TROPICAL JOURNAL OF NEPHROLOGY

The Official Journal of the Nigerian Association of Nephrology

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The aims and scope include the following:

1. *To provide a medium of exchange of ideas and knowledge of nephrology in the tropics through publication of research works, clinical experiences and relevant articles.*

2. *To promote nephrology education, clinical practice and research through publication of original research works, innovative clinical experience and authoritative review articles on topical issues.*

3. *To provide an avenue for global dissemination of consensus positions on issues of concern in tropical nephrology through publication of proceedings of consensus meetings, dedicated conferences and commissioned reviews.*

4. *To serve as a scientific link between the Nigerian Association of Nephrology and other such International Organizations all over the world.*

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Editorial

The journey so far is an encouraging one as this edition of Tropical Journal of Neprology (TJN) represents the last of Volume 3. The Editorial Board is impressed by the contributions of the membership of Nigerian Association of Neprology(NAN) and non NAN Members to the growth of the Tropical Journal of Nephrology.

There are three review articles in this edition, each of them addressing an important part of nephrology and hypertension. The article by J. A. Otegbayo is an exposition of recent development in issues relating to hepatorenal syndrome, while the role played by the metabolic syndrome in chronic kidney disease is also well treated by Dr. I. G. Okpechi, *et al.*

A reminder of the Pharmacotherapy of hypertension is well presented here by F. A. Fehintola, a Consultant Physician and Clinical Pharmacologist. I invite the entire readership of TJN to take advantage of these well written articles.

The reports of heamodialysis treatment from different dialysis centres in Nigeria have continued to be relevant to our environment and it is part of our efforts at defining problems relating to patients management in chronic kidney disease. The results from Osogbo, Port Harcourt and Ibadan would certainly supplement our efforts at developing a renal registry in Nigeria.

The case report of Fibrillary Glomerulonephritis provides an opportunity to encourage kidney biopsy and clinicopathology teaching via the pages of TJN. The maiden piece is provided by Dr. Rasheed Balogun, a USA based Nephrologist.

On behalf of the TJN Editorial Board, I thank the authors and the reviewers of these articles for a job well done.

B. L. Salako
Editor

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The Metabolic Syndrome and Kidney Disease

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ABSTRACT

The prevalence of obesity and the metabolic syndrome are increasing worldwide and reaching epidemic proportions in industrialised and developing countries. Obesity is the major driver of type 2 diabetes and it is the phenotypic hallmark of the metabolic syndrome. The global increasing prevalence of obesity has to a large extent mirrored the increase in cardiovascular diseases as well as chronic kidney disease (CKD) and its progression to end-stage renal disease (ESRD). End-stage renal disease is a devastating condition not only for the patient but also imposes a huge economic demand on the society. Several multi-ethnic societies have reported a higher prevalence of CKD and ESRD in blacks compared to whites or individuals of other ethnic groups and data from renal registries often reveal hypertension as cause of ESRD in blacks. Reasons given for this include misdiagnosis, socioeconomic status, poor access to health care and genetic differences, however, the worldwide increasing prevalence of obesity and the metabolic syndrome may contribute significantly to the high prevalence of CKD and ESRD seen in black Africans.

Keywords: *Hypertension, metabolic syndrome, obesity, kidney disease, Africans*

INTRODUCTION

The prevalence of obesity is increasing worldwide and is reaching epidemic proportions. Increasing urbanisation, unhealthy dietary patterns and sedentary lifestyles have all added to the obesity epidemic. Obesity is the major driver and phenotypic hallmark of the metabolic syndrome and has increased at a dramatic rate over the last three decades in industrialised countries. In the United States, the National Health and Nutrition Examination Surveys (NHANES) show that the prevalence of obesity rose gradually from 14.5% to 22.5%[1]. Also in Canada, the prevalence of obesity between 1985 and 1998, more than doubled from 5.6% to 14.8%[2]. This increase was not only confined to the adult population but also children and adolescents[3]. Data from the adult health section of the 1998 South African demographic and health survey (SADHS)[4] showed that the malnutrition pattern seen in adult South African population, is one of predominantly over-nutrition rather than under-nutrition with a concomitant high prevalence of obesity among the blacks of South Africa. The survey revealed that the prevalence of overweight and obesity in South African men and women was 29.2 % and 56.6 % respectively[4].

The metabolic syndrome is common but often under-diagnosed and has had different definitions since its first description[5-8]. However, the guideline of the 2001 National Cholesterol Education Program—Adult Treatment Panel III (NCEP – ATP III) (Table 1) is widely used to identify it. Generally, it is characterized by a clustering of abdominal obesity, insulin resistance / hyperinsulinemia, increased triglycerides, decreased high-density lipoprotein cholesterol, hypertension, chronic inflammation, and prothrombotic status[5, 9-10] all of which confer higher risks of incident diabetes, cardiovascular events, cardiovascular mortality and overall mortality. There are few national surveys reporting the

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prevalence of the metabolic syndrome. However, available data suggest a wide variation from one population to another[11-15]. For instance, data from the United States and Finland reported a prevalence of 27% and 14.2% respectively [13,12] while two studies from Nigeria reported a prevalence of 25.2% and 59.1% in type 2 diabetics[16,17]. Reported prevalence tends to be dependent on the sub-population studied within a given population (diabetics, specific gender, ethnicity/race, age groups). There are few studies that have reported on the prevalence of the metabolic syndrome in African countries.

A common false impression is that non-communicable diseases (NCDs) are of lesser importance than communicable diseases in most African countries. The Global Burden of Disease (GBD) study report of 1990 suggested that NCDs accounted for only 14% of the total burden of diseases in sub-Saharan Africa but that the probability of death from NCDs is higher in sub-Saharan Africa than in developed nations[18]. Studies from Tanzania have shown that the probabilities of death from a non-communicable cause are higher than that from a communicable cause[19]. As chronic kidney disease (CKD) contributes to approximately 850,000 deaths every year[20], the consequences of the increasing epidemiology of CKD continues to devastate, patients and the society. Chronic Kidney Disease is characterized by progression to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). African Americans have been shown to have a higher prevalence of incident ESRD (988 / million population) compared to Caucasians (254 / million population) and an excess risk of CKD from hypertension, diabetes mellitus and obesity[21]. Hypertensive nephrosclerosis is considered one of the most common causes of ESRD[22] and in the US, was reported as cause of ESRD in 30% of all new cases in 2002 and was found to be five times as frequent in blacks compared with Caucasians[23]. In South Africa, hypertension accounted for 45.6% of all ESRD, second only to glomerulonephritis (52.1%) from the 1994 South Africa Dialysis and Transplant Registry (SADTR) data [24]. In Nigeria, hypertension accounted for 61% of cases of CRF followed by diabetes mellitus (11%) and chronic glomerulonephritis (5.9%) [25]. The frequent "labelling" of black Africans with the diagnosis of hypertensive nephrosclerosis as cause of ESRD without histological proof by many nephrologists and in many dialysis registries has led some authors to investigate if other factors could explain the difference in hypertension - related ESRD between black Africans and Caucasians. Seedat, in a review, pointed out that improvement in treatment of hypertension over a ten-year period had led to a decline of major complications of hypertension such as stroke and myocardial infarction by about 25% but that the incidence of hypertension - related ESRD continued to increase over that same period [26]. He suggested factors such as misdiagnosis, socioeconomic status, severity of hypertension, inadequate blood pressure control and genetic differences in the black race as possible explanation for the higher diagnosis of hypertension related ESRD.

In the light of the increasing world wide prevalence of obesity and the metabolic syndrome, we sought to summarize findings from relevant clinical and experimental studies of the association between the metabolic syndrome, obesity and CKD and explore the role that each diagnostic criterion of the metabolic syndrome plays in the development and progression of CKD especially as it relates to black Africans. However the review is hampered by a paucity of data from Africa.

Kidney Disease and Metabolic Syndrome

Microalbuminuria marks the initiation of kidney disease and is believed to reflect endothelial dysfunction within the glomerulus. Several clinical studies have linked microalbuminuria / CKD with the metabolic syndrome[27,28] and a number of mechanisms have been proposed to explain this association.

(A) *Insulin Resistance*

Evidence for the central role of insulin resistance in the development of the metabolic syndrome is supported by the Bruneck Study in which the degree of insulin resistance correlated with the number and clustering of metabolic abnormalities[29]. Proposed mechanisms linking insulin resistance to the metabolic syndrome centre on three major areas:

(1) Tissue and cellular effects of mild to moderate hyperglycaemia,

(2) tissue and cellular effects of compensatory hyperinsulinemia, and

(3) the unbalanced pathways of insulin action.

Molecular studies have shown that the 2 major pathways for insulin signalling are: the Phosphatidyl Inositol-3 (PI-3) Kinase pathway which leads to the

metabolic effects of insulin and the Mitogen-activated Protein Kinase (MAPK) pathway which leads to the inflammatory effects of excess insulin[30]. In metabolic syndrome and type 2 diabetes mellitus, the pathways leading to activation of PI-3K are blocked while the MAPK pathway remains open and may even be hypersensitive[30]. This pathway can be activated by angiotensin II and leptin among others. (Figure 1) In obesity and insulin resistance there is an excess of circulating angiotensin II, leptin and insulin which means the MAPK pathway will be in an overdrive state leading to excess inflammation, endothelial damage and microalbuminuria or proteinuria as a consequence. Although other mechanisms could be involved in the initiation of microalbuminuria in metabolic syndrome patients, the MAPK pathway could be very important as insulin resistance may have been present well before the recognised phenotypic manifestations of the metabolic syndrome.

Fig. 1: The MAPK signalling pathway. Insulin, Leptin and Angiotensin II through their receptors can activate the MAPK pathway leading to the proinflammatory effects of these molecules which include endothelial dysfunction and microalbuminuria. IR – Insulin receptor, IRS 1-4 – Insulin receptor substrate protein, LEPR – Leptin receptor, AT I – Angiotensin receptor. The upstream mediators of MAPK pathway are Shc and SHP2

IRS 1-4 – Insulin receptor substrate protein, LEPR – Leptin receptor, AT I – Angiotensin receptor. The upstream mediators of MAPK pathway are Shc and SHP2.

There are studies that have reported the association between insulin resistance and kidney dysfunction both experimentally and clinically. Animal studies have shown that alterations in glomerular structure are seen very early in the metabolic syndrome and are mediated by hyperinsulinaemia and obesity. One such study in primates found that glomerular changes (hypertrophy) begin in the pre-diabetic hyperinsulinaemic phase before overt diabetes occurred with typical glomerular features[31]. The effects of glucose and insulin on the contractile response of glomerular mesangial cells to angiotensin II has also been with reports that mesangial cells grown in the presence of additional insulin will undergo contraction when treated with angiotensin II [32]. This provides a possible link between insulin and angiotensin II–mediated renal injury.

(B) *Dyslipidaemia*

Excess circulating lipids (in the form of free fatty acids - FFA) are toxic and the lipotoxic effects of the elevated FFA occur via oxidative stress, proinflammatory signalling or through the actions of ceramide. Studies using magnetic resonance spectroscopy in humans have shown that increased FFA levels directly inhibit glucose transport by causing mitochondrial dysfunction[33]. Secondly, increased reactive oxygen species in response to fatty acids activates Nuclear Factor –kappa B (NF-κB), which further stimulates the production of other proinflammatory cytokines, including TNF-α and IL-6 [34,35]. Ceramide is a product derived from long-chain saturated fatty acids and inhibits insulin-stimulated activation of protein kinase B (Akt) and the translocation of Glucose Transporter-4 (GLUT4) [36]. Ceramide and other reactive compounds such as diacylglycerol, and fatty acyl-CoA are cytotoxic and capable of inducing cell apoptosis and organ damage[37]. In the kidney, filtered fatty acids can aggravate the chronic tubular damage and inflammatory phenotype that develop during proteinuric states. Lipid loading of both glomerular and tubular cells is a common response to renal injury that contributes to the progression of nephropathy. Hunsicker *et al* [38] have reported six factors, including low serum HDL cholesterol, that independently predict a faster decline in GFR while reports from the Atherosclerosis Risk in Communities (ARIC) study[39] found high triglycerides and low HDL cholesterol, but not low-density lipoprotein cholesterol, to predict an increased risk of renal dysfunction.

(C) *Dysglycaemia*

Renal cells are stimulated by hyperglycaemia to produce humoral mediators, cytokines, and growth factors that are responsible for structural alterations such as increased deposition of extracellular matrix (ECM) and functional alterations such as increased permeability of glomerular basement membrane or shear stress[40]. Hyperglycaemia is an important risk factor for the development of diabetic nephropathy. It induces an abnormal activation of protein kinase C (PKC), which is involved in the development of diabetic nephropathy. Up regulation of PKC has been observed in the kidneys of rats with diabetic nephropathy [41] and associated with transforming growth factor-β1 (TGF-β1), fibronectin, and collagen type IV upregulation. Hyperglycaemia is also responsible for the presence of high levels of advanced glycosylation end products in patients with diabetes[42]. These glucose metabolites stimulate intrinsic glomerular cells to produce TGF-β1, which contributes to glomerular sclerosis and tubulointerstitial damage by means of an abnormal ECM production.

