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ORIGINAL ARTICLE

Phenomenon of hypoglycemia unawareness in patients with insulinoma – single center experience

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Abstract

INTRODUCTION: Insulinomas are rare neuroendocrine tumors of pancreas. Clinical manifestations include various symptoms of hypoglycemia, which is the result of insulin overproduction. Symptoms of hypoglycemia are heterogenous what most probably contributes to diagnostic delay. In this study we retrospectively evaluated clinical features of hypoglycemia. We discovered that a substantial number of patients suffered from hypoglycemia unawareness.

MATERIALS AND METHODS: We performed retrospective analysis of prospectively collected patients with histologically confirmed insulinoma. We evaluated clinical features and signs of hypoglycemia and the duration of symptoms and performed thorough review of the patients' files in order to identify whether patients had been falsely diagnosed previously. Each patient underwent 72 hour fasting test during which levels of immunoreactive insulin (IRI), C-peptide and nadir blood glucose level were obtained. Based on the clinical findings and results of 72 hour fasting test we identified a subgroup of patients with hypoglycemia unawareness. These had an episode of clinically silent hypoglycemia. We compared IRI and C-peptide levels obtained at the time of the fasting test termination in the unawareness group and the group without hypoglycemia unawareness.

RESULTS: Twenty two patients with insulinoma that had been hospitalized in our tertiary center were included in the analysis. Mean age was 51±16.7 years. The most common symptom reported by 63.6% of patients was fatigue, followed by increased appetite with consequent weight gain and the loss of consciousness, both reported by 40.9% of patients. Based on the review of clinical features and the results of the fasting test we identified a group of patients with hypoglycemia unawareness. We labeled the patient accordingly in case of the loss of consciousness in personal history as well as asymptomatic hypoglycemia or severe neuroglycopenic symptoms during the fasting test without any accompanying or preceding clinical signs. There were 7 patients with hypoglycemia unawareness in our cohort (31.8%). Patients with this phenomenon had significantly lower levels of both IRI (2.35±1.25 vs. 5.88±3.92ng/ml, p=0.01) and C-peptide (9.14±7.36 vs. 50±42.8 μU/ml, p=0.01) than the rest of the patients. Nadir blood glucose level during the fasting test showed no significant difference (9.4±8.2 vs. 12.2±8.2 months, p=0.28) in the unawareness group and the rest of the patients, respectively.

CONCLUSION: We described the phenomenon of unawareness to hypoglycemia in the patients with insulinoma. This has not been recognized in insulinoma patients yet since available evidence mostly relates to type I diabetic patients. It might lead to higher morbidity and diagnostic delay. Further studies with prospective evaluation should be performed to further confirm relatively high prevalence in patients with insulinoma.

INTRODUCTION

Insulinomas are neuroendocrine tumors that originate from Langerhans cells (beta cells) of pancreas responsible for the production of insulin. They are considered rare with an estimated annual incidence of 4 cases per 1,000,000 inhabitants per year (Vanderveen *et al.* 2010). They are more common in women with the median age of diagnosis being 45-50 years (Vanderveen *et al.* 2010; Service *et al.* 1991; Chazot *et al.* 2013).

Clinical manifestations of insulinomas include various symptoms of hypoglycemia as a result of insulin overproduction (Abboud & Boujaoude 2008). These features have been traditionally described as Whipple´s triad and include signs of hypoglycemia, low plasma glucose level and relief of these symptoms after glucose ingestion (Tarchouli *et al.* 2015). Despite being straightforward at first glance, the term "signs of hypoglycemia" is somewhat nonspecific as these are rather diverse and variable.

Indeed, biochemical criteria, together with symptoms and signs of hypoglycemia need to be fulfilled to set the diagnosis of insulinoma according to the guidelines. Diagnostic criteria proposed by ENETS and by the US Endocrine Society require the presence of symptoms and/or signs of hypoglycemia and the biochemical confirmation of endogenous hyperinsulinemic hypoglycemia (Falconi *et al.* 2016; Cryer *et al.* 2009). This includes elevated levels of insulin, proinsulin and C-peptide which are in clinical setting commonly obtained during 72 hour fasting test (Tarchouli *et al.* 2015; Falconi *et al.* 2016). However, the criteria continue to evolve and vary in different consensus documents and reviews (Falconi *et al.* 2016). Other biochemical markers (e.g. chromogranin A) are not recommended due to low specificity (Falconi *et al.* 2016; Cryer *et al.* 2009).

