3

The General Picture of Uremia

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ABSTRACT

The clinical presentation and manifestations of uremia that constitute the uremic syndrome are presented. The first descriptions of patients with advanced or "terminal" renal failure who were treated with hemodialysis are evoked to illustrate the wide range of signs and symptoms that are associated even to a moderate decrease in renal function, presently referred to as chronic kidney disease (CKD) stages 3–4. The kidney is a central organ guaranteeing the maintenance of the "milieu intérieur," where all the cells of the body are generated, develop, proliferate, and die. Chronic kidney disease, by altering the "milieu intérieur," may alter the metabolism of every type of cell or organ, leading to a wide scope of symptoms. The most frequently observed signs in daily clinical practice are summarized and put into the perspective of the renal physician. Disturbances of ion and water metabolism, hypertension, cardiovascular disease, anemia, mineral and bone disorders, endocrine, inmmunologic and neurologic syndromes are described. The addition of these clinical manifestations defines and describes each uremic patient as a specific individual. The pathophysiologic mechanisms by which each of these signs and symptoms appears and the particular compounds responsible for their occurrence, are described in depth in subsequent chapters of this issue.

The concept of an internal fluid environment in which the cells of the body live and function was introduced by Claude Bernard in 1878 (1). The vital role of the kidneys in maintaining the constitution of that environment was subsequently recognized by Peters in 1935 (2). Excretion of metabolic end products, a major homeostatic function of the kidneys, involves both glomerular ultrafiltration and renal tubular secretion.

Maintaining the optimal conditions in the fluid environment of the cells is vitally important; failure of the kidneys to perform this task is manifested in the clinical syndrome called uremia. The term "uremia" was introduced in 1840 by Piorry and L'Héritier (3). In their treatise on alterations in the blood they proposed the use of the general suffix "-emia" to denote the blood compartment and qualifying it with a specific prefix to denote the presence of an abnormality in that compartment. Thus in their terminology "uremia" literally means "urine in the blood," which reflects their view that the toxic manifestations of renal failure were a form of poisoning of the blood, a consequence of reabsorption of urine (4). Today, uremia is used clinically to describe a complex syndrome that has many interrelated features. The complexity of the uremic syndrome is due to the role played by the kidneys, not only as homeostatic but also as endocrine organs.

The word "uremia" is used to describe the state associated with the retention of nitrogenous metabolic end products and is characterized by an increased concentration of urea in the blood, the first retention product to be recognized. Later on it appeared that many other solutes were retained as well (5).

So, the uremic syndrome is attributed to the progressive retention of a large number of compounds, which under normal conditions are excreted by the healthy kidneys. As a result of this accumulation, these compounds are called uremic retention solutes, and if they are biologically/biochemically active, they are called uremic toxins. The accumulation of such compounds has a negative impact on many body functions and results in a gradual, endogenous intoxication. Retention solutes, despite being nontoxic, can still be of interest, as useful markers for other yet toxic elements.

After a considerable amount of time and effort devoted to a search for the uremic toxin, no individual compound could be accused, so far, of being the responsible for the uremic syndrome. It may well be that no one single uremic toxin will ever be identified as the toxin. The clinical syndrome of uremia should be recognized as a composite problem, involving all of the body's systems and reflecting biochemical alterations in all aspects of the constitution of the internal environment (6).

In the present special issue of *Seminars in Dialysis*, an in-depth analysis of several of the most important uremic toxins, and their effects in different biologic systems, or the modern technical tools to analyze them, will be

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provided. Our contribution to this issue aims to present the clinical features of the uremic syndrome with a mere description of their principal characteristics: what the clinical observer may see when looking at and examining a uremic patient. We will focus on the many different symptoms and signs that are presented by the person with renal disease as a whole. The mechanistic approach and the physiopathology for each of the separate clinical manifestations will certainly be described in detail in subsequent chapters of the present issue.

To present the clinical aspects of the uremic syndrome we may want to look at the descriptions of the pioneers in its treatment. They had to face receiving and handling patients expressing the uremic syndrome with the full array of clinical findings. The first reports on dialysis treatment convey the difficulties in reversing the uremic symptoms that were the most tormenting for these clinicians. J.P. Merrill (personal communication reported in Schribner et al. 1960) described being unable to prevent mental deterioration for more than a few weeks in patients with complete loss of renal function and Maher, Schreiner, and Waters reported their difficulties in maintaining the nutritional status in uremic patients despite repeated dialyses (7).

