Use of the continuous glucose monitoring system in the management of hypoglicemia in insulin autoimmune syndrome

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Introduction
Hypoglycemia is a clinical syndrome defined by a decrease in blood glucose to a level that may also show sympathetic-adrenergic and/or neuroglycopenic symptoms [1]. Among other more causes, the spontaneous autoimmune antiinsulin antibody syndrome is also associated with hypoglycemic episodes. This syndrome is extremely rare, with most reported cases occurring in Japan and in association with treatment with propylthiouracil for autoimmune thyroid disease. The disease is difficult to document in sporadic cases, and prior insulin use must be carefully excluded [2-3].

IAS is a type of autoimmune hypoglycemia characterised by hyperinsulinemic hypoglycemia due to elevated insulin autoantibodies titers (IAA), no pathological abnormalities of the pancreatic islets and no prior exposure to exogenous insulin. The other type of autoimmune hypoglycemia is type B insulin resistance syndrome, caused by antibodies directed against the insulin receptor [2].

IAS as an autoimmune disease is representative for type VII hypersensitivity, which is defined as an immunological disease that is triggered when the self-antigen (proteins or hormones) are released from the present autoantibodies in serum [4].

IAS has been found to have a higher incidence in genetically predisposed Japanese individuals with HLA-DR4 [5]. There are two major triggers of the production of IAA: viral infections/reinfections for instance mumps, rubella, Coxsackie B, influenza, hepatitis C, chickenpox [6]; and drugs, particularly drugs containing sulphydryl groups, dietary supplements containing α-lipoic acid (ALA), clopidogrel, albumin, loxoprofen-sodium [2], mostly related in patients with a history of autoimmune disorders/autoimmune polyendocrine syndromes [6].

Continuous glucose monitoring systems are used in patients with diabetes for improving glycemic control (especially to avoid episodes of severe hypoglycemia). The CGM systems are divided into several categories: professional CGM, masked to the user at the time of wear; real-time CGM (unmasked); and intermittently scanned CGM also called „flash” CGM [7]. CGM curated personal data can be accessed in real-time on personal devices and can be examined using software packages. From data analysis can be extracted a large spectrum of parameters including the number of days worn(sensor wear), the average blood glucose, glucose management indicator, glycaemic variability, time in range and percentage of time CGM is active, some of them being more intuitive and accessible to individuals [7].

Case report
Our patient, a 48-year-old Caucasian women, known with numerous osteoarticular diseases, with no personal or familial history of diabetes, was diagnosed in March 2019 with multiple episodes of hypoglycemia. The most severe episode of hypoglycemia occurred on March, 2019 confirmed at home by the paramedics, when she was found unresponsive with blood glucose of 32 mg/dl which responded well to bolus iv administration of 33% glucose solution. Other episodes have been documented in which the patient developed signs and symptoms compatible with hypoglycemia such as sweating, warmth, anxiety, tremor, nausea, behavioral changes, changes in vision and speech, confusion, dizziness associated with blood glucose below 40 mg/dl and with immediate relief of symptoms after food ingestion.

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She has been investigated for insulinoma, with a basal insulin value more than 1000 uU/ml and basal blood glucose equal to 48 mg/dl, with negative imaging results (CT, IRM, SPECT CT, echo-endoscopy). In April 2019 the patient performs an exploratory laparotomy that did not detect lesions, subsequently the episodes of hypoglycemia remitted spontaneously. Two months later IAA were performed and the serum levels were found to be more than 500 U/ml (normal value <0.4 U/ml) with normal levels of proinsulin (12.9 pmol/L) and C-peptide (2.31 ng/ml).

In October 2019, the patient performs an oral glucose tolerance test following the blood glucose and insulinemia for 5 hours and an HbA1c (value 5.27%) without finding a specific or borderline diabetic pattern. At the same presentation she was investigated for other autoimmune and endocrine diseases, informed afterwards.

At one year control, in October 2020, the IAA detected slightly higher values (10.5 U/ml), the normal value being below 0.4 U/ml.

In December 2020, she went to the endocrinology department accusing the recurrence of hypoglycemia episodes, including nocturnal ones with glycemic values on the capillary blood 35 mg/dl, with the remission of symptoms after the ingestion of carbohydrates; episodes cannot be linked to a trigger. Following the investigation performed during hospitalization of the patient we can withhold the next values of insulin antibodies >100 U/ml (<0.4 U/ml), Insulin >1000 uU/ml (2.6-24.9) to a venous blood glucose equal to 35 mg/dl, proinsulin 7.2 pmol/l (<11), C-peptide level 16,790 ng/ml (1.1-4.4), HbA1c 5.6%. She has also been investigated for thyroid and parathyroid disorders, Cushing syndrome, multiple myeloma and other viral infection including COVID-19, but none of them were confirmed.

Based on the signs and symptoms and laboratory tests, the case was interpreted as an insulin autoimmune syndrome that relapsed with unidentified triggers.

In the first phase, the patient was advised to be on a diet, frequent meals with small amounts of food, avoidance of fast absorbable carbohydrates and drugs which contain sulfhydryl groups as well as those that have the ability to absorb fast absorbable carbohydrates and drugs which contain sulfhydryl groups as well as those that have the ability to absorb fast absorbable carbohydrates and drugs which contain sulfhydryl groups as well as those that have the ability to absorb

In January 2021 we used a continuous glucose monitoring system for improving evaluations of glucose profiles obtained with diet and corticotherapy. The CGM Medtronic Guardian Connect 3 Sensor was used in real time and not blind to the patient. We performed two evaluations, for 7 days each.