(D) *Hypertension*

Approximately 70% to 80% of individuals with CKD have hypertension, and its prevalence increases as glomerular filtration rate declines [43]. Typically, significant hypertension initially affects the renal vasculature, resulting in hyaline thickening of small arteries and arterioles. Eventually, the vascular lesions can progress to vessel wall necrosis which may then extend to the glomerulus as well [44].

In the metabolic syndrome, hypertension is often related to obesity. Obesity associated hypertension is accompanied by impaired pressure natriuresis as seen in other forms of hypertension [45]. This impaired pressure natriuresis leads to salt and water retention hence to increased blood pressure. The three mechanisms that have been clearly shown to mediate the increased reabsorption of sodium in the kidneys in obesity-related hypertension are:

(i) *Increased Renal Sympathetic Activity*

Excess weight gain is associated with increased sympathetic activity, especially in the kidney [46]. In experimental dogs for instance, it has been shown that increased sympathetic activity appears to raise blood pressure mainly through the renal sympathetic nerves [46]. Hyperleptinaemia has been proposed as one of the most promising mechanisms through which obesity may increase sympathetic activity. Both acute and chronic infusions of leptin have been demonstrated to cause sympathetic activation and to chronically sustain elevated blood pressure [47, 48]. However, the mechanisms of leptin-induced sympathetic activation are still unclear, although recent studies suggest important interactions with other neurochemicals in the hypothalamus.

(ii) *Activation of the Renin-Angiotensin System (RAS)*

Obese subjects have increased plasma renin activity, plasma angiotensinogen, angiotensin-converting enzyme (ACE) activity, and plasma angiotensin-2 (ANG II) levels despite marked sodium retention and an expanded extracellular fluid volume. A significant role for ANG II in stimulating sodium reabsorption, impairing renal-pressure natriuresis, and causing hypertension in obesity is supported by the finding that treatment of obese dogs with an ANG II antagonist or ACE inhibitor blunts sodium retention and volume expansion, as well as increased arterial pressure [49]. Also, ACE inhibitors are effective in reducing blood pressure in obese humans, particularly in young patients [50]. In addition to raising blood pressure, activation of the RAS may also contribute to glomerular injury and nephron loss associated with obesity because increased ANG II formation constricts the efferent arterioles and exacerbates the rise in glomerular hydrostatic pressure caused by systemic arterial hypertension [51].

(iii) *Altered Intra-renal Physical Forces*

The intra-abdominal pressure of obese subjects is increased, reaching levels as high as 35 to 40 mmHg in some subjects with central obesity [52]. Also, the kidney is almost completely covered by adipose tissue that also penetrates into the medullary sinuses causing compression and increased intrarenal pressures[53]. It has therefore been suggested that the increased intrarenal and intra-abdominal pressures may impair pressure natriuresis in the kidneys and contribute to obesity-associated hypertension[53].

An analysis of the influence of metabolic syndrome on target organ damage (cardiac, renal and retinal) in a group of non-diabetic patients with essential hypertension has shown that the presence of the metabolic syndrome may amplify hypertension-related cardiac and renal changes, over and above the potential contribution of each single component of this syndrome[54]. Cuspidi *et al* in a cohort of hypertensive subjects reported about equal values of ambulatory blood pressures in those with and without the metabolic syndrome but found increased cardiac and extra-cardiac involvement including microalbuminuria in those with the metabolic syndrome[55].

Obesity and Kidney Disease

The World Health Organization (WHO) estimates that over 1 billion people are overweight globally, and with the current trend, the number will increase to 1.5 billion by 2015 [56]. Although a number of conditions have been associated with an increased risk for the metabolic syndrome; increased body weight plays the most important role. It was found that of all the participants in the NHANES III, the prevalence of the metabolic syndrome was 5% in subjects with normal weight, 22% in those overweight, and 60% among the obese [2].

Obesity-associated renal dysfunction (proteinuria, nephrotic syndrome, and CKD) is frequently seen in clinical practice and has been well described [57, 58]. Kambham *et al*. reported a progressive 10-fold increase in biopsy frequency of ORG from 0.2% in 1986 to 1990 to 2.0% in 1996 to 2000 in a review of over 6800 renal biopsies. Indications for biopsy were proteinuria alone or occurring with renal insufficiency and ORG was defined morphologically as FSGS and glomerulomegaly or glomerulomegaly occurring alone. They also found that patients with ORG had fewer lesions of segmental sclerosis, more glomerulomegaly, less extensive foot process effacement and less frequent doubling of serum creatinine and progression to ESRD [58].

A comparison of biopsy proven FSGS from 15 obese patients and idiopathic FSGS in 15 non-obese patients revealed heavy proteinuria but no oedema, hypoalbuminaemia or hyperlipidaemia in the obese subjects and glomerulomegaly was observed in all renal biopsies from the obese patients (mean glomerular diameter 256 ± 24 µm in obesity-FSGS vs 199 ± 26 µm in idiopathic-FSGS, $P<0.001$) [78]. With

Fig. 2: TGF-β pathways between glomerular endothelial and mesangial cells mediated by leptin. Whas lereeptin increases TGF-β1 synthesis in endothelial cells, it upregulates TGF-β type II receptor expression in mesangial cells without influencing TGF-β1 synthesis. Leptin also stimulates the synthesis of type I collagen

a mean follow-up of 82months, 50% of obese FSGS patients had developed advanced renal insufficiency or end-stage renal disease. The risk of developing progressive renal failure among obesity-FSGS patients was statistically correlated with serum creatinine and creatinine clearance at presentation [59].

Although the exact mechanisms that link obesity and renal damage have not yet been fully clarified, it can be speculated that at least some of the many inflammatory cytokines that are secreted by adipose tissue may be involved in promoting renal impairment[51]. Leptin is one of the many cytokines produced by fat cells and serum leptin levels and overall fat mass are positively correlated [62]. Massively obese patients with hyperleptinaemia tend to develop focal glomerulosclerosis [63, 64]. In the glomerular endothelial cells, leptin increases TGF-β1 synthesis and upregulates TGF-β type II receptor expression without influencing TGF-β1 synthesis in mesangial cells. TGF-β produced by endothelial cells may reach neighbouring mesangial cells and induce an amplified response because of upregulated TGF-β type II receptors (Figure 2). Leptin also stimulates the synthesis of type I collagen in mesangial cells and type IV collagen in glomerular endothelial cells. Activation of the TGF-β system by leptin eventually contributes to extracellular matrix deposition, glomerulosclerosis, and proteinuria [65].

CONCLUSION

Hypertension remains one of the most important cardiovascular diseases in the world today and major complications of hypertension such as myocardial infarction, stroke, heart failure and especially ESRD have impacted hugely on patients and the society. With the current global epidemic of obesity, the prevalence of metabolic syndrome and its associated consequences, especially those related to renal and cardiovascular diseases will continue to increase and the real challenge will be to prevent the occurrence of these consequences rather than diagnose and treat established and irreversible damages.

As obesity and the metabolic syndrome are partly responsible for the several cases of so called "hypertension- related ESRD", measures addressing the prevention and treatment of these conditions should therefore be priority for physicians who treat black hypertensives. Finally, although the components of the metabolic syndrome have been reported to be associated with kidney disease, the specific cellular pathways that lead to these associations are still

unclear. Studies on obesity, insulin resistance and inflammation and how these are associated with CKD still have to be extensively researched.

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Characteristics of Haemodialysis Patients at the University of Port Harcourt Teaching Hospital During the First Year of Operation

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ABSTRACT

Recent upsurge in the global incidence and prevalence of kidney failure especially in the developing countries such as Nigeria, has led to the emergence of haemodialysis units in the country. In 2007 a new four- machine haemodialysis unit came into operation at the University of Port Harcourt teaching hospital. This communication is a preliminary analysis of the clinical and epidemiologic characteristics of patients treated at the center in the first year of operation. During the period under study a total of 76 patients received haemodialysis treatment in the unit. They were 43 males and 33 females,(M/F=1.3:1) with a mean age of 43.01 $\pm$ 19.14 (range 10 to 79) years. The patients were mostly of the low income groups constituting 70.2%.Ethnographic distribution, reflected the local catchments population of the hospital. The indications for haemodialysis were End stage kidney failure (72.4%), Acute renal failure (14.5%), and acute-on-chronic renal failure(13.1%). Clinical status of the patients at first presentation was generally poor. Forty-two patients (55.3%) presented in advanced uremia with severe haemodynamic instability. Fifteen (patients (19.7%) presented in uraemic encephalopathy while 19(25%) presented in stable azotaemic state. Patients presenting for haemodialysis in this unit derive mostly from the low socio-economic groups. End stage kidney failure was the commonest indication for haemodialysis treatment. Most patients presented for the first time in very unstable clinical state. The findings are consistent with previous studies in other centers in Nigeria.

Keywords: *Characteristics, haemodialysis patients, University of Port Harcourt teaching hospital*

INTRODUCTION

The recent upsurge in the global incidence and the prevalence of kidney disorders, especially chronic kidney disease has created awareness of the problem, globally and even in the developing countries of the world such as Nigeria. It is estimated that well over 500 million persons worldwide suffer from some kind of kidney disorder [1]. In Nigeria, about 3-8 percent of adult medical ward admissions are as result of kidney disease and kidney failure[2, 3]. As a result there has been an increasing demand for the care of kidney failure patients in recent times in Nigeria and other resource poor countries in the sub-Saharan African countries. In response, a number of public health institution based and private healthcare provider - run kidney support services (mainly haemodialysis units) started to emerge couple of years ago in Nigeria.

Lagos University Teaching hospital (LUTH) [4] pioneered the process in 1981 followed by the University college Hospital(UCH0 [5] Ibadan in 1995. To date there are over 20 or more such centers across the country serving a population of about 140 million Nigerians. Unfortunately the history of these centers has been characterized by relatively small size, stunted growth and high attrition rates due to multiple developmental challenges [5]. As a result, chronic

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dialysis patients in Nigeria, rarely survive beyond the first year of diagnosis [5, 6]. This is in contradistinction with their counterparts in the developed countries of Europe and North-America who survive for well over 10 to 20 years on dialysis with a good quality of life [7, 8].

In 2006, The University of Port Harcourt Teaching hospital established a new Haemodialysis unit through the Federal Government/Vamed engineering company tertiary health institution improvement programme. The unit is equipped with four "FRESENIUS 4008B" model Haemodialysis machines. The unit commenced operations in January 2007.

This communication is the findings of an analysis of the epidemiological and clinical characteristics of the patient treated in the unit during the first year of operation. This will be followed by a second communication detailing the haemodialysis performance of chronic dialysis patients treated in the unit during the first year (January to December, 2007) of operations.

Objectives of the Study

- To determine the epidemiologic and clinical characteristics of patients treated in the new haemodialysis unit of the University of Port Harcourt Teaching hospital.

MATERIALS AND METHODS

The data for analysis were obtained from the clinical case records and haemodialysis case records of all patients who received haemodialysis treatment in the new haemodialysis unit of the hospital, during the period 2nd January to 31st December 2007.

In the haemodialysis unit of the hospital, to ensure safety of dialysis records a separate haemodialysis record is kept with the support of the hospital medical records department. Thus each dialysis patient has hospital clinical case record, which is in the custody of the hospital medical records department, and a Haemodialysis case record, which is kept permanently in the haemodialysis unit.

The haemodialysis case record contains three sets of records namely:

1. the demographic **data** ,
2. **baseline clinical data -** which captures the source of referral to the dialysis unit, date of first diagnosis of renal failure, the primary underlying kidney disease, other co-morbid disorders, the baseline laboratory parameters at first entry into the unit etc. Others are the pre-dialysis clinical status of the patient, a record of the immediate pre- and immediate post dialysis laboratory parameters as well as the dialysis prescription for each dialysis session,
3. **the haemodialysis monitor chart** in which the details of the proceedings of each dialysis session is recorded every half- hour for the duration of the dialysis.

The data for analysis retrospectively obtained from the patients' hospital and haemodialysis case records include the following: demographic and epidemiologic data such as age,sex, occupation, marital status, state of origin,ethno-linguistic group etc: clinical data such as the cause of renal failure, type of renal failure, primary renal disorder underlying renal failure, co-morbid clinical conditions,etc. Others include the baseline clinical and laboratory parameters at entry(pre-dialysis), such as, the over all clinical state of the patient, blood pressure,estimated creatinine clearance, haematocrit level, serum electrolytes, urea and creatinine levels, etc.

The primary kidney disorders were taken as entered in the patient case note by the consultant nephrologist in charge of the patient. There were three consultant nephrologists in the renal unit during the period under study.

Acute renal failure (ARF) was diagnosed based on relevant history of predisposing/precipitating factors (e.g. acute fluid/blood loss, ingestion of herbal mixtures etc), oligo-anuria (24-hour urine volume, <400mls), oedema, marked azotemia, metabolic acidosis, hyperkalemia, etc.

Diagnosis of acute glomerulonephritis(AGN) was based on history of an antecedent sore throat/ skin infections, facial puffiness, passage of scanty coke-coloured or smoky urine,hypertension,red-cell casts, white cell casts in the urine,azotemia,etc.Renal biopsies were not done.

