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ORIGINAL ARTICLE

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Early detection of cognitive impairment in patients with insulinoma

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Abstract

Purpose Long-standing hypoglycemia can cause cognitive impairment, and whether recurrent severe hypoglycemia impacts cognitive function in patients with insulinoma has not been studied. This study focused on exploring the cognitive function in patients with insulinoma.

Methods A prospective study was conducted to assess cognitive function in patients with insulinoma by administering the Montreal Cognitive Assessment (MoCA) questionnaire between January 2016 and July 2017, and patients with cognitive impairment were followed up to undergo the MoCA test 1 year after surgery. The MoCA scores after surgery were compared with the scores before surgery, and the associations between cognitive impairment and relevant factors were further evaluated by multiple linear regression analysis.

Results Eighteen out of thirty-four patients (53%) with insulinoma were screened positive for cognitive impairment as defined by a MoCA score <26. Performance in certain cognitive domains, including visuospatial and executive functions, delayed memory, attention, language, and abstraction, was significantly worse in patients with cognitive impairment. Multivariate analysis indicated that MoCA scores correlated significantly with tumor grade and years of education. Eight patients with cognitive impairment were lost to follow-up. The remaining ten patients with cognitive impairment showed improvements 1 year postoperatively, and seven patients recovered to normal cognitive function.

Conclusions Cognitive impairment was found in patients with insulinoma and was reversible in some patients 1 year after surgery. More studies are needed to explore the underlying mechanisms of the existence and reversibility of cognitive impairment in patients with insulinoma.

Keywords Cognitive impairment · Insulinoma · MoCA · Hypoglycemia

Introduction

Insulinoma is the most common functional pancreatic neuroendocrine tumor, with a reported incidence of 1–4 cases per million people per year [1–5]. Hypoglycemia is the manifestation of insulinoma, and in patients with insulinoma, its symptoms include confusion, weakness, dizziness, or unconsciousness [6].

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Hypoglycemia is a risk factor for subsequent cognitive impairment and dementia [7]. Notably, recurrent severe hypoglycemia in patients with diabetes produced deleterious effects on brain structure and resulted in cognitive impairment, even when blood glucose recovered to the normal range [8, 9]. Insulin or insulin analogs have succeeded in reducing hyperglycemia in patients with diabetes, but recurrent hypoglycemia is the main complication of insulin therapy. Diabetic patients with long-term recurrent hypoglycemia had poorer cognitive scores associated with cognitive disorders [10].

Recurrent severe hypoglycemia exists for several years in patients with insulinoma. Pozzessere et al. [11] reported that brain stem function in patients with insulinoma was impaired by hypoglycemia and that neurophysiological abnormalities had a long recovery period after tumor removal. To the best of our knowledge, cognitive function in patients with insulinoma and whether complete tumor resection can improve cognitive impairment have not been studied. The Montreal Cognitive Assessment (MoCA) was specifically designed to screen for mild cognitive impairment and is widely used to test cognitive function [12]. Its high sensitivity to cognitive abnormalities makes the MoCA a good screening tool for use in patients with stroke [13] and diabetes [14]. In addition, several studies reported that the MoCA was used to test the cognitive function in patients who underwent surgery, including bariatric surgery [15], lower extremity amputation [16], and cardiac surgery [17]. Thus, the current study reports the cognitive function in patients with insulinoma and the postoperative changes of cognitive function in patients with cognitive impairment by using the MoCA.

Patients and methods

This prospective study was conducted at Peking Union Medical College Hospital between January 2016 and July 2017. The inclusion criteria were (1) age ≥ 18 years; (2) diagnosed insulinoma; and (3) willingness to undergo surgery. The exclusion criteria were (1) patients who did not undergo surgery finally and (2) tumor recurrence during the postoperative 1-year follow-up. After applying the inclusion and exclusion criteria, a total of 34 patients with insulinoma were included in the study, and one patient was excluded, as she chose conservative therapy rather than surgery. The diagnostic criteria for insulinoma were the same as those that we have published previously [18, 19]. After surgery, all patients recovered to normal blood glucose levels, and they were followed up to exclude tumor recurrence. The World Health Organization (WHO) 2017 classification was used for grading the tumors [20].

