Journal of Taibah University Medical Sciences (2014) 9(3), 224–227

Taibah University

Journal of Taibah University Medical Sciences

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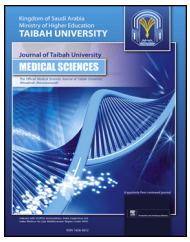

Original Article

Screening for autoimmune diseases in type 1 diabetes: Low incidence of adrenal insufficiency

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Received 11 January 2014; revised 18 March 2014; accepted 20 March 2014
Available online 9 July 2014

الملخص

الأهداف: يعتبر القصور الأولي لقشرة الغدة الكظرية (مرض أديسون) حالة خطيرة قد تؤدي للوفاة وفي كثير من الأحيان تكتشف بالصدفة وبسهولة يمكن التغاضي عنها , على الرغم أن مرض أديسون نادر الحدوث عند الأشخاص إلا أنه أكثر شيوعا عند مرضى السكري من النوع الأول .في هذه الدراسة ، استعرضنا تجربتنا في ايجاد علاقة تربط مرض أديسون عند الأطفال الذين يعانون من مرض السكري من النوع الأول خلال فترة 15 سنة من متابعتهم بمستشفى الملك خالد الجامعي بالرياض، المملكة العربية السعودية

الأساليب: تمت هذه دراسة بأثر رجعي بمراجعة حالة المرضى من واقع ملفاتهم بالمستشفى ، وشملت الأطفال والمراهقين الذين يعانون من مرض السكري من النوع الأول بمستشفى الملك خالد الجامعي في الفترة من يناير 1995 - ديسمبر 2012 . تم فحص جميع المرضى مصليا لمرض سيلياك والغدة الدرقيةو تم تقييم وظيفة الغدة الكظرية في وقت التشخيص ، و سنويا بعد ذلك عن طريق قياس هرمون الكورتيزول في الدم و هرمون الغدة الكظرية (ACTH) باستخدام الأدوات والفحوصات التجارية المتاحة . وقد تم البحث عن الأجسام المضادة لقشرة الغدة الكظرية في مريض واحد .

النتائج: في مجموعة تتكون من 305 طفلا ومراهقا من مرضى السكري من النوع الأول بمستشفى الملك خالد الجامعي تم اكتشاف مريض واحد فقط يعاني من متلازمة متعددة الغدد الصم من النوع الأول .. وكانت وظائف الغدة الدرقية غير طبيعية في 65 (21.3 ٪) من المرضى . ، 26 (8.5 ٪) من مجموع ال 65 مريضا كان لديهم دليل واضح على قصور شديد بالغدة الدرقية أما 39 مريضا (12.8) كانوا يعانون من قصور الغدة الدرقية غير ملاحظ سريريا . في ستة وعشرين مريضا (8.5 ٪) كانت نتائج خزعة الأمعاء إيجابية لمرض سيلياك .

الإستنتاجات: ليس هناك توافق دولي في الآراء بشأن مسألة الكشف مرض أديسون لدى الأطفال الذين يعانون من مرض السكري من النوع الأول . ومن واقع تجربتنا نحن لا نحبذ الكشف عن مرض أديسون لدى الأطفال الذين يعانون من مرض السكري من النوع الأول ما لم يكن هناك عامل خطورة واضح لمرض أديسون .

Abstract

Objectives: Primary Adrenocortical insufficiency (Addison's disease) is a potentially fatal condition that often develops incidentally and can be easily overlooked. Although rare in the general population, it is more common in patients with type 1 diabetes mellitus (T1D). In this study, we reviewed our experience with the occurrence of associated adrenal insufficiency (AI) in children with T1D over 15 year's period at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia

Methods: This is a retrospective hospital based study, included children and adolescents with T1D at KKUH in the period January 1995–December 2012. All patients were serologically screened for Celiac and thyroid diseases. Adrenal function was assessed at the time of diagnosis, and annually thereafter by measuring serum cortisol and adrenal corticotrophic hormone (ACTH) using the available commercial kit. Adrenal cortex antibodies (AAA) test was done by Bioscientia laboratory, Germany, in one patient.

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Peer review under responsibility of Taibah University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jtumed.2014.03.003

Results: In a cohort of 305 children and adolescents with T1D at KKUH, only one patient was found to have AI as a part of autoimmune polyendocrine syndrome type 1. Thyroid functions were abnormal in 65 (21.3%) patients. Of these, 26 (8.5%) patients have evidence of overt hypothyroidism and 39 (12.8%) patients had subclinical hypothyroidism. In twenty-six patients (8.5%), the intestinal biopsy results were positive for CD.

Conclusion: There is no international consensus on the issue of screening for AI in children with T1D. In our experience, we do not favour screening for AI in children with T1D unless there is a clear risk factor.

