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## ORIGINAL ARTICLE

# Are annual blood tests in preschool cystic fibrosis patients worthwhile?

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**Aim:** To investigate whether routine annual assessment blood tests in cystic fibrosis (CF) patients under 5 years influence management.

**Methods:** Retrospective review of the results of the first annual assessment blood tests of patients with CF less than 5 years of age during a four year period (1995–99). Management changes were identified from a follow up letter to the general practitioner or local paediatrician.

**Results:** A total of 169 patients (100 female), median age 2.2 years (range 0.3–4.9) were identified. Venepuncture was successful in 93% of patients. Of the 32 individual blood parameters measured, the overall success rate in obtaining a result was 81%. Eleven per cent of patients underwent subsequent management changes, including liver ultrasound, fasting glucose, and a short course of iron. Of particular importance, vitamin A and E concentrations were low in 9% of patients, which prompted an increase in prescribed dose.

**Conclusions:** These results support the recommendations for routine blood tests at annual review in preschool CF children. The results may help to rationalise which tests are performed and thus reduce laboratory costs.

The Cystic Fibrosis Trust recommends that all children with cystic fibrosis (CF) undergo an annual review at a specialist CF centre.<sup>1</sup> This consists of a multidisciplinary review by the CF team and specific blood tests which allow assessment of some of the clinical complications that may occur in CF<sup>2</sup> (table 1). However, despite these recommendations, some centres do not carry out the recommended blood investigations in the preschool child with CF. The reasons for this may be that venepuncture in this age group is technically difficult and may contribute to the development of needle anxiety. Secondly, it may be thought by some that blood tests in this population of relatively well children are usually normal. If this is true, routine blood tests in this age group are an unnecessary drain on resources. The aim of this study was to review whether annual assessment blood tests contribute to management in children under the age of 5 years.

## METHODS

A retrospective review of all blood tests performed at our centre at the first annual assessment was undertaken in children under the age of 5 years during a four year period (September 1995 to September 1999). Prior to venepuncture, a topical anaesthetic cream (2.5% lidocaine, 2.5% prilocaine (Emla, Astra Pharmaceuticals Ltd, Hertfordshire, UK) or 4% amethocaine (Ametop, Smith and Nephew Healthcare Ltd, Hull, UK)) was always applied. Fifteen ml of blood was taken by a paediatrician using a 23 gauge butterfly needle (Abbott Ireland, Sligo, Ireland). Values were compared to the Royal Brompton Hospital laboratory standard reference ranges and considered abnormal if outside 2 standard deviations from the mean of published normal data. One investigator (AB) reviewed all blood investigations, and management changes were identified from a contemporaneous follow up letter to the general practitioner and local paediatrician. Changes were said to occur if further investigations or change of medications were instituted.

## RESULTS

A total of 169 patients (100 female), median age 2.2 years (range 0.3–4.9) were identified. Venepuncture was successful

in 157 (93%) patients in obtaining some or all of the blood parameters requested. Of the 32 individual blood parameters measured, the overall success rate in obtaining a result was 81%. Values are expressed as a percentage of total blood tests available for the individual parameter. Table 1 presents the clinically relevant results. Of note, two children were needle phobic and were referred to a psychologist for behavioural therapy without venepuncture taking place. Overall, 18 patients (11%) underwent the following management changes: institution of iron therapy (n = 4), increased vitamin dosage (n = 8), liver ultrasound (n = 6), and fasting blood glucose (n = 2). Two of these patients had their vitamins increased and a liver ultrasound.

## Liver disease

A total of 110/152 children (72%) had raised aspartate transaminase (AST). Only 14 of these had an increased prothrombin time but had normal  $\gamma$  gluteryltransferase ( $\gamma$ GT) and alkaline phosphatase. One child with a very high alkaline phosphatase (>1000 U/l) had an increased  $\gamma$ GT and AST. The liver was architecturally normal in all six children who had a palpable liver and subsequently underwent ultrasound.

## Cystic fibrosis related diabetes (CFRD)

Nine of 149 children had a high random glucose, associated with a high glycosylated haemoglobin in two. CFRD was excluded in subsequent normal fasting sugars in these two patients.

