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Occurrence of Hypothyroidism, Diabetes Mellitus, and Celiac Disease in Emirati Children with Down's Syndrome

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ABSTRACT

Objectives: Autoimmune diseases are known to occur in people with Down's syndrome (DS), especially celiac disease, type 1 diabetes mellitus (DM), and hypothyroidism. Since there are common genetic risk factors involved in the occurrence of these autoimmune disorders, the risks would differ in different populations. We sought to determine the prevalence of type 1 DM, celiac disease, and hypothyroidism in Emirati patients with DS in Abu Dhabi, UAE. ***Methods***: Ninety-two patients with DS were investigated for the presence of anti-thyroid antibodies, antithyroglobulin, and anti-thyroid peroxidase antibodies for hypothyroidism, anti-glutamic acid decarboxylase antibodies for type 1 DM, and anti-tissue transglutaminase immunoglobulin A antibodies for celiac disease. ***Results:*** Karyotyping was performed on 89 patients. Eighty-seven had non-disjunction of chromosome 21 (97.8%), one was a mosaic, and one had translocation. Of the patients studied, 19.6% had hypothyroidism, 4.3% had type 1 DM, and 1.1% had celiac disease. Out of the 92 patients studied, 66 (71.7%) did not have any autoimmune disease, 25 (27.2%) had one autoimmune disease, and one (1.1%) had two autoimmune diseases. ***Conclusions:*** Celiac disease was the least prevalent autoimmune disease in patients with DS patients, while type 1 DM and hypothyroidism were both significantly associated with DS.

The incidence of trisomy 21, more commonly known as Down's syndrome (DS), among Emiratis is one in every 319 births (3.125/1000), which is higher than the world average of one in every 800 births. In one study, the incidence of DS was similar to that in other parts of the world (1.15 per 1000).[1,2] There is also a high rate of consanguineous marriages in the UAE.[3]

Children with DS are known to have an increased incidence of congenital heart disease and gastrointestinal anomalies as well as vision and hearing problems. Patients with DS are unique in the wide spectrum of their diseases as almost all organs are affected. They are also prone to suffer from different autoimmune conditions, which are seen at a higher frequency in patients with DS.[4] The first report of a young boy with DS who also had celiac disease was in 1975.[5] The recent estimate for the occurrence of celiac disease in children with DS is 3.2% to 16.9% of children with DS.[6] Both type 1 diabetes mellitus (DM) and thyroid disorders also occur frequently.[7,8] Autoimmune diseases are believed to have common genetic risk factors, and many of these are gender-predisposed.[9]

We sought to determine the prevalence of type 1 DM, celiac disease, and hypothyroidism in Emirati nationals with DS in the largest Emirate; Abu Dhabi. We also aimed to determine whether there were any patients with subclinical hypothyroidism and who were not taking L-thyroxin.

METHODS

We conducted an observational/cross-sectional non-interventional population study of children with DS attending Al Ain and Mafraq Hospitals in Abu Dhabi. The inclusion criteria were all children with

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DS attending the two major hospitals in the cities of Abu Dhabi and Al Ain. The population of Abu Dhabi reached 2 784 490 people in 2015, of whom 1 831 741 were males, and 952 759 were females.[10] Al Ain and Al Mafraq hospitals are two of the four main large tertiary care hospitals in this Emirate. Recruited patients were those attending these two hospitals over two years (2014 and 2015).

Ethics committee approvals were obtained from Al Ain District Human Research Ethics Committee, Al Ain Hospital Medical Research Committee, and Al Mafraq Hospital Medical Research Committee. All patients' parents gave their general consent.

Demographic data of the patients including the date of birth, age on the day seen, sex, and maternal age at child's birth were recorded. All children had their weight and height measured on the day they attended the clinic. Individual chromosomal abnormality results were registered from every child's electronic medical record.

All patients had venous blood extracted for screening for hypothyroidism (thyroid stimulating hormone (TSH) and free thyroxine (T4) levels). In addition to the formal annual screening tests, other blood investigations were requested from the same sample. These included anti-thyroid antibodies, antithyroglobulin and anti-thyroid peroxidase (TPO) antibodies, anti-glutamic acid decarboxylase (GAD) antibodies for type 1 DM, and anti-tissue transglutaminase immunoglobulin A (tTG IgA) antibodies for celiac disease.