Cognitive assessment was performed using the MoCA. A Chinese version of the MoCA questionnaire was administered to patients with insulinoma 3 days before surgery [12]. All patients who received a survey accepted the invitation. As the diagnostic criteria for insulinoma require plasma glucose ≤ 2.5 mmol/L, the blood glucose value was >2.5 mmol/L in the patients when the MoCA questionnaire was administered [21]. To assess the effect of tumor resection on the cognitive function, the MoCA was reassessed among the patients with cognitive impairment 1 year after surgery. The MoCA assesses eight major cognitive domains, including visuospatial and executive functions, naming, language, memory, abstraction, delayed recall, attention, and orientation. The maximum MoCA score is 30 points, and one additional point is added to the MoCA score if the participants have fewer than 12 years of education [22]. The cut-off score of the MoCA for cognitive impairment is <26 [23].

The patients were divided into two groups according to their presurgery MoCA scores. Group 1 consisted of patients with a MoCA score ≥ 26 who were considered to have intact cognitive function, and group 2 consisted of the patients with cognitive impairment.

Statistical analyses

Continuous data are presented as the mean ± SD or median [interquartile range (IQR)]. Categorical data were described as counts and percentages and were analyzed with the chi-square test. We used a *t*-test to analyze normally distributed continuous data, and the Mann–Whitney U test was used for nonnormally distributed continuous data. A repeated measures *t*-test was used to compare the MoCA scores before and after surgery. Multiple linear regression analysis of the MoCA score was utilized to study the association between cognitive impairment and age, gender, years of education, duration of history (the time from first onset of hypoglycemia to admission to our hospital), hypertension, tumor grade, the lowest blood glucose measured, and the longest period of hypoglycemia. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of the participants

This study included 34 insulinoma patients with a mean age of 46.1 ± 12.2 years, and the basic characteristics are shown in Table 1. The study population consisted of 17 females and 17 males, and the mean preoperative BMI was 27.1 ± 4.6 kg/m^2.

Table 1 Characteristics of all patients with insulinoma, group 1 (patients with a MoCA score ≥ 26) and group 2 (patients with a MoCA score < 26)

	All patients $N = 34$	Group 1 $N = 16$	Group 2 $N = 18$	p-value
Age	46.1 ± 12.2	42.7 ± 11.7	49.1 ± 12.1	0.131[a]
Gender				0.492[b]
Female	17	9	8	
Male	17	7	10	
Duration of disease (months)	36.0 (57.0)	36.0 (42.8)	42.0 (111.0)	0.266[c]
Glucose[d] (mmol/L)	6.0 ± 2.4	5.8 ± 2.2	6.1 ± 2.6	0.681[a]
Tumor size(mm)	15.8 ± 4.8	16.3 ± 5.2	15.4 ± 4.5	0.633[a]
Site of tumor				0.730[b]
Head-neck	15	8	7	
Body-tail	19	8	11	
Tumor grade[e]				0.006[b]
G1	19	5	14	
G2	15	11	4	
BMI (kg/m^2)	27.1 ± 4.6	25.8 ± 3.8	28.2 ± 5.0	0.139[a]
Years of education (year)				0.212[b]
1–6	4	1	3	
7–12	14	5	9	
>12	16	10	6	
Hypertension				0.028[b]
Yes	13	3	10	
No	21	13	8	
Lowest blood glucose (mmol/L)	1.7 ± 0.5	1.8 ± 0.5	1.7 ± 0.5	0.483[a]
Longest period of hypoglycemia (min)	75 (90)	60 (82.5)	120 (102.5)	0.109[c]
MoCA score	25.1 ± 3.8	28.4 ± 1.4	22.1 ± 2.6	<0.001[a]
MoCA subdomain scores				
Visuospatial/executive	3.9 ± 1.3	4.6 ± 0.7	3.2 ± 1.3	<0.001[a]
Naming	2.9 ± 0.4	2.9 ± 0.3	2.8 ± 0.4	0.201[a]
Memory and delayed recall	3.9 ± 1.3	4.6 ± 0.6	3.2 ± 1.6	0.003[a]
Attention	5.0 ± 1.5	5.8 ± 0.5	4.2 ± 1.7	0.002[a]
Language	2.0 ± 0.8	2.6 ± 0.5	1.4 ± 0.7	<0.001[a]
Abstraction	1.4 ± 0.8	1.8 ± 0.4	1.0 ± 0.8	0.003[a]
Orientation	5.8 ± 0.6	5.9 ± 0.3	5.7 ± 0.8	0.187[a]