## Pseudo-Bartter's syndrome

No child had an abnormal sodium concentration. Although two children had a low serum potassium it was not necessary to prescribe supplements. The number of high potassium

**Abbreviations:** ABPA, allergic bronchopulmonary aspergillosis; AST, aspartate transaminase; CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; ESR, erythrocyte sedimentation rate;  $\gamma$ GT,  $\gamma$  gluteryltransferase; RAST, radioallergosorbent test

**Table 1** Results of specific conditions associated with CF in the preschool child

Condition	Blood marker	% low values	% high values
Liver disease	$\gamma$ gluteryl transferase	0.7	1.4
	Aspartate transaminase	0	72.4
	Alkaline phosphatase	0.7	6.6
	Prothrombin time	2.6	14.9
	Platelets (hypersplenism)	1.3	33.6
CF related diabetes	Random or fasting glucose	6.0	6.0
	Glycosylated haemoglobin	1.6	2.4
Pseudo-Barrter's syndrome	Sodium	0	0
	Potassium	1.3	39.9
Nutrition	Cholesterol	78.4	0
	Triglycerides	0	19.8
	Albumin	9.8	0.7
	Total protein	17.8	0
	Vitamin A	9.3	0
	Vitamin E	8.6	10.9
	Calcium	0.7	19.2
	Phosphate	0	87.6
Iron status	Haemoglobin	2.7	2.7
	Iron	58.3	0.7
	Total iron binding capacity	0.9	17.9
Allergic bronchopulmonary aspergillosis	Immunoglobulin E	0	23.6
	Aspergillus specific RAST	*	62.8
	Aspergillus precipitins	*	4.5
Surrogate markers for infection	White cell count	1.3	10.7
	ESR	16.5	33.0
	IgG	6.2	1.4

Values are expressed as a percentage of total blood tests available for the individual parameters which fall outside the normal Royal Brompton Hospital laboratory limits.

\*Not applicable.

values reflect haemolysis because of technical difficulties in venepuncture in this age group.

### Nutrition

Vitamin A and E concentrations were low in 12/129 (9%) and 11/128 (9%) children respectively despite the prescription of vitamin supplementation. Albumin and total protein were reduced in 15/153 (10%) and 27/152 (18%) patients respectively. One child had a marginally low calcium, but no child had a low phosphate. Ten of 152 (7%) children had increased alkaline phosphatase levels but they were not associated with abnormal calcium or phosphate concentrations. Low concentrations of iron were seen in 85/144 (58%) patients while total iron binding capacity was increased in only 20/112 (18%).

### Infection

Two patients had a marginally raised immunoglobulin G (IgG). A total of 39/115 patients (33%) had a marginally raised erythrocyte sedimentation rate (ESR). Although 16/149 (11%) patients had a high white cell count, only three had a white cell count greater than  $20 \times 10^9/l$ . There was no association between a high ESR and high white cell count.

### Allergic bronchopulmonary aspergillosis (ABPA)

Three of 148 patients had an IgE over 1000 IU/ml, which in two was associated with a high aspergillus specific radioallergen sorbent test (RAST), but they did not have other features to suggest the diagnosis of ABPA. Although 63% (81/129) patients had a high RAST, this is a statistical quirk as the median was 0.35 IU/ml (range <0.34–100) and therefore was of no clinical significance in the majority of patients.

### DISCUSSION

Blood taking in this age group was relatively successful as more than 93% of patients had blood taken at first annual

assessment. In these patients, 80% of all results were obtained despite this being technically difficult in this age group. It was surprising that in this relatively well group, 11% of patients had management changes. It may be argued that these blood tests act as a screening tool for complications of CF and the results obtained in this study suggest that some of these conditions may begin early.

Although many children had abnormal liver function tests, those liver ultrasound examinations performed were all normal. These findings are not surprising as the prevalence of liver disease in this age group has been estimated at 0.3%,<sup>3</sup> and it is known that blood liver function tests do not correlate well with liver damage in CF. Some centres perform annual ultrasound examinations which may negate the need for annual liver function blood tests. However, it is not known which of clinical examination, biochemical, prothrombin time, or ultrasound investigation is the most sensitive screening tool for liver disease in CF. It is suggested that a fourfold rise in liver isoenzymes is associated with liver disease. Only one child in our study had such a high level. Thus, blood tests may highlight the child at risk early in disease progression and the sensitivity may be increased if combined with clinical examination with or without routine ultrasound.

CF related diabetes is a disease which occurs in the adolescent or adult with CF and is virtually unknown in the preschool child. The high random glucose values seen in our population probably reflect a high sugar load ingested just prior to venepuncture. Some centres advocate a fasting glucose, but this is inconvenient and unpleasant for young children, particularly in those who may have to travel long distances to attend the CF centre. Thus random glucose may not be a useful marker in this age group. It may be argued that this blood test could be replaced by simple urinalysis for glucose, although collecting urine is not always easy in this age group.