TSH was analyzed using the Electro-Chemi-Luminescence Immuno-Assay (ECLIA) on Cobas immunoassay analyzers (Roche Diagnostics Ltd. Rotkreuz, Switzerland) for in vitro quantitative determination of thyrotropin in human serum and plasma. The test utilizes the Sandwich principle. Free T4 was quantitatively analyzed by the ECLIA on Cobas immunoassay analyzer (Roche Diagnostics Ltd. Rotkreuz, Switzerland). The competitive principle was utilized for the test. Alegria tTG IgA antibodies test was performed on serum/plasma samples using the Orgentec Alegria Analyzer (Mayo Medical Laboratories, Rochester, USA), which provides quantitative measurement. Anti-TPO and antithyroglobulin tests were performed utilizing ECLIA by Cobas immunoassay analyzers (Roche Diagnostics Ltd. Rotkreuz, Switzerland) based on the competition assay principle. We used the Medizym anti-GAD (Life Diagnostic Lab, West Chester, USA) enzyme immunoassay (manual ELISA) for the quantitative determination of autoantibodies to GAD in human serum.

We calculated the prevalence and simple means and standard deviation (SD). Logistic regression analysis was used to determine significant factors linked with hypothyroidism in patients with DS. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio for different markers were calculated.

RESULTS

Eighty-seven of the 89 patients who had genetic studies had non-disjunction of chromosome 21 (97.8%), one was a mosaic, and one had translocation. Of all patients, 4.3% had type 1 DM, 1.1% had celiac disease, and 19.6% had hypothyroidism. Of the 92 patients studied, 66 (71.7%) did not have any autoimmune disease marker, 25 (27.2%) had one autoimmune disease marker, and one (1.1%) had two autoimmune disease markers. We had no cases of three autoimmune diseases occurring in the same individual. Forty-seven children were aged above five years among whom 15 (31.9%) were overweight and 12 (25.5%) were obese. Of the three children with DS who had type 1 DM and aged over five years, one was obese (33.3%), and two had normal body mass index. In the 11 children aged over five years with hypothyroidism, four (36.4%) were overweight, and three (27.3%) were obese [Table 1].

One patient with low GAD levels (< 2 U/mL) had type 1 DM, and two with high GAD levels (> 250 U/mL) did not have type 1 DM. Therefore, the sensitivity of the test was 75.0% while the specificity was 98.0%. The PPV was 60.0%, and the NPV was 99.0%. The positive likelihood ratio was 33.0, and the negative likelihood ratio was 0.26. GAD antibodies were high in seven of 92 (7.6%) patients with DS. The normal value of GAD is < 30 U/mL.

All 22 patients with DS who also had hypothyroidism were treated. However, nine (40.9%) of the 22 patients with associated hypothyroidism had low levels of anti-TPO and antithyroglobulin

Table 1: Data on children with Down's syndrome (DS) with associated diseases.

	DS with hypothyroidism	DS with celiac disease	DS with type 1 DM	DS with two autoimmune diseases	DS with three autoimmune diseases	Total
n	18	1	4	1	0	22
Percentage	19.6	1.1	4.3	1.1	0.0	23.9
Chromosomal abnormality	1 mosaic, 17 non-disjunction	1 non-disjunction	4 non-disjunction			1 mosaic, 21 non-disjunction
Male	9	1	2	1	0	11
Female	9	0	2	0	0	10
BMI	4 overweight* and 3 obese** out of 11	1 normal	1 obese** out of 3	1 obese**	0	4 overweight* and 3 obese**

**Overweight are those whose body mass indexs (BMIs) were > 90th percentile (equivalent to BMI > 25 in adults).*
*** Obese were those whose BMIs were > 95th percentile (equivalent to BMI > 30 in adults).*
The total column gives the total number of children with DS who had autoimmune disorders. It seems to be one less than the sum of all cases with hypothyroidism, type 1 diabetes mellitus (DM), and celiac disease. That is because one patient had two autoimmune disorders and is present in both DS with hypothyroidism and DS with type 1 DM.

Table 2: The sensitivity and specificity of anti-TPO and antithyroglobulin antibody (ATGA).

Test	Specificity, %	Sensitivity, %	Positive predictive value, %	Negative predictive value, %	Positive likelihood ratio	Negative likelihood ratio
Anti-TPO	89.0	37. 0	47. 0	84.0	3.36	0.71
ATGA	85.0	50. 0	35.0	91. 0	3.27	0.59
Both anti-TPO and ATGA	82.0	53.0	44.0	87. 0	2.96	0.58

TPO: thyroid peroxidase.

antibodies, and 13 out of 26 (50.0%) patients with high levels of anti-TPO and antithyroglobulin antibodies did not have hypothyroidism. There were 35 females and 46 males in 81 patients with DS (in whom the sex was known) giving a M:F ratio of 1.00:0.76. The number of both female and male patients with DS who had hypothyroidism was nine, resulting in 19.6% and 25.7 % of males and females, respectively, with DS having hypothyroidism. In the patients with hypothyroidism the M:F ratio was 1.00:1.31. The median age of patients with DS who also had hypothyroidism was five years (mean = 6.4 years). The sensitivity of the anti-TPO test, specificity positive likelihood ratio, negative likelihood ratio, PPV and NPV for anti-TPO, antithyroglobulin and both tests are listed in Table 2. It was determined, using logistic regression analysis, that the odds of having hypothyroidism increased by 80% when anti-TPO antibody increased by 1 SD (SD = 76).

