

# Late onset diabetes of adults (LADA) masked by co-existed adrenal failure in the context of autoimmune polyglandular syndrome 2

## Abstract

Autoimmune polyglandular syndrome type II (APS II) is a rare disease characterized by the presence of autoimmune Addison's disease in combination with thyroid autoimmune disease and/or Type 1 diabetes mellitus, with possible occurrence of other autoimmune non-endocrine disorders. The combination of the three glands diseases is even rarer and sometimes referred to as Carpenter's syndrome. A long time interval is often present between the manifestation of the first to second component of the disease which may reach decades and it is clinically unusual for a patient to present with two or more glands disorders simultaneously. In this paper, we are presenting a case of 47years old woman who was referred for evaluation of hyponatraemia when she was confirmed to have Addison's disease. Upon starting her on steroids treatment, she was re-admitted after 3weeks with non-ketotic hyperglycaemia where underlying autoimmune diabetes was confirmed. Subsequently, she was found to have an autoimmune subclinical hypothyroidism, fulfilling the criteria of Carpenter syndrome. We believe that the long standing cortisol deficiency in our patient has masked her underlying autoimmune diabetes and prevented her from having marked hyperglycaemia which was only spotted upon replacing her with glucocorticoids. Our case to the best of our knowledge is singular as the disease manifested with fully blown up picture of the three endocrine glands dysfunction with no period of latency. Despite being a rare disease in clinical practice, consequences can be life threatening if not diagnosed and treated early. Physicians should be actively looking for the presence of this disorder especially in those patients with a new diagnosis of Addison's disease who develops marked hyperglycaemia soon after initiation of steroids at small physiological doses.

**Keywords:** addison's disease, autoimmune diabetes, autoimmune polyglandular syndrome 2

Volume 3 Issue 3 - 2016

Ahmed Al-sharefi, Uzma Khan, Girhidar Tarigopula, Paul Peter, Shafie Kamaruddin, Praveen Partha

Darlington memorial hospital, Darlington, United Kingdom

**Correspondence:** Ahmed Al-Sharefi, Department of diabetes and endocrinology, Darlington memorial hospital, Darlington, County Durham DL3 6HX, United Kingdom, Tel 0044 757 448 6063, Email ahmed.alsharefi@nhs.net

**Received:** May 22, 2016 | **Published:** May 30, 2016

**Abbreviations:** APS II, autoimmune polyglandular syndrome type II

## Introduction

The diagnosis of autoimmune polyglandular syndrome type II (APS II) is challenging as the symptoms are quiet nonspecific with a long sub-clinical state where antibodies are positive without an overt clinical gland dysfunction. Historically speaking, combined occurrence of Addison's disease and chronic lymphocytic thyroiditis was first reported by Schmidt in 1926 and this coexistence was later termed as Schmidt syndrome, this was followed by Carpenter's review of 142cases of Schmidt's syndrome where a link between Schmidt's syndrome and type 1 diabetes was confirmed and the full tri-glandular disease is then termed Carpenter's syndrome.<sup>1</sup> Despite being rare disease in clinical contexts, early identification and proper hormonal replacement can prevent fatal consequences.

## Case presentation

A 47years old white-British woman was referred to the acute medical unit by her general practitioner after a biochemical finding of hyponatraemia. She gave an 8 weeks history of generalized fatigue, decreased appetite and 6 Kilogram of weight loss. She also

reported feeling of nausea, light-headedness and occasional shortness of breath. She denied any symptoms of headache, visual blurring, skin pigmentation, and polyuria and polydipsia. She had no previous medical problems and she was not on any regular medication. She had no family history of thyroid disease, diabetes mellitus or other endocrine problems. On examination there was no pallor or increased skin pigmentations her cardiovascular, gastrointestinal, neurological and respiratory examination was entirely normal. Her observations showed significant postural hypotension with a difference of 80mmHg in systolic pressure upon standing. Biochemical blood results are shown below Table 1. Her ECG was normal and in sinus rhythm. Her Chest X-ray was also normal. She underwent short synacthen test which confirmed the presence of adrenal insufficiency (Table 2). The diagnosis of an autoimmune Addison's disease was made at this stage after the finding of high ACTH level of 840ng/L (normally should be <47ng/L) and confirmed positive adrenal antibodies. An MRI of adrenal glands was normal. Treatment was started with hydrocortisone 20mg twice daily plus fludrocortisone 100 micrograms once daily. After 3days of admission, she felt better in herself and her sodium level was improving to 139mmol/L. She was discharged with a 4weeks follow up appointment. 3weeks after discharge from the hospital, her general practitioner referred her again to the ambulatory care unit, this time with high blood glucose. Her fasting blood glucose was