The low blood concentrations of vitamins A and E agree with previous studies.<sup>2-4</sup> Eleven patients (9%) had a low vitamin E concentration. This value is similar to those obtained by Feranchak *et al* who prospectively followed vitamin concentrations in a screened population of children with CF. They found that despite adequate supplementation, vitamin E concentrations remained low in approximately 10% of preschool children.<sup>4</sup> Conversely, most of the children they followed up corrected their vitamin A concentrations following supplementation. This was not the case in an audit of 100 older children (median age 9.8%).<sup>2</sup> Thirty per cent of this group had low vitamin A concentrations and 15% of patients had low vitamin E concentrations, despite the prescription of suitable vitamins. Some of the children in our study continued to have low vitamin A and E concentrations at subsequent annual assessments despite an increase in prescribed dose following the results obtained in this study (data not shown). A criticism of our study is that the measurement of vitamin concentrations is not standardised with respect to time between vitamin ingestion and venepuncture. Some centres measure fasting samples, but this is not convenient in this age group. A further confounding variable in all of these studies is that of adherence to therapy. Low vitamin concentrations may alert the physician to the patient who is not adhering to treatment, but it is recognised that, despite adequate supplementation, children with CF may become intermittently deficient in fat soluble vitamins. Thus this study has highlighted the need to routinely monitor vitamin concentrations in this age group which is consistent with the recommendations of the United States CF Foundation consensus guidelines on nutrition and the United Kingdom CF Trust.<sup>1,5</sup>

This study also highlighted other indices of poor nutrition and malabsorption in this group. A total of 116/148 children (78%) had a low cholesterol, reflecting the known incidence of pancreatic insufficiency in this disease. Furthermore, the low albumin in 10% and protein in 18% of patients confirms the known association with poor nutrition in CF, even at this age.<sup>6,7</sup> Feranchak *et al* found that hypoalbuminaemia was a significant risk factor for vitamin deficiency.<sup>4</sup> Thus blood tests in this age group may identify those patients with potential nutritional problems. Whether this method is better than a detailed dietary review and serial anthropometric measurements is unclear.

It is known that iron deficiency is common in adult patients with CF,<sup>8</sup> but it was surprising that 58% of children had low iron concentrations. Not all of these patients had an associated high total iron binding capacity, so it is probable that the low iron concentrations in most patients merely reflected chronic disease rather than true iron deficiency. Various theories for why iron deficiency occurs in CF, such as poor absorption, chronic inflammation, and increased concentration in the lower airways and sputum have been proposed. It has been shown previously that a two week course of iron increases haemoglobin concentration in patients with CF and iron deficiency<sup>9</sup>; hence four patients in our study with microcytic anaemia were treated with a short course of iron. However, some studies have shown no beneficial effect of iron supplementation, even when treated for longer periods.<sup>10</sup> Because reactive oxygen species may contribute to lung damage, a process catalysed by iron, the role of iron metabolism and iron supplementation in CF patients remains controversial.

The surrogate markers for infection and inflammation (ESR, white cell count, and IgG) in this study confirmed that only a small number of patients had clinically significant raised indices. These results are not surprising as this group of patients tend to be clinically well and many have not become chronically infected with *Pseudomonas aeruginosa*. However, it does discount the view that the young child is necessarily the well child. Although ABPA was not diagnosed in any of the children studied, it identified those children with a high IgE

and positive RAST and aspergillus precipitins. Although the blood investigations did not specifically alter management in these groups of patients, it may be argued that a role for blood tests in this age group may be the early identification of those patients at risk of subsequently developing infective complications, and results in heightened surveillance in these children.

In conclusion, this study has shown that abnormal blood tests occurred in a large number of preschool CF children which resulted in management changes in approximately 10%. Furthermore, they may highlight patients in whom there is a clinical suspicion of poor adherence and may identify patients early who are at risk of subsequently developing specific CF complications. These results support the recommendations for routine blood tests at annual review in preschool CF children.

