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Review

A review of renal disease in cystic fibrosis

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Abstract

Kidney disease is becoming increasingly common in CF. This review looks at the effect of CFTR on the kidney, the problems with measuring renal function effectively in CF, the causes and incidence of renal dysfunction, and its pathophysiology. Strategies to reduce aminoglycoside toxicity are discussed.

Keywords: Renal disease; Measurement of renal function; Creatinine clearance; Aminoglycosides; Fosfomycin

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1. Introduction

Cystic fibrosis is one of the success stories of modern medicine — whereas in the 1950s most individuals with the

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disease died before the age of 5, medical advances mean that those born in the 21st century will live into their fifth or sixth decade.

Indeed, the latest UK CF Registry (capturing nearly all the UK's >9000 patients) indicates that the median survival is already over 41 years, and very few patients die in childhood.

Furthermore, many adolescents transitioning to the adult sector can now expect to have normal or near-normal lung function, attributed to better therapy, organisation of care, and improving socio-economic factors.

However, the ageing of the CF population has brought with it unforeseen problems and complications and there has been a paradigm shift in outlook in the adult healthcare sector, from a focus on the care of lung disease to the management of a complex multi-system chronic illness. One of these complications has been the emergence of the involvement of the kidney in the CF condition. Although CFTR is found in the kidney, mainly in the proximal and distal tubules, and its inactivation can cause low molecular weight proteinuria [1], its exact role and effect in CF related kidney disease is unknown and primary renal disease is an unusual feature, in contrast to secondary renal dysfunction that is becoming increasingly common. Nephrogenesis is completed by thirty-six weeks of gestation [2]: nephron numbers are genetically determined (the human average is 1 million per kidney) and they do not regenerate. Following birth, there is a gradual decline in their number, but the attrition rate is accelerated by chronic infection, diabetes, and vascular disease, all of which can be present in CF.

Furthermore, CF individuals are in danger of acute kidney injury and the development of chronic renal disease through exposure to multiple potentially nephrotoxic agents including aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs) and immune-suppressants. Nephropathy can also result from abnormalities in salt transport [3], colonisation with *Pseudomonas aeruginosa* (*Psa*) [4], and the development of Cystic Fibrosis Related Diabetes (CFRD) requiring insulin [5].

This paper reviews the problems with measuring renal dysfunction in CF, its patho-physiology, and discusses reno-protective strategies in order to decrease the incidence of this important complication.

2. Diagnosis and screening of renal dysfunction

Renal blood flow, glomerular filtration, and tubular resorptive capacity all play their part in defining renal function. In humans, the assessment of renal function is limited to measuring the Glomerular Filtration Rate (GFR), renal blood flow, and estimation and measurement of proteinuria and creatinine clearance derived from various formulae.

Although GFR has always been considered the best clinical estimate of renal function and correlates well with both clinical severity and disturbances in renal function [6], it has its limitations. It cannot be assessed directly and is determined indirectly by measuring the clearance of suitable filtration markers that are not reabsorbed, secreted or metabolised by the kidney, such as Cr-EDTA, inulin, ^{99}Tc-DTPA and iohexol [7]. However, tests involving these markers are costly, time consuming, need intravenous infusions and accurate sample collection, all of which are problematic. Also, many CF patients do not have normal or stable serum creatinine levels, which further complicates its measurement.

GFR is also insensitive in the detection of early renal dysfunction: up to 30% of nephrons can cease to function before GFR alters, since the remainder compensate by increasing their filtration rate [8,9]. It is only with a further loss of renal tissue that GFR will reduce.

Due to the difficulty of directly measuring GFR, indirect methods based on the clearance of physiological products through the kidney have been devised. One such test is the clearance of creatinine (CCl). Creatinine, a muscle breakdown product, is produced in a predictable way in stable individuals and is only minimally reabsorbed by the renal tubules. However, because the measurement of CCl depends upon the accurate urine collection, it is subject to error in adults and impractical in young children, a number of formulae based on serum creatinine, muscle mass, and physical constants have been devised to estimate it (eCCL).

Formulae including the abbreviated Modification of Diet in Renal Disease (aMDRD) equation [10] and the Cockcroft-Gault formula (CGF) [11] are widely used clinically and have been advocated in those with CF [12]. However although these formulae are simple to use in daily practice, they are not reliable when the serum creatinine is unstable, overestimating CCl and therefore GFR when the creatinine is rising, and vice versa [13,14]. They have not been validated in CF and furthermore, this lack of validation is particularly important because many CF patients are in a hypermetabolic state [15], have diminished muscle mass, and have limited exercise capacity [16], all of which can influence creatinine production.

Data published from our own unit [17] comparing 74 adult CF patients with no previous history of renal problems and a normal range of serum creatinine, with 29 healthy age and BMI matched control subjects, showed these formulae to be unreliable. Measured creatinine clearance was compared with eCCL using various formulae: all (including the popular CGF and aMDRD-derived estimates) compared less favourably in CF patients than controls and grossly over-estimated renal function in CF patients with reduced CCl (<80 ml/min)[Table 1]. These formulae should be used and interpreted with caution in CF patients; generally they overestimate creatinine clearance and therefore understate the degree of renal dysfunction in the CF population.

Drugs such as aminoglycosides can cause proximal tubular damage, leading to acute tubular necrosis resulting in electrolyte leak from a defect in the urinary concentrating capacity and the elevated urinary excretion of certain tubular enzymes.

Hence over the past 40 years attention has been directed towards the evaluation of urinary enzymes as non-invasive biomarkers of renal tubular damage. They can be sensitive tools useful in the early diagnosis of acute renal injury before conventional laboratory assays become deranged [18–20], and they reflect sub-clinical toxicity and might have an important role in screening for early renal damage. They may also indicate the site of primary tubular damage because of their localisation in tubular lysosomes (N-acetyl-β-D-glucose-aminidase [NAG]) and