Chronic glomerulonephrits(CGN) was diagnosed based history of progressive oedema,fatigue ,anorexia, vomiting etc,anaemia,hypertension,urinary red-cell casts,azotemia and renal ultrasound scan showing bilaterally shrunken kidneys with poor cortico-medullary differentiatiation.

Of the 22 patients with CGN record of renal biopsy was obtainable only in five(22.7%) patients.Histologic examination was by light microscopy with no immunologic staining due to the lack of requisite facilities in the histopathology department of the hospital. The histologic diagnosis in the five cases

were focal glomerular sclerosis (FGS) in two patients,messangiocapillary nephropathy in two patients and membranous nephropathy disease in one patient respectively.

Diagnosis of hypertensive nephrosclerosis was based on history of long-standing hypertension, clinical markers of longstanding hypertension such as peripheral arterial wall thickening,locomotor-brachialis,displaced heaving cardiac apex etc,azotemia and kidney ultrasound scan showing bilaterally shrunken kidneys with poor cortico-medullary differentiation. None of the patients had renal biopsy done.

Diagnosis of diabetic nephropathy(DN) was based on the history of longstanding diabetes (for at least five years), significant micro-albuminuria,gross proteinuria,anaemia,azotemia hypertension, and a kidney ultrasound scan showing, a normal or enlarged kidneys with poor cortio-medullary differentiation.
Diagnosis of Obstructive uropathy was based on the presence of clinical and laboratory features of chronic renal failure in the setting of clinical, ultrasound and retrograde urographic evidence of obstruction of the urinary tract (commonest being prostatic lesions in elderly males).

Diagnosis of end-stage kidney failure was based on the presence of chronic kidney disease with an e-GFR of less than 5-15 mls per minute.

Presently all patients presenting for haemodialysis were screened for human immuno-deficiency virus(HIV), hepatitis B and C virus status. Patients testing positive for any of the three viruses were referred to centers treating such patients. Management to procure heamodialysis machines to be dedicated for the treatment of such cases.

Data Management

The data were analyzed with the aid of Epi-info computer based statistical package for biomedical research.

Averages are presented as mean $\pm$ standard deviation.Pearsons correlation coefficient(r) was used to establish relationship between quantitative variables, while Student t-test was used to measure statistical significance between variables with p-values set at 0.05.Tables are used as appropriate.

Study Limitations

The retrospective nature of the study does not ensure absolute completeness of the data. The non inclusion of patients positive for HIV, and Hepatitis B and C viruses also limited the scope of the data. The paucity of renal biopsies and the lack of electron microscopy and immunofluorecsent studies limit the accuracy of the clinical and histologic diagnosis.

RESULTS

During the period under study (January to December, 2007) a total of 76 patients were dialyzed in the haemodialysis unit of the hospital. They comprised 43 males and 33 females (M/F=1.3:1) with a mean age of 43.0 $\pm$ 19.4 years and age range from 10 to 79 years. The peak age at presentation was in the 40-49 and 50 -59 year age groups (table -1) which together were responsible for 35.5 % of the patients. There were no significant differences between the males and the females in all compared variables (P>0.05).

Students and the un-employed (31.6%), small scale business men/women (21.0 %), and junior public servants (17.6%) constituted the bulk of the patients being together responsible for 70.2% of the patients (table 2).

Table 1: Age and sex distribution

Age Group (Years)	Males	Females	Total	Percentage
10-19	3	7	10	13.2
20-29	5	6	11	14.5
30-39	5	6	11	14.5
40-49	7	8	15	19.7
50-59	10	2	12	15.8
60-69	8	2	10	13.2
70-79	5	2	7	9.2
Total	**43**	**33**	**76**	**100.0**

MEAN AGE. =43.0 $\pm$ 19.14 YEARS
AGE RANGE = 10 -79 YEARS

Table 2: Occupational group

Occupational Group	Number	Percentage
Students/Unemployed	24	31.6
Businessmen/Women	16	21.6
Senior Public Servants	7	9.2
Junior Public Servants	15	19.7
Clergy	3	3.9
Artisans	3	3.9
Full Time Housewives	8	10.5
Totals	**76**	**100.0**

Distribution of the patients in accordance with states of origin (table 3) showed that Rivers state (53.3%), Imo state (15.8%), and Abia state (10.5%)

Table 3: State of origin

State of origin	Number	Percentage
Rivers State	42	55.3
Imo	12	15.8
Abia	8	10.5
Akwa- Ibom	4	5.3
Cross-River	2	2.6
Bayelsa	1	1
Delta	3	3.9
Edo	2	2.6
Ondo	2	2.6
Total	**76**	**100.0**

collectively contributed to 81.6% of the patients. Ethno-linguistically, (table 4) the Igbo speaking group (26.3%), Ikwerres (23.7%). and the Kalabaris (10.5%) were the dominant groups collectively responsible for 60.5% of the patients.

Table 4: Ethno-linguistic groups

Ethno-Linguistic Group	Number	Percentage
Igbo	20	26.3
Ikwerre	18	23.7
Kalabari	8	10.5
Ogoni	5	6.7
Andoni	3	3.9
Ndoni	3	3.9
Engeni	2	2.6
Okirika	1	1.3
Efik/Ibibio	6	7.9
Izon	1	1.3
Bini	2	2.6
Yoruba	2	2.6
Urhobo	2	2.6
Itsekiri	1	1.3
Total	**76**	**100.0**

The commonest indication for haemodialysis in the patients were End-stage kidney disease (72.4%), and Acute renal failure (14.5%), the two indications being responsible for 86.9 % of all the the patients (table 3).

The commonest conditions causing acute renal failure were acute glomerulonephritis (18.2%), post-operative sepsis (18.2%), pre-renal renal failure(27.2%) and obstetric haemorrhages (18.2%) respectively.

Chronic glomerulonephritis (33.8%), hypertensive nephropathy (23.1%) diabetic nephropathy (21.1%) and obstructive uropathy(9.2%) were the commonest disorders responsible for chronic kidney failure in the patients.(tables 4 and 5)

Most of the patients, 42(55.5%) presented for the first time in poor and unstable clinical state, characterized by gross oedema,moderate to severe hypertension(mean blood pressure 166.4/99mmHg), moderate to severe anemia(mean haematocrit 21%), pulmonary oedema and ascites. Nineteen patients (25%) presented in a state of uraemic encephalopathy, while 15 (19.7%) patients were in a relatively stable clinical state.

The pre-dialysis baseline laboratory parameters are detailed in table 6. For this purpose, the patients are segregated into acute renal failure (ARF) and chronic renal failure (CRF) sub-groups. The mean age of the patient with CRF (46.2 $\pm$ 17.7) years was significantly higher than the mean age (29.5 $\pm$13.9) years. ($p < 0.001$) In all other parametric variables there were no significant differences between the ARF and the CRF subgroups (table 6).

DISCUSSION

The epidemiologic and the clinical characteristic of the patients in this study are quite similar to the finding in other centers in Nigeria, both past and recent studies. The mean age of the patients, primary conditions underlying both acute and chronic kidney disease as well as the late stage of illness at presentation are similar with the observations by Akinsola *et-al* in Ife [2] (1989), Ojogwu *et-al* [9] (1983) in Benin, Arije *et-al* [6] (2001) in Ibadan, Menakaya *et-al* [10] (2005) in Lagos and recently by Bosan and Ibrahim in Zaria [11](2007) .

Acute glomerulonephritis,pre-renal oliguria resulting from significant body fluid losses, Obstetric complications, post-operative sepsis, nephrotoxic herbal drug exposures etc constitute the common causes of acute renal failure while, chronic

Table 5: Primary and underlying kidney disorders

Primary/Underlying Kidney Condition	Number	Percentage
Acute Renal Failure		
Acute Glomerulonephritis	2(18.2%)	2.6
Post Operative Sepsis	2(18.2%)	2.6
Obstetric Complications	2(18.2%)	2.6
Ingestion of Nephrotoxic Herbal Potions	2(18.2%)	2.6
Pre-Renal Renal Failure	3(27.2%)	3.9
Sub-total	**11**	**14.5**
Chronic Kidney Disease		
Chronic Glomerulonephritis	15(23.1%)	28.9
Hypertensive Nephrosclerosis	16(24.6%)	19.7
Diabetc Nephropathy	6(9.2%)	21.1
Obtructive Nephropathy	1(1.5%)	7.9
Iatrogenic Nephrectomy	1(1.5%)	1.3
Multiple Myeloma	4 (6.2%)	1.3
Indeterminate	22(33.8%)	5.3
Sub-total	**6 5 (100.0)**	**85.5**
Grand Total	**76**	**100.0**

Table 6: Baseline pre-dialysis laboratory parameters at presentation

	Acute Renal Failure (n=11)		Chronic Renal Failure(n=65)		
BaselinePre-dialysi					
Parameters	MEAN ± SD	RANGE	MEAN +SD	RANGE	p- value
AGE(YEARS)	29.5± 13.9	14-47	46.2 ±17.7	12-78	P<0.001*
E-CREAT.CLEARANCE(MLS/MIN)	9.5 ± 6.3	3-18.6	8.2 ± 5.8	3.7-34.2	P>0.10
SYTOLIC BP.(MMHG)	155.6± 27.2	130-190	171.2 ±31.9	107-240	P>0.05
DIASTOLIC BP.(MMHG)	96.7 ± 19.2	70-120	102.3 ±27.9	70-140	P>0.5
SODIUM(MMOL/L)	133.8 ± 7.2	125-140	134.8 ±6.0	122-140	P>0.5
POTASSIUM(MMOL/L)	4.5 ± 0.8	4.1-6.0	4.7 ± 1.0	3.5-6.5	P>.5
BICARBONATE(MMOL/L)	14.4 ± 1.9	12-17	19.4 ±4.8	8-27	P<0.001*
UREA(MMOL/L)	30.5 ± 13.7	14.5-52	32.9 ±36.2	4.2-62	P>0.10
CREATININE(UMOL/L)	1275.7 ± 818.1	720-2730	1224.9±557.4	245-2505	P>0.5
TOTAL PROTIEN(MG/DL)	NIL	NIL	60.7 +4.0	57-65	—
ALBUMIN (MG/DL)	NIL	NIL	32 + 9.8	10-35	—
HAEMATOCRIT(%)	21.3 ± 5.4	13.9 -22.0	20.9 +6.8	10-35	P>0.05

glomerulonephritis, hypertensive nephrosclerosis, diabetic nephropathy and the obstructive uropathy constitute the commonest causes of chronic kidney disease in Nigerian adults.

In this study patients with acute renal failure were almost two decades younger than those with chronic renal failure 29.5 versus 46.2 years ($p<0.001$). The reason for this is explained by the fact that the common causes of chronic kidney disease enumerated above have their highest prevalence in people of the middle and older age groups, whereas the common causes of acute renal failure occur more commonly in adolescents and adults.

The predominance of patients from Rivers state is a mere geographic expression of the fact that the haemodialysis center is located in River state. The dominance of the Igbo ethno-linguistic group reflects the high density of people of Igbo extraction living in Rivers state. Also Igbo's from neighbouring Imo, Abia and even Anambra states come all the way to Port Harcourt for haemodialysis treatment due to the absence of such facilities in those states.

The paucity of patients from Bayelsa state (only one patient) is surprising. Bayelsa state was carved out of the old Rivers state and shares socio- cultural similarities with Rivers state. Also, Yenagoa the state capital of Bayelsa is less than two hours from Port Harcourt. The paucity of standard medical facilities in the area may account for the poor referral rate as the Federal medical center, Yenagoa is the highest and main medical facility in the area. Cases of renal failure requiring dialysis may pass unrecognized by the medical practitioners in Bayelsa.

The findings from this study show that the bulk of the patients requiring haemodialysis treatment in our center were mainly people belonging to the economically disadvantaged groups, being mainly students, fulltime house wives, junior and intermediate public servants, etc.

This pattern however, reflects the general pattern of patients attending public health facilities in Nigeria and most other developing countries. The affluent (including top Government functionaries,) in Nigeria and in most other sub-Saharan African countries usually avoid the public health facilities but prefer private or overseas medical treatment. As a result the medical facilities in public health facilities remain ill-equipped and stunted.

The high prevalence of patients from the lower economic groups have far reaching implications for the ability to pay for haemodialysis services, which is quite expensive and not subsized by government.

Previous haemodialysis service experience [6, 12] in Nigeria has identified the singular role of poverty as dominant factor in the poor dialysis outcomes of patients who commence maintenance dialysis programs in the country.

The late presentation of majority of the patients in a very un-stable clinical state as well as in state of uraemic encephalopathy also influences the short term patient outcome. Only about 6% of the patients presented in a relatively stable clinical state, the remaining 94% presented in advanced uremia with marked fluid retention, severe hypertension, haemodynamic instability, severe anemia and uremic encephalopathy(Tables 6 and 7).Mortality rates in such patients in the early stage of commencement of dialysis is usually high. Late commencement of dialysis has been demonstrated to have deleterious effect on dialysis outcomes [13, 14].

CONCLUSION

This study of the epidemiologic and clinical characteristics of patient presenting for haemodialysis at the University of Port Harcourt teaching hospital show that the clinical and epidemiologic characteristics of our patients are similar to observations in other centers in other parts of Nigeria.