Keywords: Addison's disease; Adrenocortical insufficiency; Autoimmune; Diabetes; Screening

Introduction

Type 1 Diabetes Mellitus (T1D) is the most common endocrinopathy to have clinical onset in childhood and adolescence with varied pathogenesis, clinical appearance and outcome and seriously affect patients and families life. A combination of genetic, environmental and immunological factors exerts to a T cell mediated autoimmune process targeted against the insulin producing beta cells in the pancreatic Island of Langerhans.[1] The incidence is increasing worldwide.[2]

Patients affected by T1D are at increased risk of developing other autoimmune conditions like Coeliac Disease (CD), autoimmune thyroid disorders (ATD) and AI. The national institute of clinical excellence guidance (NICE) and the American Diabetes association (ADA) included recommendations about the screening for ATD and CD in children with T1D but there was no guidance regarding screening for AI.[3,4] The issue of screening for AI in T1D is still controversial.[5–8] While Triolo et al. and Brewer et al. recommended screening, Babiker et al. and Mark et al. do not favour screening for autoimmune AD and feels that Adrenal antibodies should be requested in children with T1D only when AI is clinically suspected.[6–8]

This article reviewed our experience over more than 15 years with children and adolescents with T1D in a cohort of 305 patients at the paediatric diabetes clinic at King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia.

Materials and Methods

This is a retrospective hospital based study, included children and adolescents who were diagnosed and followed for T1D, at the paediatric diabetes clinic at King Khalid University hospital (KKUH), Riyadh, Saudi Arabia in the period January 1995–December 2012. The diagnosis of T1D was based on history of polyurea, polydipsia and weight loss, with an elevated random blood sugar of >11.2 mmol/L.

Subjects were serologically screened for other associated autoimmune diseases, at the time of diagnosis and annually thereafter. Serologically screening test for CD includes anti-glidin antibody (AGA), Anti-endomyseal antibodies (EMA) and anti-tissue transglutaminase (Ttg) antibody. Serological tests are fully automated, except EMA test which is time consuming and operator dependant. For serological tests, immunoglobulin A was also measured. In case of a positivity of one or more of these tests, the patient is referred for upper endoscopy where multiple biopsy specimens were taken. The severity of small bowel mucosal damage was reviewed by an experienced gastrointestinal pathologist and graded according to the Marsh classification from 1 to III. The diagnosis of CD is based on the revised criteria for the diagnosis of CD.

Patients were screened for the thyroid dysfunction by thyroid stimulating hormone (TSH) and free thyroxin (FT4) at the time of diagnosis, and annually thereafter. These were made by methods using commercially available kits. The quality control of the assay was monitored by the Middle East Extended Quality Assessment Scheme (MEEQAS) in Riyadh. Anti-thyroid microsomal and thyroglobulin antibodies were estimated using haemagglutination method, and a titre of 1:100 or more was considered positive. Diagnosis of subclinical autoimmune thyroiditis was based on high levels of TSH or more than 5 IU/L associated with normal FT4, while clinical hypothyroidism (overt hypothyroidism) was associated with low FT4 levels and/or goitre.

Adrenal function was assessed at the time of diagnosis, and annually thereafter by measuring serum cortisol and adrenal corticotrophic hormone (ACTH) using the available commercial kit. Adrenal cortex antibodies (ACA) test was done by Bioscientia laboratory, Germany, in one patient.

The study was approved by institutional Review Board (Ethical and Research Committee) of the College of Medicine of King Saud University (KSU), Riyadh, Saudi Arabia.

Results

All patients were serologically screened for CD; sixty-two patients (20.3%) were subsequently referred to paediatric gastroenterologist to perform upper gastrointestinal endoscopy and biopsy when the patient has one or two positive screening tests.

In twenty-six patients (8.5%) ($n = 17$ females, $n = 9$ males), the biopsy results were positive for CD with a mean of 5 years duration after the diagnosis of T1D. Their age range was between seven and sixteen years (mean 11.5) and the duration of T1D was 1.5–11.5 years (mean 5 years). The other 36 patients (11.8%) had normal biopsies and therefore, considered to have potential CD.

Thyroid functions were abnormal in 65 (21.3%) patients with a mean of 2.5 years duration after the diagnosis with T1D in 61 patients, while four patients were diagnosed with hypothyroidism before T1D. Of these 65 patients, 26 (8.5%, $n = 26$ patients) have evidence of overt hypothyroidism, i.e. high TSH and low FT4 and (12.8%, $n = 39$ patients) had subclinical hypothyroidism, i.e. TSH of more than 5 IU/L and normal free T4. Thyroid microsomal peroxidise (TPO) and thyroglobulin (TG) antibodies were done in the sera of 114 (37.4%) patients. Seventy-six (66.7%), were euthyroid, twenty (17.5%) patients were having overt hypothyroidism, while only eighteen (15.8%) patients had subclinical hypothyroidism. Interestingly, in sixteen (80%) patients with

overt hypothyroidism both TPO and TtG antibodies were positive, while in the majority of euthyroid patients (93.2%) both TPO and TtG antibodies were negative.

