A curious case of hypoglycaemia

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A 79-year-old man affected by type 2 diabetes mellitus for 10 years in therapy with gliclazide 80 mg/day was at home when, after breakfast, he started to feel cold, dizziness, tremors and he collapsed on his sofa. His glucose level was 35 mg/dl (1.94 mmol/l). The patient was taken to the Emergency Room and then admitted to the Department of Internal Medicine and Therapeutics of our hospital for further analysis given the age and the only slight improvement of the glycaemia even after a 33% glucosate administered by Emergency Room physicians.

The patient medical history included an appendectomy in his childhood, a previous hospitalisation for a coma due to a cerebral abscess, and a hospitalisation for pneumonia 10 years before. He was also affected by dementia on a cerebrovascular base, hypertension treated with amlodipine 5 mg/day, and hypercholesterolaemia in therapy with simvastatin 20 mg/day.

Hypoglycaemia is very common in patients affected by type 2 diabetes mellitus, especially in patients taking sulphonylureas [1]; in our case we excluded an overdose of the drug or wrong behaviour of the patient; we stopped the administration of gliclazide and put the patient on a dietary regimen. We also performed some examinations to evaluate the liver and the kidney functionality that gave a normal result. The glycated haemoglobin (HbA_{1c}) value showed optimal control of diabetes (HbA_{1c} 5.4%). The other analyses were normal with the exception of sodium (131 mEq/l) and glycaemia (45 mg/dl (2.49 mmol/l)), which were low. In the next 2 days, even though the patient was eating at a regular level, the glycaemia remained always under 40 mg/dl (2.22 mmol/l). We also administered some sugar and some 33% glucosate without results. Given the persistent hypoglycaemia, we were obliged to put the patient under a continuous infusion with a 10% glucosate. We also co-administered a sodium solution to avoid hyponatraemia. We searched for other causes of hypoglycaemia [2], which can be divided into: insulin-related causes such as insulinoma; not insulin related causes such as organ failure (liver, kidney, or heart), sepsis, tumours, hormone deficit.

The better way to diagnose an insulinoma is dosing glucose, insulin, pre-insulin and C-peptide after a 48-72-h fast: insulinoma is confirmed by low blood glucose, elevated insulin, pre-insulin and C-peptide. The test showed normal values of insulin and C-peptide, so we excluded the hypothesis of an insulinoma. To exclude an organ failure or sepsis, we evaluated parameters such as transaminases, creatinine, erythrocyte sed-

imentation rate, C-reactive protein, procalcitonin: in the case of our patient, they were within the normal ranges.

In the meantime, the patient did not improve, the glycaemia was always under 40 mg/dl (2.20 mmol/l), and partly due to the continuous glucose infusion, the sodium levels decreased to 109 mEq/l, despite supplementation. Furthermore, the blood pressure was low, 95/60 mm Hg, the patient was very soporous, almost comatose, and he did not eat anymore.

Severe hypoglycaemia associated with severe hyponatraemia, and with hypotension, can be due to an adrenal insufficiency; the adrenocorticotropin (ACTH) stimulation test is the most commonly used test for diagnosing adrenal insufficiency; however, during an emergency, measurement of blood ACTH and cortisol during the crisis, before glucocorticoids are given, is enough to make a preliminary diagnosis [3].

To confirm our suspicions, we dosed the levels of aldosterone, ACTH, renin at 8 a.m. and cortisol levels at 8 a.m., 2 p.m. and 8 p.m. The values were as follows: cortisol levels were very low, while ACTH levels were double the normal values. On the basis of those examinations we diagnosed primary adrenal insufficiency, also called Addison's disease. Our first priority was to treat the patient with administration of hydrocortisone 200 mg *i.v.* once a day for the first 5 days [4]. After two administrations, we achieved an improvement of glycaemia that went to 130 mg/dl (7.21 mmol/l), so we suspended the glucose infusion with also an improvement of natraemia that slowly returned to acceptable levels. The patient regained consciousness and resumed eating. After 5 days, given the improvement of the patient, we suspended hydrocortisone *i.v.* and started prednisone orally 15 mg in the morning, 5 mg in the afternoon and 5 mg in the evening taken orally.

