THE ULTRASOUND QUANTIFICATION OF CYSTIC FIBROSIS LIVER DISEASE

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ABSTRACT

Cystic fibrosis (CF) is the most common genetic inherited disease, with a live birth incidence of 1:2000 in a European population. With the advent of improved physiotherapy, nutrition and antibiotic therapy, survival has increased rapidly, however there is now mounting awareness of the increased prevalence of cystic fibrosis liver disease (CFLD).

CFLD affects between 5-30% of the CF population, and its diagnosis is difficult as there is a long sub-clinical phase. Establishing the diagnosis is also contentious as current tests for CFLD (e.g. biochemical screening, liver biopsy, clinical examination) are reported to be inaccurate in diagnosing early changes and will only permit the detection of established disease. Historically percutaneous liver biopsy has been held as the gold standard for the diagnosis and staging of the disease, but the focal nature of the disease means that liver biopsy may be inaccurate. Biopsy may also be associated with significant morbidity and mortality; so many centres are now moving away from this and seeking to develop a more sensitive non-invasive diagnostic test.

Ultrasound (USS) is a non-invasive and well-tolerated technique with an established role in the evaluation of all types of liver disease. Its use can be subjective and operator-dependent, so its value is often disregarded. Other researchers have attempted to determine its role in the quantification of CFLD, with varying degrees of success.

The case is presented for a USS scoring system used to quantify CFLD in a paediatric CF population, which has been correlated against clinical, biochemical and histological findings. The development of a series of clinical algorithms to predict the likelihood of CFLD is also discussed.

PREFACE

Background:

This study came about as a direct result of my job as a superintendent radiographer specialising in ultrasound scanning, employed in a specialist children's hospital which has tertiary level responsibilities for all aetiologies of liver disease. In my job I was required to scan children in order to evaluate their liver disease and part of this process included a routine abdominal ultrasound scan for patients prior to percutaneous liver biopsy. I had always wondered why children who had cystic fibrosis (CF), a disease affecting the respiratory system, could ever be in the situation of needing a procedure as invasive as a liver biopsy. I did not understand at that point that there was a subset of children with CF who had abnormal livers, and being naturally curious I decided to investigate this anomaly further.

After I had the opportunity to read around this subject, it became increasingly clear that there was a subset of children with CF who developed a specific type of liver disease. It was also obvious that although the pathogenesis of the disease was understood, no one was yet able to diagnose either those children who were at increased risk of developing cystic fibrosis liver disease (CFLD), or those who had already developed early CFLD. The result of this was that children were often only diagnosed when significant liver disease was already present. Realising the implications of a disease process of this nature, I decided that further investigation into this particular topic was needed, and performed a formal literature search and review. The summary of results concluded that although there were thought to be some predisposing factors these were not accurate enough to predict the incidence of liver disease, and that diagnosis was confirmed only after percutaneous liver biopsy. The problem with liver biopsy is that there is an increased risk of morbidity and mortality as it required hospital admission, general anaesthetic and was highly invasive in nature. No other appropriate test existed and there was not any reliable method for the objective staging and evaluation of disease progression.

Justification for undertaking the study:

Once a very basic preliminary literature search had been undertaken, it became progressively clear that despite large amounts of research, and even at the end of the 20th century it was still not possible to determine the causes of CFLD and that many patients were presenting late (often in late childhood and early teen years) with established liver disease. This reduced the range of available treatment options for them. A more extensive and systematic literature review was then performed, which revealed that other researchers in this field could not agree with any consistency on the prevalence, possible causative factors or even the most common age at which CFLD developed.

The nature of the disease process leads to difficulties with diagnosis, as the mechanism of the defective metabolic pathway (causing cholangiopathy[1]) meant that blood tests to evaluate liver function (LFTs) only became abnormal in the presence of established liver disease, i.e. when cholangiocyte damage had become so extensive that it had spread to involve the surrounding hepatocytes with subsequent scarring of the liver parenchyma. These LFTs were non-specific for CFLD, as any of the parameters assessed could become elevated by other factors than CFLD. To date no reliable early marker of cholangiocytes* damage has been developed, although several interesting tests have been proposed.

A 'gold standard' test had been described (liver biopsy) but this is intrinsically flawed owing to the initially patchy nature of CFLD within the liver. Even in the presence of late stage CFLD i.e. macronodular cirrhosis with clinical evidence of portal hypertension, a normal biopsy result was possible if a regenerated nodule had been sampled rather than a damaged area of tissue. Even routine clinical examination could prove misleading, as portal hypertension-related splenomegaly could be dismissed as being caused by hyper-expanded lungs, intercurrent or chronic infection. Another confounding factor was that no-one was sure of any characteristic that might increase the incidence or likelihood of developing CFLD; for example factors such as male sex, homozygous ΔF508 genotype, meconium ileus have all been proposed by different teams of researchers. Family studies have been performed by other researchers to evaluate this linkage, but these were non-conclusive in the face of siblings with disparate phenotypic expression. A recent development in the evaluation of CFLD has been investigation of the role of modifier genes, although to date nothing conclusive has been reported.