One of the major diagnostic challenges in these patients results from the diversity of clinical symptoms of hypoglycemia. These have been classically described as autonomic and neuroglycopenic, however, other neurological signs (e.g. epileptic seizures) or psychiatric signs (e.g. disorientation, aggression, confusion) have also been reported (Samoš *et al.* 2014; Graves *et al.* 2004; Ding *et al.* 2010). Misinterpretation of nonspecific symptoms and signs might lead to delayed or missed diagnosis as it does not prompt clinicians to aggressively exclude or confirm hyperinsulinemic hypoglycemia. Not surprisingly, the mean time between the symptom onset and the diagnosis is as much as few years (Tarchouli *et al.* 2015; Falconi *et al.* 2016).

Therefore, we retrospectively analyzed our cohort of patients with histologically confirmed insulinoma in terms of clinical features and biochemical parameters.

MATERIALS AND METHODS

This is a retrospective analysis of prospectively collected patients with insulinoma that were admitted to our tertiary centre from 1996-2019. Only patients with histologically confirmed definitive diagnosis of insulinoma were included in the analysis. The study was approved by the Ethical Committee of Jessenius Faculty of Medicine, Comenius University.

Firstly, we reviewed general clinical symptoms by the means of retrospective evaluation of the patients' records and files. We than calculated the mean time between the symptom onset and the diagnosis.

Secondly, we focused on the levels of biochemical parameters related to insulinoma and the result of 72 hour fasting test. This was performed in patients without proven hyperinsulinemic hypoglycemia (n=22) under standardized conditions: intensive care unit admission with continuous monitoring of vital signs, monitoring blood glucose levels every three hours and termination of the test when the blood glucose level dropped below 2.4 mmol/l or clinical symptoms or signs of hypoglycemia occurred. Blood glucose level and the level of C-peptide and insulin (immunoreactive insulin - IRI) were obtained at the time of the test termination and the patient was given 5% parenteral glucose solution. The test was considered positive when it met the following criteria: plasma concentrations of glucose ≤2.4 mmol/l, IRI levels ≥3 μU/ml and C-peptide levels ≥ 0.6 ng/ml (Falconi *et al.* 2016). A biochemical diagnosis of insulinoma was established (Falconi *et al.* 2016; Service 1995).

Thirdly, we focused on patients' symptoms during the documented episode of hypoglycemia. Indeed, we identified a subgroup of patients without any warning (autonomic) signs of hypoglycemia. We compared this subgroup of patients with the remaining group of patients in terms abovementioned biochemical parameters (levels of blood glucose, C-peptide and IRI).

Levels of blood glucose, IRI and C-peptide are expressed as mean±SEM. Unpaired t-test is used as indicated in the figure legends.

RESULTS

A total of twenty two patients (12F/10M) were included in the final analysis. The mean age at the time of diagnosis was 51±16.7 years.

All patients suffered from various symptoms and signs of hypoglycemia. The most common symptom reported by 15 patients (63.6%) was fatigue. The