BMI body mass index, *MoCA* Montreal Cognitive Assessment

p-value between group 1 and group 2:

[a]Independent-sample *t* test

[b]Chi-square test

[c]Mann–Whitney *U* test

[d]The blood glucose was tested preoperatively before the MoCA evaluation

[e]World Health Organization (WHO) 2017 classification includes (1) pancreatic neuroendocrine tumors (PanNET G1, PanNET G2, PanNET G3) and (2) pancreatic neuroendocrine carcinoma (PanNEC)

The mean preoperative blood glucose tested before MoCA evaluation was 6.0 ± 2.4 mmol/L, and no significant difference was found between group 1 and group 2. Two patients were diagnosed with multiple endocrine neoplasia type 1 (MEN1), and two patients had obstructive sleep apnea syndrome (OSAS). One patient had lacunar infarcts, and another patient underwent brain surgery because of glioma.

Hypoglycemia and preoperative treatment in the participants

The lowest blood glucose measured in the participants was 1.7 ± 0.5 mmol/L, and a comparison of the values in group 1 and group 2 revealed no significant difference ($p = 0.483$, shown in Table 1). The median value of the single longest

period of hypoglycemia was 75 min in this cohort; and the duration of hypoglycemia in group 2 was 120 min and was longer than that in group 1 (60 min), although this difference was not significant ($p = 0.109$). Common symptoms in patients with insulinoma were loss of consciousness, sweating, memory impairment, visual disturbance, barylalia, and dizziness. The prevalence of all hypoglycemic symptoms was not significantly different between group 1 and 2, as shown in Supplementary Table 1. Preoperatively, all patients usually ate food to relieve hypoglycemic symptoms, and nine of the 16 patients (56%) in group 1 had regular additional meals as suggested by the doctors compared with the five patients (28%) in group 2, although the difference was nonsignificant ($p = 0.163$).

Cognitive impairment in patients with insulinoma

Eighteen (53%) patients with insulinoma were classified as having cognitive impairment according to the MoCA score (Table 1). The mean value of the MoCA score in all patients was 25.1 ± 3.8. The mean MoCA score was 22.1 ± 2.6 in group 2, which was significantly lower than 28.4 ± 1.4 in group 1 ($p < 0.001$). Analysis of the MoCA subscores showed that five domains were significantly impaired, namely, visuospatial-executive ($p < 0.001$), memory and delayed recall ($p = 0.003$), attention ($p = 0.002$), language ($p < 0.001$), and abstraction ($p = 0.003$) among the patients with cognitive impairment.