[1] Cholangiopathy – damage to the epithelial cells (*cholangiocytes) lining the biliary ductules

Focus then shifted away from trying to determine the causes of CFLD, towards attempting to improve diagnostic tests. As ultrasound technology (US) has improved over the last decade of the 20th century, different centres have concentrated on its role in the earlier diagnosis of CLFD. These studies have rarely focused on children exclusively, using only either a very small percentage of the total group, or concentrating on adults, who already have established CFLD. Research involving children can be difficult, not only because of issues relating to competency to give consent and recruitment into trials, but also because of the emotive nature of researching a life-limiting disease and problems relating to anxiety of the parents and children of having to deal with another possible facet of CF. Many aspects of medical treatment for children are limited by the fact that owing to the expense of obtaining a license for use of drugs on people under 18, many treatments are used off-license, and this may also be a factor dissuading people from performing research involving children.

This has created a large gap in the knowledge of CFLD, its aetiology and progression. It has generally become understood that the average age of diagnosis of CFLD is within mid-childhood (defined in this instance as between 8 to 10 years of age), and that no cases tend to be diagnosed after puberty. Consequently more attention is now being placed on analysing the childhood aspects of CFLD to see if more conclusive information can be found.

So why was this study necessary?

Essentially, because no previous work had been carried out to investigate the role of up to date ultrasound in an exclusively paediatric group. Upon determining the sonographic characteristics of CFLD from current literature, the author felt that with modern ultrasound equipment it should be possible to provide a more effective means of evaluating children with CFLD. The aim of the study was therefore to develop a scientifically tested ultrasound based scoring system using all the conventionally accepted US markers for CFLD and portal hypertension, which could then be used in combination with the other generally available (if flawed) methods of routine surveillance to determine whether the diagnostic sensitivity could be increased, and which had the potential to be used for the longitudinal follow-up of patients as a quantitative individual monitor of the potential progression of their disease.

There was also the potential to re-define the clinical care pathway for CF patients, if the scoring system was successfully validated. Details of current practice (at the time of writing) for the surveillance and management of CF patients are discussed in Chapter 3, where the results of a nationwide survey of clinical management are presented.

The proposed ultrasound scoring system had been introduced in a simplistic form for my MSc dissertation (Pearson 2000). This study had originally intended to validate the use of the proposed scoring system in a clinical environment; however this was not possible (due entirely to the initial inconsistency in reports) and therefore forced a shift in focus of the MSc. Instead it was used as a means of testing inter and intra-observer variation and reliability[2] to ensure the consistency of ultrasound reports, as well as to see how easy it would be to use clinically. In the MSc it had been established as easy to use with good inter and intra-observer consistency but this was only possible after the introduction of a short period of relatively informal training. It was only after that study was complete that it could become possible to validate the scoring system clinically. Should the proposed scoring system prove reproducible and valid in a larger population, then a new clinical care pathway could be formulated for the improved care of CF patients, subject to widespread adoption by the clinical community.

A positive and supportive research culture has always been present at the author's place of work, and the author was already recognised as fully competent in the field of paediatric liver ultrasound. Facilities existed for the recruitment of patients with CFLD from a comprehensive database of liver disease, and encouragement for the recruitment of a normal cohort of patients for comparison was facilitated by the interest and support of the CF physicians. The concept of the study was based upon an extended literature review of the sonographic features of CFLD and portal hypertension, as well as critical evaluation of other work that had previously been carried out in this field.

A full and complete account of the methods and processes by which this research was underpinned and carried out, as well as the outcomes of the process can be found in the following chapters.

In summary, this research was necessary in order to fill a gap in the knowledge and treatment of CFLD and with the aim of furthering clinical care in this area. It was performed under good conditions, although specific advantages and disadvantages will be discussed in more detail.

[2]Inter and intra-observer testing gives an indication as to how reliable the measurement under test is. Consecutive analyses should not differ significantly from each other. In this instance the testing was performed by repeat analysis of 10 scans selected at random from a list of patients with CFLD. Each scan was scored by 5 individual observers, and repeated after an interval of time. The results were compared for consistency, which highlighted the need for training. The scores were then repeated after training, which showed a marked improvement in consistency on an inter and intra-observer basis.