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Original article

The role, yield and cost of paediatric faecal elastase-1 testing

Nicholas Williams [a], Mary Moriatis [b], Georgina M. Chambers [c], Chee Y. Ooi [a, d, *]

[a] Sydney Children's Hospital Randwick, Sydney, Australia
[b] Department of Clinical Chemistry, South Eastern Area Laboratory Services, Randwick 2031, Australia
[c] Centre for Big Data Research in Health and the School of Women's and Children's Health, The University of New South Wales, Sydney NSW, Australia
[d] Discipline of Paediatrics, School of Women's and Children's Health, Medicine, University of New South Wales, Sydney, Australia

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ABSTRACT

Objective: Faecal elastase-1 (FE1) is a sensitive marker for exocrine pancreatic enzyme insufficiency. Pancreatic insufficiency (EPI) leads to maldigestion and subsequent poor weight gain. Thus, FE1 is performed as work-up for children with failure to thrive (FTT). However, EPI in the paediatric population outside of cystic fibrosis (CF) is rare. This study aimed to identify the indications for FE1 testing and their diagnostic yield in children. The secondary aim was to evaluate the cost per case of EPI detected for the various indications.

Design: All FE1 tests performed on children (0–18 years) at a tertiary paediatric hospital in Sydney, Australia between 2010 and 2013 (inclusive) were identified. A retrospective chart audit was performed to identify the indication for testing FE1. The diagnostic yield based on FE1 cut-offs <200 and < 100 μg/g were assessed.

Results: The most common indication for testing FE1 was "FTT only" (71/216, 32.9%), however, in this cohort of patients, FE1 was least likely to be positive with only 2 out of the 71 (2.8%) patients returning a positive result. In comparison, CF was the second most common indication for testing (60/216, 27.8%), but nearly half (48.8%) of tests returned a positive result in this cohort. The cost per case detected (FE1 <200 μg/g) reflected the test yield with an average cost per positive test of $262.50 (AUD2015) for FTT with short-gut syndrome and $420.00 (AUD2015) for CF-related indications.

Conclusion: Our study shows that for patients with isolated failure to thrive, FE1 testing is low yield and costly.

Introduction

Exocrine pancreatic insufficiency (EPI) in children is either primary or secondary, and in the vast majority is caused by cystic fibrosis (CF) [1]. Other primary pancreatic diseases in the paediatric population are rare [2]. Secondary EPI can occur with chronic states of malabsorption such as celiac disease [3].

Clinically, because pancreatic enzymes are required for the digestion and absorption of fats, starch and protein in the small bowel, patients with EPI will typically present with steatorrhoea, chronic diarrhoea and subsequent weight loss or poor weight gain. Thus, EPI is a differential diagnosis for failure to thrive (FTT), which is a common paediatric presentation estimated to occur in 3.7% of children in the United States, but up to 16% of children under 5 years of age when developing countries are included [4]. However, the differential diagnosis for children presenting with FTT is broad and involves almost all organ systems. It is often classified as either "organic" or "non-organic", reflecting that FTT can be caused by factors beyond the child. In clinical practice, FTT is often the result of inadequate caloric intake, and includes biological, environmental and psychosocial contributors [5,7]. In addition to FTT, pancreatic function testing is also considered in the evaluation of chronic diarrhoea and for monitoring of pancreatic function in patients with acute recurrent or chronic pancreatitis.

The gold standard for detecting EPI is the direct pancreatic stimulation test, which is now rarely performed due to its complexity, expense, radiation exposure and invasive nature [1]. As far as indirect and non-invasive pancreatic function testing is

* Corresponding author. Sydney Children's Hospital, Discipline of Paediatrics, School of Women's and Children's Health, Level 3, High Street, Randwick, NSW 2031, Australia. Tel.: +61 2 93821752; fax: +61 2 93821787.
E-mail address: keith.ooi@unsw.edu.au (C.Y. Ooi).

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concerned, the three-day faecal fat collection is considered the alternative gold standard. However, it is both cumbersome and labour intensive, and fails to identify the underlying aetiology of malabsorption. In contrast, faecal elastase-1 (FE1) testing is a relatively easy, non-invasive test that has been shown to be a sensitive method of detecting EPI in paediatric patients [6]. FE1 testing can be performed easily on a single, random stool sample. Furthermore, with the use of monoclonal assays, FE1 measurements are not affected in patients taking pancreatic enzyme replacement therapy (PERT) [7].

It is likely that FE1 and other tests like it, which are relatively easily performed and non-invasive, are contributing to the exponential rise of laboratory tests worldwide. Currently, laboratory tests are doubling in rate every 5–10 years, which is out of keeping with the increasing and aging population [8]. This has significant fiscal implications at a time when healthcare budgets are under increasing pressure and laboratory tests are being scrutinized by cost-effective analyses. With no clear evidence or current guidelines to inform clinicians of appropriate testing of FE1, it is likely that this test is being ordered for a wide range of indications, some of which are unlikely to result in a diagnosis of EPI.