The bulk of the patients presenting for haemodialysis derive from the lower socioeconomic brackets of the society. This has far reaching implications on the ability to sustain long term dialysis. Late presentation in unstable clinical state is predominant which also has implications for overall patient outcome.

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Pharmacotherapy of Hypertension

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ABSTRACT

Hypertension is responsible for considerable morbidity and mortality all over the world affecting black population more than the Caucasian population. Hypertension is the leading non-communicable disease in Nigeria with a prevalence rate of 11% amongst adults aged 15 years and above. Most cases of hypertension are classified as idiopathic or primary hypertension for lack known aetiology and generally respond to pharmacotherapy. This article reviews the available drugs used in the control of hypertension emphasis been on pharmacologic classification, mechanism of action as well as adverse drug reactions associated with their use. Physicians are reminded of the central role of thiazides in lowering blood pressure and encouraged to watch out for adverse drug reactions as a possible cause of treatment failure.

INTRODUCTION

Hypertension is defined as sustained elevation of blood pressure 140/90 mmHg, a level that has been associated with significant cardiovascular risk [1]. Transient elevation of blood pressure may occur as a result of increased activity, emotion or illness. Blood pressure also varies at different times of the day. Hypertension may be described as primary or benign (essential) when there is no obvious disorder causing it. This type of hypertension is different from secondary hypertension where there is a primary disorder known to be responsible for the sustained elevation of blood pressure. Blood pressure is the product of cardiac output (CO) and the peripheral resistance (PR) and the basis of control of hypertension using various anti-hypertensive drugs revolves around this equation. Thus, drugs with capacity to reduce one or both variables of cardiac output and peripheral resistance could serve as a remedy for hypertension [2].

Hypertension is commoner amongst black population than Caucasian population [3]. Hypertension is responsible for considerable morbidity and mortality being one of the leading causes of deaths all over the world. In Nigeria, Hypertension is the leading non-communicable disease and is found in more than 11% of 15 years or older adults [4].

Treatment of hypertension involves pharmacotherapy as well as non-pharmacologic means including lifestyle modification. This article is intended to discuss anti-hypertensive drugs with particular reference to class mechanism of action, adverse effects and clinically important drug interactions.

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Pharmacology of Anti-hypertensive Drugs

Classes of antihypertensive:

Drugs for the treatment of hypertension have been conventionally grouped on the basis of mechanism and/or site of action and further differentiated using their chemical classes. Below are the main classes of drugs used in the treatment of hypertension.

- Thiazide and thiazide-like diuretics
- Centrally acting sympatholytic drugs
- Ganglion blockers
- Adrenergic neurone blocker
- Adrenergic receptor blockers
    - Beta adrenergic receptor blockers
    - Apha adrenergic receptor blockers
    - Mixed α and β adrenergic receptor blockers
- Calcium channel blockers
- Vasodilators
- Angiotensin Converting Enzyme inhibitors (ACEI)
- Angiotensin II Receptor Blockers (ARB)
- Renin inhibitors

Thiazide and Thiazide-like Diuretics

Thiazide and thiazide-like diuretics are the most commonly used antihypertensive all over the world [5, 6]. Diuretics alter Na^+ balance and have generally been used as mono-therapy for treatment of hypertension and have also served in enhancing antihypertensive effects of most other drugs particularly vasodilators. Thiazides interact with Na^+ - Cl^- symporter in the kidneys leading to increased salt and water excretion and therefore reduced cardiac output. However, the initial contraction of extracellular volume returns to normal even with the continued use of thiazides and it has therefore been hypothesized that thiazides maintain reduction of blood pressure by reducing tone of vascular smooth muscle thus leading to reduction of peripheral resistance [7]. The group includes: chlorothiazide, hydrochlorothiazide, chlorthiazide, bendroflumethiazide, hydroflumethiazide, chlothalidone, indapamide, metolazone.

Thiazides exhibit variable rate and extent of absorption though generally good. Oral bioavailability may be almost 100% as in the case of bendroflumethiazide to hydroflumethiazide and chlorthalidone with 50-65% to as low as less than 20% in the case of chlorothiazide [8]. Elimination half lives are also variable and may be as short as 1.5 hours for chlorothiazide and as long as about 2 days for chlorthalidone. Renal excretion occurs mostly but biliary excretion of about 10% has been documented in chlorthalidone and metolazone.

Clinically significant adverse effects of thiazide include erectile dysfunction and acute gout, Hypokalaemia, hyponatremia, hypochloraemia, hypomagnessemia, metabolic alkalosis and hypercalcaemia are common even when minimum effective doses of thiazides are used. When thiazides are used in combination with angiotensin converting enzyme inhibitors (ACEI) hypokalaemia may be mitigated but in most cases a potassium sparing diuretics or potassium supplement is co-administered with thiazides to prevent hypokalemia and its consequences. Hypercalcaemia results from inhibition of renal excretion of calcium and this may be explored in the treatment of osteoporosis or hypercalciuria. Other adverse effects of thiazides include: hyperglycaemia, paraesthesia, vertigo, headache, anorexia, nausea, diarrhoea, vomiting, cholecystitis, pancreatitis, photosensitivity, skin rash, blood dyscrasia [2]. Hyperglycaemia mirrors hypokalaemia and it has been observed that hyperglycaemia is reduced when potassium supplement is given as the same time [9]. Total cholesterol and LDL cholesterol as well as triglycerides are increased with chronic use of thiazide diuretics. Thiazide diuretics are to be avoided in individuals who are hypersensitive to sulphonamides. Thiazides may diminish the effects of anticoagulants and uricosuric agents and increase adverse effects of digitalis, Lithium and vitamin D. Their antihypertensive effect may be blunted by non-steroidal anti-inflammatory drugs (NSAIDs).

In most instances thiazide and thiazide-like diuretics have often been combined with potassium sparing diuretics particularly Amiloride and Triamterene to protect against loss of potassium. Potassium sparing diuretics block re-absorption of sodium at the late distal convoluted tubules as well

as the collecting ducts thus preventing the normal exchange of potassium and Hydrogen ions for sodium thus reducing potassium loss. They have variable absorption in the gastrointestinal, tract triamterene is relatively well absorbed whereas amiloride is poorly absorbed.

Centrally Acting Sympatholytic Drugs

The centrally acting sympatholytic drugs are α-methyldopa, guanabenz, guanfacine and clonidine, they stimulate pre-synaptic α-2 receptor in vasomotor centre on the brain stem to decrease sympathetic out-flow with reduction in peripheral vascular resistance as well as cardiac output with consequent lowering of blood pressure. Methyldopa requires conversion to α-methyl-norepinephrine and is therefore a pro-drug [10].

Methyldopa is useful in the treatment of mild to moderate hypertension as it lowers blood pressure by reducing peripheral vascular resistance with variable reduction in cardiac output. On chronic use methyldopa tends to cause fluid and salt retention which may blunt its antihypertensive action and diuretics may be needed to remedy it. Renal blood flow is maintained and renal function is unaltered with prolonged treatment. Patients with renal insufficiency are more sensitive to antihypertensive effect of methyldopa but it is unknown if the reason is reduced excretion or increased CNS uptake. Maximal antihypertensive effect occurs between 6-8 hours after oral or intravenous administration and effect may last for 24 hours. It has especial application in the management of hypertension in pregnancy as a result of its established safety profile. Concentration of methyldopa in the blood has minimal relevance to its antihypertensive effect since it is a pro-drug that is metabolised to the active drug in the brain. Methyldopa is absorbed in the gastrointestinal tract by an active amino acid transporter and uptake into the brain is also by active transport. The elimination half life is about 2 hours both the sulphate conjugate and other metabolites are excreted via the kidneys. Adverse effects include drowsiness, depression, dry mouth, Parkinsonian-like features, reduced libido, hyper-prolactinemia, haemolytic anaemia, fever, hepatitis [2]. Discontinuation of the drug is usually sufficient in case of hepatitis and the drug is better avoided in patients with hepatic disease. Other rare adverse effects are leukopenia, thrombocytopenia, myocarditis, pancreatitis and diarrhoea [2].

Adrenergic Neurone Blockers

Examples include Reserpine and Guanadrel. Others are Guanethidine, Debrisoquine, Bretylium, Bethanidine. Reserpine prevents storage of catecholamines in the vesicles and therefore exposed to metabolizing enzymes leading to depletion of sympathetic neurotransmitter which is sometimes referred to as pharmacological sympathectomy. Reserpine induced depletion of biogenic amines correlates with sympathetic dysfunction and anti-hypertensive effect. Both peripheral resistance and cardiac output are reduced thus ensuring the lowering of blood pressure.

Similar to Methyldopa the concentration of Reserpine found in the systemic circulation is a poor reflection of its antihypertensive effect. Efficacy of Reserpine is enhanced by diuretics, a combination of which enjoys widespread use in developing countries. Depression is a major adverse effect of Reserpine and the drug must be discontinued at the first sign of this. Other adverse effects of adrenergic neuron blocking agents include sedation, postural hypotension, parkinsonian signs, nightmares, nasal stuffiness, fluid retention and delayed ejaculation.

Ganglion Blockers

Of all the Ganglion blockers only Trimethaphan remain relevant in the clinical management of hypertension as others have become extinct particularly in view of availability of newer drugs with better efficacy and safety profile. Trimethaphan is a quarternary ammonium compound which inhibits transmission of nerve impulses in both sympathetic and parasympathetic ganglia. It is known to produce visual disturbances. It is administered intravenously to treat hypertension and to induce controlled hypotension during surgery. Major adverse effects include marked hypotension and syncope, constipation, paralytic ileus, urinary retention and cycloplegia.

Beta–Adrenergic Receptor Antagonists

These agents competitively antagonize effects of catecholamine at beta receptors. These drugs are widely used alone or in combination for the treatment of hypertension. Atenolol and metoprolol, bisoprolol, esmolol are β-1 selective agents and theoretically spare the β-2 receptors on the respiratory tract unlike propranolol, nadolol, timolol, pindolol which lack such selectivity. They are both negatively chronotropic and ionotropic reducing both rate and force of contraction of the heart. Also β receptor antagonists prevent renin

release from the juxtaglomerular cells and reduce circulating angiotensin II, potent vasoconstrictor.

Propanolol is a non selective β-adrenergic receptor blocker effective in treatment of mild to moderate hypertension. It does not produce postural hypotension. When given orally it is well absorbed and achieves peak plasma concentration in 1-3 hours but bioavailability is low due to high first pass effects. Propranolol is well tolerated though its adverse effects include cardiac failure, gastrointestinal disturbances, bronchoconstriction, lassitude, sleep disturbances including nightmares and insomnia and erythematous rash. In addition to treatment of hypertension β-blockers are clinically used in angina pectoris, cardiac tachyarhythmias and in secondary prevention of myocardial infarction.

Alpha-Adrenergic Antagonists

Peripheral vasoconstriction is mediated by α-1 receptors in the vascular wall an effect that is antagonized by α adrenergic receptor antagonist. There are selective α-1 receptor antagonists like prazosin, terazosin, doxazosin, tamsulosin while the nonselective alpha antagonists include phentolamine, phenoxybenzamine and tolazoline.

Prazosin antagonizes α-1 receptors thus producing vasodilatation and reduction in vascular resistance. It is able to reduce blood pressure in both supine as well as standing positions. It is often administered with diuretics which mitigate its tendency to cause fluid retention.

Prazosin is extensively metabolized in the liver. Oral bioavailability is about 50% and half life is about 3 hours. The drug is highly plasma protein bound and the duration of action is about 8 – 10 hours. Adverse effects include postural hypotension, headache, dizziness, salt and water retention, nasal stuffiness.

Mixed α- and β- Antagonists

An example is Labetalol which antagonizes both α-1 and β- adrenergic receptors thus resulting reduced peripheral resistance as well as reducing cardiac output. It is of particular application in the treatment of hypertension of phaeochromocytoma. Labetalol is well absorbed orally though extensive first pass effect results in bio-availability of 20-40%. The drug undergoes oxidation and glucuronidation in the liver and it is mainly excreted in urine as the glucuronide conjugate. Elimination half life is about 8 hours. It is also available for intravenous use in hypertensive emergencies. Adverse effects include tiredness, difficulty in micturition, postural hypotension, epigastric pain. Hepatic injury has been reported in few cases [11].

Carvedilol, Bucindolol, Celiprolol and Nebivolol are third generation β adrenergic receptor blockers with significant α-1 receptor antagonistic activity like Labetalol. All of these drugs possess capability to reduce blood pressure [12-17]

Vasodilators

Clinically relevant vasodilators include sodium nitropruside, hydralazine, diazoxide and minoxidil. These drugs through different molecular mechanisms produce vascular smooth muscle relaxation and vasodilation and consequently reduce peripheral resistance and blood pressure. For example sodium nitroprusside releases nitric oxide (NO) which in turn activates Guanylyl cyclase to produce vasodilation whereas minoxidil through its metabolite minoxidil N-O sulphate activates K+ channel which leads to hyperpolarisation and smooth muscle relaxation. In chronic management of hypertension orally administered minoxidil are given in combination with diuretics, hydralazine is also used in combination with a diuretic to avoid fluid retention, a common factor with all vasodilators. Sodium nitropruside is the drug of first choice in the treatment aortic dissection. Diazoxide is an alternative. Common adverse effects of vasodilators other than fluid retention are: Increased heart rate and myocardial contractility as well as increased oxygen demand. Pericardial effusion and hypertrichosis are other adverse effects specific for those using minoxidil whereas sodium nitroprusside may cause cyanide poisoning and lactic acidosis if infused in excessive dose.

