Chronic Toxic Nephropathies—Diagnosis and Management

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ABSTRACT

As a result of industrial and medical progress, man is exposed to an ever-changing array of chemicals, drugs and biological products. The kidneys are extremely vulnerable to chronic toxic effects of these substances. Although acute renal failure, nephrotic syndrome and renal tubular disorders result from acute nephrotoxicity, chronic renal failure with renal failure and hypertension result from chronic nephrotoxicity.

Heavy metals, analgesic agents and antimicrobials are the common nephrotoxic substance producing chronic renal disease. Medical management consists of preventive exposure measures and early detection of nephrotoxicity by modern industrial medicine. In addition, early clinical diagnosis with appropriate management may prevent the need for chronic hemodialysis and renal transplantation.

Introduction

Progress in civilization and medical science exposes man to an increasingly large number of nephrotoxic agents such as metals, chemicals, biological products and drugs. The kidney is extremely sensitive to the chronic effects of these agents. This toxic injury occurs at different renal sites owing to a variety of mechanisms (table I). The interstitium of the kidney is the most vulnerable part; thus, interstitial nephritis results from exposure to heavy metals and drugs and, subsequently, chronic renal failure results.

In only a minority of cases is the pathological damage reversible. When the primary damage is vascular involvement, malignant hypertension may develop. An example of this is radiation nephritis. In others, when chronic damage occurs to the glomeruli, membranous glomerulonephritis may lead to nephrotic syndrome. This may result from long-term use of ammoniated mercury skin creams. A toxin such as alcohol, when chronically ingested, may not directly affect the kidney, but may affect the liver and lead indirectly to a renal disease such as tubular acidosis.

Heavy Metals

The earliest chronic toxic nephropathy resulted from heavy metal exposure on ingestion. Chronic lead ingestion was probably the first heavy metal recognized
for its nephrotoxic effect. The high incidence of lead nephropathy was first observed in Queensland, Australia between 1870 and 1920 when small children ate chips of lead base paint or licked the sweet tasting lead paint off porch railings. Lead nephrotoxicity was almost exclusively limited to the tropical areas of Queensland where the characteristic verandas were the only place European children could play in both a safe and cool place. As lead-free paint was increasingly used in Queensland, the incidence of chronic renal failure fell to the low levels observed in other parts of Australia.

In general, acute lead poisoning does not usually result in chronic nephropathy. Animal studies relate chronic lead nephropathy to factors such as dietary calcium, presence of iron deficiency, exposure to sunlight and vitamin D.

Patients with chronic lead nephropathy have a markedly elevated bone lead content. This is considered a prerequisite for diagnosis when the patient presents with terminal renal failure of uncertain etiology. The characteristic microscopic findings in renal biopsy are large intra-nuclear inclusion bodies which may fill the entire nuclei of proximal tubular cells. Associated with the severe non-specific lead induced interstitial nephritis are laboratory findings in the urine of glucosuria, aminoaciduria and increased urinary levels of lead, and delta aminolevulinic acid. Some patients may have copra-porphyrin, urobilin and bile pigments. These findings are not pathognomonic of lead nephropathy. A characteristic clinical finding of lead nephropathy is an associated acute gouty arthritis. In other forms of chronic renal failure, hyperuricemia is not associated with gout.

Chronic renal failure owing to interstitial nephritis also, occasionally, results from arsenic, silver and iron. The nephrotoxicity induced by these and other metals is, however, usually acute and reversible.

Another industrial health hazard is cadmium. Originally, cadmium was thought to result in tubular damage; however, glomerular damage is the primary pathology. Again, the diagnosis is dependent on a specific clinical history related to occupational exposure. Cadmium nephrotoxicity is characterized by a peculiar low molecular weight proteinuria. Unlike the proteinuria of the nephrotic syndrome, cadmium proteinuria precipitates with nitric acid but not by boiling. Cadmium urinary protein migrates as an alpha globulin rather than the usual albumin. Cadmium has been used to plate ice cube trays. Foods and beverages with an acid pH can be a source of cadmium poisoning.

Mercury is a rare, although well known, cause of the nephrotic syndrome. This nephrotoxicity is found in workers in the pesticide, disinfectant and paint manufacturing industries. Iatrogenic causes are equally important with this compound, however. In the past, the chronic use of mercurial diuretics produced a membranous glomerulonephritis and subsequently the nephrotic syndrome. Later, mercury ointments became a popular non-prescription treatment for fungal dermatoses. Becker et al reported three cases in which the nephrotic syndrome was well shown to be due to anti-fungal compounds. These patients appeared to have

**TABLE I**

<table>
<thead>
<tr>
<th>Toxic Substance</th>
<th>Pathological Site of Damage</th>
<th>Clinical Features of Chronic Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin, gold, mercury &amp; cadmium</td>
<td>Glomeruli</td>
<td>Glomerulonephritis, Nephrotic syndrome</td>
</tr>
<tr>
<td>Radiation</td>
<td>Vasculature &amp; Interstitium</td>
<td>Malignant hypertension &amp; uremia</td>
</tr>
<tr>
<td>Analgesic agents, lead</td>
<td>Interstitium</td>
<td>Chronic uremia</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Liver disease</td>
<td>Renal tubular leading to hyperglobulinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glomerulosclerosis</td>
</tr>
</tbody>
</table>

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at least a partial response to high dose prednisone therapy.