A more general clinical picture is wonderfully presented in the reports on the first successful dialysis treatments. The first dialysis survivor had to stop working at the age of 39 because of weakness, vomiting, and headaches (7). On admission he was barely able to walk, his speech was thick, and his sensorium clouded. He had uremic tremors and exudates and hemorrhages in his fundi. He had water retention, hypertension, and dyspnea with cardiac enlargement and pulmonary congestion on chest X-ray. Other patients (no. 2 of the Scribner's report) presented increased fatigability, dyspnea on exertion, muscle cramps, irritability and lethargy, periorbital and ankle edema, anorexia, and nausea (8). All these individual clinical features (and many others) may coexist, be absent or differ in intensity in a single patient with uremic syndrome.

Therefore, the clinical manifestations of uremia are rather nonspecific and may involve any system of the body. The renal physician may see a patient with vascular disease and hypertension, anemia, gastrointestinal symptoms, mineral and bone disorders (previously called renal osteodystrophy), disturbances of ion and water metabolism, endocrine dysfunction, immunologic as well as neurologic diseases which may present or evolve up to uremic coma. The principal clinical features are summarized in Table 1.

In what follows, we will describe each of these clinical elements in more detail to give a more complete view, although certainly not comprehensive, of the signs and symptoms that may be observed in the uremic syndrome.

TABLE 1. Principal clinical features of uremia

Central nervous system	Diurnal somnolence, night insomnia, disorders of the memory and the concentration, asthenia, headache, confusion…
Peripheral nervous system	Polyneuritis, restless legs, cramps
Gastrointestinal	Anorexia, nausea, gastroparesia, parotiditis, stomatitis
Hematologic	Anemia, haemostasis disorders
Cardiovascular	Hypertension, atherosclerosis, coronary artery disease
Skin	Itching, skin dryness, calciphylaxis
Endocrinology	Growth impairment, impotence, infertility, sterility
Osteoarticular	Secondary hyperparathyroidism, osteomalacia, β2-microglobulin amyloidosis
Nutrition	Malnutrition, weight loss, muscular catabolism
Immunity	Low response rate to vaccination, increased sensitivity to infectious diseases
Biochemical	Metabolic acidosis, hyperphosphatemia, hyperkaliemia

The Uremic Syndrome

Disturbances of Ion and Water Metabolism

The kidney is the central organ maintaining water and ion homeostasis. In addition to the ion cell-transport abnormalities described in uremia (9), which may have a major impact on cell metabolism, changes in ion metabolism may cause, directly or indirectly, many of the symptoms observed in the uremic syndrome. When Na^+ intake exceeds the renal excretory capacity, a net positive Na^+ balance occurs, hypertension worsens, and pulmonary oedema may appear participating in the so-called uremic pneumonitis (10). Fortunately, the damaged kidneys are able to adapt even at the advanced stages of renal disease and generally maintain a close to neutral Na^+ balance (11). As a result, although Na^+ and water retention is commonly observed among chronic kidney disease patients, it will not permanently increase and will be partially limited by the adaptative capacities of the kidneys (11).

Water retention with hyponatremia may exacerbate central nervous system symptoms (Table 1). Although hyponatremia may occur in chronic renal failure, its incidence is lower than could be expected, because of the capacity of the damaged kidneys to adapt to the decline in their function (12).

Hyperkalemia is frequently observed in advanced renal disease, and may present with diarrhea, skeletal muscle dysfunction or if severe, cell membrane potential disturbances, and cardiac arrest. In addition to potassium, other ions have their metabolism altered in renal disease. Hypercalcemia may worsen hypertension, or central nervous system symptoms, or be associated with nausea, vomiting, abdominal pain, and diarrhea, while hypocalcemia may present with paresthesias, tetany or seizures, hypotension, arrhythmia, and heart failure among other manifestations. Frequently observed in renal patients, the disturbances in calcium–phosphate metabolism are also associated with dermatologic manifestations, such as pruritus, dystrophic calcifications and if severe, calciphylaxis (Fig. 1).