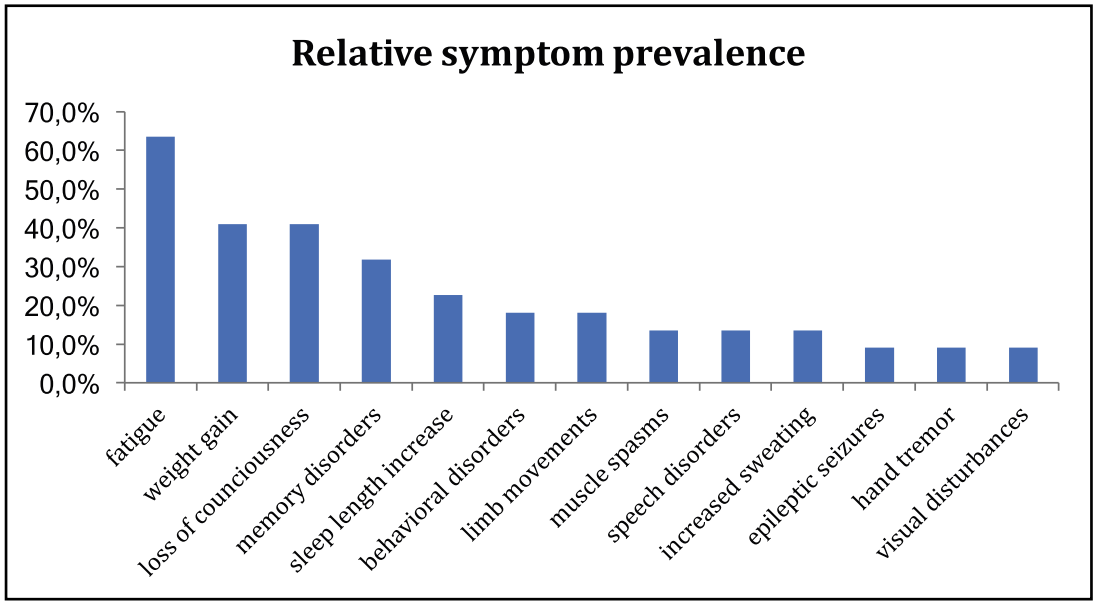

Fig. 1. Relative prevalence of symptoms of hypoglycemia (n=22). The most prevalent is fatigue, followed by weight gain and the loss of consciousness. By contrast, symptoms labeled as "classic", e.g. sweating or hand shaking are less prevalent - present in 13.6 and 9.1% of patients, respectively.

second most common was increased appetite with consequent weight gain and the loss of consciousness. These were both reported by 9 patients (40.9%). The duration of the loss of consciousness varied from short-term with spontaneous awakening and not requiring medical intervention to severe hypoglycemic coma requiring injection of parenteral glucose or glucagon. Interestingly 5 patients (22.7%) reported problems waking up with substantial increase of the length of sleep. This was pronounced in a single patient whose first symptom was extremely long sleep lasting for almost 24 hours and the inability to wake up well. During the hospitalization differential diagnostic process revealed insulinoma being responsible for this condition. In 7 patients (31.8%) memory disorders were present, ranging from short-term to long term amnesia. In 4 patients (18.1%) behavioral and thinking disorders were present with episodes of aggression, disorientation, confusion and internal tension.

Other features reported were epileptic seizures (9.1%), muscle spasms (13.6%), upper and lower limb movements (18.2%), hand traces (9.1%), speech disorders (13.6%), increased sweating (13.6%), and visual disturbances in terms of diplopia (9.1%). Relative prevalence of these features is provided in the comprehensive table (Fig. 1).

The review of patients' files (n=22) showed that a substantial group (n=7) of patients had been incorrectly diagnosed before being sent for evaluation to our institution. 7 patients (31.8%) had been diagnosed and treated for neurological disease or psychiatric disorder (4 patients for the transient ischemic attack, 1 patient for epilepsy, 1 patient for postherpetic encephalitis and 1 patient was treated for severe psychoorganic syndrome). Not surprisingly, the overall average time from symptom onset to final diagnosis of insulinoma in the whole group of patients was 14.3 months (range 0 – 72 months).

Subsequently we reviewed biochemical results and outcomes of the 72 hour fasting test obtained during the hospitalization. The test was performed in all 22 patients and was positive all patients, nadir glucose levels were available in 19 patients and IRI and C-peptide levels were available in 17 patients. Analysis of the symptoms and results of the fasting test lead to unexpected identification of a subgroup of patients (7 patients, 2 females and 5 males) that had no warning (autonomic) symptoms of hypoglycemia. We labeled the patient as having as having unawareness to hypoglycemia if he had the episode of the loss of consciousness in personal history together with asymptomatic hypoglycemia or severe neuroglycopenic symptoms during the fasting test without any accompanying or preceding clinical signs.

Based on these findings we compared the biochemical results (blood glucose level, C-peptide and IRI level) between the group of patients with and without hypoglycemia unawareness. The average value of the nadir *blood glucose level* during the fasting test in the unawareness subgroup compared with the rest of the patients was 1.85±0.14 and 1.98±0.69 mmol/l, respectively (p=0.33, NS, n=19). Average *C-peptide level* was significantly lower in the unawareness subgroup compared with the rest of the patients (2.35±1.25 vs. 5.88±3.92ng/ml, respectively, p=0.01, n=17). Average *IRI level* in the unawareness group was also significantly lower in the unawareness subgroup compared

