

Late Onset Bartter Syndrome in Type 2 Diabetes Mellitus Scarcely Compensated: A Case Report Study

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Type 2 diabetes mellitus and obesity, both characterized by an increasing incidence, are strictly associated to one another so that the specific definition diabetes [1,2] has been coined to describe the medical condition occurring in concomitance of these two diseases. Obesity and insulin resistance are frequently associated with type 2 diabetes mellitus pathophysiology and this concurrence has been described in literature [3,4]. Furthermore, diabetes often coexists with other major illnesses such as hypertension, dyslipidemia, hyperuricemia. The concomitance of these diseases is commonly known as Metabolic Syndrome. Diabetes and obesity are influenced by both familiar and environmental factors. Type 2 diabetes occurring in family is able to affect biochemical markers, anthropometric factors and cardiovascular risk also in normoglycemic patients; such an event may induce a predisposition to obesity which can be enhanced by environmental factors thus leading to cardiovascular complication [5-7].

Bartter Syndrome is a familial autosomal recessive condition, characterized by hypokalaemia with normal kaliuresis, hyperreninaemia with secondary hyper-aldoosteronism and by an overproduction of prostaglandins by the kidneys. Several hypotheses, including a vascular insensitiveness to angiotensin, a defect of sodium or chloride reabsorption, the excess of atrial natriuretic factor or a general abnormality of membrane permeability have been developed, however so far its pathophysiology is still unknown. Bartter syndrome can be associated with other autoimmune diseases such as Scleroderma and Sjogren Syndrome [8]. This syndrome is rare but sometimes envisaged in patients with unexplained hypokalaemia and its treatment can be difficult and disappointing (Figure 1).

In this case report we describe the case of a severe uncompensated Type 2 diabetic patient, insulin treated, with grade 2 obesity, dyslipidemia, uncompensated hypertension and albinism, diagnosed and successfully treated for late onset Bartter syndrome.

Cases and Method

C.M.L first arrived to our outpatient clinic at the age of 62. She was albino, with family history of type-2 diabetes (her mother, in old age) and history of atrophic retinopathy due to albinism itself, systolic hypertension, atrial fibrillation since 2 years, and nephrolithiasis recurrence. In spite of an uncompensated (mainly systolic) hypertension, her cardiac function was decently compensated and it had been previously assessed by basal ECG, cardiac sonogram, myocardial scintigraphy and ECG under pressure, all resulted as normal. She was under medication with Spironolactone 100 mg per day. Micro albuminuria in the 24 hours was absent, and there was a mild renal impairment with creatinine levels of 1.7 mg%. Uremia fell within normal reference ranges. Her BMI was 36.2 and her glycated haemoglobin was 14.2%, in spite of an intensive insulinization with more than 50 IU per day (20 IU Lantus® at 11 p.m., 10 IU Apidra® at breakfast, lunch and dinner) inducing several Late onset Bartter Syndrome in Type 2 Diabetes Mellitus scarcely compensated: a case report study severe hypo-glycemic events during the week. For this reason, the patient was very scared by a further increase in insulin therapy. The patient reported former allergic reaction to metformin without showing any documentation, so that no insulin sensitization

therapy had been previously added to the insulin therapy itself. Sodium, Calcium and Chloride levels were normal. No record of potassium levels was made available.

Patient's mood was almost depressed (depression was assessed using DSM-IV-TR criteria with Hamilton depression rating scale score of <20). The woman had a very low level of motivation, for she was convinced that anything else could be done for her since all the treatment options had already been tested, revealing unsuccessful. Lastly, she persistently complained about an intense and enduring sensation of fatigue, preventing her even from doing normal activities of daily living, such as making the bed in the morning.

During a long interactive visit, we persuaded the woman to try with a new approach. A mild antidepressant was inserted in the overall therapy, as suggested by the Italian Society of Diabetology-SID guidelines [9-12]. Allergometric tests were requested for metformin and repaglinide medication and, in the meantime, pioglitazone was added to the therapy [13], thus reducing the total amount of insulin administration. Basal bolus therapy with Lantus® 20 IU was left unchanged (rapid insulin at mealtime was removed from the therapy), pioglitazone was added at a dosage of 30 mg/day and fluoxetine 20 mg/day was added in the morning, associated with alprazolam 0.75 mg/ml (0.5 gtt at night time).

As to what concerns the dietary regimen, a cognitive-behavioral treatment leading towards a low glycemic index scheme has been started. A daily aerobic physical activity plan consisting in 30 to 40 consecutive minutes with exercise bike has been introduced; daily glycemic controls to be done on an empty stomach in the morning and 2 hours after principal meals (breakfast, lunch and dinner) have been prescribed. A follow up visit for glycemic control was scheduled 20 days later. At the follow up visit, glucose levels were improved and the patient seemed to have developed a positive behavior towards the new regimen. Pressure levels were improved as well. However, severe fatigue had remained unchanged, highly reducing the patient's ability to perform physical activity. Small adjustments in the alimentary scheme were made and a new visit was scheduled 30 days later for new analysis and glucose monitoring.