Calcium Channel Blockers

Calcium channel blockers reduce peripheral resistance by causing relaxation of vascular smooth and vasodilation [18]. Examples are: Diltiazem, Verapamil, Nimodipine, Isradipine, Nifedipine, Felodipine, Amlodipine, Bepridil, Nicardipine. Calcium channel blockers are broadly classified into: first generation which include: Diltiazem, Verapamil, Nifedipine, and second generation which include: Amlodipine, Felodipine, Nimodipine, Lacidipine. Chemical classification of Calcium Channel Blockers is as follows:

Dihydropyridines e.g. Nifedipine, Nicardipine, Amlodipine, Felodipine

Benzothiazepines e.g. Diltiazem

Phenylalkylamines e.g. Verapamil

Diarylaminopropylamine e.g. Bepridil

They are as effective in the treatment of mild to moderate hypertension but preferably in combination with diuretics [5].

All calcium antagonists are well absorbed in the gastrointestinal tract when given orally. They are extensively metabolized. Verapamil and diltiazem are available for both oral and parenteral administration. They have limited oral bioavailability due to first pass effect and are highly plasma protein bound. Amlodipine has a long elimination half life so it is given once a day whereas Nifedipine, verapamil, diltiazem have shorter elimination half life are given more frequently except in slow release formulation which permits once daily dosing.

Adverse effects include: peripheral oedema, palpitation, dizziness, transient hypotension and flushing. Others cough, wheezing, pulmonary edema, nausea, abdominal pain, constipation, rash, somnolence, worsened myocardial ischaemia has been reported in few studies.

Angiotensin Converting Enzyme Inhibitors (ACEI)

Renin converts circulating angiotensinogen to angiotensin I which in turn is converted to a potent vasoconstrictor agent angiotesin II by an enzyme known as angiotensin converting enzyme (ACE). The ACE inhibitors inhibit the conversion of agiotensin I to angiotensin II thus reducing peripheral resistance and blood pressure. Examples of ACE inhibitors are Enalapril, Quinapril, Ramipril, Benazepril, Lisinopril, Fentiapril, Pivalopril. There is increasing evidence that angiotensin converting enzyme inhibitors are better than calcium channel blocker in hypertensives who also have diabetes [19-21].

ACE-Inhibitors are classified into three chemical classes or as pro-drug depending on whether the drug is immediately active or requires activation after administration. The three chemical classes are: dicarboxyl-containing group, for example, Enalapril, Quinapril, Lisinopril; sulphhydryl-containing group, for example Captopril, Pivalopril and Fentiapril; the phosphate-containing group has fosinopril as an example. Enalapril, Trandolapril, Fosinopril, Qiunapril and Ramipril are examples of pro-drugs whereas Captopril, Lisinopril, Pivalopril are immediately active on administration. ACE inhibitors are generally cleared by the kidneys thus the need for dose adjustment in renal impairment. Only Fosinopril and Spirapril are exceptions as they enjoy significant elimination by the liver. Antacids reduce absorption of ACE inhibitors and non-steroidal anti-inflammatory drugs such as aspirin antagonize their antihypertensive effects.

Captopril is rapidly absorbed following oral administration and its oral bioavailability is about 70% when taken in empty stomach. This bioavailability reduces to about 30-40% if taken with food. Captopril is distributed to most tissues in the body with notable exception of central nervous system. The half life of captopril is about 3 hours.

Adverse effects include first dose hypotension which may be observed just like in the case of prazosin and small dose is usually advised while introducing the drug. Other adverse effects include hyperkalaemia, cough, angioedema, glycosuria, neutropenia, dysgeusia, macula-papular rash. Angioedema is a potentially serious adverse effect and has been ascribed to accumulation of bradykinin and blacks are at greater risk [22]. Hyperkalemia may be worsened when co-administered with potassium-sparing diuretics like Amiloride. Alteration in sense of taste, allergic skin rashes, drug fever was observed in 10% of patients with high dose of captopril. ACE-inhibitors are contraindicated pregnancy due to fetal malformation particularly pulmonary hypoplasia. Fetal growth retardation, neonatal anuria and neonatal death may also occur.

Angiotensin II Receptor Antagonist

Drugs that competitively antagonize angiotensin II at the receptor site block the vaso-constrictive effect of angiotensin II thus reducing peripheral resistance and blood pressure. Candesartan, Eprosartan, Losartan, Valsartan, Temilsartan, Irbesartan are examples currently in use in the management of chronic hypertension.

Losartan has comparable therapeutic uses with Captopril [23, 24]. Like most angiotensin receptor blockers losartan has low oral bioavailability. It achieves peak plasma concentration within 3 hours of oral administration and has half life of about 3 hours. Losartan is about 90% plasma protein bound. Phase I metabolism involves CYP 2C9 and CYP3A4 and subsequent glucuronide conjugation in the liver. Excretion involves the kidneys as well as the liver.

Losartan and other angiotensin receptor blockers are well tolerated been known to cause angioedema in much fewer cases than ACEI [8]. Losartan may also cause hypotension and fetopathy.

It can also cause hyperkalaemia when used with potassium sparing diuretics such amiloride.

Rennin Inhibitors

Rennin inhibitors act upstream in the biosynthesis of Angiotensin II by inhibiting conversion of angiotensinogen to angiotensin I [25]. Examples include: Remikiren, Enalkiren, Aliskiren.

Remikiren is rapidly and almost completely absorbed but oral bioavailability is poor due to hepatic first pass effect. Remikiren is metabolized in the liver and excreted in the urine as well as bile with a short half life of less than 2 hours. Antihypertensive effect is enhanced by co-administration with thiazide such as hydrochlorothiazide [26, 27]. Remikiren like other inihibitors of Renin-Angiotensin-Aldosterone pathway must be used cautiously with potassium sparing diuretics in order to avoid hyperkalaemia. Other reported untoward effects are include hypersensitivity, gastrointestinal disturbances, nausea and vomiting.

CONCLUSION

In conclusion it is appropriate to note that thiazides diuretics play central role in the management of hypertension and this cuts across ethnic and racial divide [28, 29]. Thiazides are used alone or in combination with other antihypertensive drugs and in all circumstances the minimum effective dose should be preferred. Antihypertensive drugs, both the newer renin inhibitors and the relatively well established ACE inhibitors and angiotensin receptor blockers remain very useful in the management of both uncomplicated and complicated forms of hypertension. The possibility of adverse drug interaction should always be considered especially whenever medication seems to be failing the patient.

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A Review of Hepatorenal Syndrome

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ABSTRACT

Renal dysfunctions are not uncommon occurrences in liver cirrhosis and hepatorenal syndrome (HRS) is a major one with a very high morbidity and mortality. The major pathophysiological mechanisms have been mostly unravelled, consisting of splanchnic vasodilation and renal cortical vasoconstriction. These vascular anomalies stem from endogenous release of vasodilatory biomolecules such as nitric oxide in the face of high hepatic sinusoidal pressure and portal hypertension. The vasodilatation leads to ineffective tissue perfusion and subsequently triggering the release of vasoconstrcting substances via the rennin-angiotensin-aldosterone system, thus leading to a vicious cycle. Therapeutic intervention is anchored on the reversal of the splanchnic vasodilation and renal ischaemia. Measures that have shown promise include the use of vasopressin analogues like terlipressin or ornipressin, and alpha adrenergic agonists like midodrine and norepinephrine. The use of these vasoactive substances have been combined effectively with plasma expanders especially albumin infusion, using extracorporeal albumin dialysis (ECAD). The most effective therapy however is liver transplantation, though the mortality of this procedure is higher than in non-HRS patients. Transjugular intahepatic potacaval shunt (TIPS) has also been found useful, with good patient selection. Prevention of HRS is principally by prevention of precipitating factors like spontaneous bacterial peritonitis, gastrointestinal haemorrhage and depletion of the intravascular volume.

Keywords: *Hepatorenal syndrome, cirrhosis, ascites, portal hypertension.*

INTRODUCTION

The liver and the kidneys are both essential to sustenance of life in humans and as such disease conditions in either or both tend to present with dire consequences if not treated early. Joint failure of both organs often occurs and may manifest in several settings. Three major ways of joint failure of both organs particular stand out. These are pseudohepatorenal syndrome, Stauffer's syndrome and the hepatorenal syndrome (HRS), with the first two being much rarer. Pseudohepatorenal syndrome describes a clinical condition of joint failure of both organs in which the hepatic failure has no aetiologic contribution to the renal failure [1], while Stauffer's syndrome, also known as the reversed hepatorenal syndrome, describes a liver failure which occurs in a setting of renal cell carcinoma [2]. Stauffer's syndrome has been linked to intravascular coagulation as a result of the presence of circulating fibrinogen: fibrin degradation product complexes [3]. By far the commoner of the three and most explored is the hepatorenal syndrome, a reversible and functional renal failure that occurs in a setting of advanced liver disease, usually advanced liver cirrhosis with ascites and acute liver failure (ALF). Hepatorenal syndrome is one of the major life-threatening complications of cirrhosis, others being hepatic encephalopathy, dilutional hyponatraemia, variceal haemorrhage, spontaneous bacterial peritonitis (SBP) and ascites [4]. Approximately 10% of patients with advanced cirrhosis will develop hepatorenal syndrome [5], with

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90% dying in 10 weeks of onset of the complication, the median survival being 1.7 weeks [6]. In view of this dismal outlook in its prognosis, more research efforts need to be deployed into unravelling the pathobiology and mapping out of novel therapeutic interventional approaches. The objective of this review is to briefly highlight the current trends in the pathogenesis, diagnosis and treatment modalities of hepatorenal syndrome.

Classification

In 1996, the International Ascitic Club led by Vicenti Arroyo proposed the definition and the diagnostic criteria of the hepatorenal syndrome in cirrhosis [7] which was adopted in preference to the previous Sassari's Diagnostic Criteria of 1978 [8]. The diagnostic criteria as shown in Table 1, describes the major and minor criteria. The minor criteria, however need not be present for diagnosis to be made.

Table 1: International Ascites club's diagnostic criteria of hepatorenal syndrome [7, 9].

Major criteria

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low glomerular filtration rate, as indicated by serum creatinine of >1.5 mg/dl or 24-h creatinine clearance <40 ml/min
- Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs.
- Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhoea) or renal fluid losses (weight loss >500 g/day for several days in patients with ascites without peripheral oedema or 1,000 g/day in patients with peripheral oedema)
- No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline
- Proteinuria <500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Additional criteria

- Urine volume <500 ml/day
- Urine sodium <10 mEq/L
- Urine osmolality greater than plasma osmolality
- Urine red blood cells <50 per high power field
- Serum sodium concentration <130 mEq/L

Based on the adopted criteria, two types of HRS were classified. Type 1 is characterized by a severe and rapidly progressive renal failure, which has been defined as doubling of serum creatinine reaching a level greater than 2.5 mg/dl in less than 2 weeks. Although type-1 HRS may arise spontaneously it frequently occurs in close relationship with a precipitating factor, such as severe bacterial infection, mainly SBP, gastrointestinal haemorrhage, major surgical procedure or acute hepatitis superimposed to cirrhosis [7, 9]. The type- 2 HRS has a less severe course with a slower progression of renal impairment and better prognosis, the major problem being renal failure with refractory ascites. They may however develop type-1 HRS with the presence of infections or other precipitating factors.

Aetiopathogenesis

The aetiopathogenetic mechanism underlying the development of HRS is still a subject of intense research studies for the hepatologist, nephrologists and the basic scientist. Current scientific evidence suggests that there is concurrent severe renal vasoconstriction and splanchnic vasodilatation [9, 10, 11, 12]. Splanchnic vasodilatation occurs in cirrhosis with ascites as a result of portal hypertension that sets in motion the elaboration of vasodilators such as endogenous nitric oxide (eNOS), prostaglandins, natriuretic peptides, calcitonin gene-related peptide, vasoactive intestinal peptide among others [9, 13, 14, 15]. In addition to these vasodilating agents, there is also accumulating evidence of resistance to the effect of vasoconstrictor agents in advanced cirrhosis with portal hypertension. As a consequence of the vasodilating mediators, there is systemic hypotension and ineffective perfusion pressure in spite of the expanded plasma volume and hyperdynamic circulation. The hypotensive effects of the vasodilators lead to stimulation of the baroreceptor mechanisms and subsequently the stimulation of vasoconstrictor mechanisms via the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS) and antidiuretic hormone (ADH) and later endothelin [16-20]. It has been found that urinary excretion of vasodilators produced in the kidneys like adenosine, prostaglandin E2, 6-keto prostaglandin F1 alpha and kallikrein are reduced in HRS [18, 21]. To reinforce the vasoconstrictor theory as a major contributor to HRS, a study by Boyer and his colleagues showed that administration of non-steroidal anti-inflammatory analgesic drugs (NSAID)

to patients with cirrhosis and ascites resulted in diminished renal blood flow and glomerular filtration rate (GFR) due to the prostaglandin inhibiting effect of NSAID [22]. This later finding suggests that there might be reduction in prostaglandin synthesis in the kidneys in the presence of circulating vasoconstrictors. Perfusion anomalies associated with HRS are not, however, limited to the inbalance in the vasoactive substances because of evidence of cardiac dysfunction which has been aptly titled cirrhotic cardiomyopathy.

