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Hypoglycemia and Reduced Insulin Dosage in an Adolescent with Type 1 Diabetes Mellitus (T1DM)

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Abstract

A 16-year-old male with T1DM diagnosed without ketoacidosis showed a progressive reduction in insulin requirements after the honeymoon phase, with frequent hypoglycemia despite correctly dosing adjustment (maximum IR: 0.68 U/kg/day). Fifteen months later, a further reduction in insulin requirement (0.57 U/kg/day) was noticed, associated with suboptimal glycemic trend. Celiac disease and autoimmune thyroid involvement were excluded. Adrenocorticotropic Hormone (ACTH) values were elevated (418.30 pg/ml at first control and 304.8 pg/ml at the second one (n.v.: 7.2- 63.3 pg/ml) and baseline morning cortisol levels at 8.00 were in the range requiring evaluation (9.1 µg/dl and 7.4 µg/dl, n.v.: 2.47-19.5 µg/dl). The association of reduced insulin requirement during pubertal development and after honeymoon phase, unexplained hypoglycemic episodes and high ACTH values induced to suspect adrenal insufficiency. Diagnosis was confirmed after two stimulation ACTH tests with insufficient cortisol peak at 30' (10.15 µg/dl and 9.64 µg/dl respectively). Renin levels were high in upright (472.5 µUI/ml; n.v. 2.8 to 39.9 µUI/mL) and in lying down positions (282.1 µU/ml; n.v.: 4.4-46.19 µUI/ml), with levels of aldosterone in the lower range both in upright and lying down positions (5.82 ng/dL, n.v. 4.4-46.1 ng/dL and 5.88 ng/dL, n.v. 1.88-25.67, respectively). The abdominal MRI showed normal adrenal glands; tuberculosis and X-linked adrenoleukodystrophy were excluded. Adrenal anti-cortex antibodies were positive (> 1:40). Autoimmune adrenal insufficiency was treated with oral hydrocortisone (8.98 mg/m^2/day) and fludrocortisone (0.1 mg/day); blood electrolytes, ACTH and renin were monitored. Replacement therapy was adjusted (up to 13.7 mg/m^2/day of hydrocortisone, fludrocortisone unmodified) in order to obtain reduced hypoglycemia, improved mood, asthenia and blood pressure values; increased insulin requirement was observed after starting replacement therapy (up to 0.75 U/kg /day).

Abbreviations

T1DM: Type 1 diabetes mellitus; GADA: Glutamic acid decarboxylase antibodies; IAA: Anti-Insulin autoantibodies; BMI: Body mass index; ACTH: Adrenocorticotropin hormone; LDCT: Low-Dose corticotropin stimulation test; MRI: Magnetic resonance imaging; VLCFAs: Very long chain fatty acids

Introduction

T1DM management relies on basal/bolus subcutaneous insulin injections, self management of disease, adequate meal plan and regular physical activity. Insulin requirement must be tailored according to patient's age, pubertal stage, lifestyle habits. During adolescence a higher insulin dosage is required, due to the physiological insulin resistance induced by growth hormone and sexual steroids. Hypoglycemic crisis is the most serious acute complication in type 1 diabetes, and is a life-threatening condition. Otherwise, long term neurological impairment due to severe and recurrent hypoglycemic events are reported. Primary goals of diabetes care are to allow well being, regular growth and development, to avoid hyper/hypoglycemic spikes, and to prevent the onset of acute and chronic complications.

Aim

The aim of the present case report is to consider autoimmune conditions other than celiac and autoimmune thyroid diseases as responsible of unexplained hypoglycemic events in patients with type 1 diabetes.

Patient presentation

In January 2015, a 16-year old adolescent was admitted for newly-diagnosed T1DM [random plasma glucose 309 mg/dl, pH 7,44, serum bicarbonate 22,6 mmol/l, HbA1c 9,83% (n.v. 4-6%), serum C- peptide 0,5 mmol/l (n.v. 1.1-4.4 ng/ml). GADA levels were 9.71 U/ml (n.v. 0-0.9 U/ml), IAA levels were 2.32 U/ml (n.v. <0.4 U/ml)]. Height and pubertal development were normal. One week later after therapeutic education and meal program he was discharged with multiple daily insulin injections (1 long-acting analogue and 3 pre-prandial short-acting analogues; insulin requirement 0,5 U/kg/day). Family history was positive for autoimmune thyroid disease (mother and maternal grandmother). Regular follow-up in outpatient section was uneventful. One year later HbA1c levels was 7.2% and total day insulin dose 0.7 U/kg/day. The clinical examinations revealed height 177.2 cm (50°-75° percentile for age) weight 55.6 Kg (10°-25° percentile for age) and BMI: 17.7 kg/m^2, pubertal stage G5 PH5; no main abnormalities were observed. Because of satisfactory metabolic control and self-management of diabetes no therapeutic change was suggested. The patient was evaluated 4 months later: a further reduction in total daily insulin dose (0.6 U/kg/day) due recurrent episodes of unexplained hypoglycemia was noticed; he also complained muscular weakness, asthenia and depressed mood. At physical examination height 178.6 cm (50°-75° percentile for age), weight 55.8 kg (10°-25° percentile for age); BMI 17.5 Kg/m^2; blood pressure 109/72 mmHg, HbA1c levels 6.6%.