Factors related to cognitive impairment in patients with insulinoma

Patients with tumor grade 1 (G1) were more likely to have cognitive impairment than patients with tumor grade 2 (G2) ($p = 0.006$), and more patients were diagnosed with hypertension in group 2 than in group 1 ($p = 0.028$). The differences in the remaining basic characteristics were nonsignificant between group 1 and group 2; these variables included age, gender, duration of disease, tumor size, tumor site, BMI, years of education, lowest blood glucose, and longest period of hypoglycemia (shown in Table 1). The median duration of disease in patients with G1 was 48.0 months, which was significantly longer than 12.0 months in patients with G2 ($p = 0.008$). The cognitive impairment rate in patients with G2 was 27% (4/15), which was significantly lower than 74% (14/19) in G1 patients ($p = 0.006$).

Multiple linear regression analysis was used to study the relationship between various factors and the MoCA score (Table 2). In the model for the total MoCA score, patients with G1 were associated with worse MoCA performance ($p = 0.048$), and education level also had a significant effect on the MoCA score, with less education associated with lower performance ($p = 0.003$ and $p = 0.002$ for 7–12 years of education and 1–6 years of education, respectively). Age, gender, duration of disease, hypertension, lowest blood glucose value, and longest period of hypoglycemia did not seem to be associated with the MoCA score.

Table 2 Multiple linear regression analysis of the factors associated with the preoperative MoCA score in patients with insulinoma ($n = 34$)

MoCA total score	B	SE	t	p-value
Age	−0.069	0.048	−1.444	0.162
Gender	−1.477	1.004	−1.471	0.154
Years of education				
>12	Ref.			
7–12	−3.543	1.072	−3.304	0.003
1–6	−6.268	1.829	−3.427	0.002
Duration of disease	0.002	0.006	0.432	0.670
Hypertension	−0.766	1.184	−0.647	0.524
Tumor grade	2.292	1.101	2.083	0.048
Lowest blood glucose	0.138	1.162	0.118	0.907
Longest period of hypoglycema	−0.006	0.004	−1.606	0.121

SE standard error, *B* regression coefficient, $R^2 = 0.555$

Postoperative reversibility of cognitive impairment in patients with insulinoma

Eight patients with cognitive impairment were lost to follow-up. Seven out of ten patients (70%) with cognitive impairment recovered to normal values, and the postoperative score of the MoCA test in the remaining three patients was 22.7 ± 3.2, which was significantly higher than 20.3 ± 3.0, the score they had received before surgery ($p = 0.020$). The total postoperative MoCA value was 26.2 ± 3.0 for patients with cognitive impairment, which was significantly higher than the MoCA value before surgery ($p = 0.037$). Among the subgroup analyses, the MoCA scores of the visuospatial and executive functions ($p = 0.001$), delayed memory ($p = 0.049$), and language ($p = 0.018$) domains were significantly improved after surgery (shown in Table 3).

Discussion

In this study, we found that 53% of patients with insulinoma were screened positive for cognitive impairment in the situation without hypoglycemia. Insulinoma patients with tumor G1 or fewer years of education had worse MoCA performance. Furthermore, we explored the postoperative cognitive changes among patients with cognitive impairment and found that all followed-up patients with cognitive

Table 3 Comparison of MoCA score in ten followed-up patients with cognitive impairment before and after surgery using a repeated measures *t*-test

	Before surgery	After surgery	*p*
MoCA total score	22.2 ± 2.6	26.2 ± 3.0	0.037
Visuospatial/executive	3.4 ± 1.0	4.4 ± 0.7	0.001
Naming	2.7 ± 0.5	2.7 ± 0.5	0.896
Memory and delayed recall	3.1 ± 1.4	3.9 ± 1.1	0.049
Attention	4.2 ± 2.0	5.7 ± 0.9	0.267
Language	1.3 ± 0.9	1.8 ± 0.7	0.018
Abstraction	1.1 ± 1.0	1.4 ± 0.7	0.082
Orientation	5.8 ± 0.4	5.8 ± 0.4	–

impairment improved, and 70% of the patients recovered to normal cognitive function 1 year after surgery.