Pathology

There is usually no histopathological damage in the kidneys of patients with HRS and harvested kidneys from HRS patients have functioned efficiently when transplanted. Thus suggesting that the renal dysfunction in HRS is of a functional nature. Similarly, liver transplantation in HRS leads to complete reversal of the renal dysfunction. There are however some peculiar chemical pathological findings, apart from liver function test abnormalities, that highly suggest HRS when present. One of such biochemical anomalies is dilutional hyponatraemia, which is defined as serum sodium less than 130mEq/L in the presence of an expanded extracellular fluid volume, as indicated by the presence of ascites and or oedema [23]. This phenomenon which occurs in about 30%-35% of hospitalised patients with cirrhosis and ascites is due to impaired water excretory capacity of the kidneys as a result of activation of antidiuretic hormone. This however is a late occurrence in advanced cirrhosis. Other biochemical anomalies are as shown in Table 1.

Diagnosis

Traditionally, functional renal disease is said to occur when the following are present, viz: oliguria, low urine sodium concentration, urine-to-plasma osmolality ratio greater than unity, normal fresh urine sediment and no proteinurria. HRS is classified as a functional renal failure and is a diagnosis of exclusion. This is because there are several types of renal dysfunction in liver disease and HRS has specific diagnostic criteria as delineated in Table 1. There are major criteria, which must be present and other criteria that do not necessarily have to be present for a diagnosis of HRS to be made [7, 9], are referred to as minor.

Investigation

In investigating HRS, a reduced glomerular filtration rate (GFR) must be established. However, this may be misleading, as cirrhotic patients usually have reduced muscle mass, thus leading to a deceptively low or normal serum creatinine levels in the face of significant renal impairment. Also, because the liver manufactures urea, the decompensated cirrhotic liver produces less urea. This aberration may be responsible for cases of false negative diagnosis of HRS [9, 24, 25]. The general consensus, therefore, is a creatinine level above 1.5mg/dl or creatinine clearance of less than 40ml/min [7]. In addition, serum and urinary sodium and osmolalities, urinary protein, sediments and daily volume as well as ultrasonography of the kidneys, ureters and bladder to exclude obstruction, need to be carried out (Table 1). It should however be noted that cirrhotic patients with superimposed acute tubular necrosis may present with features of HRS and rarely HRS patients may present without avid sodium retention [26, 27].

Complications

Complications of HRS are not quite distinguishable from the symptoms and are mainly the consequences of acute renal failure in addition to the complications of the underlying cirrhosis. These are coagulopathy, multiple organ dysfunction, dyselectrolytaemia, oliguria among others.

Treatment

Although spontaneous recovery occurs in about 3.5% of HRS [6], treatment modalities that increase survival have witnessed some advances in recent times and may be either surgical or pharmacological. Precipitating factors such as large volume paracentesis and spontaneous bacterial peritonitis, if identified, also need to be treated. The choice treatment is, however, liver transplantation, though mortality and complications after a liver transplantation is higher than is observed among non-HRS transplant recipients [28,29]. Pharmacological therapy mainly takes advantage of the pathophysiological mechanism of HRS which is hinged on intense renal cortical vasoconstriction and splanchnic vasodilatation associated with hypotension in patients with advanced cirrhosis with portal hypertension and refractory ascites. The best approach is a combination of systemic vasoconstrictors and plasma expanders, which lead to improvement in the mean arterial pressure and renal perfusion, as well as reversal of HRS, as described in a recent review by Barada [30]. Useful splanchnic vasoconstrictors include vasopressin analogues (ornipressin and terlipressin) and alpha-

adrenergic agonists (norepinephrine and midodrine), while the plasma expanders include albumin and fresh frozen plasma. Side-effects of the splanchnic vasoconstrictors include ischaemic features like angina and sometimes arrhythmias, especially with ornipressin [31]. Some studies have shown benefits in combining midodrine with octreotide, a somastotatin analogue that inhibits the release of endogenous vasodilatory agents like glucagons and vasoactive intestinal peptide. Others have combined misoprostol and sub-pharmacological doses of dopamine. A pilot study also showed a reversal of HRS in 83% of patients when norepinephrine was combined with albumin and frusemide [32]. Other modalities of therapy that have shown variable benefit include transjugular intrahepatic portacaval shunt (TIPS) and extracorporeal albumin dialysis/molecular adsorbent recirculation system (ECAD/MARS) [33, 34].

Prognosis

Hepatorenal syndrome generally has a poor prognosis, with the type 1 being worse, as it is characterised by a rapidly progressive renal failure. HRS has a ten week mortality rate of about 90% and median survival of 1.7 weeks [6]. Current approaches to management have improved the prognosis with reversal of HRS in 83% of patients being reported [32]. The major problem in type-2 HRS is refractory ascites with moderate renal failure and it carries a better prognosis than type-1.

Prevention

Available preventive measures for HRS are measures taken to tackle the major known precipitating factors such as large volume paracentesis, gastrointestinal haemorrhage and spontaneous bacterial peritonitis. Other measures include ensuring effective circulation and adequate mean arterial pressure in patients with liver cirrhosis by infusion plasma expanders and judicious use of diuretics.

The Future

A number of clinical trials that may improve the grim prognosis in HRS are still ongoing. There are efforts towards development of aquaretic drugs which are specific antagonists of tubular effects and release of antidiuretic hormone. They will be useful in normalising renal water metabolism [35].

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A Two Year Review of Patients with Chronic Kidney Failure Undergoing Haemodialysis in a New Dialysis Centre in Nigeria: Any New Lesson?

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ABSTRACT

Chronic kidney failure (CKF) is a devastating medical, social and economic problem for the patients, their families and the country. Reports from Nigeria had shown increase in hospital prevalence rates of CKF. This study reviewed the first two year data of patients with CKF who were dialyzed in a new dialysis centre in Southwest Nigeria to determine whether any progress has been made in terms of referral pattern, pre-dialysis management and to determine if there is any change in the prevalent causes of CKF compared to earlier reports from the same region. This retrospective study evaluated patients with CKF dialyzed between December 2004 and December 2006. Seventy one patients (52 males, 19 females) with CKF were dialyzed during the study period. The mean age of the study population was 43.3 ± 18.9 years. The prevalent causes of CKF were hypertension and chronic glomerulonephritis. Three-quarters of the patients were transfused and 68 patients (96 %) commenced dialysis within one week of referral to a nephrologist and had no pre-dialysis care. Three patients had arteriovenous fistula before commencement of dialysis. Five patients had dialysis for more than 8 weeks and none of the patients was able to sustain dialysis for a year or had kidney transplantation. This report showed that CKF still affects our patients in their productive years with late referral to nephrologist. Our patients had little or no pre-dialysis care and were not able to sustain dialysis therapy for an appreciable time in view of cost with attendant high mortality.

INTRODUCTION

Chronic kidney failure (CKF) represents the end of the continuum of chronic kidney disease (CKD). It is defined as glomerular filtration rate (GFR) less than 15 mL / min and / or the presence of symptoms of uraemia [1]. Chronic kidney failure is a devastating medical, social and economic problem for the patients, their families and the country as a whole[2]. The prevalence of CKF has been increasing in the developed countries at a rate of 7 – 8 % in the last 10 years [2-4]. Although there is no population data of CKF in Nigeria, there is a suggestion that the incidence of CKF may be increasing judging by hospital admission rates [5-8]. In the 1960s, CKF accounted for 1.6 % of the hospital admissions [5]. On the other hand, reports from the 1980s documented hospital prevalence rates varying from 3.6 % to 8 % [6-8].

The main treatment of CKF is renal replacement therapy (RRT) either in the form of dialysis [haemodialysis (HD) or peritoneal dialysis (PD)] or ultimately kidney transplantation. The availability and quality of dialysis programme largely depend on the prevailing economic conditions, the political – social structures, overall health care facilities and the health care funding strategies of various countries [9, 10]. There have been a number of reports on CKF patients on dialysis in Nigeria [5-8, 11, 12]. These reports have pointed out the prevalent causes of CKF in Nigeria and various problems encountered in the management of these patients.

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The aim of this study was to review the data of the Ladoke Akintola University of Technology Teaching Hospital (LTH) haemodialysis centre, Osogbo, Osun State in the first two years, compare our findings with earlier reports from other centres in the south western part of the country (Nigeria) and propose possible solutions toward improving the management of patients with chronic kidney failure.

Keywords: *Chronic kidney failure, haemodialysis, Sub-Urban centre in Nigeria.*

SUBJECTS AND METHODS

The study was carried out at the Ladoke Akintola University of Technology Teaching Hospital (LTH) haemodialysis centre, Osogbo, Osun State, Nigeria. The centre commenced operation in December, 2004. In view of its central location, it serves as a referring centre for neighbouring states such as Kwara, Ondo, and Ekiti States. The centre only offers haemodialysis for now.

Ethical approval for the study was obtained from the Ethical Committee of the LAUTECH Teaching Hospital.

The study population consisted of all consecutive patients with CKF that underwent haemodialysis at the centre between December 2004 and December 2006. Information obtained from the patients' folders or case notes and dialysis records included age, sex, educational status, referral source, record of transfusion and number of units transfused, vascular access, creation of artero-venous fistula (AVF), use of erythropoietin, pre-dialysis use of phosphate binders, blood pressure at first dialysis, number of dialysis sessions and the duration of dialysis. The hepatitis B and C and human immunodeficiency virus (HIV) status of the patients were also noted.

The inclusion criteria were patients with CKF based on the history, physical examination, biochemical and ultrasound findings. Chronic kidney failure was defined Attempts were made to diagnose the underlying aetiology of the CKF from the clinical data obtained on each patient. Patients who were more than 40 years with previous history of hypertension, presence of other hypertensive target organ damage, and absence of cellular cast on urine microscopy were classified as having hypertensive nephrosclerosis. Patients with severe hypertension (i.e. systolic blood pressure e" 180 mm Hg and or diastolic blood pressure e" 110 mm Hg), presence of exudates, haemorrhages with or without papilloedema and presence of microscopic haematuria were classified as having malignant hypertension. Patients with proteinuria, presence of cellular casts on

Table 1: Baseline clinical and laboratory characteristic of the study population

Patients' Characteristics	Number (%)
Gender	
Male	52 (73.2)
female	19 (26.8)
Age group (years)	
< 20	7 (9.8)
20 - 39	26 (36.6)
40 - 59	19 (26.8)
e" 60	19 (26.8)
Mean age	43.3 ± 18.9
Systolic blood pressure (mm Hg)	
< 140	16 (22.5)
140 – 159	16 (22.5)
160 – 179	18 (25.4)
e" 180	21 (29.6)
Diastolic blood pressure (mm Hg)	
< 90	42 (59.1)
90 – 99	9 (12.7)
100 – 109	8 (11.3)
e" 110	12 (16.9)
Serum electrolytes, urea and creatinine	
Sodium (mmol / L)	135.2 ± 8.6
Potassium (mmol /L)	4.4 ± 1.1
Chloride (mmol / L)	100.7 ± 9.6
Bicarbonate (mmol / L)	22.2 ± 3.1
Calcium (mmol / L)(n = 22)	2.02 ± 0.26
Inorganic phosphate (mmol /L) (n = 19)	2.1 ± 0.9
Uric acid (mmol /L) (n = 25)	649.6 ± 230.9
Urea (mmol / L)	36.7 ± 11.3
Creatinine (µmol/ L)	1420. 6 ± 649.3
Packed cell volume (%)	20.0 ± 4.9

Table 2 : Aetiology of chronic kidney failure in the study population

Aetiology of Chronic Kidney Failure (%)	Number
Hypertension	29 (40.8)
Malignant Hypertension	2 (2.8)
Chronic glomerulonephritis	22 (31.0)
Diabetes mellitus	5 (7.1)
Autosomal dominant polycystic kidney disease	3 (4.2)
Obstructive uropathy	4 (5.6)
Unknown	6 (8.5)

microscopy were classified as having chronic glomerulonephritis. Patients with clinical and ultrasound findings in keeping with urinary tract obstruction were classified as having obstructive uropathy. Patients with history of diabetes mellitus, proteinuria, diabetic retinopathy and normal or increased kidney sizes on ultrasound and absence of active urinary sediments were classified as having diabetic nephropathy.