The patient denied alcohol abuse or other improper lifestyle habits. Routine blood exams were performed including screening for celiac, thyroid and adrenal disease. Normal results were observed, except for mild hyponatremia (134 mEq/L, n.v. 135-145), high ACTH (418.30 pg/mL, n.v. 7.20-63.3) and at 8.00 am morning cortisol level was 9.12 µg/dL (n.v. 2.47-19.50), in the range requiring evaluation. These findings were confirmed in a second detection. Due to the association of decreased total daily insulin requirement, unexplained hypoglycemic episodes and high ACTH levels, adrenal insufficiency was suspected. To confirm the diagnosis LDC Test (Synachten 1 µg i.v.) was performed. Cortisol level of 9.54 µg/dL at baseline, increased to 10.15 µg/dL after 30'(n.v. > 22 µg/dL after ACTH stimulation [1]. High plasma renin levels both in orthostatism and in clinostatism (472.5 µU/mL and 282.1 µU/mL, respectively) with normal aldosterone levels both in orthostatism and clinostatism (5.82 ng/dL and 5.88 ng/dL, respectively) were documented. Abdominal MRI showed normal morphology of adrenal glands; the negative intradermal injection with Mantoux technique excluded adrenal insufficiency secondary to tuberculosis and normal values of VLCFAs excluded the X-linked adrenoleukodystrophy. On the contrary, adrenal cortex antibodies were detected (> 1:40) suggesting an autoimmune etiology. Other organ- and non organ-specific autoantibodies were negative. Oral replacement therapy with hydrocortisone (8.9 mg/m^2/day) and mineralocorticoid (fludrocortisone 0.1 mg/day) was started with rapid improvement in glyco-metabolic control, mood, asthenia and blood pressure values; it was also noticed a progressive increase in total daily insulin dose up to 0.9 U/kg/day after starting replacement therapy. At the last follow-up visit HbA1c was 7.3%, insulin requirement was 0.75 U/kg/day associated with a satisfactory glyco-metabolic control. Hydrocortisone dosage was 12 mg/m^2/day and fludrocortisone 1.5 mg/day.

Discussion

Historically, the most common cause of adrenal insufficiency was tuberculosis. At present the majority of cases of Addison disease is due to an autoimmune process, even if worldwide infectious diseases like tuberculosis and fungal infections (Histoplasmosis, Cryptococcus) are still responsible. In patients with Addison disease other autoimmune conditions including T1DM, hypoparathyroidism and thyroid disease are frequently observed.

Adrenal insufficiency, whether primary or secondary, is a life-threatening relatively rare condition in childhood and adolescence and signs and symptoms may be nonspecific leading to delayed or missed diagnosis. Sometimes the diagnosis is made in case of medical emergency like adrenal crisis, and unrecognized adrenal insufficiency may cause morbidity and even death [2]. Replacement steroid therapy is mandatory and in case of critical illnesses corticosteroid insufficiency may worsen. In such cases a strong and prompt increase of steroid dosage is required to prevent clinical worsening up to death. Families should be taught how to manage therapy in case of fever, intercurrent illnesses or stressful events, like accidents, surgery. Our patient showed a particular presentation of adrenal insufficiency, characterized by unexplained recurrent hypoglycemia associated with abrupt decrease of insulin requirement, despite pubertal age and absence of honeymoon phase. In T1DM unexplained recurrent hypoglycemia and reduced insulin requirement even if nonspecific, should arise suspicion for Addison disease. These features usually precede other main clinical characteristics of Addison disease, like adrenal crises and skin hyperpigmentation.

In our patient, glucocorticoid deficiency was associated with both enhanced insulin sensitivity and lower gluconeogenesis response leading to an increase risk of hypoglycemia. Furthermore, appropriate glucocorticoid replacement was followed by a higher

insulin requirement and restoration of normal blood glucose values; high plasma renin activity with normal or low serum aldosterone levels, detected at the time of diagnosis, showed normalization after replacement therapy. Addison disease is a chronic, severe disorder of the adrenal cortex resulting in decreased production of glucocorticoids, mineralocorticoids, and androgens, and a concomitant increased secretion of ACTH aimed to stimulate the adrenal gland. Two clinical forms of adrenal insufficiency are described: Addison disease within syndromes characterized by autoimmune involvement of several organs and named Autoimmune Polyendocrine Syndromes (APS-1 and APS-2), and Addison disease as an isolated condition. In developed countries an autoimmune mechanism is recognized as the most common etiological factor of adrenal insufficiency (70-90%) and genetically susceptible individuals develop autoantibodies toward adrenal cortex and/or the 21-hydroxylase enzyme and eventually lose the ability to produce cortisol; the second cause is represented by tuberculosis of the adrenal gland (10 to 20%).