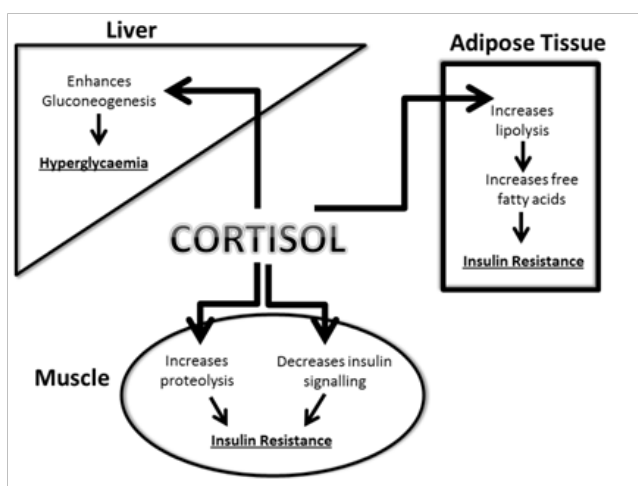
18.6mmol/L and a repeat HbA1c was 53mmol/mol. The diagnosis of type 1 diabetes mellitus was further supported by a low C-peptide level 0.25nmol/L (normal range 0.34-1.8nmol/L )and positive Glutamic acid decarboxylase antibodies of 276U/mL (normally less than 25U/mL). She was started on Insulin therapy with long and short acting insulin .On subsequent follow up, a repeat thyroid function test showed a TSH level of 7.36mU/L (normal range0.35-5.5mU/L) and positive thyroid peroxidase antibodies of more than 1300ku/L ( normal range 0-59Ku/L ). Levothyroxine replacement was initiated. Given the autoimmune evidence of adrenal, thyroid and pancreas involvement, the patient was diagnosed as having Carpenter’s Syndrome (a rare variant of autoimmune polyglandular syndrome 2).

**Table 1** Initial biochemistry results

Test	Value	Normal range
Sodium (mmol/L)	122	135-145
Potassium (mmol/L )	4.5	3.5-5.3
Urea (mmol/L)	5.7	2.5-7.8
Creatinine (umol/l)	54	50-110
Random plasma glucose (mmol/L)	9.7	11-Apr
HbA1C (mmol/mol)	43	<42
TSH (mU/L)	4.3	0.35-5.5
ACTH (ng/l)	840	9 am <47, midnight<10

**Table 2** Short synacthen test results

Baseline cortisol(nmol/l)	236(normal range >140nmol/l)
Cortisol 30minutes after I.V Synacthen(nmol/l)	247(550nmol/L, with an increment greater than 200nmol/L.)



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

## Discussion

Autoimmune polyglandular Syndromes are a heterogeneous group of diseases in which an immune driven process results in destruction and impaired function of at least two endocrine glands. The involvement of two or more glands is necessary for the diagnosis, however, other non-endocrine autoimmune diseases are often present such as pernicious anaemia, coeliac disease, vitiligo, gonadal failure

and rarely, myasthenia Gravis.<sup>2,3</sup> The extent to which glands are affected , the age of onset and genetic aetiology can distinguish APS into type I and APS type II in which Adrenal cortex involvement is always present , whereas in APS type III adrenal failure was not described.<sup>4</sup> In contrast to APS type II and APS type III, APS type I is a disease of childhood or early adolescence that is characterized by the presence of chronic mucocutaneous candidiasis, hypoparathyroidism and Addison’s disease, thus it is sometimes referred to as autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED) and is usually of an autosomal recessive inheritance.<sup>5</sup> APS type II is much more common than type I, and is usually a disease which affects adults, mostly females in the third and fourth decade of life, with an estimated prevalence of 1.4-2/10000 in the general population.<sup>6</sup> The pathogenesis of autoimmune tissue destruction in APS II is believed to be secondary to cellular mediated immunity and loss of self-tolerance, which is triggered by an external antigen stimulus in genetically susceptible individuals.<sup>7</sup> Two genes have shown to be associated with APS type 2 including HLA genes on chromosome 6 and CTLA-4 gene on chromosome 2, of which HLA appears to have the strongest gene effect.<sup>3,7</sup> The combinations of gland diseases and the time period when this becomes clinically evident is variable. In one retrospective study for a series of 106 patients,<sup>8</sup> the most frequent association was the co-occurrence of type 1 diabetes and thyroid disease (56.2%) and less commonly was the occurrence of diabetes and Adrenal disease (26%). With regards to time interval, the longest interval of time was between type 1 diabetes and thyroid disease (10.3years) but a short time between Addison’s disease and thyroid disease (1.4years). Clinically speaking, APS II usually starts with a single disease (e.g Type 1 diabetes, Graves’ disease, Hashimoto thyroiditis or Addison’s disease) and after a variable period of latency the second component of the disease appears, thus, it is clinically hard to find simultaneous occurrence of two or more autoimmune endocrine diseases in one patient.<sup>1</sup> Our patient’s presentation was unique as the syndrome blew up simultaneously with the finding of an autoimmune Addison’s disease, diabetes and subclinical hypothyroidism with no latency period. The patient was diagnosed with Addison’s disease, then after 21days, type one diabetes was found which raised our suspicion that the two components may have existed together from the beginning. Cortisol stimulates gluconeogenesis and enhances peripheral insulin resistance (Figure 1). In patients with pre-existing type 1diabetes a decrease in insulin requirement or an increasing frequency of hypoglycaemia could be the first sign of adrenal failure.<sup>9</sup> Hence, the onset of diabetes in patients who have Addison’s disease can be masked due to impaired gluconeogenesis and increased sensitivity to insulin associated with cortisol deficiency. In our patient, we noted that during her initial presentation with Addison’s disease, her random blood glucose and glycosylated haemoglobin were in the pre-diabetes range. We believe that this is because she was sensitive to the small insulin reserve she had, protecting her against marked hyperglycaemia, which only 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 points toward in immune origin of diabetes.

