A Case of Insulinoma Presenting As Circadian Rhythm Sleep Disorder

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ABSTRACT We report the case of a 17-year-old female first presenting as circadian rhythm sleep disorder, then later diagnosed as insulinoma. The patient demonstrated severe deterioration of academic performance in high school classes six months prior to examination. She also had disordered dietary habits, including copious late-night consumption progressing to reversal of daytime and nighttime activities. The patient was examined by a psychiatrist and diagnosed with circadian rhythm sleep disorder. Somnolence developed and worsened thereafter, and the patient was transported by ambulance to our facility. The patient was silent and almost non-verbal at admission, suggesting a mental disorder. However, hypoglycemia persisted despite the opportunity for adequate food intake after admission. Additional investigation and extensive test results showed an insulin/glucose ratio of 0.64 (17.8 μ U/ml / 28 mg/dl). Abdominal magnetic resonance imaging (MRI) demonstrated a 15 $\times$ 10 mm tumor at the border of the pancreatic head and body. Insulinoma was diagnosed, and the tumor was excised. Hypoglycemia and circadian rhythm sleep disorder disappeared completely after surgery, and the patient was discharged. The Japanese literature shows that approximately 10% of insulinomas present various mental symptoms. Chronic hypoglycemia symptoms are also sometimes difficult to differentiate from mental disorders, and careful observation is required in emergency room settings.

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Key words: hypoglycemia, mental disorder, somnolence, insulin, pancreatic tumor

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Introduction

Many patients are treated in the emergency room for complaints of various mental symptoms. When irregular symptoms are observed, it can be difficult to differentiate mental, central nervous system, and metabolic disorders, as well as the overlap thereof. The classically cited symptoms of insulinoma are Whipple's triad:¹⁾ (1) Symptoms are known or are likely to be caused by hypoglycemia. (2) A low glucose level was measured at the time of symptoms (<50 mg/dl). (3) Relief from symptoms occurs when glucose level is raised to normal. However, insulinoma sometimes presents as mental disorders and is a condition

easily misdiagnosed²⁾. We report a case of insulinoma presenting as circadian rhythm sleep disorder and deteriorating school performance, which was diagnosed as insulinoma from extensive test results.

Case Report

A 17-year-old female was transferred to our emergency room for a complaint of somnolence. Information ascertained from the parents was as follows. From childhood, the patient tended toward silent social closeting in her own room. High-school marks were excellent but declined suddenly six months prior to examination. Napping in school became frequent, which drew the concern of teachers. The patient also showed disordered dietary habits, including copious consumption from late night until early morning. Fixed meals were sometimes skipped in favor of computer-game use. Due to persistent reversal of daytime and nighttime activity, the patient was examined by a private psychiatrist who diagnosed circadian rhythm sleep disorder. Dietary imbalance was observed, but there was no excess

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Fig. 1. Gadolinium-enhanced abdominal magnetic resonance imaging image.

caffeine consumption, smoking, or drug use. Subsequently, somnolence developed, waking ceased, and the family called an ambulance.

Vital signs at admission were as follows: Consciousness level of Japan Coma Scale (JCS) III-100 and Glasgow Coma Scale (GCS) E1 V1 M4; respiratory rate 20/min; heart rate 80/min; blood pressure 126/74 mmHg; body temperature 36.2 °C. Physical findings on examination were 155 cm height, 55 kg weight, and Body Mass Index 22.9. There were no head wounds and no other abnormal findings.

There were no abnormal values on peripheral blood analysis and biochemical analysis of serum except for a low level of glucose (28 mg/dl). Urinalysis results showed no abnormal findings, and toxicological screening by Triage® was also negative. After intravenous injection of 40 ml of 40% glucose, blood sugar was 55 mg/dl, and consciousness had improved to Japan Coma Scale I-1. Although the disturbance of consciousness was improved, the hypoglycemia remained unexplained, and the patient was admitted.