The rate of cognitive impairment in this study was much higher than the reported 3–17% of elderly people (>65 years) [24]. All patients with insulinoma experienced severe hypoglycemia, and long-term recurrent severe hypoglycemia might contribute to the high rate of cognitive impairment observed in the study. As the only essential source of energy for brain cells, glucose is instantly used by the brain, given the inability to store or synthesize it. Severe hypoglycemia impairs the hippocampus and results in cognitive impairment [25]. Acute hypoglycemia induces disruptions to brain activities that require high attention and concentration; thus, working memory and delayed memory are impaired [26]. In addition to its acute effects, long-term recurrent severe hypoglycemia exposure has deleterious effects on brain structure and memory function [8]. In patients with diabetes, recurrent severe hypoglycemia leads to impaired cognitive function and is a risk factor for cognitive decline [27, 28]. The duration of the disease ranged from 3 to 360 months in this study, and the median duration of disease in group 2 was longer than that in group 1, although the difference was nonsignificant.

Tumor grade was associated with cognitive function in patients with insulinoma. The biological behavior of tumors was evaluated by two markers, namely, Ki-67 immunohistochemical staining and mitotic index. The WHO and the European Neuroendocrine Tumor Society divided pancreatic neuroendocrine tumors into three grades, G1, G2, and G3, according to Ki-67 values and the mitotic index [20, 29]. Higher tumor grades usually indicate more aggressive pancreatic neuroendocrine tumors [30]. In this study, the survival rate of patients with different tumor grades was not the focus. In fact, this study determined that G1 indicated worse MoCA performance than G2. Peter Wolf et al. [31] thought that lower initial blood glucose and higher levels of insulin and c-peptide were related to worse tumor grading during a 72-h-fast test in patients with insulinoma. Thus, patients with G2 may be more likely to present more serious clinical symptoms of hypoglycemia, which may help family members or the patients themselves recognize hypoglycemia so that it can be corrected in a timely manner, potentially decreasing the amount of time spent in a hypoglycemic state and decreasing the potential dangers to the brain. In addition, our study revealed that G2 was associated with a shorter duration of the disease, which might indicate less time to have experienced hypoglycemia.

The postoperative MoCA score was significantly improved in patients with cognitive impairment, and most patients recovered to normal cognition function after a long postoperative period. Spontaneous chronic hypoglycemia has caused many neurophysiological abnormalities in patients with insulinoma, and improvement of such abnormalities required a long recovery time, at least 6 months after surgery [11]. Thus, we assessed patients and administered the MoCA 1 year after the surgery. The improvement in cognitive function after surgery might be attributed to the following two factors. One was that blood glucose levels in patients recovered to within a normal range, and the brain injury caused by hypoglycemia was no longer occurring. Postoperative blood pressure recovery might be the other factor that contributed to the improvement in cognitive function. This study revealed that the rate of hypertension was much higher in patients with cognitive impairment, although the difference was not significant in the multivariate analysis. Hypertension could cause brain ischemia, hemorrhage, brain atrophy and amyloid accumulation, all of which contribute to the progression from cognitive impairment to dementia [32]. One study [18] reported that blood pressure had normalized in most patients with insulinoma 1 year after surgery. The improved metabolic changes caused by tumor resection might play a role in the recovery of cognitive function.

As the reported incidence of insulinoma is 1–4 cases per million people per year [1–5], the small number of patients is one of the limitations of our study. It would have been better to expand the sample size and decrease the rate of loss to follow-up. In addition, the underlying mechanisms contributing to the postoperative improvement of MoCA need to be studied further.

Conclusions

In conclusion, this study indicated that cognitive impairment exists in patients with insulinoma and that tumor removal could improve cognitive function. The underlying mechanism of postoperative cognitive recovery needs to be studied in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol (S-K654) was approved by the Institutional Ethics Committee of PUMCH, Chinese Academy of Medical Sciences.

Informed consent The authors declare that they have no conflict of interest.

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