Late Onset Diabetes of Adults (LADA) Masked By Coexistent 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 47 years 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 3 weeks with non-ketotic hyperglycaemia where an 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 develop marked hyperglycaemia soon after initiation of steroids at small physiological doses.

Keywords: Addison’s disease; Autoimmune diabetes; Autoimmune polyglandular syndrome 2

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 142 cases 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 [1]. Despite being rare disease in clinical contexts, early identification and proper hormonal replacement can prevent fatal consequences.

Case Presentation

A 47 years 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 80 mmHg 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 840 ng/L (normally should be <47 ng/L) and confirmed positive adrenal antibodies. An MRI of adrenal glands was normal. Treatment was started with hydrocortisone 20 mg twice daily plus fludrocortisone 100 micrograms once daily. After 3 days of admission, she felt better.
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in herself and her sodium level was improving to 139 mmol/L. She was discharged with a 4 weeks follow up appointment. 3 weeks 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 18.6 mmol/L and a repeat HbA1c was 53 mmol/mol. The diagnosis of type 1 diabetes mellitus was further supported by a low C-peptide level 0.25 nmol/mL (normal range 0.34-1.8 nmol/mL ) and positive Glutamic acid decarboxylase antibodies of 276 U/mL (normally less than 25 U/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 7.36 mU/L (normal range 0.35-5.5 mU/L) and positive thyroid peroxidase antibodies of more than 1300 ku/L (normal range 0-59 ku/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.

| Test                      | Value | Normal range |
|---------------------------|-------|--------------|
| Baseline cortisol (nmol/l)| 236   | (normal range > 140 nmol/l) |
| Cortisol 30 minutes after 1V Synacthen (nmol/l) | 247 (550 nmol/L, with an increment greater than 200 nmol/L) |

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 [2,3]. 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 adrenal failure [4]. 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 [5]. 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 [6]. 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 [7]. Two genes have shown to be associated with APS type 2 including IL2, IL10 and CTLA-4 gene on chromosome 6 and CTLA-4 gene on chromosome 2, of which IHLA appears to have the strongest gene effect [3,7]. The combinations of gland diseases and the time period when this this becomes clinically evident is variable. In one retrospective study for a series of 106 patients [8], 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 was between type 1 diabetes and thyroid disease (10.3 years) but a short time between Addison’s disease and thyroid disease (1.4 years). 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 [1]. 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 21 days, 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 1 diabetes a decrease in insulin requirement or an increasing frequency of hypoglycaemia could be the first sign of adrenal failure [9]. 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 12 years 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 1 DM in view of positive HLA genes on chromosome 6 and the autoimmune syndrome 2.
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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 [9]. 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, an oral glucose tolerance test should be performed to confirm the presence of type 1 diabetes [11]. 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 [12]. 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 [12]. 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.

References

1. Betterle C, Lazzarotto F, Presotto F (2014) Autoimmune polyglandular syndrome Type 2: the tip of an iceberg? Clin Exp Immunol 137(2): 225-233.
2. Kahaly GJ (2012) Polyglandular Autoimmune Syndrome Type II. La Presse Medica1e 41: e663-e670.
3. Jaume JC (2011) Endocrine Autoimmunity. In: Greenspan’s Basic & Clinical Endocrinology Gardner, (9th edn), Ed D-G Shoback, McGraw-Hill, New York, p. 43-44.
4. Dittmar M, Kahaly GJ (2003) Polyglandular Autoimmune Syndromes: Immunogenetics and Long-Term Follow-Up. J Clin Endocrinol Metab 88(7): 2983-2992.
5. Wass J, Owen K (2014) In Oxford Handbook of Endocrinology and Diabetes. (3rd edn), Oxford University Press, Oxford, UK, pp. 270.
6. Betterle C, Zanchetta R (2003) Update on autoimmune polyendocrine syndromes (APS). Acta Biomed 74(1): 9-33.
7. Graves L, Klein R, Walling A (2003) Addisonian crisis precipitated by thyroxine therapy: A complication of Type 2 Autoimmune polyglandular syndrome. Southern medical journal 96(8): 824-827.
8. Munif F, Elleuch M, Hajji R, Fourni H, Masoudi H, et al. (2014) Autoimmune polyglandular syndrome type II epidemiological, clinical and immunological data. J Endocrinol Metab 4(4): 101-109.
9. Gherbon A (2014) Epidemiological aspects of polyglandular autoimmune syndrome type II in a group of adults with thyroid disease and diabetes mellitus. European scientific journal 10(3): 31-40.
10. Aijaz N, Blanco E, Lane H, Thomas E (2003) Type 1 Diabetes Mellitus Masked by Primary Adrenal Insufficiency in a Child with Autoimmune Polyglandular Syndrome Type 2. Clinical Pediatr 42(1): 75-77.
11. Kahaly G (2009) Polyglandular autoimmune syndromes. European Journal of endocrinology 161: 1-20.
12. Eisenbarth G, Gottlieb P (2004) Autoimmune polyendocrine syndromes. N Engl J Med 350(20): 68-79.