After 30 days, glucose levels were dramatically reduced, HbA1c levels were 8.2%. The patient was highly motivated from the reduction of insulin therapy: no other hypoglycemic episodes resulted from the

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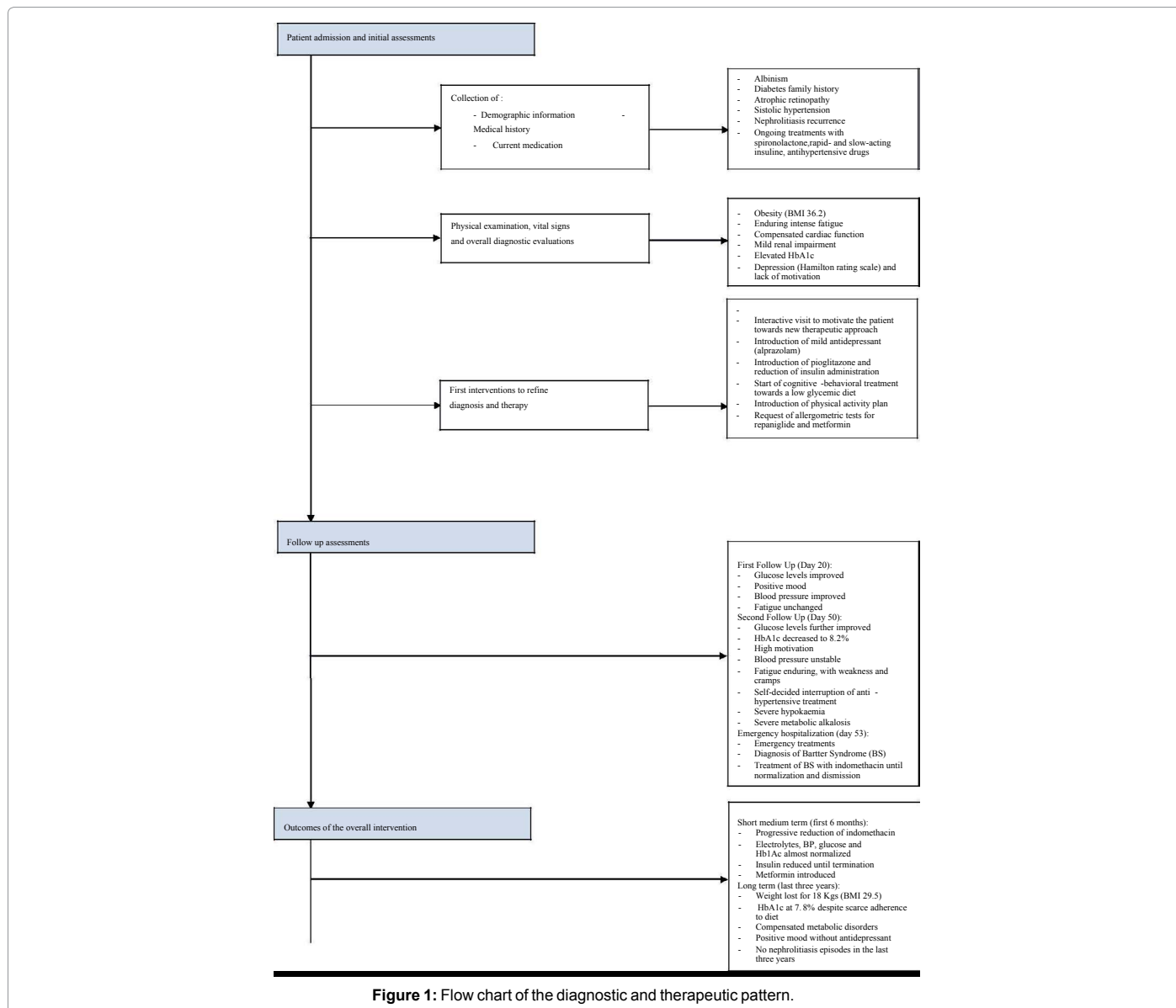


Figure 1: Flow chart of the diagnostic and therapeutic pattern.

