CASE REPORT

Lead poisoning secondary to hyperthyroidism: report of two cases

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Abstract

With long-term exposure to lead, lead accumulates in bone, where it is stored for years. These quiescent lead stores are mobilised when increased bone turnover occurs, and latent lead toxicity may then become symptomatic. Although Graves' disease is a common cause of increased bone turnover, to date hyperthyroidism has been implicated in lead poisoning only twice. We describe herein two cases of hyperthyroidism, one caused by toxic multinodular thyroid enlargement, the second by Graves' disease, leading to lead poisoning. Treatment of hyperthyroidism with radioactive iodine cured both hyperthyroidism and lead poisoning and no chelating agent therapy was necessary. Lead poisoning is an important environmental health problem, and physicians must be aware of the endocrine disorders such as hyperthyroidism and hyperparathyroidism that increase bone turnover, favouring lead mobilisation. Atypical symptoms should draw the physician's attention to the possibility of lead poisoning, particularly in workers with occupational exposure to lead and in areas where lead poisoning is endemic.

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Introduction

About 1200 deaths were attributed to occupational lead poisoning in England and Wales between 1900 and 1933 (1). During the past 50 years deaths from lead poisoning have become rare, because of progress in diagnosis and legislation aimed at reducing the hazards presented by large-scale industrial use of lead and lead compounds. A large, well-conducted population survey was carried out in the early 1980s to assess blood lead concentrations of lead in areas with differing levels of environmental lead pollution (2). Some of the highest blood lead concentrations were found in areas with high concentrations of lead in the water supply.

Lead is one of the most important and widely distributed pollutants in the environment. Attention has recently focused on the deleterious effects of subclinical lead poisoning, as distinct from acute lead poisoning, which has become rare. Long-term exposure leads to accumulation of lead in bone, where it is stored for years (3, 4). These quiescent lead stores are mobilised when increased bone turnover occurs, and latent lead toxicity may then become symptomatic. Although hyperthyroidism increases bone turnover, it has unusually and rarely been implicated in the pathogenesis of lead poisoning, and only two cases have been reported. We describe herein two cases of lead

poisoning induced by hyperthyroidism and discuss the pathogenesis of this intoxication.

Case reports

Patient 1

An 82-year-old woman with no previous relevant medical history was referred to our clinic for hyperthyroidism. She had mild hypertension, which was not treated, and had had a cholecystectomy and a unilateral oophorectomy for a benign cyst more than 40 years previously. She was admitted to another hospital because of a loss of independence and it was there that paucisymptomatic hyperthyroidism was diagnosed. She was referred to our clinic for aetiological investigation and treatment.

On her admission to hospital, her temperature was 36.6 °C, pulse 80 beats/min and arterial pressure 170/80 mmHg. She was 160 cm tall; her weight was 47 kg, but had been 50 kg 4 months earlier. Her appetite was good, but she was nervous and anxious. On examination, a multinodular thyroid goitre was found that was diagnosed as toxic by thyroid scintiscanning. Thyrotropin (TSH) concentration was 0.02 mU/l (normal range (NR) 0.25–4.0); free thyroxine (fT₄) concentration was 29.3 pmol/l (NR 11–25).

Several symptoms, although also common to hyperthyroidism, suggested possible associated lead poisoning: fatigue, insomnia, irritability, extra pyramidal syndrome, decreased memory recall and ability to concentrate, confusion and labile hypertension. Despite the lack of specificity of such symptoms in an elderly woman, she had lived for a long time in an area of endemic lead poisoning and this led us to investigate possible lead poisoning in her case. Test results were indeed consistent with lead poisoning: delta-aminolaevalulinic acid (ALA) dehydratase activity was $0.11 \mu\text{mol}$ (protoporphyrinogen) PBG/ml erythrocytes/h (NR >0.30), erythrocyte protoporphyrin concentration was $2370 \mu\text{mol/l}$ erythrocytes (NR 300–1120); the $\text{CaNa}_2\text{-EDTA}$ provocative test result was $491 \mu\text{g}$ lead/24 h (NR ≤ 300). As the test results suggested that lead poisoning was not severe, we decided to treat the hyperthyroidism and avoid chelation therapy, which may cause kidney damage in the elderly. Propranolol was given in a low dose, and $37 \times 10^7 \text{ Bq}$ (10 mCi) radioactive iodine was also given. This treatment of the hyperthyroidism alone led to a complete recovery of both thyroid function (TSH concentration 0.73 mU/l (NR $0.25\text{--}4.0$); fT_4 concentration 23.9 pmol/l (NR $11\text{--}25$)), and lead intoxication (ALA dehydratase activity was $0.35 \mu\text{mol}$ PBG/ml erythrocytes/h (NR >0.30); erythrocyte protoporphyrin concentration $1590 \mu\text{mol/l}$ erythrocytes (NR 300–1120)). The continued increase in concentration of erythrocyte protoporphyrin after treatment was due to the long half-life of erythrocytes. The decrease in erythrocyte protoporphyrin concentrations, associated with normalisation of ALA dehydratase activity, is a sign that lead poisoning has been cured.