Hypertension

Hypertension is a major feature of the uremic syndrome. It may appear during the first stages of renal

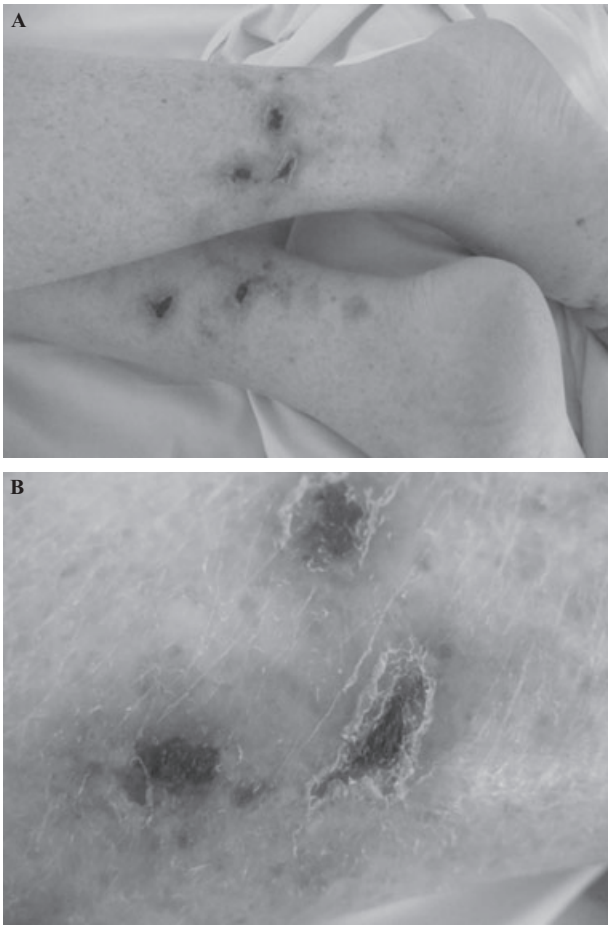

FIG. 1. Skin lesions of calciphylaxis. A 66-year-old obese woman (155 cm and 107 Kg of body weight) with diabetic nephropathy, presented painful subcutaneous lesions with mottled violet discolorations that evolved into central necrotic ulcerations. Her iPTH was >1900 pg/ml in spite of hyperparathyroidism treatment that sequentially included phosphate binders, vitamin D3 derivatives, and calcimimetics. Surgical parathyroidectomy was scheduled. Panel B shows a closer view of the three lesions of the left leg shown in panel A.

disease or even precede it and be at its origin. When present, hypertension hastens the decline of renal function and its incidence and severity increases while renal disease progresses. It is observed in >90% of the patients with end-stage renal disease, and it is corrected by dialysis treatment in many cases (13,14). On the other hand, renal failure has been demonstrated to worsen hypertension and cardiovascular disease: the prevalence of retinopathy and especially, malignant retinopathy is greater for a given level of hypertension in the patients with renal disease when compared to those with essential hypertension (15). In addition, cardiovascular mortality increases when glomerular filtration rate declines, from the very early stages (16). The mechanisms by which renal disease may participate in hypertension result from factors altering cardiac output (extracellular body fluid and salt accumulation, angiotensin II, aldosterone, norepinephrin, atrial natriuretic factor, glomerular filtration rate decrease, sympathetic nervous system activation, baroreceptor sensitivity), total peripheral resistance (pressors: angiotensin II, norepinephrine, vasopressin, intracellular calcium, and depressors: prostaglandin E2, prostacycline, kinins, atrial natriuretic peptide), or both.

