis has been reviewed. Historically, the clinical and pathological features of the disease were first noted in 1897, but it was not until 1940, during the London Blitz, that the entity began to gain its importance. The etiological and pathogenic factors of the disease have been reviewed; the main subdivisions being traumatic injuries and a large number of non-traumatic insults to the body. The mechanism of the disease is discussed, with especial reference to the changes in renal circulation which occur during the pathogenesis of the disease process. Pathological findings have been covered, both as to the gross appearance and microscopic features of the kidney in lower nephron nephrosis. An account has been made of the clinical features of the disease, which includes signs and symptoms, physical findings, and laboratory studies, which aid in making a diagnosis of the syndrome. Treatment has been presented in regard to general supportive measures, as well as special therapeutic aids in combating anuria and impending uremia.

CONCLUSIONS

Lower nephron nephrosis is a disease entity with which every practicing physician should be familiar. The etiology of the syndrome is great and varied, so that almost any practitioner, regardless of the limitation of his field, could conceivably be put to the task of diagnosing and treating a patient who is suffering from this type of anuria.

The important facts to keep in mind are the wide variety of conditions which can precipitate the syndrome. In this way early diagnosis will be facilitated. Early diagnosis and treatment are of prime importance if the high mortality rates attributed to lower nephron nephrosis are to be decreased.

It is necessary for the physician to understand the mechanism by which the disease is produced, as well as the pathology and clinical features, in order to give logical and proper treatment to the patient.

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