Experimental and Clinical
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Case Report

Chronic intestinal Giardiasis with isolated levothyroxine malabsorption as reason for severe hypothyroidism – Implications for localization of thyroid hormone absorption in the gut

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Summary: We report a case of isolated levothyroxine malabsorption in the course of chronic intestinal giardiasis, leading to severe hypothyroidism. Infection with Giardia lamblia was proved histologically by jejunal biopsy. Treatment with metronidazole resulted in complete elimination of parasites and recovery of regular intestinal thyroid hormone absorption. Stable euthyroidism was accomplished with common replacement doses of orally administered levothyroxine.

Introduction

Despite concurrent replacement therapy with high doses of levothyroxine, some patients might be seen with clinical and biochemical evidence of hypothyroidism. Recently, 4 patients were reported with hypothyroidism receiving supraphysiological doses of levothyroxine sodium which were unable to restore and maintain euthyroidism. In all cases intestinal malabsorption was supposed but could be excluded by absorption studies showing a normal increase of serum T_4 concentrations after oral administration of 1 mg levothyroxine. Therefore, the authors concluded that noncompliance with therapy, mimicking levothyroxine malabsorption, is the main reason for ineffective treatment with thyroid hormones (Ain et al., 1991). Nevertheless, genuine levothyroxine malabsorption has been reported under various circumstances (Hays, 1988). Levothyroxine sodium, the usual preparation for oral replacement therapy, is probably absorbed in the small intestine and its bioavalibility is approximately 81% (Fish et al., 1987; Hays, 1968). In principle, each intestinal disorder associated with mucosa alteration might led to malabsorption including levothyroxine. Impairment of levothyroxin absorption has been observed in the setting of congestive heart failure, in severe hepatic cirrhoses, in short-bowel syndrome and after jejunoileal bypass procedures (Azizi et al., 1979; Bevan and Munro, 1986; Hays, 1968; Stone et al., 1984; Surks et al., 1973). Interactions between levothyroxine and various drugs, like cholestyramine, sucralfate and antacids may also reduce intestinal absorption

(Northcutt et al., 1969; Sperber and Liel, 1992; Vick and Wennerberg, 1989).

Case report

We report a 62-year-old female who has been treated with radioiodine and near-total thyroidectomy for hyperthyroidism due to Graves' disease at the age of 54. Postoperative oral thyroid hormone replacement was initiated with a daily dose of 150 µg levothyroxine sodium. One year later when she was referred for control she complained of tiredness and sensitivity to cold. Further symptoms were stiffness and aching of muscles, hair loss, dry skin and brittle nails. Her voice became husky and chronical constipation had developed. Clinically, the patient presented the typical picture of myxedematous hypothyroidism with palor and cold thickened skin, nonpitting edema, periorbital puffiness and mental and physical lethargy. The ECG showed peripherial low-voltage and ST-changes suspicious of coronary artery disease. Laboratory tests revealed a markedly elevated serum cholesterol up to 450 mg/dl. Noncompliance with levothyroxine therapy was strictly denied and drug taking in due form was confirmed by the daughter of the patient. Serum T_4 was 21 nmol/l (normal range: 64–180), serum T_3 was 0.7 nmol/l (normal range: 0.9–3.1) and serum TSH was 72.8 mU/l (normal range: 0.35–4.5), confirming severe hypothyroidism. Subsequently, the levothyroxine dose was raised stepwise up to 2000 µg per day without achieving euthyroidism. A change of the replacement regime by giving liothyroxine alone or in combination with levothyroxine was also ineffective in removing hypothyroidism. The patient, therefore, was treated with intravenously-administered levothyroxine in a dose of 500 µg twice weekly for at least 3 years. Then, after discontinuance of levothyroxine injection for 4 weeks, she was admitted to the hospital for reevaluation. On admission day serum free T_4 was 2.8 pmol/l (normal range 10.3–29.6), serum T_3 was 1.2 nmol/l and serum TSH was 58.0 mU/l and the patient appeared clinically hypothyroid again. Inpatient evaluation revealed normal gastrointestinal roentgenograms and an inconspicuous endoscopic aspect of the upper gastrointestinal mucosa. Fecal fat and chymotrypsin concentration was normal. Serum ferritin, cobolamin and folate were also found within the reference range. Disaccharidase deficiency was excluded by the hydrogen breath test. In contrast, a 5 h urine D-Xylose excretion of only 1.93 g (normal >4.5 g) suggested markedly impaired carbohydrate absorption. Histological examination of duodenal and jejunal biopsies showed a regular intestinal mucosa organisation