The first evaluation, period B was between 16-th of January – 22-nd of January, respectively the second evaluation, period A was between 30-th January – 5-th of February.

At the first monitoring, we increased the dose of corticosteroid from 15 mg/day to 20 mg/day, keeping it to a low-dose, to avoid side effects while maintaining the immunosuppressive effect; at the second monitoring we returned to the initial dose.

We noticed that the episodes of hypoglycemia became rarer, the patient seeing the glycemic trend in time, thus she was able to prevent episodes of hypoglycemia.

Episodes of hyperglycemia in both periods were in a low percentage (1%), with values in the range of 180-250 mg/dl, possible in the context of carbohydrate intake with high glycemic index. But in our case, as we can see on the graph, the highest value of blood sugar was 180 mg/dl.

In the graph we can observe two graphical representations, figure B, the first monitoring period respectively figure A, the second monitoring period. We found out that episodes of hypoglycemia were reduced in the second monitoring, respectively in figure A compared to the first monitoring; the patient intervened quickly to prevent hypoglycemia. By reducing episodes of hypoglycemia, we observed an increase time spent in range without increasing time above range.

After 2 months of corticosteroid therapy, the IAA titer was 32.9 U/ml (normal range: <10 U/ml), we observed a decrease in the frequency of episodes of hypoglycemia. In this context we decided to reduce the dose of prednisone to 10 mg/day, with gradual decrease of doses until cessation of therapy.

Subsequently, after another 6 months during which the patient had few episodes of mild hypoglycemia, a new analysis of insulin antibodies was performed, with titer within normal limits (value: 7.4 U/ml, normal range: <10 U/ml). Evolution of the patient’s antibody levels can be seen in table 1.

**Discussions**

Diagnosis of IAS must be taken into consideration in differential diagnosis of hypoglycemia in any non-diabetic patient or in patients without a record of exposure of exogenous insulin. [8] First of all, Whipple triad must be documented alongside spontaneous hypoglycemic episodes or after a 72 hours fasting test correlated with high serum insulin levels to demonstrate hyperinsulinemic hypoglycemia [9].

Nonetheless, differential diagnosis of hyperinsulinemia between exogenous insulin administration and endogenous forms needs to be performed. Therefore C-peptide and proinsulin seric concentrations point out the source of high insulin levels [9]. If high or inappropriate levels of C-peptide and proinsulin are detected then hyperinsulinemia is most probably due to an endogenous cause (IAS or insulinoma), oppositely low levels of C-peptide and proinsulin which indicate administration of exogenous insulin [2].

For the diagnosis of IAS the gold standard consists in analysis of insulin antibodies in serum [9]. A pathogenetic role in the development of IAS is played by IAA that are immunoglobulin directed against endogenous insulin molecule and they can be included in different Ig classes,
but they are more often IgG, respectively IgM and IgA in few cases [10]. The defining attributes of IAA is that they have high binding capacity and low affinity [11].

In spite of the fact that most cases of IAS are triggered by the administration of a drug or an infection/reinfection [2,4,9,12,13], in the described case, no potential trigger factor could be identified for IAS. Also, no correlation could be found between a trigger and the recurrence of hypoglycemic episodes that took place after a year and a half, after the spontaneous remission.

Based on the initial data, the case was interpreted as an insulinoma, despite negative imaging investigations (CT, MRI, CT spectrum, echo-endoscopy). An exploratory laparotomy was performed with intraoperative pancreatic ultrasound without detecting lesions. Later, the surgery proved to be unnecessary and it could have been avoided if insulin antibody dosing and the diagnosis of IAS had been considered.

An interesting finding in this case was the spontaneous remission of hypoglycemia episodes after surgery although the titer of anti-insulin antibodies showed increased values > 500 U/ml (<0.4) two months later. A plausible explanation for this phenomenon could be that the insulin antibodies dosed at the time of relief of hypoglycemia had higher affinity constant and lower binding capacity against human insulin as described by Eguchi et al [10] in a Japanese study that showed the connection between the hypoglycemia and longitudinal changes of serum IAA.

Few cases of hypoglycemia in IAS have been described in the literature in which continuous glycemic monitoring has been used to monitor and evaluate IAS and to individualize treatment in the absence of consensual agreement [3,14].

Continuous glucose monitoring systems are widely used among people with diabetes. They have been shown to be useful in assessing the patient's time in range, as well as the time below range and the time above range [7].

The use of this monitoring system, in this case in real time, has proved to be very useful in quantifying variations in the glycemic trend, hypo- and hyperglycemia. It has

Table I. Evolution of the patient's antibody levels

<table>
<thead>
<tr>
<th>Anti-insulin antibody level (U/ml)</th>
<th>May 2019</th>
<th>October 2020</th>
<th>December 2020</th>
<th>February 2021</th>
<th>August 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500</td>
<td>10.5</td>
<td>&gt;100</td>
<td>32.9</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>IAA normal values (U/ml)</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
also been useful in preventing episodes of hypoglycemia with potentially life-threatening by fast administration by the patient of carbohydrates after consulting the glycemic trend [14].

Our case report confirms the interest in the use of the CGM in autoimmune hypoglycemia and encourages its use to prevent severe episodes of hypoglycemia.

Ethical conduct of research informed consent was obtained from the patient involved in this study.

Authors' contribution
ARP: Writing – original draft, funding acquisition, investigation, conceptualization, project administration, data curation
CMR: Conceptualization, Writing – original draft, project administration, data curation, software
GR: Validation, Visualization, formal analysis, supervision
IMP: Write- review & editing, validation, methodology, resources, supervision

Conflict of interest
None to declare.

References