Cardiovascular Disease

Although heart-related diseases are seldom the first clinical manifestation of renal disease, chronic kidney disease patients have a high incidence of cardio-vascular disease and a significantly increased mortality risk as a result of it (17). Coronary artery disease presenting as angina and acute myocardial infarction is commonly observed in chronic kidney disease, but also cardiac arrhythmia, valve dysfunction (generally due to valve calcification), and cardiac insufficiency frequently accompany the natural history of chronic kidney disease. From the early days of renal medicine it was identified that chronic kidney disease patients develop "accelerated atherosclerosis" (18). In addition to hypertension, other established ("traditional") factors may participate in the increased cardiovascular morbidity and mortality in chronic kidney disease patients, such as left ventricular hypertrophy, dyslipidemia, diabetes, smoking, male sex, and age (19). However, these "traditional" factors do not fully explain the higher incidence in cardiovascular disease observed in chronic kidney disease patients (20), and other "novel" cardiovascular disease—risk factors, such as inflammation, endothelial dysfunction, sympathetic overactivation, protein energy wasting, oxidative stress, vascular calcification, and volume overload, frequently observed in chronic kidney disease patients, have been involved (reviewed in 21).

Anemia

The fate of anemic patients with CKD has completely changed with the introduction of human recombinant erythropoietin (EPO). Renal failure—associated anemia is normocytic, normochromic, and secondary to many different etiologic factors. We distinguish the factors decreasing erythropoiesis from those decreasing red cell survival. Deficient response to EPO (decrease in EPO synthesis and increase in EPO resistance), iron deficiency, aluminium toxicity (uncommon since the introduction of proper water treatment for dialysis and the abandon of Al containing salts), hyperparathyroidism, and folate deficiency result in a decreased erythropoiesis. Hemolysis, acute or chronic, and hypersplenism decrease red cell survival. Uremic toxins may act both, decreasing erythropoiesis and red cell survival. In that respect PTH has been suspected to suppress erythropoiesis. Secondary hyperparathyroidism has been identified to increase EPO resistance (22) and improvement of secondary hyperparathyroidism by parathyroidectomy (23) or by vitamin D3 derivatives (24) is followed by a clear improvement in anemia and allows reducing EPO doses or EPO withdrawal (25).

Anemia may be the first accompanying sign motivating referral to the nephrologist, and therefore is of particular importance. It has also been improved in patients

with stage 3–5 of chronic kidney disease, by the extension of the treatment with erythropoiesis stimulating agents to this population.

Gastrointestinal Symptoms

Gastrointestinal manifestations are typically observed in the uremic syndrome with advanced renal failure. As it has been commented above, the patient described by Scribner et al. presented nausea and vomiting. Towards the stage 5 of the CKD, patients complain of lack of appetite, bitterness, and metallic taste as well as selective disgust for specific aliments, frequently the meat. The appearance of these gastrointestinal symptoms is often the announcement to start dialysis treatment. On the other hand, gastrointestinal symptoms may result in malnutrition, which in turn, may aggravate existing inflammation and heart failure, accelerate atherosclerosis, and increase susceptibility to infection (26). The association of malnutrition, inflammation, and atherosclerosis constitutes the MIA syndrome that has been described in chronic kidney disease patients and has an exceptionally high mortality rate (26).

Mineral and Bone Disorders (previously termed renal osteodystrophy)

Mineral and bone disorders may be observed quite early in chronic kidney disease. Typically, they are associated with secondary hyperparathyroidism and include proximal muscle weakness, bone pain and fractures, growth retardation in children and skeletal deformities (Fig. 2), arthritis and periarthritis, itching, soft tissue calcifications and calciphylaxis (Fig. 1). They also include hypertension and myocardial failure as well as life-threatening complications that may result from heart block and valve calcification (27).

Endocrine Dysfunction

A variety of endocrine disturbances may be observed in the uremic syndrome. Parathyroid dysregulation has already been commented; thyroid metabolism abnormalities, gonad and adrenocortical dysfunction may also be observed. The mechanisms leading to these disturbances are diverse: a decrease in production of the hormone can be observed for EPO and the active form of vitamin D with advancing renal disease, whereas a decrease in the metabolic clearance of different hormones leads to an increase in serum levels of follicle stimulating hormone, luteinizing hormone, prolactin, growth hormone, melanocyte-stimulating hormone, and gastrin. Decreased production of the active form of a hormone in the corresponding organ may also be observed, for testosterone or triiodothyronine, as well as blunted feedback response with associated abnormal hormone secretion for luteinizing hormone, corticotropin and prolactin, and end-organ resistance for insulin and parathyroid hormone.