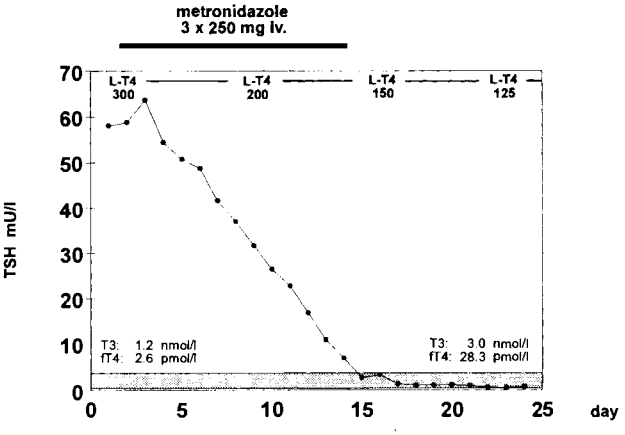

Fig. 1 Serum TSH levels before, during and after metronidazole treatment (the reference range is indicated as shaded area). Duration of metronidazole therapy and oral replacement doses of levothyroxine (in µg) are given at the top. Serum thyroid hormone concentrations at hospital admission and prior to release are also shown (reference ranges: T3 0.9–3.1 nmol/l; fT4 10.3–29.6 pmol/l)

with only minor inflammation signs in the duodenal specimens. In the jejunal biopsies moderate cellular mucosa infiltration was found with a slightly decreased villus/crypt ratio. Furthermore, at the mucosal surface a large number of Giardia trophozoites could be identified. An intravenous therapy with metronidazole was performed (250 mg, for threetimes daily) for 2 weeks and histological control after treatment showed complete eradication of intestinal parasites with improvement of mucosal alteration. Simultaneously, thyroid hormone replacement was changed again into an oral regime, with an initial dose of 300 µg levothyroxin per day which was reduced stepwise down to 125 µg per day prior to hospital demission. Follow-up of serum thyroid hormone parameters during therapy showed rapid restoration of euthyroidism suggesting normalization of intestinal levothyroxin absorption (Fig. 1). In the following years the patient was in a stable euthyroid state with a daily oral replacement dose of 125 µg levothyroxine.

Discussion

This is the first report, to our knowledge, of levothyroxine malabsorption in the course of infectious intestinal disease. Giardia lamblia is a multiflagellar protozoon that parasitizes the human duodenum and jejunum. Clinical manifestations appear to be caused by an impairment of the absorptive capacity of the gut, particulary for fat and carbohydrates. Infection with Giardia lamblia is known to be facultatively associated with watery diarrhea in the acute state and malabsorption signs

in its chronic form (Marsden, 1978). In our patient severe hypothyroidism despite high-dose thyroid hormone replacement therapy was the only symptom pointing to an underlying intestinal disorder. Probably, the leading symptom of Giardiasis, diarrhea, was superimposed by altered gut motility caused by thyroid hormone deficiency. Causal relationship between jejunal Giardiasis and ineffective levothyroxine treatment was proved by complete normalization of serum thyroid hormone parameters during metronidazole administration (Wolfe, 1982). In rats, levothyroxine is shown to be absorbed predominantly in the colon and in the ileum and less efficiently in the duodenum and the jejunum (Chung and van Middleworth, 1967). The main site of thyroid hormone absorption in man is not clear. Absorption studies with tracer doses of oral ^{125}I-levothyroxine sodium in patients with surgically shortened bowel indicated that residual length of bowel was positively correlated with the amount of levothyroxine absorption. Absorption of T_4 found in the presence of duodenum only was negligable suggesting that this is not the important site. Ileum function in T_4 absorption could not be assessed because none of the investigated patients had an intact ileum (Stone et al., 1984). The results of short bowel studies are confirmed by our observation of impaired levothyroxine absorption during infection with a selective small intestine parasite. Therefore, on the contrary to rats, appreciable colonic levothyroxine absorption in man seems to be less probably. Furthermore, the ileum also seems not to be the main absorption site in humans because Giardiasis is usually limited to the proximal small intestine. We conclude, from literature data and our own observations, that intestinal thyroid hormone absorption in humans is predominantly focused on the jejunum.

We recommend that patients suffering from hypothyroidism despite adequate exogeneous thyroid hormone replacement, may undergo subtle gastrointestinal examination including biopsies of the small intestine mucosa. Infection with Giardia lamblia can be accompanied by altered thyroid hormone absorption, even in the absence of other malabsorption symptoms.

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