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Short communication

Zinc therapy for night blindness in cystic fibrosis

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Abstract

This is the first report of a supplemented CF patient presenting with clinical vitamin A deficiency to be successfully treated with zinc therapy alone. Therefore in addition to retinol supplementation, normalizing serum zinc levels may be important in maintaining the vitamin A status of CF patients. The interactions and synergistic effects between the two micronutrients are discussed.

Keywords: Night blindness; Cystic fibrosis; Zinc therapy

1. Introduction

Night blindness in cystic fibrosis (CF) is rare, but may occur with vitamin A deficiency secondary to malabsorption [1]. Some patients develop nyctalopia despite oral vitamin A supplementation [2,3]. We successfully treated such a patient with zinc sulphate alone and discuss the interactions between the two micronutrients.

2. Case report

A 23 year old woman with CF was referred to the West of England Eye Unit with a two week history of ocular discomfort, difficulty seeing in dim light and colours assuming a green hue. She was diagnosed with CF after presenting with meconium ileus at 5 weeks of age (δF_{508} homozygote; sweat test Na^{+}104-mmol/l), and had complications of adhesions requiring small bowel resection as a child. In addition, she had cystic fibrosis-related diabetes and severe respiratory impairment (FeV_1 1.45 l, FVC 1.97 l, PEF 280 l/min). Medical therapy at the time consisted of oral prednisolone 10 mg, nebulised colomycin, budesonide/formoterol fumarate inhalations, and insulin. Daily oral supplementation included pancreatic enzymes, vitamin A 4000 IU, vitamin D 400 IU, multivitamins (vitamin A 5000 IU, vitamin D_3 600 IU, vitamin $B_{1,2\&3}$,vitamin C), vitamin E 400 IU, vitamin K 10 mg, ferrous sulphate 400 mg, and calcium carbonate/vitamin D_3 400 IU.

Visual acuity was 6/9 in each eye and there was no red–green colour deficit. Focal areas of keratinisation (Bitot's spots) were present on the interpalpebral conjunctivae with bilateral diffuse corneal punctate epitheliopathy. Posterior segment examination was normal. Serum vitamin A was low, 0.2 mg/l (1.5–4.2), but had been less than 0.7 mg/l for the previous 5 years, despite compliance with vitamin supplementation. A serological zinc deficiency was also present, with levels measured at 8.1 μmol/l (11.4–24.8). There was no evidence of fat malabsorption clinically, but her BMI was low (19.6), and there were deficiencies in other fat soluble vitamins (vitamin D 7.5 ng/ml (25–50), vitamin E 6.4 mg/l (11.6–37.1), normal clotting profile). No fat studies on stool were performed however. Hepatic enzymes were mildly deranged (ALT 47U/l (5–31), ALP 108U/l (34–102), but synthetic function (bilirubin, albumin) was normal.

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An electroretinogram (ERG) was performed, which showed no response to rod stimulation with a dim blue flash (Fig. 1A) and reduced A and B wave amplitudes to a bright white flash in dark-adapted conditions. Cone responses were normal. Treatment was commenced with oral zinc sulphate 220 mg tds alone (Zincomed®, 50 mg elemental zinc per 220 mg tablet). Within 1 week there was a dramatic improvement in the symptoms of nyctalopia and signs of xerophthalmia, with recovery of serum zinc levels (12.1 μmol/l). Serum vitamin A levels remained low however, at 0.2 mg/l. Repeat dark-adapted ERG demonstrated a clear rod response, indicating full restoration of rod photoreceptor function (Fig. 1B).

3. Comment

Zinc is absorbed by enterocytes in the proximal small intestine, and zinc deficiency has been associated with malabsorption syndromes such as CF [4]. In CF, unabsorbed fat specifically interferes with the re-absorption of endogenous zinc [5], and this, together with prior small bowel resection, may have contributed to the zinc deficiency in this case. Furthermore, iron supplementation has been shown to inhibit zinc absorption in the human small intestine [6].

The knowledge of zinc metabolism in the eye is fragmentary. Much of the evidence for its role in retinal function comes from interaction studies with other nutrients, a few naturally occurring diseases and *in vitro* studies [4]. It is known that zinc interacts with taurine and vitamin A in the retina, modifies plasma membranes in the photoreceptors, regulates the light-rhodopsin reaction within the photoreceptor, modulates synaptic transmission and serves as an anti-oxidant in both the retinal pigment epithelium and retina [4]. Although zinc deficiency was previously thought to impair retinol dehydrogenase activity, it is now known that this enzyme is zinc independent [7]. However, numerous other enzymes important in the visual cycle may be zinc dependent. Zinc deficiency can depress the hepatic synthesis of retinol-binding protein (RBP) and lead to lower concentrations of RBP in the plasma, which is required for mobilization of retinol from the liver [8]. In addition, there may be a specific role of zinc in the conversion of β-carotene to retinol via the enzyme 15-15 dioxygenase [9].