Even after admission, speech was virtually negligible, and communication was difficult. The initial diagnosis was therefore schizophrenia, circadian rhythm sleep disorder, eating disorder, or another such mental disorder. Questioning indicated that the patient withdrew into her own room and pursued irregular activities to the point of daytime and nighttime reversal, sometimes not eating for up to 20 hours, which was the assumed cause of hypoglycemia. However, hypoglycemia persisted even after admission, despite the opportunity for regular and adequate oral intake, and the cause was further investigated.

Additional test results predicated on insulinoma were

Fig. 2. Selective angiography findings for the celiac artery.

as follows: Blood insulin/glucose (IRI / glu) ratio was 0.64 (17.8 μ U/ml / 28 mg/dl) > 0.3. Insulin during hypoglycemia was IRI 10.9 μ U/ml > 6, and C-peptide CPR during hypoglycemia was 4.56 ng/ml > 0.6. Blood insulin and C-peptide values were high despite low blood sugar, clearly fulfilling the 1976 diagnostic criteria of Fajans et al³⁾ and the 1995 diagnostic criteria of Service⁴⁾ for blood testing.

Enhanced abdominal computed tomography did not show a pancreatic tumor. Nonetheless, abdominal MRI demonstrated a weak T1-weighted signal at the border of the pancreatic head and body, a 15 $\times$ 10 mm lesion slightly enhanced by gadolinium (Fig. 1).

Selective angiography findings for the celiac artery demonstrated a 15 mm diameter hypervascular tumor supplied by the dorsal pancreatic artery (Fig. 2).

Accordingly, pancreatic endocrine tumor and insulinoma were diagnosed. The pituitary gland, thyroid gland, parathyroid gland, and adrenal gland were normal, negating multiple endocrine neoplasia.

The clinical diagnosis was insulinoma, and limited resection of the tumor was performed. The pathological diagnosis of the specimen was insulinoma. Hypoglycemia and circadian rhythm disturbance disappeared completely after surgery, and the patient was discharged.

Discussion

This case included late night waking activity and overeating, leading at times to excess drowsiness during school classes and impairment of social activities. A discrepancy consequently developed between the circadian sleep rhythm of the patient and the schedule imposed environmentally. Based on the diagnostic criteria of the Diagnos-

Table 1. Case reports of insulinoma distinguished with difficulty from mental disorders in Japan.

Age	Sex	Misdiagnosed Insulinoma cases	Interval to diagnosis	Journal of Publication	Year
25	Male	Epilepsy	4 month	J Med Soc South Hokkaido	2001
50	Male	Confusional arousal	4 month	Jpn J Clin Psychiatry	2000
29	Female	Schizophrenia, Hallucination, Delusion	3 months	Clinic All-round	2000
77	Female	Dementia, Memory lapse, Depression	3 months	Jpn J Geriat	1998
57	Female	Depression, Epilepsy, Hysteria	6 years	Jpn J Clin Psychiatry	1995
62	Female	Schizophrenia	2 years	J Saitama Med Soc	1995
23	Male	Epilepsy	2 years	Jpn J Clin Psychiatry	1990
51	Female	Menopausal disorders	10 months	Jpn J Clin Psychiatry	1990
46	Female	Hallucination	1 year	Jpn J Clin Psychiatry	1990
28	Female	Memory lapse, Anorexia nervosa	7 months	Bull Kanagawa Psychiatr Assoc	1988
62	Female	Memory lapse, Wandering	8 years	The Biliary tract & pancreas	1987

tic and Statistical Manual of Mental Disorders, Fourth Edition⁵⁾, a circadian rhythm sleep disorder was diagnosed.

Insulinoma is an endocrine tumor causing hypoglycemia. In an investigation⁶⁾ of 358 cases of insulinoma during the 10-year period of 1991-2000, symptoms at the initial manifestation of insulinoma included many attributable to hypoglycemia; the most frequent being loss of consciousness (28.2%) and disturbance of consciousness (16.8%), followed by hypoglycemia (15.4%), convulsions (4.7%), and sweating. However, note should be taken that approximately 10% of these cases included various mental symptoms not initially suggestive of hypoglycemia, including behavioral abnormalities (3.9%), drowsiness (1.4%), irritation (1.1%), memory lapse (0.8%), sleep daze (0.6%), insomnia (0.3%), wandering (0.3%), soliloquy (0.3%), delirium (0.3%), and depression (0.3%). Previous, separate statistical research studies⁷⁻⁹⁾ also indicated a largely similar pattern.

