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CASE REPORT

Insulin Autoimmune Syndrome as Part of Pre-Clinical LADA

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Abstract: Hypoglycemia presents relatively typical symptoms. However, when it occurs spontaneously – like in insulin autoimmune syndrome – it is difficult to perform scheduled biochemical tests at the laboratory. The study presents the case of a 31-year-old Caucasian female whose recurrent hypoglycemia symptoms were the reason for further diagnostics. The final results revealed a positive test for insulin autoantibody and glutamic acid decarboxylase autoantibody. Therefore, not only the potential causes of hypoglycemia but also an active autoimmune process typical for latent autoimmune diabetes in adults were confirmed. It was concluded that autoimmune hypoglycemia can be a part of the autoimmune process associated with diabetes and pre-diabetes in adults.

Keywords: autoimmune hypoglycemia, latent autoimmune diabetes, insulin autoantibodies, pre-clinical diabetes

Introduction

There are many factors causing hypoglycemia that are not related to hypoglycemic treatment. They include: pancreatic islets cell tumors, ectopic insulin secretion, paraneoplastic production of IGF-1 and IGF-2, autoimmunological failure of organs which can release glucose – liver or kidney, sepsis, undernutrition, inadequate secretion of cortisol, growth hormone, glucagon, epinephrine, alcohol overconsumption, or reactive factors, eg, functional hypoglycemia.[1] Hypoglycemia is characterised by relatively typical symptoms resulting from the stimulation of the adrenergic system, and also from neuroglycopenia, if it persists for a longer period of time. Nonetheless, in order to confirm that the reported symptoms in fact result from a low glucose level, low concentration of glucose in blood should be confirmed by biochemical test and it should be simultaneously demonstrated that the symptoms subside after consumption of carbohydrates. Those typical symptoms form the criteria of Whipple's triad.[2,3] As most of the hypoglycemia cases other than those resulting from blood-glucose-lowering treatment occur spontaneously, it is difficult to predict situations in which they might occur and, therefore, plan the timely performance of biochemical tests at the laboratory.[4] The situation when low glucose levels cannot be confirmed in the laboratory leads to the diagnosis being missed as the causes of hypoglycaemia are investigated only when hypoglycaemia is confirmed. On the other hand, due to the fact that most cases of hypoglycemia in the population of patients not receiving blood-glucose-lowering treatment stem from bad habits (for example, reactive hypoglycemia),[2,3] many adult patients experience only mild symptoms which do not concern the patient or the physician in a considerable way.

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Hyperinsulinemic hypoglycemia, known as Hirata's disease or IAS (insulin autoimmune syndrome), can be one of the causes of hypoglycemia. It is a rare disease, especially in the Caucasian population.[5,6] An interaction of the anti-idiotypic autoantibodies against IAA (insulin autoantibodies) could displace bound insulin from the insulin autoantibodies, resulting in hypoglycemia in patients who have not yet been diagnosed with diabetes and are not treated with insulin. The disease frequently undergoes self-remission, which can also be the reason for underdiagnosis. Meanwhile, it is known that IAA involved in the above-mentioned process play also an important role in the development of T1DM (type 1 diabetes mellitus). Moreover, IAA are present even in patients who have not been diagnosed with diabetes yet but who belong to the diabetes risk group. Being initial autoantibodies, they are encountered more frequently than GADA (Glutamic Acid Decarboxylase Autoantibodies) which usually appear at later stages of the autoaggression process.[7] Although the IAA are associated with an early autoimmune process in children, they can also constitute autoantibodies in LADA (Latent Autoimmune Diabetes in Adults).[8,9] Even though the autoimmunisation process is sometimes taken into consideration as the reason for hypoglycemia during the diagnostic process thereof, autoimmune hypoglycemia being the first pre-clinical symptom of autoimmune diabetes in the adult population has not been described so far.

Case Presentation

The patient provided informed oral consent for the publication of her case details through teleconsultations (due to the risk of SARS-CoV-2 pandemic), which was recorded and witnessed. All the obtained data came directly from the patient; they were the patient's property and were voluntarily provided by the patient to the authors, and thus the institutional approval was not required to publish this case details.