RESULTS

Seventy one patients with chronic kidney failure (52 males, 19 females) had hemodialysis during the study

Table3: Published studies on chronic renal failure in south west Nigeria

	Akinsola *et al.*[6]	Salako *et al.*[12]	Arije *et al.*[11]	Alebiosu *et al.*[13]
Number of patients	100	67	141	153
Period of study (yrs)	3	3	3	11
Gender Male	64	55		
Female	36	12		
Mean age ± SD (years)	33.4 ± 12.9			39.6 ± 14.8
Age range (years)	12 – 61		15 - 81	14 – 72
Aetiology of CRF (%)				
CGN	50 (50.0)	32 (47.8)		63 (41.2)
Hypertension	25 (25.0)	26 (38.8)		40 (26.1)
Diabetes mellitus		3 (4.4)		20 (13.1)
ADPKD		2 (3.0)		
CPN		1 (1.5)		
HIVAN		1 (1.5)		
Miscellaneous	9 (9.0)			
Unclassified	16 (16.0)			
Others		2 (3.0)		
Mean serum Cr (µmol / L)	1167 ± 849	2113		619 ± 424
Range serum Cr(µmol /L)	203 - 3253	309 – 4703		
Mean serum urea (mmol /L)		91.3		77.9 ± 34.9
Mean serum K (mmol/L)		4.8		4.7 ± 1.3
Serum bicarbonate (mmol/L)		19.3		17.8 ± 9.9
Mean plasma Ca (mmol /L)		1.87		1.87 ±0.45
Mean serum inorganic phosphate (mmol / L)		2.45		2.13 ± 1.13
Mean serum albumin (g/dL)				3.6 ± 1.2
Mean parked cell volume (%)		21.6		
Number of patients dialysed			141	34
Number of dialysis sessions				
d" 3 sessions			86 (61.0)	21 (61.8)
4 – 20 sessions			44 (31.0)	13 (38.2)
e" 21 sessions			11 (8.0)	
Mean SBP ± SD (mm Hg)				167.3 ± 15.5
Mean DSP ± SD (mm Hg)				106.0 ± 28.6

Key to Table. *CRF – chronic renal failure, CGN – chronic glomerulonephritis, ADPKD – autosomal dominant polycystic kidney disease, CPN – chronic pyelonephritis, HIVAN – Human immunodeficiency virus associated nephropathy, Cr – creatinine, K – potassium, Ca – calcium, SBP – systolic blood pressure, DBP – diastolic blood pressure*

Fig. 1: Duration of dialysis in chronic renal failure patients

period. Table 1 shows the baseline clinical and laboratory characteristics of the patients. The male to female ratio was 2.7: 1. The mean age of the study population was 43.3 ± 18.9 years (range 16 to 86 years). Fifty two patients (73.2 %) were under 60 years of age. Sixty-eight out of the 71 patients (95.8 %) were referred to the centre and had to commence dialysis within one week of referral.

The aetiology of CKF is as shown in table 2. The leading causes of CKF in the study population were hypertension, glomerulonephritis and diabetes mellitus. The aetiology of CKF could not be determined in 6 (8.5 %) of the population.

Figure 1 shows the duration of dialysis in the study cohort. Forty two patients (59.2 %) had dialysis for < 2 weeks while only 5 (7.0 %) had dialysis for > 8 weeks. None of the patients had dialysis for a year or had kidney transplantation before their demise. Fifty patients (70.4 %) had d" 5 sessions of dialysis, 14 patients (19.7 %) had between 6 and 10 sessions, 4 patients (5.6 %) had between 11 and 20 sessions of HD and only 3 patients (4.2 %) had > 20 sessions of HD. Two patients had AVF before commencement of HD and 3 patients had AVF fashioned after commencement of HD. At commencement of dialysis, 57 patients (80.3 %) had blood pressure e" 140 / 90 mm Hg. Five patients (7.0%) were hepatitis B surface antigen (HBsAg) positive and only one patient had antibody to hepatitis C virus.

Fifty three patients (74.6 %) had blood transfusion and 136 units of blood were transfused. Forty patients out of the 53 patients transfused (75.5 %) had been transfused before referral for dialysis. Only 5 patients (7.0 %) had erythropoietin during the course of their management.

DISCUSSION

The mean age of the study population was 43.3 ± 19.1 years with majority of the patients (73.2 %) under the age of 60 years. This is not different from earlier reports from Nigeria as shown in table 3 but differs considerably from reports from developed countries where majority of patients requiring dialysis are over 60 years of age. For example, two –thirds of total dialysis patients in Japan are more than 60 years of age. Likely reasons suggested for the age difference in patients in developing compared to developed countries included the delay in detecting renal diseases and the failure in instituting measures in retarding progressive renal disease, both of which result in faster progression to end stage kidney disease (ESKD).

The male to female ratio is 2.7: 1. Earlier studies from south western Nigeria as shown in table 3 have documented a male preponderance in the dialysis population [6-8, 11, 12]. Reasons put forward to explain this gender difference included inherent proneness of males to developing chronic kidney disease, the faster progression of CKD in males and

the higher prevalence and severity of hypertension in males compared to pre-menopausal females.

Hypertension and chronic glomerulonephritis were the leading causes of CKF in this study population. This finding did not differ from findings from earlier studies as shown in table 3. The prevalence of hypertension in Nigeria is between 15 to 20% [15, 16] and studies have shown that blood pressure control rates are poor [17]. It is therefore not surprising that hypertension is still the leading cause of CKF in our population. Diabetes accounted for 7.1 % of the causes of CKF in the population. Though diabetes is the leading cause of CKF in most developed countries, it accounts for between 2 to 13.1 % of CKF in Nigeria from earlier reports [6, 13]. However, an increasing trend of diabetes as a cause of chronic kidney failure in Nigeria has been reported by Alebiosu *et al* [18]. This is likely due to the fact that many Nigerian patients with diabetes are surviving longer due to improvement in the medical care and are now developing diabetic nephropathy which tends to set in with increased duration of diabetes.

Most of the patients' first contact with nephrologists was when they had developed uraemia and needed urgent dialysis. Thus, none of the patients had a functioning permanent vascular access or had been started on erythropoietin before commencement of dialysis. In addition, majority of the patients had been transfused before referral for dialysis and most had inadequately controlled blood pressure. This finding is not peculiar to Nigeria. Reports from developed countries estimated that 20 to 50 % of patients starting dialysis are late referrals [19, 20]. Patients referred late to nephrologists experienced a greater degree of blood transfusion, a lower prevalence of permanent vascular access at initiation of dialysis, substantial underuse of anti-hypertensive medications, erythropoietin and phosphate binders [19]. Also, these patients experienced an earlier initiation of haemodialysis therapy and significantly poorer survival than patients who are referred early to nephrologists [19, 20]. Reasons for non-referral to nephrologists include non-recognition of early renal insufficiency, and non-nephrologists' attitudes and perception towards pre-dialysis care and in some health care systems or cases, physician concerns about loss of income [19].

Virtually all our patients could not sustain long term dialysis which eventually led to their death. This was because the patients had to pay for dialysis and patients' finances dictate the frequency and duration of therapy. A report by Arije *et al* showed that 70.8 % of the patients were able to remain on dialysis for less than 1 month and only 1.9 % remained on dialysis for over 12 months [11]. In a situation where the cost of one dialysis session is more than the lowest minimum monthly wage in the country, it is not surprising that patients were not able to sustain long term dialysis.

The issue of ethical appropriateness in starting RRT in a patient with limited resources who will most likely discontinue therapy after depleting all family resources and savings has been raised. However, it is ethically and morally inappropriate to withhold treatment from these patients particularly when patients' family members are initially willing to make any sacrifice to preserve life and believed that patients will recover from the illness despite all physicians' counsel [10]. It is after emotions and resources have been exhausted that it finally dawns on the family members that treatment cannot be sustained.

The implications of our findings are many. First, there has not been any significant change in the various causes of chronic kidney failure in the country over time. This should provide the country with a template for planning prevention programme towards reducing the burden of CKD. Preventive measures should involve targeted screening for urinary abnormalities, hypertension, diabetes, cardiovascular disease and other recognizable risk factors for CKD and the development of comprehensive team-based care for patients with known hypertension, glomerulonephritis and diabetes.

Second, the disease continues to affect our people in their productive years and most patients continued to die due to their inability to sustain dialysis treatment in view of the high cost. Thus, the country is being robbed of its work force and families are being deprived of bread winners with dire negative social consequences for the families and the nation. Unfortunately, there is no national renal registry. Therefore, the exact incidence and prevalence of chronic kidney failure in the population, its burden on the health care system and the outcome of these patients are not known. The recent move by the Nigerian Association of Nephrology (NAN) to establish a national registry is in the right direction. This will help in defining the burden of CKD in Nigeria and also arm the association with relevant data necessary to influence health care policy makers to make decisions that will effectively address CKD.

Most patients cannot sustain long term dialysis due to the high cost. A way out of this problem may be to seek alternative funding aside from that provided by the government. In doing this, we can learn from the National Kidney Foundation of Singapore (NKFS) by forming workable partnerships with pharmaceutical companies, private corporations with a "social conscience", non-governmental organizations, organized religious groups and individuals [21]. The pharmaceutical companies can help by providing dialysis machines at much reduced cost, providing equipment related to PD, developing training programs for allied health professionals and patients and providing widespread availability of erythropoietin for chronic dialysis patients at reduced cost [21]. The government in turn can encourage these companies by providing tax relief and reducing import duties on dialysis products while working on the ultimate aim of facilitating local production which will reduce cost. In initiating and sustaining this partnership, there must be transparency in the handling of funds and fulfilment of set-out objectives [21].

Third, most of our patients were referred quite late to nephrologists. This finding suggests the need for improved communication between nephrologists and other health care providers since early referral to nephrologists ensure adequate and necessary pre-dialysis care and promote a healthier transition to dialysis therapy. Patients should be referred to nephrologists when the glomerular filtration rate is < 30 mL / min [1].

The limitations of this study included the small number of the study population though it is unlikely that the findings will be different even if this review was done later on. Second, the aetiological diagnosis of CKD was not based on histology of kidney biopsies. Thus mis-classification of aetiology is possible.

In conclusion, this study showed that CKF continues to affect Nigerians in their productive years and was associated with high mortality due to inability of our patients to sustain long-term dialysis. Also, patients were still being referred quite late to nephrologists with little in way of good pre-dialysis care. There is a need to institute measures directed at detecting CKD and controlling factors that initiate and promote progression of CKD. In improving the survival outcomes in these patients, alternative sources of funding in addition to that provided by the government may help with the provision of renal replacement therapy.

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Uremic Pruritus in Patients with End Stage Renal Disease, in Ibadan, Nigeria

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ABSTRACT

Pruritus is a disabling symptom in patients with chronic renal failure. There are no reports of this symptom in patients with renal failure in our environment. We looked at the prevalence and pattern of pruritus in patients with end stage renal disease and underlying associated cutaneous features in them. Questionnaire assessing the presence, pattern, severity and sites affected with pruritus were administered to the patients with end stage renal disease. Their skin was examined for associated clinical features. One hundred and twenty patients with end stage renal disease where recruited in to the study. Thirty two (26.7%) of the patients had pruritus out of which 22 were males. Twenty one (65.6%) of the patients were receiving haemodialysis while the others were on conservative management. The age range of the patients was 22-78 years with a mean of 42.96±15.83 years. Pruritus was generalised in 75% of the patients. It was localised to the face in 6%, upper limbs 3%, lower limbs 9%, scalp 3% and the trunk in 3% of the patients. Xerosis was found in 80% of the patients with generalized pruritus. We concluded that pruritus is a symptom of end stage renal disease in this environment and occurs more in patients receiving haemodialysis. Most of our patients had mild to moderate pruritus. Xerosis was an accompanying feature of generalised pruritus in these patients.

Keywords: *Uremic pruritus, End Stage Renal disease*

INTRODUCTION

Pruritus is a common symptom of end stage renal disease and is also known as uremic pruritus or renal itch. Although commoner in patients on haemodialysis [1, 2, 3] it is also seen in patients on conservative management for ESRD [1, 4]. Once it starts, it usually becomes persistent until there is renal transplantation [5]. Associated skin changes seen in the patients include xerosis (dryness of the skin) or complications of pruritus itself such as excoriation, lichenification and impetiginisation of the skin [2].

The pathogenesis of uremic pruritus is still not clear but appears to be multifactorial. A variety of factors have been suggested for its aetio-pathogenesis. They include secondary hyperparathyroidism [6], mast cell proliferation and degranulation [7], pruritogenic cytokines [8], deranged divalent ion metabolism [9], defective sweating[10] and abnormal pattern of cutaneous innervations [11]. None of these studies have found these factors to be major or universal. However, atrophy of the sebaceous glands and the secretory and ductal portions of the eccrine sweat glands have been demonstrated in patients with end stage renal disease [12]. These results in lower surface lipids and a reduction in the water content within the stratum corneum possibly contributing to pruritus. Significantly less hydration of the stratum corneum in pruritic dialysis patients has been demonstrated [13]. Recently, the role of inflammation and pro inflammatory factors on the

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occurrence of pruritus indicate that uremic pruritus may be a systemic phenomenon due to dysfunctional regulation of immunologic parameters [14].

We looked at the prevalence and pattern of pruritus in patients with end stage renal disease the University College Hospital Ibadan Oyo State.