The cases diagnosed after more than a year of neurological treatment as epilepsy, dementia, schizophrenia, and other such disorders should also be noted. **Table 1** shows literature search results for Japanese case reports of insulinoma difficult to differentiate from mental disorders and other such causes. Academic presentations in psychology have also described cases in which unidentified complaints existing for more than a year were treated with antipsychotics and antiepilepsy drugs, while hypoglycemia was never checked; cases difficult to differentiate from senile dementia; and cases overlapping mental handicap.

In the case of our experience, lucidity of consciousness was restored after excision of insulinoma, and speech returned gradually. The fact that, in this case, school performance that was formerly excellent deteriorated rapidly makes it highly plausible in our opinion that onset occurred

not in childhood, but approximately six months previously. Some reports^{10, 11)} concerning brain damage caused by hypoglycemia in elderly individuals suggests that, in diabetic patients, dementia may be caused by the persistence of chronic unperceived hypoglycemia. We experienced a case of insulinoma manifested as circadian rhythm sleep disorder and decreased academic performance.

The diagnosis of hyperinsulinemic hypoglycemia is often delayed. Reported intervals from onset of symptoms to time of diagnosis range from 10 days to more than 20 years. We inferred that some factors for recognition of insulinoma are as follows: 1) Many physicians do not suspect insulinoma because its incidence is very low. 2) Many physicians cannot detect tumors by abdominal echography testing because small tumors often grow slowly, and glucose and insulin levels are usually not examined all at once. 3) Counterregulatory hormonal responses camouflage symptoms of hypoglycemia and diminish the deterioration of cognitive function during hypoglycemia. Symptoms from chronic hypoglycemia are therefore difficult to differentiate from mental disorders, and careful observation is required in emergency room settings.

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症例報告

概日リズム睡眠障害を呈したインスリノーマ

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要旨 概日リズム睡眠障害と学業成績低下で発症し、精密検査の結果インスリノーマと診断された17歳の女性患者を報告する。患者は幼少期より無口で自分の部屋に引きこもりがちであった。高校での学業成績は優秀であったが、受診する半年前から学業成績が急激に悪化した。学校では居眠りが多くなり、教師から注意されるようになった。深夜から早朝にかけて多く食事するなど食生活が乱れた。定時の食事を摂らずにコンピュータをし続けることもあった。昼夜逆転の生活が続いたため、精神科の開業医を受診し、DSM-IV診断基準により概日リズム睡眠障害と診断されていた。その後、傾眠がちとなり覚醒しなくなったため、家族が救急車を要請し当院救急外来へ搬送された。入院時より無口で殆ど口を利かず、統合失調症・概日リズム睡眠障害・摂食障害など精神障害が疑われた。しかし入院後に十分な食事を摂ることが出来るようになったにも拘わらず低血糖が続いたため、更に原因検索を行った。血中インスリン 17.8 μ U/ml / 血糖 28 mg/dl = 0.64。腹部MRIで膵頭部・体部境界にガドリニウムで造影される15×10mmの腫瘍あり。インスリノーマと診断し、腫瘍核出術が行われた。手術後、低血糖および概日リズム睡眠障害は消失・軽快し退院した。救急外来には、様々な精神症状を主訴に受診する患者も多い。時に精神疾患なのか、中枢神経系疾患や代謝性疾患なのか、またそれらのオーバーラップなのか判別が難しいこともある。インスリノーマの典型的症状はWhippleの3徴候といわれる。本邦における集計ではインスリノーマが様々な精神症状で発症することが約10%あるとされる。精神科で年余にわたり、てんかん・認知症・統合失調症などとして加療されたのち診断された症例報告も散見されている。慢性的低血糖症状は、ときに精神疾患と鑑別が難しいこともあり、注意が必要である。

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