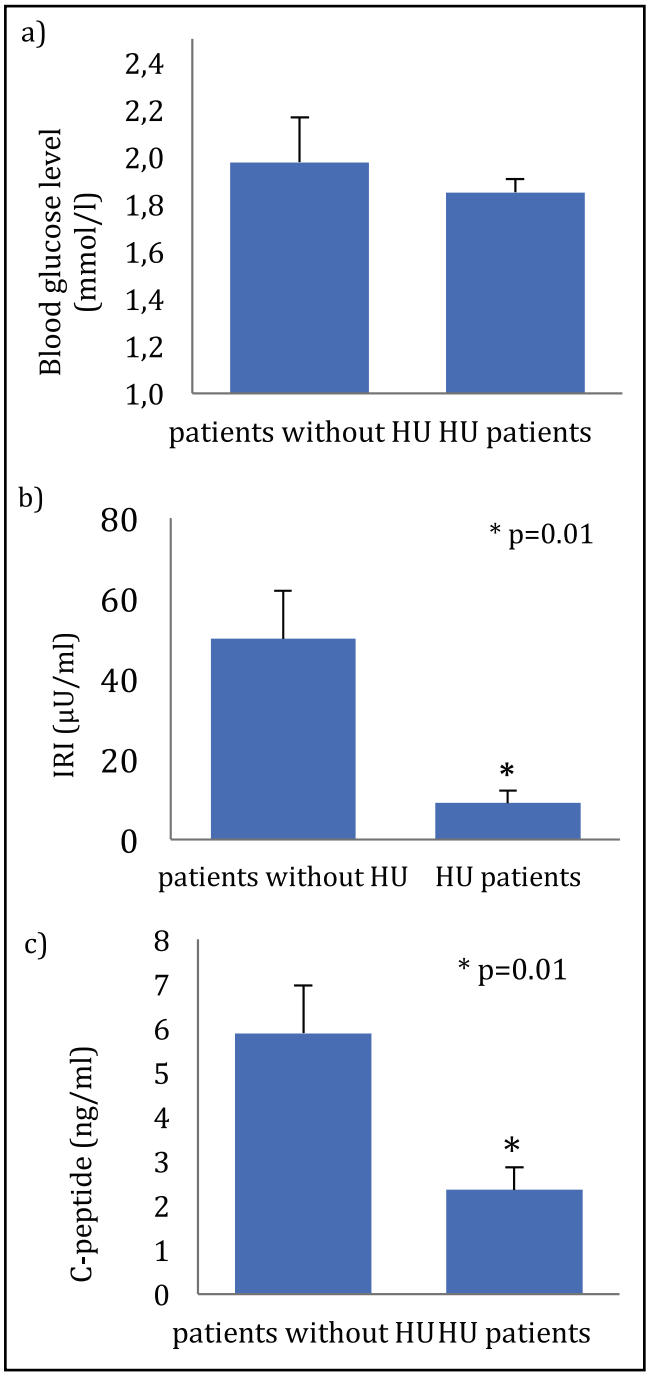

Fig. 2. Blood glucose, IRI and C-peptide levels of the patients with and without features of hypoglycemia unawareness (HU). These were obtained during the 72 hour fasting test. Levels of IRI (b) and C-peptide (c) are significantly lower in the group of patients with hypoglycemia unawareness (n=17, p=0.01 in both cases). Contrary to these, nadir glucose level (a) obtained during the test did not show statistically significant difference between the groups (n=19, p=0.33). Unpaired t- test is used.

with the rest of the patients (9.14±7.36 vs. 50±42.8 µU/ml, respectively, p=0.01, n=17) (Fig. 2 a, b, c). However, the mean time to diagnosis was not significantly different in patients with hypoglycemia unawareness (9.4±8.2 months) compared to the patients without this syndrome (12.2±8.2 months) (p=0.28).

DISCUSSION

The main outcome of our study is the identification of a subgroup of patients with insulinoma suffering from hypoglycemia unawareness which has been traditionally associated with type I diabetic patients. Arguably, lack of hypoglycemic symptoms might lead to increased morbidity and diagnostic delay. Rigorous evaluation of patients with only histologically confirmed insulinoma further supports our results.

In this study we summarized clinical signs and symptoms and selected biochemical parameters in 22 patients with confirmed insulinoma. Similarly to other studies there was relatively higher prevalence in women and the mean age at diagnosis was almost 50 years (Service *et al.*1991; Shao *et al.* 2018).

Patients presented with variable clinical manifestations of hypoglycemia. Analysis of the prevalence of particular symptoms in our cohort revealed that the most common clinical symptoms were fatigue, followed by weight gain and loss of consciousness, memory disorders and behavioral disorders. Similar study to ours reports the most prevalent symptom loss of consciousness in 54% followed by tremor in 25% of patients with insulinoma (Anakal *et al.* 2014). Another study of 40 patients summarizes that the most prevalent was loss of consciousness (75%), fatigue (27.5%) and behavioral changes (30% of patients) (Shao *et al.* 2018). Retrospective review of 79 patients reported the most common presenting symptom confusion (86%), followed by excessive sweating (57%) and drowsiness (58% of patients) (Peltola *et al.* 2021). Different results of relative symptom prevalence are not surprising considered the heterogenity of clinical signs of hypoglycemia. The aspect of patients' subjective perception and interpretation of symptoms of hypoglycemia might also to a certain degree confound these results.