Immunologic Alterations

Chronic kidney disease is associated with severe alterations of the immune system. Infections are responsible for a large part of the mortality in hemodialysis patients, and vaccination is mostly ineffective, particularly in advanced stages of chronic kidney disease. Although improvement in vaccines may reduce the nonresponse rates in hemodialysis patients (28), whenever possible, it is preferable to vaccine the patients in the early stages of renal disease, when the primary immune response has not been sensibly diminished (28,29).

Acquired immunity disturbances in HD patients concern mainly the T-lymphocyte and the antigen-presenting cell (APC) (30). Patients with chronic renal failure

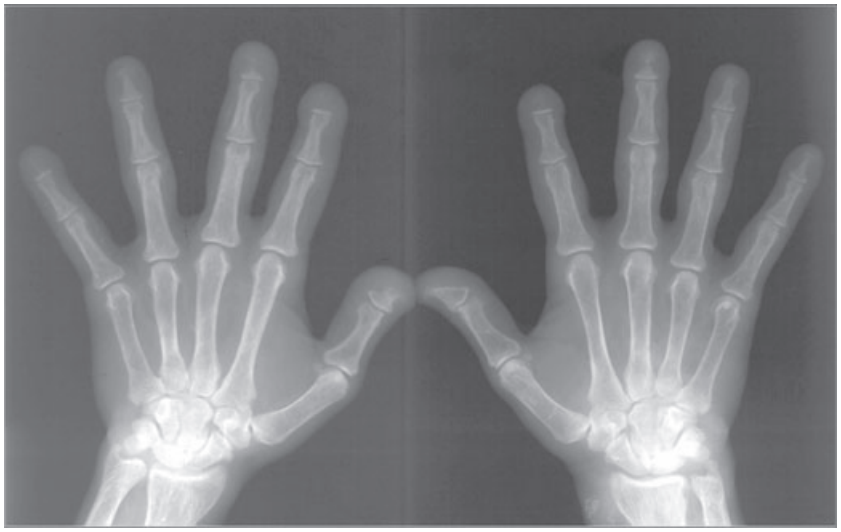

FIG. 2. Bone resorption in severe secondary hyperparathyroidism. X-rays of a 20-year-old man who was wheelchair bound at presentation, with diffuse pain; he was pale, had proximal muscle weakness and could not stand up; he was sitting with a twisty attitude and evident thorax deformity. His PTH level appeared to be >2000 pg/ml. These X-rays are given as an example of bone resorption, as can be appreciated at different degrees in all fingers, with a complete disappearance of the final phalanx of both index fingers.

show a defective function of costimulation derived from APCs leading to impaired activation of effector lymphocytes (31). The mechanisms involved in immune system deficiency in chronic kidney disease, including also the inflammation mentioned above, were nicely reviewed and put into perspective with a putative link with uremic toxicity by Descamps-Latscha (32).

Neurologic Disorders

Neurologic manifestations are among the most concerning features with which dialysis pioneers had to deal (33). They include central nervous system signs, such as decreased attention and cognition, imprecise memory, slurred speech, asterixis and myoclonus, seizures, daytime drowsiness, tendency to sleep and obtundation, disorientation and confusion, and eventually coma. They also include peripheral neurologic manifestations such as burning disesthesia, restless leg syndrome, increased muscle fatigability and cramps (Table 1).

Conclusion

The uremic syndrome is a sum of many different manifestations appearing with the decline of renal function. It is a complex clinical entity which involves nearly all the systems of the body corresponding to the "milieu intérieur" as it was described by Claude Bernard (1). Research in uremic toxicity has achieved remarkable progress during recent years, mainly because of the collaboration between renal physicians and scientists and the rational use of the new tools allowing the identification of molecules with relevant roles in the pathogenesis of uremic syndrome. Tools for early, noninvasive diagnosis of renal disease or for risk evaluation of its appearance are already waiting to be used. The arrival of dialysis dramatically improved the uremic syndrome and changed the survival expectations of those patients with end-stage renal disease. We hope that our efforts will allow improving the prevention and treatment of end-stage renal disease by opening new endeavors in the understanding of the physiopathology of this complex clinical entity.

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