A 31-year-old Caucasian female patient, BMI (body mass index): 26 kg/m2 in 2019 and 24.4 kg/m2 after approximately a year, who had been unsuccessfully trying to get pregnant for 4 years, was hospitalised due to periodically occurring symptoms consistent with hypoglycemia (hunger, trembling hands, excessive sweating, anxiety). The symptoms would occur after excessive physical effort or long breaks (length not specified) between meals, but sometimes also 2–3 hours after a meal, and would disappear after consuming simple carbohydrates. The patient's family history revealed that her grandmother suffered from T2DM (type 2 diabetes mellitus). The patient did not consume alcohol and smoked approx. 10 cigarettes a day. To her knowledge, she was not suffering from any chronic diseases and she did not use any medications including those that may provoke IAS.[5]

The patient's laboratory basic parameters were within the normal range (glucose, blood cell morphology, transaminases, creatinine, urea, uric acid, ionogram, magnesium, urine test, serum C-reactive protein, lipid profile, TSH – thyroid stimulating hormone), except for slightly elevated concentration of bilirubin, during the first and the second hospitalisation (1.6 and 1.45 mg/dl, respectively). Additional tests and parameters were also normal and included: thyroid ultrasound, abdominal ultrasound, anti- TPO (thyroid peroxidase), anti- TG (thyroglobulin), HbA1c (glycated hemoglobin). Daily in-hospital glycemic profiles measured using a glucometer (both postprandially and randomly) showed glucose levels between 83 and 113 mg/dl (4.62–6.28 mmol/l) but hypoglycemia signs or symptoms never occurred during the hospitalizations. The calculated HOMA IR was 0.87 for the results from the first period, during which metformin was not administered and were calculated from OGTT (0-1-2-3 hours): glucose: 78–178-111-91 mg% (4.3–9.9-6.2–5.1 mmol, respectively); insulin: 4.5–62.1–34.4–15.7 μU/mL. The fasting C-peptide level was 1.08 ng/mL. Based on the clinical picture and the patient's results, the first diagnosis proposed was "hyperinsulinism without IR (insulin resistance)", and behavioral treatment as well as metformin were recommended. The diagnosis, however, was changed to "reactive hypoglycemia" as the patient reported worsening of the symptoms between the first and second hospitalisation. Due to her poor tolerance of metformin (recurrent morning diarrhea, recurrent abdominal pain), the patient ceased to take the medicine and reported relief – but not resolution – of hypoglycemia signs and symptoms at the ambulatory follow-up visit. Glycemia measured at home with the use of a glucometer was not lower than 70 mg% (3.89 mmol) after the discontinuation of metformin, however, prior measurements (before the first hospitalisation as well as when patient was taking metformin) were not available. During the ambulatory follow-up visit the results of anti-GAD65kD were available (blood sample for the test was collected during the second hospitalisation), and were confirmed to be positive (anti-GAD = 653.8 IU/mL; N<10 IU/mL; ELISA - enzyme-linked immunosorbent assay method) by the negative results of other tests: ICAs (Islet Cell Cytoplasmic Autoantibodies; N<1:10, IFA-indirect immunofluorescence assay), anti-HBs (ECLIA – Electrochemiluminescence immunoassay method), HCV antibodies (ECLIA), ANA (AntiNuclear Antibodies,

ELISA method). Due to the fact that the positive test result indicated an autoimmune process typical of diabetes mellitus, an ambulatory test for IAA and a repeated anti-GAD test were ordered. Results of both tests were positive (IAA = 0.59 U/mL; N<0.4 U/mL and anti-GAD = 526.6 IU/mL; ELISA method in both) and the final diagnosis – pre-clinical LADA – was made. The patient was told to regularly visit a diabetologist, conduct tests typical for DM diagnosis and follow the low glycemic index (GI) diet.

Treatment

After the first hospitalisation, which was followed by the proposed diagnosis, the patient was prescribed metformin, in an increasing dose from 500 to 1500mg. Even at the low dose, the prescribed treatment resulted in the occurrence of a much greater number of signs and symptoms of hypoglycemia as well as more side effects than before the beginning of the treatment. Therefore, the medication was withdrawn at an ambulatory visit after the second hospitalisation. Even though metformin can constitute a useful treatment in hyperinsulinism, primarily at the stage of prediabetes preceding T2DM, it can also cause exacerbation of hypoglycemia as it inhibits glucose release from the liver. In our opinion, therefore, there was no indication for metformin whatsoever, despite the previous suggested diagnosis of hyperinsulinism, due to the reported symptoms and signs of hypoglycemia, even if they were not biochemically confirmed.

Outcome and Follow-Up

After the discontinuation of metformin, the results of repeated ambulatory OGTT (after approximately 4 weeks) were as follows: 90–86-76 mg% (5.0–4.8-4.2 mmol, respectively) and insulin: 6.1-35-32.3 (uU/mL). The final fasting glucose (one week ago) was 120/6.67 (mg%/mmol). The patient is not undergoing any treatment, except for the implementation of healthy habits.