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#### COMMENTARY

Some years ago, when I was an SHO, I questioned a consultant about the reasons for requesting a routine chest x ray on a patient who was clinically well. I was told that it was important to "keep one step ahead of the patient". That response satisfied me at the time, and I have used the quote from time to time when explaining to parents the reasons for undertaking investigations in children who have no overt clinical problems. Nowadays, clinicians and families are likely to require more tangible evidence of benefit before agreeing to children undergoing detailed investigations, particularly if these may be uncomfortable or distressing. Jaffe *et al*'s retrospective review is therefore a welcome attempt to address this issue with respect to routine annual blood tests in young children with cystic fibrosis (CF).

Annual review of patients with CF has been practised for some time in most CF centres in the UK and is now recommended by national guidelines.<sup>1</sup> The aims of annual review are numerous, but include the need to screen for asymptomatic disease outside the respiratory system. Most of these screening investigations require blood tests. As much of the treatment recommended for children with CF is directed

towards preventing clinical deterioration and improving long term outcomes and survival, the notion of being able to detect complications at an early, subclinical stage is one which fits well with the whole ethos of clinical management.

One of the difficulties in assessing this paper is that, in clinical practice, each screening blood test result is not considered in isolation when the annual review is discussed with parents and appropriate action is considered. An example of this is the early detection of CF-related liver disease, where there is no satisfactory screening test and by the time the disease can be diagnosed with certainty, there is often irreversible cirrhosis. In assessing whether any changes were significant, one would consider not only the results of liver function tests, but also clinical findings of enlarged liver or spleen and liver ultrasound appearances.

A second difficulty is that a single measure provides limited information which may not trigger a change in management and results are always considered in the context of previous ones. For example, it is recommended by some that biochemical liver disease should only be considered to be present if liver function tests were abnormal on two consecutive annual reviews.<sup>2</sup> In a child with borderline iron deficiency anaemia one would be more inclined to treat with iron if these findings persisted despite dietary advice.

The benefits of obtaining information from blood tests are much broader than those considered in this study. First of all, in the UK and other countries, national CF databases are now collecting data prospectively about incidence and prevalence of complications of CF, such as liver disease and nutritional status. Analysis of longitudinal data from such large databases

will provide important information about risk factors, prognosis, and possible strategies for prevention.<sup>3</sup> Without information from blood tests, such data will be incomplete.

Secondly, Jaffe *et al* have assessed changes in management, but there are other important outcomes from annual review. It provides everyone with an opportunity to discuss the child and his/her progress in detail and is regarded by most families as a useful and rewarding exercise. Parents, who are generally as well informed as their doctors, are often very gratified to hear about a normal result. This is particularly the case in a recently diagnosed child, where it is important to assess whether previously abnormal results have improved. While I agree with Jaffe *et al*'s recommendations, I feel that the most compelling reasons for having a complete dataset of information in young children at annual review were not evaluated in this study.

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## ARCHIVIST

### Health of boys in secure care

**B**oys in secure care because of serious or persistent offending are clearly a highly selected population at high risk of mental health problems. The mental health needs of boys in four secure units have been assessed (L Kroll and colleagues. *Lancet* 2002;**359**:1975–9; see also Commentary, *ibid*: 1956–7).

Ninety-seven boys aged 12–17 years were assessed on admission to secure care and while still in care 3 months later. More than a third of the children had been in social services care before admission, more than half had had at least two previous care placements, and almost three quarters were not attending school. They had committed serious or repeated offences (42 boys had committed offences that if committed by an adult would carry an expected prison sentence of 14 years or more). The mean age was 14.9 years, mean reading age 11.4 years, and mean reading comprehension age 9.9 years. Twenty-six had an IQ under 70.

At the time of admission the mean number of cardinal mental health problems per child was 8.5. Depression, anxiety, aggression, drug or alcohol misuse, and social and educational problems were all common. In some aspects the needs were well met. These included education, substance misuse, self care, and diet. After 3 months the mean number of cardinal problems had fallen to 2.9 but often problems persisted or new problems arose. Some problems were probably contained by secure care rather than managed successfully. Admission itself appeared to precipitate depression, anxiety, or post-traumatic stress in some boys. Assessment and provision for mental health needs was deemed inadequate. Three important needs are highlighted: better treatment for emotional disorders, better assessment and treatment for aggressive behaviour, and better treatment for substance misuse.

In the USA innovative approaches to the problems posed by young offenders include special drug courts, mental-health courts, and peer courts in which fellow adolescents play important parts. New approaches to sentencing include "multisystem therapy" and "wraparound" community based sentences

Young serious offenders have many mental health needs and current provision is inadequate. Newer legal approaches and sentencing provisions need to be considered along with better health services.