The primary aim of this retrospective study was to investigate the indications for testing FE1 and to evaluate the yield of FE1 for these various indications. The secondary aim was to evaluate the cost per case of EPI detected for the various indications.

Methods

Subjects

Children 0–18 years old who had FE1 performed at Sydney Children's Hospital Randwick, New South Wales, Australia between January 1st, 2010 and December 31st, 2013 were identified through the hospital pathology service (South Eastern Area Laboratory Services) database. A retrospective chart review was performed to determine the primary indication for FE1 testing. This study was approved by the SCH Network Human Research Ethics Committee (LNR/14/SCHN/280).

The indications for FE1 testing were grouped into the following categories:

1. Cystic fibrosis (CF)-related – (i) as part of the diagnostic workup for suspected diagnosis of CF with patients eventually receiving either a diagnosis of CF or not CF, (ii) for monitoring of exocrine pancreatic status in pancreatic sufficient patients to monitor for progression of pancreatic disease from pancreatic sufficiency to insufficiency [9,10], or (iii) for confirmation of EPI in patients with an established diagnosis of CF but who did not undergo previous exocrine pancreatic function testing.
2. Failure to thrive with chronic diarrhoea;
3. Failure to thrive associated with short gut syndrome (as defined by small bowel length <100 cm in the 1st year of life) [11];
4. Failure to thrive only – as the primary manifestation and not associated with chronic diarrhoea or short gut syndrome;
5. Chronic diarrhoea without FTT;
6. Pancreatitis – to monitor for exocrine pancreatic status following recurrent episodes of acute pancreatitis or in chronic pancreatitis;
7. Other – for any indication which did not meet the preceding categories.

Faecal elastase-1 assay

Faecal elastase-1 was measured in duplicate from spot stool samples with an enzyme-linked immunosorbent assay (Schebo Biotech Kit, Biotech AG, Germany). The spot stool samples were first homogenised using a vortex mixer to ensure a complete extraction of pancreatic elastase-1. Results were expressed as micrograms (μg) of elastase-1 per g of stool. The limits of detection were 15–500 μg/g. For the purposes of the study, results <200 μg/g were considered positive (or abnormal) [6,7]. We also evaluated, as a sub-analysis, the yield of FE1 based on a cut-off of <100 μg/g as this cut-off was previously reported to provide excellent sensitivity and specificity to distinguish between pancreatic sufficiency and insufficiency in children [6].

Costs of FE1 testing (in Australian Dollars)

The cost of a FE1 assay to each patient was $140, as advised by the hospital pathology service provider finance department. This includes the direct costs of the FE1 kit and the labour to process the assays, as well as indirect and overhead costs. Dividing the sum of the cost of the tests by the number of positive EPI results for each clinical indication was performed to provide a broad estimate of the average cost per EPI detected.

Statistical analysis

Variables were described as mean (standard deviation (SD)) or median (interquartile range) depending on the normality of data distribution.

Results

A total of 220 FE1 tests were performed on 164 patients between 2010 and 2013. The mean (SD) age at time of testing was 3.6 (4.5) years. Ninety-seven of 164 (59%) patients were males. Inpatient and outpatient collection were equally represented with 110 of 220 (50%) tests ordered in each setting. Four results were excluded as no indication could be identified following chart review, resulting in 216 tests suitable for analysis. The most common indication for FE1 testing was FTT only (71; 32.9%), followed by CF-related (60; 27.8%), chronic diarrhoea without FTT (29; 13.4%) and FTT with chronic diarrhoea (25; 11.6%).

Of the 216 FE1 tests, 41 results were less than 200 μg/g and were therefore considered as "positive" tests (Table 1). The CF-related cohort had the largest number of positive tests (20; 48.8%), followed by FTT associated with short-gut syndrome (8; 19.5%) and FTT with chronic diarrhoea (5; 12.2%). The diagnostic yield varied according to the various indications (Tables 1 and 2). Despite "FTT only" being the most common indication, only 2 tests (2.8%) returned a positive result. The FTT with short-gut syndrome cohort returned the highest yield with eight positive results of the total 15 tests (53.3%), followed by CF-related (20/60, 33.3%).

Of the two patients within the FTT cohort who had a FE1 result <200 μg/g (31 μg/g & 36 μg/g), one was subsequently diagnosed with Pearson Syndrome (a mitochondrial disease which results in exocrine pancreatic dysfunction). The second patient had a history of poor weight gain following removal of a long-segment Hirschprung's disease but did not meet the diagnostic criteria for short-gut syndrome.

When only FE1 levels <100 μg/g were considered "positive", the total number of positive FE1 results was 29/216 (13.4%). The finding of FE1 <100 μg/g according to the different indications are summarised in Tables 1 and 2. The majority (19/20) of the CF-related tests with a result <200 μg/g remained positive when the FE1 threshold was lowered to <100 μg/g. The one patient who had a result >100 μg/g (199 μg/g) went on to have a repeat FE1 test of <100 μg/g and was subsequently commenced on PERT. In contrast to the CF-related results, the FE1 yield halved in the FTT with short-

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