Overt Addison disease is preceded by a long-lasting asymptomatic interval, followed by subtle clinical manifestations up to adrenal insufficiency. Main symptoms are persistent vomiting, anorexia, hypoglycemia, unexplained weight loss, malaise, ill-defined fatigue, muscular weakness, hypotension, and craving for salt. The most specific cutaneous sign of primary adrenal insufficiency is generalized hyperpigmentation of the skin and mucosal surfaces, due to high plasmatic levels of melanocyte stimulating activity of β-lipotropin, originating from the same precursor as ACTH. Laboratory tests can confirm clinical diagnosis: hypoglycemia, hyponatremia, hyperkaliemia, acidosis, high levels of ACTH and cortisol deficit [1]. Furthermore, adrenal antibodies, detectable in more than 90% of subjects with autoimmune Addison disease, represent a marker with the higher predictive value in young patients [3]. Screening of antibodies toward adrenal cortex (Adrenal Cortex Autoantibodies, ACA) or steroidogenic enzymes (CYP21A2 and 21 hydroxylase) is recommended in patients with T1DM, hypoparathyroidism, and Autoimmune Polyendocrine Syndrome type 1 and type 2 [2,3]. If detectable, yearly monitoring with an ACTH stimulation test is performed to allow early diagnosis of Addison disease and prevent adrenal crisis [4].

Addison disease treatment consists of urgent lifelong glucocorticoids replacement, with clear counseling about the need for stress dose steroids for illnesses and prior to surgical procedures [4]. In some cases, supplementation with mineralocorticoids in mandatory. In adolescents with T1DM Addison disease is rarely encountered, and symptoms are sometimes nonspecific. Correct diagnosis of Addison disease requires a high degree of clinical suspicion and since the disease is a life-threatening condition, several investigators recommend periodical screening of adrenal function in all T1DM patients, specifically if other autoimmune diseases are associated (i.e. against thyroid gland) [5]. In an adolescent with T1DM, Addison disease should be suspected in case of recurrent hypoglycemic episodes, unexplained decrease of insulin requirement and improvement of metabolic control, fatigue, weight loss, hyponatremia and hyperkaliemia. The confirmation of diagnosis is based on low serum morning cortisol and high ACTH levels. Screening procedures allow to detect asymptomatic children and adolescents with positive adrenal antibodies; high ACTH levels suggest the presence of adrenal insufficiency [6]. Risk factors for adrenal insufficiency in patients with T1DM include a history of other autoimmune conditions, in particular thyroid disease, as reported in a case series of 4 adolescents with pre-existing T1DM who developed Addison disease [7]. Three out of 4 patients showed unexplained hypoglycemia and the other one showed unawareness hypoglycemia; all cases reported unexplained improvement in diabetes metabolic control. Only one patient showed skin hyperpigmentation [8]. Skin darkening, especially in the sun-exposed areas, otherwise a hallmark sign of primary adrenal insufficiency, can be less evident if the disease is of short duration. In all 4 patients a positive personal and family history of other autoimmune conditions has been reported, in particular celiac and/or thyroid autoimmune diseases and Autoimmune Polyendocrine Syndrome type 2.

A study in 491 newly diagnosed children with T1DM aimed to define the prevalence of additional autoimmune conditions reported 1% positivity of antibodies to 21-hydroxylase, while overt Addison disease was found only in 20% of the positive patients [9]. Noteworthy, all young patients with T1DM and adrenal autoantibodies develop Addison disease during the follow-up period. A different clinical presentation with faster progression to overt adrenal failure in younger children than in adults has been reported, indicating that different autoimmune responses may be evoked at various age periods [10]. More recently, a young adolescent with T1DM and autoimmune thyroid disease who reported recurrent hypoglycemia secondary to glucocorticoid deficiency and increased insulin sensitivity was diagnosed with an Addison disease [11]. We suggest to investigate adrenal function in children and adolescents with T1DM in case of unexplained hypoglycemic events and/or decreased insulin requirement. In the majority of cases, symptoms are nonspecific, requiring a high index of clinical suspicion. Long-term follow up is mandatory, since incomplete forms are more common in pediatric age. If the diagnosis and treatment are delayed, acute adrenal insufficiency carries a high morbidity and mortality.

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The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest

The authors have no conflict of interest to disclose

Contributors' Statement Page

Dr. Giuseppe d'Annunzio conceptualized and designed the study, drafted the initial manuscript and reviewed and revised the manuscript.

Dr. Erica Ricci and Giuseppe Patti collected data and contributed to the draft of initial manuscript.

Dr. Flavia Napoli, Maria Cristina Schiaffino, Nicola Minuto and Gianluca Piccolo took care of the patient, collected data and supervised data collection.

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