Diagnosis of exocrine pancreatic insufficiency in cystic fibrosis by use of fluorescein dilaurate test

Sir,

Professor Cuschieri and colleagues suggest that use of fluorescein dilaurate in an oral pancreatic function test may, by detecting different levels of pancreatic function, differentiate between patients with cystic fibrosis who do not require exogenous enzyme supplementation and those who do. The authors also propose the fluorescein dilaurate test as a screening test for pancreatic insufficiency to reduce the number of false positive diagnoses of cystic fibrosis. Examination of their data leaves me sceptical of these claims made on behalf of the test, for the following reasons.

1. The implicit suggestion in this paper, that positive correlation of fluorescein dilaurate test result with faecal chymotrypsin value indicates this test to be semi-quantitative in assessing pancreatic function, is unsupported; I know of no evidence that faecal chymotrypsin correlates well with more direct measurements of exocrine state. Had faecal chymotrypsin values from the control group been presented, I suspect the overall correlation between faecal chymotrypsin and fluorescein dilaurate test result would have been very poor.

2. The authors chose a cut off point of 20 for the fluorescein dilaurate test result, above which level gross pancreatic hypofunction was held to be excluded. A single patient with cystic fibrosis had a urinary fluorescein dilaurate value above this figure but also experienced no change in bowel habit once enzyme supplements were withdrawn. If, on further investigation, this patient was confirmed to have pancreatic sufficiency, the fluorescein dilaurate test as a screening test for pancreatic disease would seem to be no more sensitive than a clinical history of steatorrhoea. If, on the other hand, this same patient was shown indeed to have pancreatic insufficiency the fluorescein dilaurate test would have proved to be less sensitive than a simple measurement of faecal chymotrypsin, low in all the group with cystic fibrosis.

3. We are told little about the controls other than that they were healthy. The fluorescein dilaurate test results show a very wide scatter (13.2-62.2), with three of the 15 giving values of 20 or below—that is, by the authors’ criteria, indication for further investigation of pancreatic function. Used as a screening test for pancreatic disease, 20% false positive results give a specificity of only 80%. I wonder if the faecal chymotrypsin values in controls might have proved considerably more specific?

A simple, non-invasive test of pancreatic function with both high sensitivity (positivity in disease) and high specificity (negativity in absence of disease) together with the ability to delineate degrees of functional capacity must be considered yet to be found.

Reference


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Recurrent neural tube defects, risk factors and vitamins

Sir,

Wild and her colleagues conclude that the highly significant difference in recurrence rates of neural tube defects between mothers who took periconceptual vitamins and those who did not, in the study reported by Smithells and his colleagues, was due to vitamin supplementation. They argue this on the basis that no significant confounding was found with certain factors such as social class or immediately prior miscarriage.

There are two problems with the paper. The first problem is that statistical re-analysis of the existing data cannot overcome bias that may have been introduced through patients presenting themselves and complying with supplementation being, in any case, at a relatively low risk of having a neural tube defect pregnancy. Allowing for known confounding factors cannot, of course, avoid bias from unknown ones. Although the authors conclude that bias from unknown confounding factors is unlikely to be of importance, we believe that in this particular instance it may have been critical. Most cases of neural tube defects, including recurrences, cannot be predicted by known means, indicating that the main risk factors are still unrecognised and could therefore exert a substantial confounding effect. Also adjusting for certain variables that might be confounding factors, but in fact were not, and then showing that adjustment for these variables did not alter the magnitude of the association is uninformative.

It does not alter the strength of the evidence concerning whether the association was causal or due to bias.

The second problem relates to social class, and this has been the subject of previous publications. One of us, with Professor Polani, has shown that some bias was introduced because, as expected, women in the vitamin supplementation group who took extra vitamins tended to be of higher social class than women who did not; they were also, by virtue of their social class, less likely to have a further pregnancy associated with a neural tube defect. We used data from the first cohort of pregnancies in the vitamin supplementation study conducted by Smithells and his colleagues. In a letter replying to our paper they said that if data from both the first and second cohorts were aggregated no social class confounding was evident (the conclusion that Wild and her colleagues reach again in their present paper). Our response to the letter still
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