

# Loss of consciousness in a helicopter pilot as plausible first sign of insulinoma: a case report

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## SUMMARY

*A 50-year-old man who worked as a helicopter rescue pilot transiently lost consciousness while piloting a helicopter rescue. In the diagnostic process, all tests for the main possible differential diagnoses of loss of consciousness (cardiological and neurological) were performed and yielded normal results. Blood chemistry tests revealed recurrent fasting hypoglycemia and Chromogranin A was at the upper limit of normal. Fine needle aspiration guided by endoscopic ultrasonography was used to diagnose insulinoma-type neuroendocrine tumor of the pancreas. According to the Italian policies, the occupational physician aims to maintain professional skills without neglecting flight safety. A careful analysis of the relationship between the characteristics of the state of health of the aviator and his specific work needs was carried out, and he was given the opportunity to continue working as a rescue pilot thanks to medical therapies associated with organizational interventions in the workplace.*

## INTRODUCTION

In 2020, we diagnosed an insulinoma-type neuroendocrine tumor in an aviator who has been working as a helicopter rescue pilot for approximately 10 years. Helicopter emergency medical service (HEMS) is a pre-hospital first aid service that has become increasingly important since the early 1980s, not only in Italy but also throughout Europe (1, 2). Usually, HEMS conventional rescue team is made up of two groups: flight crew (pilot and helicopter hoist winchman), who is responsible for deciding whether or not the mission is feasible, and health personnel (doctors and nurses). HEMS

is a job with a high risk of injury, especially at night. Landing is the phase of flight most often associated with accidents due to collision with an unseen obstacle (3).

Insulinoma is a rare neuroendocrine tumor. Its incidence is 1-3/million population/year. Less than 10% of cases are malignant. There is an age-specific incidence peak in the fifth decade of life. The biologically active peptide secreted is insulin, and the tumor is located in the pancreas in 99% of cases (4). Several cases of insulinoma have been described in the scientific literature, however, the issue of work implications of this rare diagnosis is often not given due attention. Clinical manifestation of insulinoma

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includes episodes of loss of consciousness due to hypoglycemia. This clinical manifestation can make some work activities dangerous. This complex case required the management of a rare disease, which, when it was diagnosed in a helicopter pilot, had serious implications on the pilot's possibility to continue performing his duties.

## CASE DESCRIPTION

In May 2019, a 50-year-old man who worked as a helicopter rescue pilot transiently lost consciousness while piloting a helicopter rescue during a day shift. The incident lasted approximately 1 min and 20 s and took place a few meters from the ground during the landing phase. Fortunately, it ended without anyone being injured because the pilot regained consciousness and control of the helicopter. He had no memory of what happened during the period he lost control of the aircraft due to unconsciousness. The pilot had never experienced any symptom until the day of the accident. Even during the moments preceding loss of consciousness, he denied hypoglycemic symptoms or other types of malaise. Relevant pathologies in his clinical history included a diagnosis of mild obstructive sleep apnea syndrome (OSAS) in 2018 and obesity class 1. He was put on low-calorie diet and it was suggested to him to take curcumin (1.5 g per day) for the purpose of losing weight: a weight loss of approximately 10 kg was achieved from December 2018 to May 2019. After the accident, the pilot was temporarily suspended from his job pending examinations.

## RESULTS

The first investigations performed at the Istituto di Medicina Aerospaziale "A. Mosso", Aeronautica Militare, Milan, in Fall 2019 (echocardiogram, electroencephalogram with sleep deprivation, magnetic resonance imaging of the brain, neck, and cervical spine, eco-color Doppler of the epiaortic vessels, electrocardiogram, and 24hECG) excluded cardiac and neurological pathologies. Subsequent investigations performed in Winter-Spring 2020 at the Clinica del Lavoro, Milan, revealed: recurrent fasting hypoglycemia <70 mg/dl (mean, 53 mg/dl range,

46-60 mg/dl) without hypoglycemic symptoms and with repeated blood insulin levels at the upper limit of normal range (19.4 -18.4 n.v. 2.6-25.0 mIU/L) that lead us to calculate a Turner Index of 61.33 (normal values <30) and pose the clinical suspicions of insulinoma; Chromogranin A at the upper limit of normal in the two samples, normality of C-peptide, and cortisolemia. Abdominal ultrasound (US), and confirmed by computed tomography (CT) scan, revealed a nodule in the pancreas head. US fine needle aspiration biopsy (FNAB) and CT FNAB were inconclusive. Fine needle aspiration guided by endoscopic ultrasonography (EUS) was then used and a diagnosis of neuroendocrine tumor (NET) of the pancreas: (well differentiated neuroendocrine tumor of the pancreas G1, positive for chromogranin (according to WHO 2017)) was made.