Discussion

According to the current knowledge,[10] the patient presents pre-clinical type of LADA which was confirmed by two positive tests for autoimmune diabetes mellitus. Reported symptoms of hypoglycemia, which were never biochemically confirmed, constituted the starting point for the initiation of the extended diagnostics. It is very unusual to start the diagnostic process without laboratory tests revealing a low level of glucose, and the case should be considered an incidental diagnosis, which is also confirmed by the unusual repeated results of anti-GAD (there is still insufficient information about the role of changes in titers of different autoantibodies), and unjustified use of metformin. However, the result of the final autoimmune test (IAA) can potentially explain hypoglycemia symptoms in the patient, and determine the diagnosis of Hirata's disease. Although a big disproportion between the concentration of insulin and C-peptide, which is typical for autoimmune insulin syndrome, was not confirmed in the patient, it should be remembered that it depends on the time of the test (during the symptoms and biochemical hypoglycemia, which was the case of our patient), as well as on the laboratory assay used. However, the case fits into the proposed definition of IAS.[10] Rare hypoglycemia occurred several months before pre-clinical LADA; it became the reason for the investigation, and finally - the diagnosis, despite the initial misdiagnosis. Although hypoglycemia could be considered as the result of the autoimmune process, it has not been observed to be the first symptom of autoimmune diabetes in the adult population so far. It stems from the fact that the symptoms of diabetes are related to and result from hyperglycemia, not hypoglycemia, and the presence of the detected autoantibodies does not always result in the development of the disease.[11] To summarize, after obtaining positive results of the second autoantibody test, it was determined that the patient was at a high risk of typical latent autoimmune diabetes in the future, which is now defined as the first stage of the disease. The patient should control her glycemia on a regular basis and the measurement of C-peptide should be considered. Adequate insulin treatment should be initiated after the patient reaches the level of blood glucose concentration defined for DM. The spontaneous resolution of symptoms of hypoglycemia in IAS as well as gradual decrease in the concentration of endogenous insulin in LADA, which is responsible for lower production of antibodies to insulin, should be associated with gradual disappearance of hypoglycemia symptoms in the patient.

There is no indication that the patient should require insulin therapy.[12] Also, metformin will not reduce the risk as there are no data that the medicine can protect beta cells from the autoimmune process. Due to the fact that the pathogenesis of LADA is known to include both autoimmunity and insulin resistance,[13,14] behavioral treatment (diet and physical activity) should also be followed to maintain good insulin sensitivity and to protect patients from cardiovascular complications in the future.

In cases of recurrent symptoms typical of hypoglycemia, it seems advisable to deepen the diagnosis with atypical causes. In the absence of confirmation of reactive hypoglycemia, monitoring of blood glucose over several days using real-time continuous glucose monitoring –

rtCGM, or intermittently scanned continuous glucose monitoring – isCGM, should be considered due to the paroxysmal and unpredictable nature of other types of hypoglycemia. Those methods could be also useful to prevent hypoglycemia episodes after diagnosis. When the autoimmune background of hypoglycemia is suspected, other autoimmune conditions should also be looked at. Behavioral treatment can be helpful in patients prone to low blood glucose levels. Frequent small meals low in carbohydrates during the day and cornstarch, which is slowly absorbed, in the evening to prevent night and/or fasting hypoglycemia should be recommended.[15,16] Also, acarbose, which delays carbohydrate absorption, can be a useful option. Some severe cases may also require corticosteroids, rituximab, or even plasmapheresis.[5]

Conclusion

The symptoms of hypoglycemia led to further diagnostics that revealed not only the potential reasons for those symptoms but also an active autoimmune process typical for LADA.

Although the low level of glucose was not detected during the accumulation of symptoms observed at the ambulatory visit, the typical course suggested that hypoglycemia was the reason. At least three diagnoses were proposed during the diagnostic process (hyperinsulinism without insulin resistance; reactive hypoglycemia; preclinical LADA) which is quite typical if the results do not clearly identify the disease. The rare Hirata disease was not considered during the diagnostic process, but eventually seemed to be associated with the whole clinical picture.

Bullet Points

1. Hypoglycemia can constitute an indicator of pre-clinical LADA.

2. Insulin autoantibodies should be assessed if symptoms of hypoglycemia are present.

3. The autoimmune hypoglycemia can be a part of the autoimmune process associated with diabetes.

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Disclosure

The authors report no conflicts of interest in this work.

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