The Endocrine Trifecta: Rarer Presentation of a Rare Disease

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Introduction

Autoimmune Polyendocrine Syndrome (APS) type 2 is rare disease comprising of:

- Autoimmune Addison's disease, in combination with
- Thyroid autoimmune disease and/or
- Type 1 diabetes mellitus
- Other non-endocrine autoimmune diseases can be a part of the syndrome

Uniqueness of the Case

The combination of the three autoimmune endocrine diseases is very rare and sometimes referred to as Carpenter's syndrome. Only few cases have been reported in literature.

Our patient's presentation was unique as the syndrome blew up with almost simultaneous onset of autoimmune Addison's disease, type 1 diabetes and subclinical hypothyroidism, with almost no latency period.

Case Report

- **History**: 47 years old Caucasian woman, previously fit and well, referred with hyponatremia and 8 weeks history of fatigue, anorexia, dizziness and weight loss (6.3 kgs).
- **Examination**: There was significant postural drop in systolic blood pressure on standing (80 mmHg). However, there was no skin or mucosal pigmentation.
- **Investigations**:

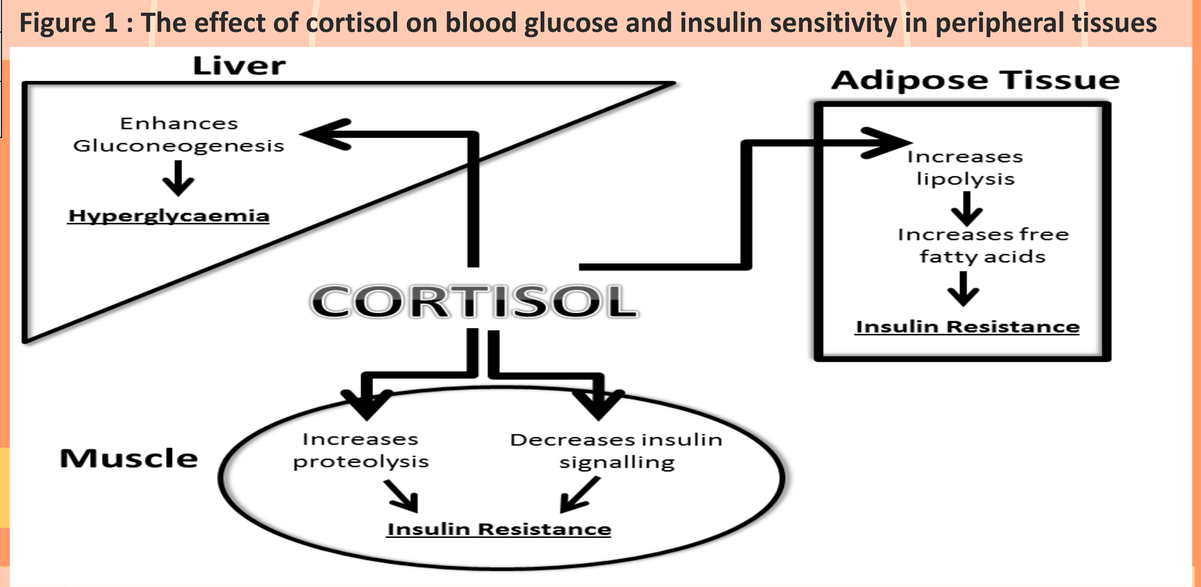
Tests	Results	Normal range
Sodium (mmol/l)	122	135-145
Potassium (mmol/l)	4.5	3.5-5.3
eGFR (ml/min)	90	>90
Random plasma glucose (mmol/l)	9.7	4-11
HbA1c (mmol/mol)	43	<42
TSH (mU/L)	4.3	0.35-5.5
ACTH (ng/l)	840	9 am<47, midnight <10

Baseline cortisol (nmol/l)	236 (range >140)
Cortisol 30 minutes after Synacthen 250 mcg i.v. (nmol/l)	247 (normal response: 550 , with an increment greater than 200)

Initial diagnosis & treatment : Diagnosis of Addison's disease was confirmed with positive adrenal antibodies (along with failed short synacthen test and raised ACTH). She was started on replacement with hydrocortisone 20 mg twice daily and fludrocortisone 100 micrograms daily.

Clinical course & final diagnosis: She was referred again after 3 weeks of discharge from the hospital with hyperglycaemia **[**random glucose 18.6 mmol/l, HbA1c 53 mmol/mol**]**. Diagnosis of type 1 diabetes was supported by a low C-peptide **[**0.25 nmol/l**;** range 0.34-1.8 nmol/l**]** and positive GAD antibodies **[**276 U/ml**;** range <25 U/ml**]**. Repeat TSH was suggestive of subclinical hypothyroidism **[**TSH 7.36 mU/L, FT4 & FT3 normal**]**. Thyroid peroxidase antibody was strongly positive **[**>1300 kU/l**;** range 0-59 kU/l**]**. So, diagnosed as having APS-II or Carpenter's syndrome (combination of Addison's disease, type 1 diabetes and autoimmune thyroid disease).

Figure 1 : The effect of cortisol on blood glucose and insulin sensitivity in peripheral tissues



Discussion

- Autoimmune Polyendocrine Syndromes (APS) are a heterogeneous group of autoimmune diseases causing impaired function of at least two endocrine glands. Non-endocrine autoimmune diseases are often present.
- The inheritance of APS-II is complex, with genes on chromosome 6 playing a major role.
- APS-II usually starts with a single disease (e.g Type 1 diabetes, Graves' disease, Hashimoto thyroiditis or Addison's disease) and a long time interval is usually present between the manifestations of the first to second/third component of the disease.
- Our patient is unique as type 1 diabetes was confirmed within a month of diagnosis of Addison's disease, and she developed autoimmune subclinical hypothyroidism shortly thereafter.
- We believe that the long standing cortisol deficiency in our patient had masked her underlying autoimmune diabetes and prevented her from having marked hyperglycaemia which was only evident upon replacing her with glucocorticoids. Figure 1 describes the effect of cortisol on blood glucose and insulin sensitivity.
- During her initial presentation with Addison's disease, her random blood glucose and glycosylated haemoglobin were in the pre-diabetes range. Cortisol deficiency made her sensitive to the small insulin reserve she had, protecting her against marked hyperglycaemia, which became overt when steroids therapy was initiated . Her diabetes was not secondary to steroids as she was confirmed to have low level of C-peptide and positive anti GAD antibodies, all pointing towards an immune origin of diabetes.

Conclusion

- Carpenter's syndrome is rare and only few cases have been reported in literature. Our case to the best of our knowledge is singular as the syndrome manifested with all the features presenting almost simultaneously within a short time span.
- Although it is a rare disease, the consequences can be life threatening if not diagnosed and treated early.
- Long standing cortisol deficiency related to Addison's disease can mask underlying autoimmune diabetes.
- It is recommended that all patients with idiopathic endocrine deficiencies should be screened for insufficiencies of other endocrine organs.

References:

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