Gold, another iatrogenic toxin, produces the nephrotic syndrome. It is used in treating patients with rheumatoid arthritis. Some patients with rheumatoid arthritis and gold treatment have subsequently developed systemic lupus erythematosus (SLE) and it is possible that they initially had SLE masquerading as rheumatoid arthritis or that lupus was precipitated by a hypersensitivity reaction to gold.\textsuperscript{18}

Balkan nephritis is limited to certain mountain valleys in Romania, Bulgaria and Yugoslavia. It is characterized by interstitial nephritis and a clinical course resembling a toxic nephropathy. It is probably an example of a toxic nephropathy in which the etiologic agent has not yet been identified. Extensive studies\textsuperscript{8} have suggested trace metals, radiation, dietary fungi and aflatoxins; however, no specific substance has been proven the cause.

**Hydrocarbons**

Another recently recognized cause of glomerular disease is hydrocarbon solvents. Beirne and Brennan\textsuperscript{4} found that six of eight patients with anti-glomerular basement membrane antibody mediated glomerulonephritis had an extensive history of exposure to industrial solvents. Various petroleum products, including paint removers, degreasing solvents, hair sprays and painting solvents, were suspected. A patient with nephrotic syndrome associated with terminal uremia and a long history of solvent exposure has been studied by the present authors. All these patients had inadequate ventilation at the place of work. Most of these patients developed irreversible renal failure; however, future disease could probably be prevented by better industrial ventilation. To prevent industrial solvent-induced nephropathy, the solvent industry could create occupational medical departments designed to prevent a toxic industrial environment.

**Heroin and Alcohol**

Social change and medical progress have led to the discovery of nephropathies owing to heroin and alcohol which were not previously known. Heroin produces the nephrotic syndrome owing to a glomerulonephritis.\textsuperscript{16} The serum Beta 1C globulin is usually reduced. Immunopathological studies reveal focal and segmental deposits of immunoglobulins in the glomeruli. A high percentage of these patients develop irreversible renal failure. Adrenal corticosteroids and immunosuppressive drugs have no beneficial effect.

Chronic alcohol ingestion has no direct toxic effect on the kidney but does have several indirect effects. The hypergammaglobulinemia found in alcoholic cirrhotics is well known\textsuperscript{14} to lead to proximal renal tubular acidosis.

Glomerulosclerosis has occasionally occurred in some patients with chronic alcohol ingestion. Another example is alcoholic cardiomyopathy with mural thrombi and subsequent embolization to the renal arteries and renal infarction.

**Antibiotics**

Antimicrobials cause toxic nephropathy under certain circumstances. Early preparations of sulfa led to chronic renal failure by crystallization and subsequent obstruction in the kidneys. The highly soluble sulfonamide compounds available today do not crystallize, but an occasional patient\textsuperscript{18} develops interstitial nephritis and necrotizing angiitis.

Today, the most serious nephrotoxicity is seen with the aminoglycoside antibiotics, particularly kanamycin and gentamicin. Both drugs\textsuperscript{18,19} lead to necrosis of the proximal and, less often, the distal tubules. Azotemia occurs in 10 percent of patients treated with normal doses of
kanamycin and is likely to be severe and irreversible in the presence of mild underlying renal disease or in the presence of other nephrotoxic drugs.

Gentamicin, like streptomycin, is less nephrotoxic than kanamycin but can also lead to chronic renal failure in the presence of underlying renal disease or excessive dose.¹⁹ Because of the narrow margin between therapeutic and toxic levels, the aminoglycoside antibiotic agents should be given on a milligram per kilogram of body weight basis. Aminoglycosides are also toxic when applied topically to open wounds. They are not absorbed by normal skin but usually are absorbed through the mucous membranes of broken skin leading inadvertently to high blood levels and subsequent nephrotoxicity. Unrecognized absorption of other topically applied antibiotics, such as bacitracin, neomycin and polymyxin, may also produce nephrotoxic damages. Although not related chemically, the antifungal agent Amphotericin B is highly toxic to the tubules. It can produce potassium wasting and leads to chronic renal failure.

