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CASE REPORT

AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE 1 (APS-1): MORE THAN CHRONIC MUCOCUTANEOUS (CMC) DYSTROPHY, HYPOPARATHYROIDISM (HP) AND ADRENAL INSUFFICIENCY (AAD)

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ABSTRACT

We report an eight year-old Saudi girl who was diagnosed to have chronic-mucocutaneous-candidiasis (CMC), and hypoparathyroidism (HP) i.e. autoimmune polyendocrine syndrome type 1 (APS-1). She was shortly manifested symptoms and signs of autoimmune adrenal insufficiency (AAD). During the course of follow-up, and within a short period of time she developed hypothyroidism with positive anti-thyroid antibodies, type 1 diabetes mellitus with elevated glutamic acid decarboxylase 65 (GAD 65), celiac disease, small bowel biopsy proved, pernicious anemia, kerato-conjunctivitis. She died at the age of 14, with acute hepatic failure, due to an autoimmune hepatitis, and over-wheeling sepsis. The spectrum of APS-1 was highlighted.

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INTRODUCTION

Autoimmune polyendocrine syndrome type 1(APS-1), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autosomal recessive disorder (Abonen *et al*., 1990, Betterle, 1998, Eisenbarth and Gottlieb, 2004, Owen and Cheethem, 2009, Saderbergh *et al*., 2004), caused by mutations in a single gene on chromosome 21q22.3 named AIRE (autoimmune regulator) (Mathis and Benoist, 2007). APS-1 is characterized by multiple organ-specific autoimmunity as well as ectodermal manifestations (Abonen *et al*., 1990). The disease usually begins in childhood with chronic mucocutaneous candidiasis, and later the patients' contract autoimmune destruction of endocrine as well as non-endocrine organs resulting in a variable phenotypes.

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In this report, we present a patient with APS-1 who developed variable autoimmune endocrinopathy.

Case History

An eight year-old Saudi girl presented to the emergency room with tetany. No clinical evidence of malabsorption, and she was otherwise normal. She had history of recurrent attacks of mucocutaneous candidiasis since infancy. Her parents were first degree relatives and had two other children presented at the same time with autoimmune polyendocrine syndrome type 1 (APS-1). Her serum calcium was low at 1.7 mmol/L (normal; 2.1-2.6), inorganic phosphate was high at 2.3 mmol/L (normal; 1.4-2.1) with normal alkaline phosphatase and serum magnesium. Serum parathyroid hormone was low at, 3.5 pg/ml (normal; 5-15), serum cortisol and adrenocorticotropin hormone (ACTH) were normal. AIRE gene mutation was confirmed. The diagnosis of APS-1 was entertained and started on oral calcium and 1-α-calcidol. A year later she manifested symptoms and signs of adrenal insufficiency, with low serum

cortisol 180 nmol/L (normal; 150-650) and high serum ACTH 195 pg/ml (normal; 10-55). The diagnosis was confirmed by a flat cortisol response in a short synacthen test. Adrenal cortex antibodies (ACA) was performed (Bioscientia Laboratory, Germany) and was positive. During the course of follow-up, and within 6 months, she was discovered to have autoimmune thyroiditis, low-free thyroxine (FT4) of 11 pmol/L (normal 10-25), and high thyroid stimulating hormone (TSH) of 150 iu/L (normal; up to 5). Thyroid microsomal peroxidase (TPO) and thyroglobulin (TG) antibodies were done in the sera, haemagglutination method, and were positive. She was also developed type 1 diabetes mellitus, with elevated glutamic acid decarboxylase 65 "GAD 65" antibodies. Serologically, screening test, for celiac disease (CD) which included anti-gliadin antibodies (AGA), anti-endomyseal antibodies (EMA) and anti-tissue transglutaminase (tTG) antibodies were suggestive of CD, which was confirmed by small bowel biopsy. Pernicious anemia and kerato-conjunctivitis then developed. At the age of 14 years, she died with acute hepatic failure and over-wheeling sepsis.

DISCUSSION

Autoimmune polyendocrine syndrome type 1 (APS-1), is a rare autosomal recessive disorder associated with the mutation in the AIRE gene (Mathis and Benoist, 2007) and characterized by chronic mucocutaneous-candidiasis (CMC) which generally presents earlier in life, usually infancy, and multiple organ-specific autoimmunity affecting first the hypoparathyroid. It usually occurs after CMC and before auto-adrenal insufficiency (AAD). AAD is usually associated with the 21-OH antibodies (Soderbergh *et al*., 1998, Abonen *et al*., 1990, Betterle *et al*., 1998, Soderbergh *et al*., 1996). Autoimmune polyendocrine syndrome type 1 (APS-1) is also associated with variable auto-antibodies against various organs, as in our patient. It can be rapid in occurrence. Type 1 diabetes mellitus has been described in up to 15% of patients with APS-1 (Betterie, 1998), majority of them had islet cell antibodies (Gylling *et al*., 2000). The first description of autoimmune thyroiditis in APS-1 was in 1964, and since then, other reports indicated that up to 10% of APS-1 patient developed thyroiditis (Betterle 1998). Our patient was symptomatic with elevated thyroid-microsomal antibodies. The association of malabsorption with autoimmune polyendocrine syndrome type 1, APS-1 is rare and contributed to celiac disease (Kumar *et al*., 2001). This can lead to other deficiencies such as pernicious anemia. Autoimmune hepatitis has been described in up to 30% of APS-1 patients (Betterle, 1998). The age clinical presentation ranged from 5 to 20 years, and the clinical course could vary from asymptomatic to fulminant hepatic failure, as in our patient.

Acquired asplenia or splenic dysfunctions are rare and expose the patient for significant risk of fulminant bacteremia especially from encapsulated bacteria (Pollack *et al*., 2009). Patients should be worked up for this and given the appropriate preventive measures. Finally, although APS-1 is a rare disorder, it can have associated severe and life-threatening conditions. Our patient represents the severe form of the disorders.

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