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Tenuous link between chronic fatigue syndrome and pyruvate dehydrogenase deficiency

OPINIONS

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Researchers studying the energy metabolism of patients with chronic fatigue syndrome have reached the conclusion that these patients have impaired pyruvate dehydrogenase function, but their measurements are not consistent with the changes we see in patients with primary genetic pyruvate dehydrogenase deficiency.

A cross-sectional study published in December 2016 found a change in the pattern of amino acids in the plasma of patients with chronic fatigue syndrome. Gene expression in white blood cells and energy metabolism in muscle cells was also found to have changed (1). The authors interpret the results as an expression of functional inhibition of the enzyme pyruvate dehydrogenase, and they postulate dysregulation of the enzyme complex as a possible key factor in the pathogenesis associated with chronic fatigue syndrome.

The study received extensive media coverage (2, 3), and the link to pyruvate dehydrogenase is published without reservations as an established fact (4, 5). At our laboratory we are now receiving samples for metabolic screening from patients with suspected fatigue syndrome. On the basis of my own experience

with biochemical diagnostic workup for pyruvate dehydrogenase deficiency, I would like to point out weaknesses in the study that should have prompted much greater caution in the conclusions.

Criticism of method and interpretation

The plasma amino acid concentrations of 200 patients and 102 healthy control persons were examined in the study. The researchers found significant differences between the two groups, but the implications of this are uncertain because they did not adhere to established diagnostic workup for pyruvate dehydrogenase deficiency, and because the samples were not taken in a standardised manner.

The amino acid pattern is not consistent with what we see in patients with primary pyruvate dehydrogenase deficiency

Pyruvate dehydrogenase deficiency results in an increased concentration of pyruvate, in muscle and nerve cells, for example. Pyruvate is converted into lactate and the amino acid alanine. Alanine is the only amino acid that is expected to be outside the reference range in plasma and cerebrospinal fluid in cases of primary pyruvate dehydrogenase deficiency (one and a half times to twice the upper reference limit) (6). However, the study reports a tendency to a *lower* alanine level in these patients. It is surprising that this striking discrepancy is not mentioned in the article.

Failure to standardise sampling may explain the difference between the groups

A fasting sample is strongly recommended for assaying plasma amino acid concentrations, because levels vary substantially with diet, and also naturally over a 24-hour period, by up to 10–15 % (6). In the study, non-fasting amino acid patterns with small differences are compared; significance is attached to differences down to 3 %.

It is very strange that the authors do not make greater reservations about diet as a confounding factor, when they themselves have shown that diet affects precisely the group of amino acids that they use in their argument for pyruvate dehydrogenase deficiency.

The study found significant differences between fasting and non-fasting patients. The fasting patients were therefore excluded in subsequent statistical work. The authors should then also have made clearer reservations to the effect that a possible concealed discrepancy between patient group and control group with respect to diet and sampling might be an alternative explanation for several of the differences they found. Systematic dietary differences between the groups are not inconceivable.

Gastrointestinal symptoms (abdominal pain, nausea, irritable bowel etc.) are some of the consensus criteria for the diagnosis (7). There have been earlier reports of special dietary habits among patients with chronic fatigue syndrome

(8).

What about the pyruvate/lactate ratio and direct measurement of pyruvate dehydrogenase activity?

The pyruvate/lactate ratio in plasma may distinguish patients with pyruvate dehydrogenase deficiency from other patients with hyperlactacidaemia. The ratio therefore plays a central part in the biochemical workup of pyruvate dehydrogenase deficiency (9).

The pyruvate/lactate ratio was not determined in the study. This is unfortunate, because the ratio could have provided important evidence for, or against, pyruvate dehydrogenase deficiency. Direct determination of enzyme activity in cells is also a key factor in routine diagnosis of pyruvate dehydrogenase deficiency. It is strange that this was not performed in the study of muscle cells cultured in the presence of patient serum.

Specific link to chronic fatigue syndrome requires several control groups

The expression pattern of genes associated with the pyruvate dehydrogenase complex differed between the patient group and the control group in the study. This is an interesting result, but the study does not provide grounds for interpreting the difference as specific to chronic fatigue syndrome.

According to the consensus criteria, the patients have had a "substantially reduced activity level" lasting for "at least six months" (7). It is well known that genes associated with the *entire* energy metabolism (including pyruvate dehydrogenase complex) are changed by immobilisation (10). Musculature grows and dwindles depending on the activity level; different expression patterns between the two groups in this study are therefore only to be expected. Before the expression pattern can be linked specifically to chronic fatigue syndrome, the patients must be compared not only with healthy subjects, but also with other patient groups who experience a similar reduced activity level, for example patients with stroke, broken bones, renal failure or severe depression.

The study also found that the energy metabolism of muscle cells in vitro changed in the presence of serum from patients with chronic fatigue syndrome. It is interesting that this can be shown experimentally, but this observation cannot be used either as a link specifically to chronic fatigue syndrome. Here, too, more control groups consisting of patients with a reduced activity level for other reasons are needed. For example, the study shows reduced production of high-energy phosphates (ATP) in vitro. In a mouse model in which cultivated muscle cells are exposed to serum from individuals with muscular atrophy and chronic renal failure, ATP production is also reduced (11).

Chronic fatigue syndrome is not typical of primary genetic pyruvate dehydrogenase deficiency

The authors suggest that pyruvate dehydrogenase deficiency is a key to the pathophysiology of chronic fatigue syndrome. Chronic fatigue is not a typical symptom of patients with primary genetic pyruvate dehydrogenase deficiency, either the severe or the mild form (9). This requires a comment, but is not mentioned at all.

Objective assessments called for

Research on metabolic mechanisms associated with chronic fatigue syndrome is interesting, and the major work of Fluge et al. may generate hypotheses that are well worth investigating further. But the authors have been too quick to state almost categorically that pyruvate dehydrogenase deficiency is a part of the pathophysiology underlying chronic fatigue syndrome. At present, the link between detected amino acid changes and pyruvate dehydrogenase deficiency is too tenuous, and the change in gene expression and energy metabolism too non-specific for so categorical a conclusion.

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