Similar findings were reported in the paediatric literature, which relates to a 12years old girl who had Grave’s disease since the age of 4, then presented with signs and symptoms of adrenal insufficiency. After few days of replacement with glucocorticoids she was found to be hyperglycaemic and subsequently started on insulin and diagnosed to have type 1DM in view of positive anti-GAD and anti-islet cell antibodies.<sup>10</sup> The approach to individuals with more than one endocrine gland failure should include auto-antibodies testing

for patients and family members plus testing for end organ damage, as this will identify individuals who require hormonal substitution therapy and those who are at risk of developing a glandular failure in the future.<sup>9</sup> In any patient with autoimmune Addison's disease, screening for other auto-antibodies like thyroid peroxidase antibodies, Thyroglobulin, glutamic acid decarboxylase 65 (GAD 65) and islet cell Abs is recommended giving the frequent association of Addison's to other autoimmune disorders and in those who have anti GAD antibodies positive, an oral glucose tolerance test should be performed to confirm the presence of type 1 diabetes.<sup>11</sup> The mainstay of treating APS type II is by the replacement of each component hormonal deficiency, however it is crucial for adrenal failure to be treated prior to starting thyroxine to avoid precipitating adrenal crisis.<sup>12</sup> For Adults with APS II who have Addison's disease and/or diabetes, annual monitoring of thyroid function is recommended as the presence of thyroid peroxidase antibodies usually precedes overt hypothyroidism.<sup>12</sup> In our patient, she had an evidence of subclinical hypothyroidism and high titre of TPO antibodies with mild increase in TSH level, She was commenced on Levothyroxine 100 micrograms once daily and kept under regular follow up.

### Acknowledgements

None.

### Conflict of interest

Author declares that there is no conflict of interest.

### References

1. Betterle C, Lazzarotto F, Presotto F. Autoimmune polyglandular syndrome Type 2: the tip of an iceberg? *Clin Exp Immunol*. 2014;137(2):225–233.
2. Kahaly GJ. Polyglandular Autoimmune Syndrome Type II. *La Presse Medicale*. 2012;41:e663–e670
3. Jaume JC. Endocrine Autoimmunity. In: Greenspan's Basic & Clinical Endocrinology Gardner, 9th ed. New York: Ed D-G Shoback, McGraw-Hill; 2011:43–44p.
4. Dittmar M, Kahaly GJ. Polyglandular Autoimmune Syndromes: Immunogenetics and Long-Term Follow-Up. *J Clin Endocrinol Metab*. 2003;88(7):2983–2992.
5. Wass J, Owen K. In: *Oxford Handbook of Endocrinology and Diabetes*. 3rd ed. Oxford, UK: Oxford University Press; 2014. 270p.
6. Betterle C, Zanchetta R. Update on autoimmune polyendocrine syndromes (APS). *Acta Biomed*. 2003;74(1):9–33.
7. Graves L, Klein R, Walling A. Addisonian crisis precipitated by thyroxine therapy: A complication of Type 2 Autoimmune polyglandular syndrome. *Southern medical journal*. 2003;96(8):824–827.
8. Munif F, Elleuch M, Hajji R, et al. Autoimmune polyglandular syndrome type II: epidemiological, clinical and immunological data. *J Endocrinol Metab*. 2014;4(4):101–109.
9. Gherbon A. Epidemiological aspects of polyglandular autoimmune syndrome type II in a group of adults with thyroid disease and diabetes mellitus. *European scientific journal*. 2014;10(3):31–40.
10. Aijaz N, Blanco E, Lane H, et al. Type 1 Diabetes Mellitus Masked by Primary Adrenal Insufficiency in a Child with Autoimmune Polyglandular Syndrome Type 2. *Clinical Pediatr*. 2003;42(1):75–77.
11. Kahaly G. Polyglandular autoimmune syndromes. *European Journal of endocrinology*. 2009;161:11–20.
12. Eisenbarth G, Gottlieb P. Autoimmune polyendocrine syndromes. *N Engl J Med*. 2004;350(20):68–79.