Patient 2

A 46-year-old man with no previous history of lead poisoning was referred to our clinic for a relapse of hyperthyroidism. He was employed as a salesperson in a hypermarket. He had experienced a first episode of Graves' disease 1 year earlier, and had been treated with $37 \times 10^7 \text{ Bq}$ (10 mCi) radioactive iodine. There was no evidence of lead poisoning during his previous stay in hospital.

The main symptoms on his present admission to hospital were a 7 kg weight loss, tachycardia (about 120 beats/min), fine resting tremor of both hands, and diarrhoea. On physical examination, he presented with marked 'lid lag', mild exophthalmos (19 mm right, 15 mm left, NOSPECS IIc, IIIa, IVo, Vo, VIo), a generally enlarged murmuring thyroid gland, and symmetric hyperreflexia. Moreover, he complained of symptoms that had never occurred during former episodes of Grave's disease: abdominal pain, fatigue, insomnia, irritability, and decreased memory recall and ability to concentrate. TSH concentration was 0.02 mU/l (NR $0.25\text{--}4.0$); fT_4 concentration was 26.8 pmol/l (NR $11\text{--}25$).

Serum concentrations of glucose, urea, creatinine and amylase were normal. Cholesterol concentration was slightly low and alkaline phosphatases slightly high (256 mU/ml (NR $70\text{--}210$)). Lead poisoning was diagnosed, although the patient had moved out of the area of endemic lead poisoning 3 years earlier. ALA dehydratase activity was $0.27 \mu\text{mol}$ PBG/ml erythrocytes/h (NR >0.30) and erythrocyte protoporphyrin concentration was $1590 \mu\text{mol/l}$ erythrocytes (NR 300–1120); the $\text{CaNa}_2\text{-EDTA}$ provocative test result was greater than $800 \mu\text{g}$ lead/24 h (NR ≤ 300). Treatment with propranolol and hydroxyzine was begun and a $55.5 \times 10^7 \text{ Bq}$ (15 mCi) dose of radioactive iodine was given. All symptoms resolved within 3 months after treatment of the hyperthyroidism alone. TSH concentration was 0.18 mU/l (NR $0.25\text{--}4.0$); fT_4 concentration was 14.8 pmol/l (NR $11\text{--}25$). TSH concentrations were still low 3 months after treatment, because of thyrotrophic inertia. The normalisation of fT_4 , which occurred in parallel with the disappearance of symptoms, was consistent with the hyperthyroidism being cured despite the low TSH concentration. Lead intoxication was shown to be cured: ALA dehydratase activity was $0.88 \mu\text{mol}$ PBG/ml erythrocytes/h (NR >0.30) and the erythrocyte protoporphyrin concentration was $304 \mu\text{mol/l}$ erythrocytes (NR 300–1120).

Controls

To determine whether hyperthyroidism *per se* could affect ALA dehydratase activity and erythrocyte protoporphyrin concentrations, we measured both parameters in 20 consecutive hyperthyroid patients living outside areas endemic for lead poisoning and with no occupational risk of lead poisoning. None of these analyses gave values outside the normal ranges: mean ALA dehydratase activity was $1.22 \pm 0.25 \mu\text{mol}$ PBG/ml erythrocytes/h (NR >0.30) and the erythrocyte protoporphyrin concentration was $824 \pm 174 \mu\text{mol/l}$ erythrocytes (NR 300–1120).