MATERIALS AND METHODS

One hundred and twenty patients diagnosed with ESRD who gave their consent where included in the study. A questionnaire was administered by the investigators. This was to assess the relevant bio-data, presence, pattern and severity of the pruritus in the patients. Uremic pruritus was defined as pruritus around the period of the present illness without any other obvious reasons. Patients with pruritus were examined. Patients with known pruritic dermatoses were excluded from the study.

RESULTS

One hundred and twenty patients with end stage renal disease where recruited in to the study. Thirty two (26.7%) of the patients had pruritus out of which 22 were males. Twenty one (65.6%) were receiving haemodialysis' while the others were on conservative management. The age range of the patients was 22-78 years with a mean of 42.96 ±1 5.83.There was no correlation between age, sex, duration of treatment and pruritus. Pruritus was generalised in 75% of the patients, localised to the face in 6%, upper limbs 3%, lower limbs 9%, scalp 3% and the trunk in 3% of the patients. Xerosis was found in 80% of the patients with generalised pruritus.

DISCUSSION

Pruritus is one of the commonest symptoms in patients with ESRD especially in those on dialysis. Prevalence rates vary between 12-90% in patients with chronic renal failure [15, 16]. It would appear that higher prevalence rates about 40% and above have been reported in those on continuous dialysis. Figures as low as 12% was recorded in Senegal where a significant number of patients were unable to afford dialysis [15]. Twenty seven percent of our patients had pruritus and this occurred more in patients on haemodialysis. It has been suggested that the haemodialysis itself may contribute to the pruritus or prolong the lives of patient long enough for the pruritus to develop [1, 4]. During dialysis it is believed that several cytokines including interleukin-1 are released following contact with plasma and the dialysis membrane[8]. Interleukin 1 has been postulated to induce the release of potentially pruritogenic substances [17]. It was earlier suggested that accumulation of non- dialyzable middle molecules in haemodialysis patient stimulated free nerve endings contributing to pruritus [18].

Although haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) have been found to contribute to uremic pruritus, CAPD contributes 10-14% less (the contribution of CAPD) is 10 – 14 % less than HD). This may result from a more effective elimination process of possible pruritogenic substances by the peritoneum when compared to the artificial membranes in haemodialysis [7]. Most studies had reported development or worsening of pruritus during dialysis or on the day after dialysis, only one of our patients had worsening of pruritus 12 hours after dialysis. We were not sure if this was due to the small number of patients we had on dialysis. Virtually most studies have reported no correlation between age, sex and duration of treatment and pruritus. This was also our experience in this study.

In 75% of our patients, pruritus was generalised and of mild - to moderate- intensity in 97% of the patients. Generalised pruritus appears to be a common finding in most studies [1, 2, 3]. A report from Israel had 70 % of patients with generalised pruritus with 50% [19] moderate intensity while those in Morocco had 65.7% of their patients with generalised pruritus and 78.3% with mild intensity [20]. Localised pruritus appears to be less common.

Amongst patients that had pruritus, 80% of them had xerosis (dry skin). Other studies had reported prevalence rates of xerosis of 66.6% to 93.1% [3, 21] in patients with uremic pruritus. Some studies showed a correlation between severity of pruritus and xerosis while others did not show any correlation. We did not notice any association between pruritus and severity of xerosis in our study. It has been suggested that the xerosis in these group of patients is due to atrophy of epidermal and dermal appendages [21]. Significantly less hydration of the stratum corneum in pruritic dialysis patients has been demonstrated. Some authors have reported an increase in vitamin A levels and elevated retinol which has been linked with xerosis in patients with ESRD and suggested it may be the aetiology of the pruritus [1]. Other authors have not found an association between vitamin A levels and pruritus in uremic pruritic patients [22].

We found it interesting that none of the patients had complained to their primary physicians about pruritus, possibly because it was not disabling in them.

In conclusion, pruritus is a symptom of end stage renal disease in this environment and occurs more in patients receiving haemodialysis. In most of our patients, pruritus was mild to moderate in severity. Xerosis is an accompanying feature of generalised pruritus in these patients.

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Renal Clinico-Pathology Teaching Case: Fibrillary Glomerulonephritis

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CASE REPORT

A 39-year-old Caucasian man with a history of hypertension for 5-8 years was referred to the renal clinic for evaluation of asymptomatic nephrotic-range proteinuria. At the time of his initial visit he had no specific complaints suggestive of a potential etiology. His past medical history was remarkable for chronic low back pain secondary to lumbar spine compression fracture in the 1980s, morbid obesity, obstructive sleep apnea, gastroesophageal reflux disease and depression. Social and family history were noncontributory. Prescription medications included tramadol, atenolol, klonopin and paroxetine.

On physical examination, he was an obese man in no apparent distress. Vital signs revealed BP of 120/74, a pulse rate of 100 beats per minute, and a temperature of 37.3 degrees Celsius. The rest of the physical examination was unremarkable. It

Table 1: Initial visit laboratory results

Na	142 (135-145	WBC	9.6 (4-11k/uL)
K	mmol/L)	Hg	15.4 (14-18 g/dL)
Cl	4.2 (3.5-4.5	Hct	45.4 (40-52%)
HCO3	mmol/L)	Platelets	236 (150-450
Bun	106 (97-107	Hep B Surf Ag	k/uL)
Cr	mmol/L)	Hep B Surf Ab	Negative
Calculated GFR	26 (22-29 mmol/L)	Hep C Ab	Negative
Uric acid	14 (9-20 mg/dL)	HIV	Negative
Total Protein	1.3 (0.7-1.2 mg/dL)	C3	Negative
Albumin	65 ml/min/1.73m2	C4	146 (83-156
Bilirubin	8.9 (3.5-7.2 mg/dL)	RF	mg/dL)
Alk phosphatase	7.4 (6-8.3 g/dL)	Cryoglobulin	19 (10-38 mg/dL)
AST	4.5 (3.5-5.7 g/dL)	ANA	<20 (<30 IU/ml)
ALT	0.7 (03-1.2 mg/dL)	Anti-DS-DNA	Negative
HgA1C	49 (40-150 U/L)	SPEP	Negative
LDL	25 (<35 U/L)		Negative
24 hour urine protein	43 (< 55 U/L)	UPEP	No anomalous immunoglobulins
Urinalysis	5.6 (< 6%)		No anomalous immunoglobulins

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showed no lower extremity edema, ascites, rash or synovitis. Results of the initial laboratory tests are listed in table 1.

Renal Biopsy Findings

On light microscopy, 15 glomeruli were identified, one of which was globally sclerotic. The other fourteen demonstrated mild to moderate mesangial matrix expansion and hypercellularity (Figure 1). There was minimal tubular atrophy and interstitial fibrosis. A scant lymphoplasmacytic infiltrate was primarily subcortical. Small arteries displayed medial hypertrophy. Congo red staining with and without potassium permanganate incubation was negative. Immunofluorescence (IF) with antisera specific for IgG, C3, and kappa and lambda light chains demonstrated 2+ positivity in the mesangium (on a scale of trace to 3+) (Figure 2). There was 1+ positivity with anti-sera specific to IgM and C1q. Immunofluorescence with anti-sera specific for IgA and fibrin was negative. Electron microscopy (EM) revealed deposition of randomly arranged, non-branching 15 nm fibrils, predominantly in the mesangium and focally in the glomerular basement membrane (Figure 3).

Figure 1: Light microscopy. Glomeruli demonstrate mild to moderate mesangial matrix expansion and hypercellularity (H&E, original magnification 200x).

Figure 2: Immunofluorescence microscopy. Staining with antiserum to kappa light chain demonstrates 2+ smudgy mesangial positivity. Similar staining for IgG, C3, and lambda light chain was observed. IgA was negative. (anti-kappa light chain, 400x).

Figure 3: Electron microscopy. Randomly arranged fibrils are deposited predominantly in the mesangium. For orientation, a glomerular basement membrane is included in the top right (uranyl acetate and lead citrate, 12000x).

No immune complexes or tubuloreticular inclusions were identified. Based principally on the ultrastructural findings, a diagnosis of fibrillary glomerulonephritis was made.

DISCUSSION

Fibrillary glomerulonephritis (GN) is an uncommon form of glomerular disease found in approximately 0.5-1% of native kidney biopsies. It was originally described as "Congo-red negative amyloidosis" by Rosenmann and Eliakim in 1977 [1]. Usually an idiopathic disorder, it has been linked to chronic hepatitis C infection in one study [2]. The average age at presentation is 45 years. Main clinical features include proteinuria (virtually 100%), often nephrotic range (50-70%), hematuria (60-70%), renal insufficiency (55-70%), and hypertension (65%) [3-5]. Fibrillary GN is a primary renal disorder and serologic tests for complement levels, lupus antibodies, rheumatoid factor, anti-neutrophil cytoplasmic antibodies and anti-glomerular basement membrane antibodies are usually negative or within the normal range.

Renal biopsy with ultrastructural examination of the specimen is required for a definitive diagnosis

of fibrillary GN. Light microscopic findings are nonspecific, as the lesion manifests a variety of histologic patterns, including mesangioproliferative (as in the patient discussed above), diffuse proliferative, membranoproliferative, crescentic, membranous, and diffuse sclerosing. Rosenstock *et al* described IF findings in 61 patients with fibrillary GN. Ninety six percent displayed positivity for IgG, 52% for IgM, 30% for IgA, 83% for C3, 41% for C1q, and 96% for both kappa and lambda light chains [4]. The ultrastructural appearance is pathognomonic, showing randomly oriented fibrils in the mesangium (in 98% of cases) and/or the glomerular basement membrane (in 90% of cases). The fibrils are usually 15-25 nm in diameter, larger than those seen in amyloidosis, which are typically 6-10 nm. Although overlap in fibril size in fibrillary GN and amyloidosis may occur, staining with Congo red reagent readily distinguishes these two conditions [7]. Subendothelial or subepithelial distribution of fibrils is seen in < 15% of cases [4].

The clinical course of fibrillary GN is that of subacute progression to end stage renal disease (ESRD). Approximately 50% of patients will require renal replacement therapy within 2-6 years. The prognosis appears to be somewhat dependent on the histologic pattern found on light microscopy with the worst prognosis observed in patients with a diffuse sclerosing pattern on initial biopsy (~7 months to ESRD) and the best prognosis seen in those with membranous lesions (~87 months to ESRD) (4). There is no proven treatment for fibrillary GN. Cytotoxic agents and/or steroids, chlorambucil, plasmapheresis and NSAIDS have been tried with limited success. Response to therapy may again depend on the histologic appearance, and patients with glomerular crescents on light microscopy may respond better to immunosuppressants. Dickenmann *et al* reported successful clinical remission in 3 patients with normal renal function and nephrotic range proteinuria at the time of diagnosis, when they treated with high dose prednisone and nonspecific therapy with an angiotensin converting enzyme inhibitor [6].

Renal transplantation is an option for fibrillary GN patients who progress to ESRD. Recurrence was 50% in one small study [3], however, the rate of disease progression appears to be slower than in the native kidney.

Immunotactoid Glomerulopathy

In contrast to fibrillary GN, immunotactoid glomerulopathy (ITG) is morphologically characterized by parallel arrangement of microtubular deposits in the mesangium and in the glomerular basement membrane [8]. The size of microtubules in ITG is in general larger than in fibrillary GN, usually > 30nm and can be up to 90nm. As in fibrillary GN staining with Congo red reagent is negative and ultrastructural examination of the glomerular tissue is essential for diagnosis.

Clinical features of ITG largely overlap with those of fibrillary GN and almost universally include proteinuria (nephrotic range 80%) with hematuria (75%), hypertension (85%) and renal insufficiency (45%) being frequently present. Association of ITG with several systemic diseases including monoclonal gammopathies, lymphoproliferative disorders, autoimmune conditions and chronic hepatitis C infection has been described in several case series [4, 5], therefore diagnosis of ITG should prompt a search for these conditions. While it has been suggested that prognosis may be better in patients with ITG [9], this was not confirmed in later publications [3, 4].

Whether fibrillary GN and immunotactoid glomerulopathy (ITG) are separate entitities is still a subject of significant debate. Brady [5] and Pronovost *et al* [3] suggest that it is too early to make a clinical distinction as the two conditions have a significant overlap in clinical presentation, fibril size and prognosis. On the other hand, Alpers *et al* [7, 10] and Rosenstock *et al* [4] contend that fibrillary GN and ITG should be separated since the latter has a higher coexistence with serious systemic illnesses.

Teaching Points

- Fibrillary glomerulonephritis (GN) is an uncommon form of glomerular disease found in approximately 0.5-1% of native kidney biopsies.
- Presentation is usually with proteinuria, often nephrotic range. Hematuria and renal failure also occur but less often.
- Diagnosis is made by ultrastructural appearance of randomly oriented fibrils in the mesangium . The fibrils are usually 15-25 nm in diameter, larger than those seen in amyloidosis, which are typically 6-10 nm. Congo red staining is negative.

- Clinical course of subacute progression to end stage renal disease, approximately 50% of patients will require renal replacement therapy within 2-6 years.
- No proven effective treatment. Cytotoxic agents and/or steroids, chlorambucil, plasmapheresis and NSAIDS have been tried with limited success. Renal transplantation is an option.

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