glycaemia self-monitoring tests, and fasting glucose were around 100 mg/dl. On the contrary, blood pressure was not stabilized anymore, fatigue was still extremely intense and inferior arts cramps had arisen. In fact, due to the above reported extreme weakness, the patient had autonomously decided to gradually reduce the anti-hypertensive therapy until a complete interruption, in order to relieve the fatigue. Haematic electrolytes were normal, but the blood testing had revealed a severe hypokalemia. Due to the interruption of the anti-hypertensive medication, we decided to further investigate the nature of hypokalemia and hypertension, by testing the levels of vanilmandelic acid, renin and aldosterone, and by performing a haemo-gas analysis. In the meanwhile, allergometric tests resulted as negative for metformin, and a potassium supplementation therapy was started. Three days after, the patient came back with the blood testing: renin had extremely increased both in orthostatism (1.123 ng/ml/h with normal values ranging from 2.5 to 40 ng/ml/h) and in clinostatism (856 ng/ml/h with normal values ranging from 1.5 to 20 ng/ml/h). Aldosterone had extremely increased too, both in orthostatism (2.956 ng/dl with normal

values ranging from 30 to 220 ng/dl) and in clinostatism (1.837 ng/dl with normal values ranging from 20 to 125 ng/dl). Severe metabolic alkalosis had occurred in concomitance with severe hypokalemia while blood pressure was high and the patient still felt extremely fatigued. The patient was urgently hospitalized at the Obesity and Metabolic Disease Unit of the Catholic University Hospital in Rome where, following the emergency interventions including bicarbonate, rehydration and potassium supplementation, a renal sonogram revealed normal kidneys with no obstruction of the renal artery, and a nephrologist consultation confirmed the suspicion of a late onset Bartter syndrome.

The patient was immediately treated with a prostaglandin inhibitor (indomethacin at high dosage, 150 mg 3 times per day), associated with gastro protection, and was then dismissed after normalization of the vital parameters. The patient was then followed every 20-30 days. Within the following 6 months, renin and aldosterone levels progressively reduced and indomethacin regimen could be lowered up to 25 mg once a day. Potassium and other electrolytes returned within the normal ranges; Blood pressure was normalized without the need of any drug although a

beta-blocking therapy at low dosage for cardiac protection (propranolol 10 mg/day) has been maintained; Glucose levels were significantly reduced and HbA1c was 7.0%. Insulin therapy was gradually reduced until termination; Pioglitazone was then associated with metformin at increasing dosage; afterwards, pioglitazone was suspended and the patient remained under metformin 1000 mg 3 times per day.

One year later the patient had lost weight for 18 kilograms, thus reaching a BMI of 29,5. HbA1c had gradually increased up to 7.8% due to a scarce adherence to dietary regimen. Repaglinide 1 mg was inserted at mealtime, and metformin reduced to 500 mg per meal due to gastrointestinal complications. Dyslipidaemia and hyperuricemia remained well compensated, as well as hypertension. Now, glycated hemoglobin ranges from 6.8 to 7.6%, the patient mood is significantly increased and no antidepressant therapy is required. Renal function, together with acidosis and alkalosis control, is kept under regular monitoring. Electrolytes are maintained within normal levels without the need of any regular pharmacological supplementation. No further episode of nephrolithiasis has occurred over the last 3 years.

Discussion

Bartter Syndrome as primary cause of hypertension and fatigue in adults is commonly underestimated, despite it is known that this disease may occur even at a late onset, mainly in association with autoimmune diseases and/or metabolic syndrome [14-17].

Bartter's Syndrome (BS) comprises a range of overlapping autosomal recessive renal salt-losing phenotypes, characterized by hypokalaemia metabolic alkalosis. The various levels of penetrance of the syndrome and consequently the age of occurrence may depend from the kind and the quantity of genetic mutations [18]. Bartter Syndrome has been described once in association with oculocerebral hypopigmentation, a specific case of Albinism, together with mental retardation and hypoacusis [19] but, to our knowledge, there are no other reports of this illness linked to albinism, in adult life with no mental retardation. Our patients had no mental retardation and a very late onset development of Bartter Syndrome, even if it cannot be excluded that signs and symptoms of the illness might have appeared earlier in life without being diagnosed for several years. The family history of type 2 Diabetes in the patient may have enhanced her cardio-vascular complication as well.

Conclusions

Hypertension in type 2 diabetes and metabolic syndrome, mainly if uncompensated, should always be investigated in depth since it may be caused by other hidden illnesses. To this aim, prior to impute all the signs and symptoms to the underlying Metabolic Syndrome, physicians should very carefully evaluate the patient and, as strongly recommended by the relevant guidelines, perform a global renal assessment.

Bartter Syndrome is not usually considered as a possible cause of hypertension in adult patients [20,21]. However, since sporadic occurrence of late onset forms of this disease have been reported, it should be taken into consideration in type 2 diabetic patients with metabolic syndrome and electrolyte disorders associated with extreme fatigue. Hyperinsulinization should be avoided in obese patients with unstable glycemic control, in order to reduce hypoglycaemic event thus promoting a better quality of life. Antidepressant therapy should be taken into consideration in depressed-anxious patients in order to improve glycemic control therapy compliance.

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