Discussion

Lead poisoning not only has industrial and environmental sources, but is endemic in several European areas where the water supply is dispensed via lead pipes. Lead is leached from pipes into drinking water, particularly when the water is acidic and corrosive (5, 6). In adults, barely 10% of ingested lead is absorbed from the gastrointestinal tract (7). Once absorbed, lead accumulates in three compartments: blood, soft tissues and bone. Constant exposure results in the accumulation of lead in blood (where 95% of the lead is associated with the erythrocytes) and soft tissues, until a 'steady-state' is reached. Sixty to ninety percent of the body's lead burden is deposited in the skeleton as insoluble, quiescent tertiary lead phosphate (3, 4), which may be stored for up to 30 years.

The best understood toxic effect of lead is its influence on haem synthesis. Lead inhibits two important enzymes implicated in this process: ALA dehydratase and ferrochelatase. Chronic exposure to lead leads to the incorporation of zinc into the porphyrin ring to produce erythrocyte zinc protoporphyrin (ZPP). Several screening tests, based on the effects of lead on haem synthesis, are used to detect chronic exposure to lead; ZPP assay is the most widely used, and measurement of ALA dehydratase activity is used in France (1, 6, 8, 9). In chronic lead poisoning, blood concentrations of lead are not particularly high (10), so blood lead measurements are not useful in screening for chronic lead poisoning. There are few and non-specific symptoms of chronic lead poisoning (abdominal and muscle pain, asthenia, arthralgia, irritability, depression, altered sleep, memory disturbances and hyperactivity in children) (11), so screening tests (ZPP and ALA dehydratase assays) should be performed for all cases of suspected chronic exposure to lead.

Factors that affect calcium distribution also affect lead distribution. For example, high phosphate intake favours storage in bone, and vitamin D promotes deposition of lead in bones. Parathyroid hormone and dihydrotachysterol mobilise the lead in bones, leading to greater concentrations in blood (10). High alkaline phosphatase concentrations reflect the increase in bone turnover. Several conditions known to increase bone turnover, such as pregnancy (12–14), chemotherapy (15–17), tumorous infiltration of bone (18), or postmenopausal osteoporosis (19), may be associated with the mobilisation of lead in bone stores, leading to chronic lead poisoning. Hyperthyroidism is known to increase bone remodelling (20–22). Therefore, hyperthyroidism may also result in lead poisoning. Nevertheless, until now, only two cases of lead poisoning have been reported in association with hyperthyroidism (23, 24). In the first report, a young patient was wounded by a bullet which remained in his leg for more than 3 years. (23). He experienced hyperthyroidism and his blood lead concentration was high ($>100 \mu\text{g}/100 \text{ ml}$). Treatment with both antithyroid (propylthiouracil) and chelating agents was necessary. The second case report concerned a 37-year-old woman who was exposed to lead in the environment (24). She complained of fatigue, sleep disorders, difficulty in concentrating, abdominal pain, and several signs of hyperthyroidism. Both blood lead and erythrocyte protoporphyrin concentrations were high.

In the cases reported in this article, both patients were living in the Vosges, where water is acidic and unpolluted. Lead pipe lines have been used for many years in this mountainous region, so chronic lead 'administration' via the water supply may, after several years, give rise to lead poisoning. In both our patients, lead poisoning was demonstrated by clinical (albeit non-specific, with several signs common to hyperthyroidism) and biological features, including high blood

concentrations of erythrocyte zinc protoporphyrin, low ALA dehydratase activity in circulating blood cells and high lead concentrations in the urine during the $\text{CaNa}_2\text{-EDTA}$ provocative test. Hyperthyroidism *per se* does not affect ALA dehydratase activity and erythrocyte protoporphyrin concentrations, as none of the tests performed in 20 hyperthyroid patients living outside the area of endemic lead poisoning had ALA dehydratase activity or erythrocyte protoporphyrin concentrations outside the normal ranges.

Our two case reports highlight two phenomena. An increase in bone turnover secondary to hyperthyroidism may lead to the liberation of lead stores from bone into the blood stream and, furthermore, such lead poisoning may develop even when there has been no lead 'administration' for several years, as observed in patient 2, because the lead stored in bone may be mobilised over a period of years.

These two cases demonstrate that a metabolic disease involving a high rate of bone remodelling is able to generate clinical symptoms of lead poisoning. Lead poisoning is a major environmental health problem and physicians must be aware of the endocrine disorders, such as hyperthyroidism and hyperparathyroidism, that lead to increased bone turnover and possible lead mobilisation. Atypical symptoms should draw the physician's attention to the possibility of lead poisoning, particularly in workers with occupational exposure to lead or in areas where lead poisoning is endemic.

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