## DISCUSSION

The initial plausible doubt that the aviator's loss of consciousness could be due to an underlying insulinoma-type neuroendocrine tumor was supported by the finding of recurrent hypoglycemia on blood chemistry tests and elevated serum chromogranin A levels. The original description of Whipple's triad to suspect insulinoma consists of symptoms of hypoglycemia (commonly including headache, diplopia, blurred vision, confusion, dizziness, lethargy, sweating, and weakness), plasma glucose level of  $\leq 2.2$  mmol/l ( $\leq 40$  mg/dl), and relief of symptoms with administration of glucose (5). Hypoglycemic symptoms are not specific, and insulinomas can mimic several pathological conditions. Therefore, in the diagnostic process, all tests for the main possible differential diagnoses of loss of consciousness (cardiological and neurological) were performed and yielded normal results. The 2012 ENETS Consensus Guidelines for Diagnosis of Insulinomas has established the following criteria for insulinoma diagnosis: documented blood glucose levels  $\leq 2.2$  mmol/l ( $\leq 40$  mg/dl); concomitant insulin levels  $\geq 6$   $\mu$ U/ml ( $\geq 36$  pmol/l;  $\geq 3$  U/l by ICMA); C-peptide levels  $\geq 200$  pmol/l; proinsulin levels  $\geq 5$  pmol/l; -hydroxybutyrate levels  $\leq 2.7$  mmol/l, and absence of sulfonylurea (metabolites) in the plasma and/or urine. General markers

such as serum chromogranin A may support the presence of a neuroendocrine tumor and can be helpful for monitoring during the course of the disease (6).

Recurrent fasting hypoglycemia and elevated chromogranin A levels were consistent with the clinical suspicion. Furthermore, the suspicion of insulinoma was reinforced by the finding of a small pancreatic nodule on radiological tests such as ultrasound, CT, and fluorodeoxyglucose (18F-FDG) positron emission tomography examinations. Unfortunately, both ultrasound fine needle aspiration and CT-guided needle biopsy of the pancreatic lesion were not conclusive for diagnostic purposes. Currently, the most used and reliable diagnostic method for locating a suspected pancreatic insulinoma is Endoscopic Ultrasound (EUS). A recent meta-analysis evaluated the sensitivity and specificity of EUS for the diagnosis of insulinoma, as 81% and 90%, respectively (7). Therefore, fine needle aspiration guided by EUS was performed and the diagnosis of insulinoma was confirmed using immunohistochemistry.

Insulinoma can be treated using medical and surgical therapy. Indications for surgery depend on clinical symptom control, tumor size/location/extent, malignancy, and metastatic spread. Insulinoma is frequently a benign tumor and often a single lesion located in the pancreas. Surgical treatment can be complicated due to the difficulty in identifying lesions when they are small (<1 cm), which is not uncommon in this type of tumor. Medical treatment for insulinoma requires small frequent meals to prevent hypoglycemic episodes. Medical treatments using drugs that inhibit the release of insulin from the pancreatic  $\beta$ -cells (e.g., diazoxide) are also often required. Somatostatin can be useful in preventing hypoglycemia in patients with somatostatin receptor subtype 2-positive tumors (6).

In our case, it is possible that several factors acted synergistically, ultimately resulting in the aviator's loss of consciousness. It should be noted that the aviator had recently been diagnosed with mild OSAS and obesity class 1 (body mass index: 30-35 kg/m<sup>2</sup>). Therefore, the aviator had decided to follow a low-calorie diet with consequent moderate weight loss. Moreover, with the aim of losing weight, he

had started taking a nutraceutical product called curcumin, at 1.5 g per day. A recent systematic review found that the maximum effect of curcumin in reducing waist circumference was achieved at a dose of 2 g/day (8). The effect of curcumin includes increased insulin sensitivity. Furthermore, the irregular meal intake, which often occurs during shifts, weighs on carbohydrate metabolism. Therefore, shifts, irregular diet, intake of an insulin-sensitizing nutraceutical and increased insulin secretion due to the insulinoma, are all factors that may have contributed to the episode of loss of consciousness.

The aviator with a new diagnosis of insulinoma has been working as a helicopter pilot since 1996 and as a helicopter rescue pilot since 2009. The working hours consist of 12-hour shifts, of which approximately 8 per month are night shifts. During a shift, the actual hours spent flying the helicopter are approximately 2-3 h. The health surveillance of the pilots consists of diagnostic tests and medical examinations every six months at the Institute of Aerospace Medicine. No clinical problems emerged during the health surveillance checks. The glycemic checks carried out until then were also normal.

This patient's management requires a multidisciplinary collaboration. Hypoglycemia risk has to be taken into account and could represent a problem for the health and safety of both the pilot and crew. It must be considered that in the worst-case scenario, loss of consciousness could result in the occurrence of extremely serious accidents (9). A careful analysis of the relationship between the characteristics of the specific work needs and the state of health of the aviator was carried out (10). In our case, the aviator has not had any further hypoglycemic symptoms or other unconscious episodes since he stopped the curcumin therapy and started a diet with regular meals. Considering the size of the tumor and its benignity, a conservative approach using medical therapy and close follow-up of the lesion was chosen for this initial phase. According to the Italian policies, the Occupational Physician (OP) aims to maintain professional skills without neglecting flight safety. We concluded that while waiting for the decisive surgical intervention, the aviator could continue to work as a helicopter rescue pilot only if there is another experienced pilot on board. The pilot will have

to undergo a six-monthly specialist medical follow-up. This case is anecdotal about how the OP in collaboration with other medical specialists has made it possible to preserve professional skills without sacrificing the health and safety of the worker (10, 11).

**DECLARATIONS OF INTEREST:** THE AUTHORS DECLARE NO CONFLICT OF INTEREST

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