Of all patients, a 9 years girl presented with adrenal insufficiency with low serum cortisol and high adrenocorticotrophine (ACTH) 195 pg/ml ($N = 10-55$ pg/ml). The ACA was 6.8 mcg/dl ($N = 10-25$ mcg/dl) and the diagnosis was confirmed by a flat cortisol response in a short synacthin test. Serum rennin and aldosteron levels were not done. The patient also developed hypoparathyroidism and chronic candidiasis, therefore a diagnosis of autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), APS type 1, with a positive AIRE gene mutation, was made. Six months later, she developed T1D and found to be hypothyroid, also with positive TPO and TtG antibody. She was diagnosed with CD based on small bowel biopsy, a year later. She died at 14 years of age because of worsening of her autoimmune hepatitis which she also developed eventually. She had other three siblings with the same syndrome. Otherwise none of the patients had signs or symptoms or biochemical evidence of adrenal insufficiency prior to or after the diagnosis of T1D.

Discussion

Patients with T1D have increased risk of other organ specific autoimmune disorders including ATD, CD, and AI (Addison's disease).[9–12] Addison's disease is a potentially life threatening condition caused by an immune mediated destruction of the adrenal cortex. The combination of Addison's disease with T1D and/or ATD is known as autoimmune polyendocrine syndrome type 2 (APS-2). T1D commonly precedes the development of AI in most patients with APS-2.[13–15] It is a rare disease and usually presents with non-specific symptoms, the diagnosis can be easily overlooked and require a high degree of clinical suspicion. After the appearance of antibodies to the adrenal cortex and/or 21 hydoxylase, the first evidence of AI is usually increased in plasma rennin activity, with a low normal or low serum aldosteron concentration, reflecting salt loss because of failing zona glomerulosa. Several months to years later, zona fasiculata dysfunction becomes evident initially by a raised serum ACTH level followed by a decreasing serum cortisol response to ACTH stimulation, and finally by a decreasing basal serum cortisol concentration, and the appearance of symptoms.[16]

Addison's disease is relatively rare (0.01%) in general population. However, the prevalence is reported to be high among patients with T1D (0.8–1.2%). The prevalence of adrenal autoantibodies is even higher (1.3–2.3%). The risk of adrenal autoimmunity and Addison's disease in T1D is even greater when anti-thyroid autoimmunity is detected.[16]

Adrenal autoantibodies may be useful markers for the prediction of progression to Addison's disease in children with higher predictive values than adults. Antibodies can be measured against several steroidogenic enzymes (21 hydoxylase) and adrenal cortex autoantibodies (ACA). They are present in the serum of more than 90% of patients with autoimmune Addison's disease, although negative antibodies do not rule out autoimmune AI. ACA positive children have been reported to have a higher rate of progression to overt Addison's disease. This suggests the importance of screening.[17–20]

The development of adrenal insufficiency in patients with T1D should be suspected in any patient presenting with unexplained hypoglycaemia or reduced insulin requirements.[20]

Autoimmune diseases are usually preceded by a long preclinical phase before becoming overt.[21] This phase can be identified by the presence of autoimmune antibodies as markers of disease progress. Such identification might allow immunological treatment, in some cases, whereby disease is prevented.[21] Alternatively, perhaps life-threatening, yet treatable conditions, such as AI could be avoided.[21] Further work is needed, for most of autoimmune associated diseases, to assess the natural history of disease progression and predictive value of autoimmune antibodies testing in healthy individuals.

Conclusion

As yet, there is no international consensus on screening for AI in children and adolescents with T1D. In our experience, there is very low incidence of AI during routine assessment of children with T1D compared with much higher incidence of CD and ATD.

Recommendations and limitations

We do not favour routine screening for AI in children with T1D unless there is a clear risk factor in the history and clinical examination. However, extended follow-up for this cohort of patients will be important to determine the natural history of the development of AI. This study is limited because it only utilises serum cortisol and ACTH to screen for AI. ACA was only performed in the APS-1 patient who in fact was diagnosed with AI prior to T1D.

Conflict of interest

None.

Authors contribution

Idea conceived by: Amir Babiker and Nasir Al Jurayyan
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Data collection: Shariefa El Issa, Nasir Al Jurayyan, Amir Babiker
Manuscript drafting and review: Amir Babiker, Nasir Al Jurayyan, Shariefa El Issa, Sarar Hamza, Hessah Al Otaibi
Confirmation of a final manuscript: Amir Babiker, Nasir Al Jurayyan, Shariefa El Issa, Sarar Hamza, Hessah Al Otaibi

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