Zinc deficiency has been implicated in rod dysfunction and a patient with liver cirrhosis and night blindness was reported to show an improvement in rod ERG's after treatment with oral cholagogues, and this was attributed to recovery of deficient serum zinc levels and liver function [10]. Morrison et al. demonstrated a rapid recovery in cirrhotic patients with impaired dark adaptation and low serum zinc levels on zinc supplementation alone [11]. There appears to be an interaction between zinc and vitamin A in patients suffering from various pathological conditions that severely compromise hepatic function, such as alcoholic cirrhosis, CF and idiopathic haemochromatosis [8]. In humans, cross-sectional studies have more often than not shown a weak linkage between vitamin A and zinc status [8]. However randomized trials have failed to show a consistent effect of zinc supplementation on vitamin A status [8]. Circulating zinc and vitamin A levels appear unrelated in well-nourished states, but tend to co-vary in marginally nourished individuals, with co-existing zinc and vitamin A deficiencies [8]. Intestinal vitamin A malabsorption may be due to specific effects of zinc deficiency beyond any generalized effects of malnutrition. Thus zinc deficiency may result in a secondary vitamin A deficiency that is reflected in low serum vitamin A concentrations [7]. Conversely, severe vitamin A deficiency may reduce absorption and lymphatic transport of zinc by altering the synthesis of zinc-dependent binding protein [8].

Low serum vitamin A levels occur frequently in clinically stable, retinol-supplemented CF patients [12]. However due to the absence of a statistical correlation between hepatic and plasma levels of retinol in CF, serum retinol does not reflect

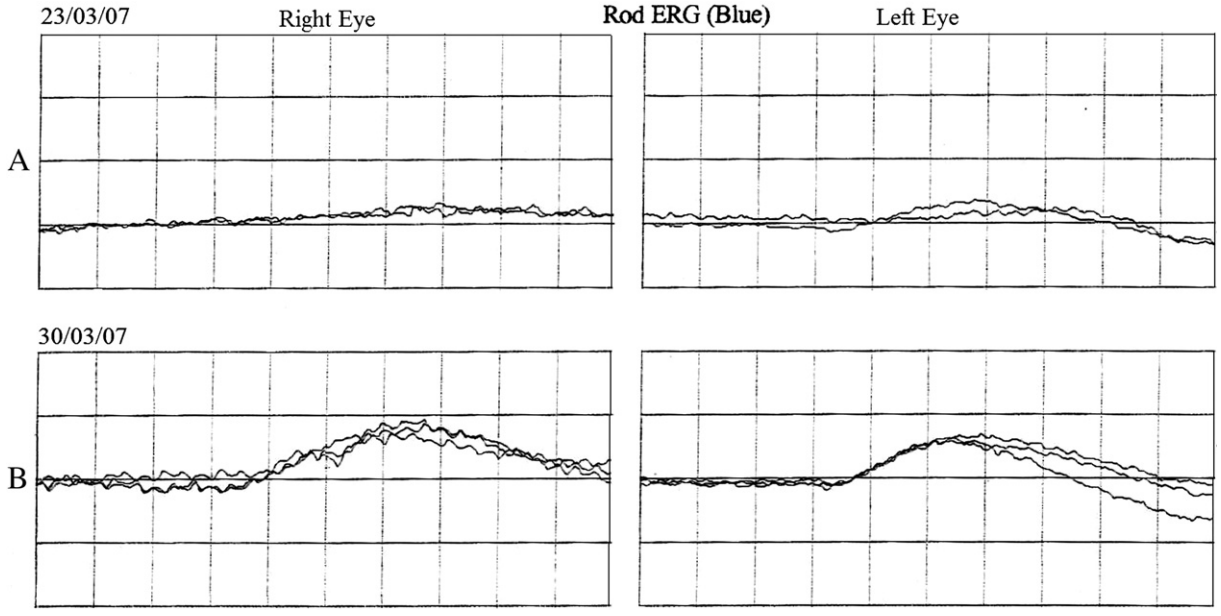

Fig. 1.

vitamin A status [12]. A defective mobilization of vitamin A from liver storage tissues has been proposed as the reason for this, which indeed may be due to a co-existing zinc deficiency. Thus even in the presence of adequate hepatic vitamin A reserves, night blindness may occur when zinc deficiency exists [7]. However, to date, studies regarding zinc-related vitamin A deficiency in CF have been inconclusive [8].

A proportion of CF patients on oral vitamin A supplementation have abnormal dark adaptation and conjunctival xerosis due to vitamin A deficiency [13]. Some patients with abnormal dark adaptation do not respond to increasing their vitamin A intake until zinc supplements are administered [13]. In CF patients with vitamin A deficiency, therapy can be commenced with intramuscular water soluble vitamin A 30 000 IU [14]. However in this case it was difficult to source locally. Furthermore, high-dose vitamin A supplementation should be given with caution due to its potential for hepatotoxicity and risk of intracranial hypertension [12]. It was previously thought that among zinc deficient subjects, zinc on its own may not resolve night blindness or poor dark adaptation, but acts only to potentiate vitamin A in preventing night blindness [7]. This is the first report of a supplemented CF patient presenting with clinical vitamin A deficiency to be successfully treated with zinc supplementation alone.

Therefore in addition to retinol supplementation, normalising serum zinc levels may be important in maintaining the vitamin A status of CF patients. A routine enquiry as to whether patients were experiencing problems seeing at night would seem worthwhile. The European consensus on nutrition in patients with CF recommends up to 10 000 IU daily of fat soluble vitamin A, to maintain serum concentrations within the normal range. If serum concentrations are found to be low, despite supplementation to these levels, consideration should be given to patient compliance and zinc levels should be measured [15].

Conflict of interest

None of the authors have financial and/or personal relationships with other people or organisations that could inappropriately influence this work.

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None.

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