Case Report
Auto-Insulin Antibodies Due to Methimazole in a Patient with Myasthenia Gravis and Graves Disease
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Abstract
We report an elderly man who suffered from episodes of severe life-threatening hypoglycemia during exacerbation of his chronic obstructive airway disease. He presented with ocular myasthenia gravis, followed six months later by Graves’ disease with thyrotoxicosis and ophthalmopathy. Two months later, he then presented as severe hypoglycemia at midnight and was found to have insulin autoimmune syndrome. Upon literature search, it was noted that this combination of autoimmune polyendocrine syndrome was rarely reported worldwide except in Japanese. Though aetiology is unknown, correct identification was important to enable immediate appropriate treatment. Our case highlighted the complexity of disease in the elderly. Clinician’s alertness to this condition and timely treatment may prevent catastrophic outcomes.

ABBREVIATIONS
APS: Autoimmune Polyendocrine Syndrome

INTRODUCTION
Hypoglycemia in the elderly is a life-threatening condition. Whereas nocturnal confusion may be feature of cognitive decline, hypoglycemia remains an important, common and treatable cause. Diabetes mellitus with drugs such as insulin, alcohol and sepsis constitute ninety percent of cases of hypoglycemia in a hospital emergency room [1]. In seemingly well elderly individuals who developed spontaneous hypoglycemia, insulin autoimmune syndrome and insulinoma are treatable conditions that need to be differentiated. The concomitant presence of other autoimmune diseases such as autoimmune polyendocrine syndrome, biochemical tests and the presence of insulin antibodies help to differentiate the two diseases.

CASE PRESENTATION
An 82 year-old gentleman, who smoked and had history of pulmonary tuberculosis and chronic obstructive pulmonary disease, was seen in Neurology clinic for reversible right ptosis. Ocular myasthenia gravis was diagnosed because of positive tension test, presence of anti-striated muscle antibody and anti-acetylcholine receptor antibody (7.39 nmol/L. Reference < 0.45nmol/L). CT scan did not demonstrate any thymoma. He responded to pyridostigmine treatment and remained well until six months later when he complained of diplopia. There was right eye proptosis and fixed right eye gaze palsy. Blood tests showed thyrotoxicosis with suppressed thyroid stimulating hormone TSH < 0.01 mIU/L and elevated free thyroxine FT4 24.8 pmol/L. Anti-thyroid microsomal antibody titre was elevated at 1600 nmol/L. CT orbits confirmed Graves’ ophthalmopathy. There was diffuse right extra-ocular muscle enlargement and mild prominence of left inferior and superior rectus muscles, mild right proptosis and prominence of right superior ophthalmic vein with evidence of apical crowding on right side. He was treated with Carbimazole. For the dysthyroid eye disease, he was treated with prednisolone while radiotherapy was arranged. Two months later while he was still taking Prednisolone 20 mg daily orally for treatment of Graves ophthalmopathy, he was hospitalised for exacerbation of chronic obstructive pulmonary disease. He was noted to have recurrent confusion and sweatiness at 2 and 3 am with low Hemoglucostix level. This was reversible with oral glucose drinks. Hypoglycemia was confirmed with glucose 1.1 mmol/L, concomitant insulin > 900 mIU/L (Reference: fasting < 18) and C-peptide 1.66 nmol/L (Reference 0.27-1.27). The second set on another day also showed similar results- spot glucose 1.1 mmol/L, insulin > 900 mIU/L and C-peptide 1.25 nmol/L. Urine toxicology was negative for oral hypoglycemic agent and he was not receiving insulin. A low dose one microgram synacthen test showed baseline cortisol 351 nmol/L at 9 am. It rose to 526 nmol/L 30 minute after stimulation. Insulin autoimmune syndrome was suspected. Because of this differential diagnosis
and he was clinically euthyroid at that time (FT4 8.3 pmol/L). Carbimazole was withdrawn. Insulin antibodies were detected and was elevated 22.2 U/ml (ref <0.4). Despite withdrawal of Carbimazole, he continued to have recurrent fast nigh hypoglycemic attack in early morning. He was treated with Diazoxide up to 50 mg every 8 hours. By then most of his glucose ranged from 5 – 8 mmol/L.

Three months later, he was hospitalized again for chest infection and was found to have hyperglycemia. Diazoxide was stopped and his blood glucose remained normal. A second set of synaethen test was performed because of prolonged steroid treatment. It showed mild inadequacy, i.e. cortisol 305 nmol/L at baseline and 441 nmol/L 30 minute after stimulation. He was replaced with physiological low dose of hydrocortisone.

**DISCUSSION**

Insulin autoimmune syndrome is a disease characterized by spontaneous hypoglycemia, high concentration of insulin and positive insulin antibodies. Hirata first reported this condition in 1970 [2]. More than 300 cases have since been reported in Japan [3]. There appeared to be an ethnic difference in this condition. Worldwide case reports were scanty. There was a strong association with human leukocyte antigen Class II alleles DRB1*0406 [4]. In the Japanese population, the most prevalent age of onset was 60-69 years. No special age predisposition had been found in Caucasians or Asians excluding Japanese. Most Asian cases were associated with Graves’ disease and treatment with methimazole. In the Japanese series, 42% were found to be associated with medication containing a sulfhydryl group, whereas some were associated with autoimmune disease such as systemic lupus erythematosus. The cause remains unknown. One possible mechanism is that sulfhydryl group may work as a reducing agent which cleaves the disulfide bond of insulin and allows the DRalfa-DRB1*0406 complex on the antigen-presenting cells to bind insulin A chain, hence activating the self- insulin-specific T-helper cells [5]. The prognosis is generally good with most hypoglycemia resolved within three months’ time [3]. Discontinuing methimazole and the addition of Diazoxide in our case eventually led to hyperglycemia in three months, suggesting that insulin antibodies were no longer present. The transition from recurrent hypoglycemia to hyperglycemia would be the proof of the medication induce anti-insulin antibody syndrome. Our patient is probably the oldest reported case. One important differential diagnosis in this elderly age group is insulinoma. Indeed in the literature, it has been reported that laparotomy has been exercised for the use of methimazole in this clinical context.

In summary, we report a rare interesting case of elderly man who had autoimmune polyendocrine syndrome complicated by severe life-threatening hypoglycemia caused by insulin autoimmune syndrome. Increased awareness of these conditions can save the patient from suffering the outcomes of devastating hypoglycemia and prevent unnecessary operation. Caution had to be exercised for the use of methimazole in this clinical context.

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**REFERENCES**