Addison's disease can be due to autoimmune disorders [5-7]: adrenal insufficiency occurs when at least 90% of the adrenal cortex has been destroyed. As a result, often both cortisol and aldosterone are lacking. Sometimes only the adrenal glands are affected; sometimes other endocrine glands are affected as well, as in poly-endocrine deficiency syndrome. Suspecting an autoimmune disorder [8], we wanted to search for auto-antibodies directed against adrenal glands, but we could not perform that test because our laboratory was not equipped for that kind of examination. However, suspecting a poly-endocrine deficiency syndrome [9], given the diabetes and the primary adrenal insufficiency, we checked the status of the thyroid gland and we found hypothyroidism with a high thyroid stimulating hormone (TSH) and lower free thyroxine 4 (fT4). Anti-peroxidase auto-anti-

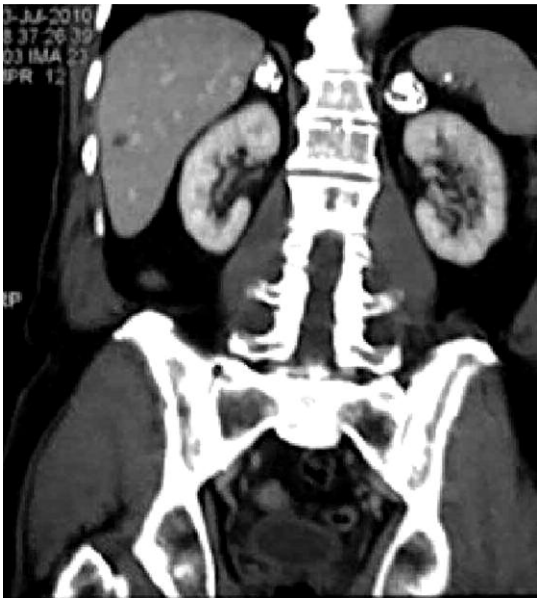

Figure 1. Computed tomography scan

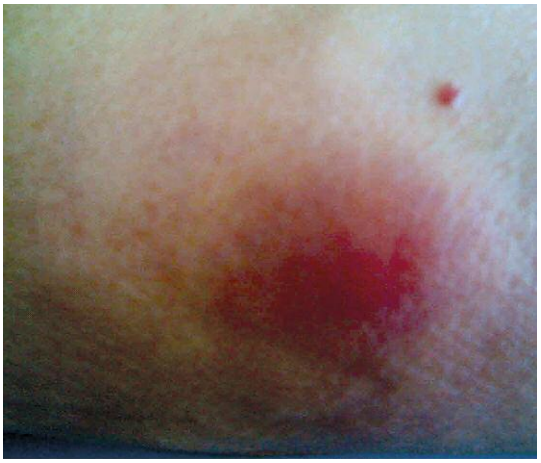

Figure 2. Tuberculin skin test

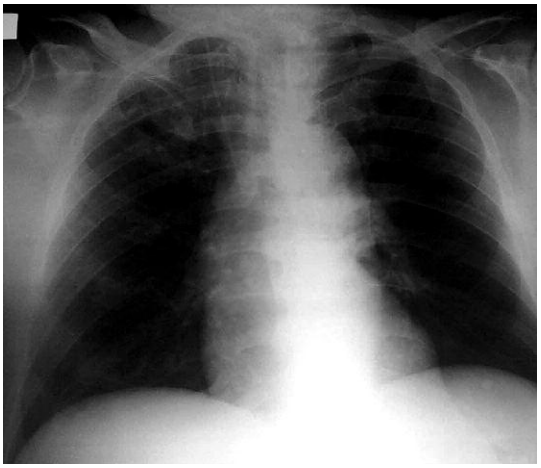

Figure 3. Thorax X-ray

bodies and anti-thyroglobulin auto-antibodies were both increased. We started supplementation with levothyroxine 25 μg/day. We also better interrogated the relatives of the patient, searching for previous symptoms or causes responsible for the Addison's disease; our interrogation was not useful to identify other Addison-related symptoms, but we discovered that, when the patient was young, he had a not well specified "pneumonia" and that he was a cow milker.

Another less common cause of Addison's disease is tuberculosis [6, 7]; tuberculosis is an infection that can destroy the adrenal glands, and it accounts for less than 20% of cases of Addison's disease in developed countries. Given the past of the patient, we performed a computed tomography (CT) scan of the adrenal glands; the CT scan showed that the adrenal glands were bigger than normal (maximum diameter of 33 mm for the right one and 42 mm for the left one) and that there were diffuse calcium deposits over the entire glands (Figure 1).

Those characteristics are very common outcomes of tuberculosis; on those bases, we performed a tuberculin skin test that gave a positive result, with a maximum diameter of 3 cm (Figure 2). The thorax X-ray showed evidence of previous tuberculosis with the presence of some calcified nodules in the base of the left lung and in the middle-upper lobe of the right lung (Figure 3). The patient did not show any signs of active tuberculosis; however, to be sure, we performed a search for the mycobacterium in the sputum that was negative.

At the end of our research, we concluded that the hypoglycaemia of our patient was due to a primary adrenal insufficiency caused by previous tuberculosis that damaged his adrenal glands, and probably his pancreas, and also his thyroid, constituting a poly-endocrine deficiency syndrome.

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