Interestingly, we observed that a substantial proportion of our patients had no warning symptoms of hypoglycemia. These patients had either no symptoms during hypoglycemia or severe neuroglycopenic symptoms – loss of consciousness without any accompanying or preceding clinical signs. To the best of our knowledge only few case reports of the syndrome of hypoglycemia unawareness in insulinoma have been published yet (Pérez-Pevida *et al.* 2016; Suminaga *et al.* 2019; Sugawa *et al.* 2018; Ferreira *et al.* 2020; Wexler *et al.* 2018). The ability to respond to hypoglycemia is the result of neural and hormonal response to low blood glucose level that triggers sympatoadrenal response (Szadkowska *et al.* 2018; Hartill *et al.* 2018).

Although our study was not designed to elucidate the pathogenesis of hypoglycemia unawareness, some suggestions on the pathogenetic background can be made. Mitrakou *et al.* (Mitrakou *et al.* 1993) followed by others (Szadkowska *et al.* 2018; Stanley *et al.* 2019) suggest that recurrent or severe episodes

of hypoglycemia are responsible for the development of this phenomenon. Their study (Mitrakou *et al.* 1993) performed on 6 insulinoma patients concluded that hypoglycemia itself induces unawareness of the autonomic symptoms and decrease of the contraregulatory hormonal responses (Mitrakou *et al.* 1993). This is different from the concept that has been suggested for type I. diabetes patients where hypoglycemia unawareness is believed to be the consequence of exogenous insulin treatment. Another study focused on hypoglycemia unawareness in type I diabetic patients linked this phenomenon to recurrent hypoglycemia. However, the responsible mechanism is unknown. Several hypotheses have been suggested. One of them illustrates the connection between HU and changes the glucose metabolism and transport in brain (Criego *et al.* 2005). The second one discusses the effect of changes in the concentration of neurotransmitters in brain (gamma – aminobutyric acid – GABA) where the increase of GABA levels in ventromedial hypothalamus leads to reduced glucagon and epinephrine response to hypoglycemia (Chan *et al.* 2011). Although there is significant improvement of knowledge of the mechanisms of HU, further research is needed to verify the pathophysiology of this phenomenon (Martin – Timon & Del Canizo Gomes 2015).

Our observations support the findings presented by Mitrakou *et al.* (Mitrakou *et al.* 1993) as in our cohort, both IRI and C-peptide levels were significantly lower in the unawareness subgroup (Fig. 2 b, c). Indeed, rather hypoglycemic episodes themselves than insulin overproduction seem to be responsible for hypoglycemia unawareness syndrome development. Although this cannot be automatically applied on diabetes patients, this concept warrants further investigation.

We consider recognizing and purposeful searching for this phenomenon in insulinoma patients important for a couple of reasons. Firstly, these patients are potentially dangerous to themselves as their only symptom is sudden loss of consciousness without any prodromal manifestations. Secondly, severe hypoglycemia might lead to irreversible structural changes in brain leading to cognitive dysfunctions and behavioral disorders (Szadkowska *et al.* 2018). Thirdly, as mentioned above, relatively high prevalence of loss of consciousness in other cohorts, arguably, this phenomenon might be underdiagnosed (Anakal *et al.* 2014; Shao *et al.* 2018).

Our study has limitations. The most prominent is the retrospective nature of the study and relatively small number of patients. We, however, believe that this is partially overcome by rigorous evaluation of patients with histologically confirmed insulinoma. Another limitation is that the study lacks information about the precise time of the termination of the fasting test (e.g. the hour of duration) and whether this was due to symptoms or biochemical evidence of hypoglycemia.

CONCLUSION

We identified a subgroup of patients with insulinoma with the phenomenon of hypoglycemia unawareness. This should be considered in the management of patients being evaluated for sudden loss of consciousness or other symptoms that might be regarded as neuroglycopenic. Further research in fields of its pathophysiological explanation and evaluation in larger cohort of patient should be performed.

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STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Jessenius Faculty of Medicine in Martin (JFM CU), Comenius University in Bratislava and every patient underwrote approval for use gained data for scientific purposes during admission.

CONFLICT OF INTEREST STATEMENT

"The authors have no conflicts of interest to declare."

AUTHOR CONTRIBUTIONS

Nosáková, Bánovčin, Ďuríček contributed to the conception of the research; Nosáková, Demeter, Uhrík, Božíková, Hyrdel conducted the data interpretation; Nosáková, Ďuriček drafted the manuscript; Nosáková, Bánovčin, Ďuričekrevised and edited the manuscript for content; all authors read and approved the final version of the manuscript.

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