Methicillin and long-term high dose penicillin have now been shown¹ to lead to interstitial nephritis with the clinical traits of fever, dermatological lesions and eosinophilia. The renal failure is usually reversible. No glomerular abnormalities or arteritis have been noted. A recent report⁶ describes a case of methicillin-associated interstitial nephritis in which a methicillin antigen was found bound to the tubular basement membrane and in which circulatory antibodies reactive with normal human and monkey tubular basement membrane were detected.

Analgesics

In 320 newly diagnosed patients with chronic renal failure, Murray and Goldberg¹⁵ found a seven percent incidence of analgesic nephropathy. Our incidence is approximately 12 percent. Patients with analgesic nephropathy ingested more than 3 kg of phenacetin and aspirin combination before the onset of azotemia. The main problem in failure to diagnose drug nephrotoxicity as the cause of renal disease is the failure of the referring physician to consider the diagnosis of analgesic ingestion. Previous studies⁸ had shown that papillary necrosis and infections were major factors in analgesic nephropathy. Only two patients out of 20 with analgesic nephropathy had both papillary necrosis and infection. Thus, the diagnosis of analgesic nephropathy is even more difficult for the referring physicians.

Presenting history and clinical data can vary widely with the same nephrotoxic drug. In Table II are illustrated three of our patients with analgesic nephropathy. Each had in common a long history of analgesic intake and subsequent reversibility of renal failure when the analgesic agents were discontinued. Multiple mechanisms of pathogenesis of the chronic interstitial nephropathy of analgesics, including anti-inflammatory effects, salicylates as uncoupling agents, hypokalemia, manufacturing contaminants (acetate-4-chloranilid), methemoglobinemia, and sulfhemoglobinemia, sensitivity reactions and predisposition

<table>
<thead>
<tr>
<th>Patient</th>
<th>B.N.</th>
<th>L.P.</th>
<th>G.U.</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of analgesic ingestion</td>
<td>Varied with Darvon compound &amp; APC</td>
<td>5 years</td>
<td>10 years</td>
</tr>
<tr>
<td>Prior renal disease</td>
<td>Arteriolar nephrosclerosis</td>
<td>Toxemia</td>
<td>None</td>
</tr>
<tr>
<td>Mental status</td>
<td>Confused</td>
<td>Oriented</td>
<td>Stuporous</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Interstitial nephritis</td>
<td>Interstitial arteriolosclerosis</td>
<td>Unremarkable</td>
</tr>
</tbody>
</table>

| TABLE II |
| Wide Variations in Presenting Histories and Clinical Data with the Same Toxin |
have been suggested. In most series both aspirin and phenacetin are simultaneously involved and it appears that the combination is required for the nephropathy to occur. Phenacetin is entirely metabolized to N-acetyl-p-aminophenol (acetaminophen), which is an oxidizing agent. Salicylates inhibit oxidative defenses and, therefore, chronic oxidation appears to be the best explanation of the fact that both phenacetin and aspirin are implicated together. The fact that phenacetin is entirely converted to acetaminophen suggests that with the increasing use of this agent, the incidence of analgesic nephropathy will therefore become common.

Treatment of analgesic nephropathy includes discontinuing the drug. Even in patients with chronic renal failure owing to chronic analgesic nephropathy and requiring hemodialysis, the authors have observed that patients will not require hemodialysis after 8 to 11 months if analgesic agents are stopped.

In figure I is illustrated the clinical course of a patient who recovered sufficient renal function subsequently to become pregnant and to give birth. Although anemia rapidly became severe at the start of dialysis, the patient’s general well-being allowed reduction of hemodialysis treatments to twice per week. She was dialyzed less frequently and her serum creatinine continued to fall slowly over the next few months. During the eight months, her hematocrit was noted to increase gradually. Dialysis was reduced to once per week and the patient had her first menstrual period in over a year. At that point, hemodialysis was terminated. She became pregnant almost immediately. Her renal disease had no affect on her pregnancy and her serum creatinine continued a slow decline. Delivery of a seven lb healthy male infant was by Caesarean section.

Radiation

Chronic radiation nephritis may progress to renal failure even after partial resolution of acute radiation nephritis. The patient with radiation nephritis has a slow decline of renal function years after the initial radiation. An unusually large number of patients with chronic radiation

![Figure 1. The clinical course is shown of a patient who ingested large quantities of APC and who subsequently developed chronic renal failure. The black line graph represents serum creatinine as a measure of renal function. The dotted line represents hematocrit with the ordinate on the right. The initial serum creatinine was 16.0 percent and dialysis was begun three times per week, as shown on the solid bar graph.](image-url)
nephritis develop malignant hypertension owing to necrotizing arteriolitis. When radiation occurs many years earlier, the history of radiation exposure may not be considered. The physician is usually led on a fruitless diagnostic search for polyarteritis or other diffuse renal diseases. Patients receiving radiation therapy to one side of the body for neoplastic disease may develop hypertension which is relieved by unilateral nephrectomy of the affected kidney.

Bibliography