The one patient with celiac disease had high levels of anti-tTG IgA antibodies (36 U/mL) while most of the others had an approximate level of 2 U/mL. This patient, therefore, had an 18-fold increase in tTG IgA antibody levels.

DISCUSSION

DS is one of the most common causes of mental retardation, and its incidence is approximately one in 319 live births (3.125 per 1000) in Emiratis,[1] which is high even when compared with other countries in the region like Saudi Arabia where the incidence is one in 554 live births (1.8 per 1000).[11] One of the reasons for this could be advanced maternal age, with mothers bearing children until their fifties and having higher parity. Other reasons could also be the inability to perform abortions if an antenatal diagnosis of DS is made. As everywhere else, most children with DS (97.8%) in the present study had non-disjunction of chromosome 21, while 1.1% were mosaics and 1.1% had a translocation.

Growth charts have been constructed for patients with DS in the UAE;[2] in children aged 10–13 years old, 32% were overweight and 19% were obese. In our study group, almost 31.9% were overweight and 25.5% were obese, which suggests that the sample selected were representative of the UAE DS population. The prevalence of obesity and overweight in ages 13–17 years in the general UAE population was 9.94% and 15.16% in females and 6.08% and

14.16% in males, respectively.[12] Children with DS were significantly more overweight and obese than the general population. The rates of overweight and obesity were similarly elevated in children with autoimmune disorders. The possible determinants of obesity are increased leptin, decreased resting energy expenditure, bad diet, other associated conditions, and decreased physical activity. Although children with DS have lower resting energy expenditure, this is not enough to explain the increase in overweight or obesity.[13]

Patients with DS are known to have an increased incidence of autoimmune disorders.[4] However, there have been only a few reports where three autoimmune disorders (DM, celiac disease, and hypothyroidism) have occurred in the same individual with DS.[14] In the present study there was only one patient with DS (1.1%) who suffered from two disorders (DM and hypothyroidism) while 27.2% suffered from one autoimmune disorder.

Celiac disease is a multifactorial disorder resulting from the interaction of HLA-DQA1 and HLA-DQB1 allelic variants and environmental factors. Definitive diagnosis of the condition is made by finding typical histological changes in tissues obtained from small bowel biopsy. However, serological markers, most commonly elevated IgA antibodies to tTG, or anti-endomysial antibodies exist, which makes the diagnosis possible without a biopsy, but confirmation can only be made after a biopsy. Both these markers have a high sensitivity (95%) and specificity (100%). According to guidelines published by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition[15] diagnosis of celiac disease may be made without a small bowel biopsy in only a few specific circumstances such as a symptomatic child with highly elevated tTG IgA (> 10× the upper limit of normal), a second blood sample showing an elevated endomysial antibody, and HLA haplotype consistent with celiac disease (DQ2 or DQ8).

The prevalence of celiac disease in patients with DS has been reported to range from a very low 1% in Turkey[16] to anywhere ranging from 5% to 18% in the US and Europe[6,7,17–20] with the highest prevalence in Sweden.[18] Celiac disease was found to occur in 18 of the 284 children with DS, aged between 2 and 15 years, giving a prevalence rate of 6.3% in Barcelona, Spain.[17] Anti-endomysial antibodies and antigliadin antibodies were found to be positive in 94% and 78%, respectively, of patients with DS who also had celiac disease. Prevalence of celiac disease in DS in the Arab world ranges between 2% and 3.8%;[21,22] however, in Tunis, a North African Arab country, the prevalence was 10%, but the numbers were small and a small bowel biopsy was performed for confirmation of diagnosis.[23] We screened 92 DS patients for the presence of tTG IgA antibodies and found only one case of celiac disease (1.1% of DS patients), a finding similar to the study in Turkey, and significantly less than Saudi Arabia, other Arab countries, European countries, and the US. In Emiratis with DS there was no indication that there was any link between DS and celiac disease. However, the numbers of studied patients were too small for a conclusion to be made on the association of celiac disease with DS.

The occurrence of hypothyroidism with DS is not only more common in adult DS sufferers (12%) but also in neonates in whom the frequency is 0.7%, which is 28-times more frequent than in normal newborns.[24,25] One study found the incidence of hypothyroidism to be one in 141 DS neonates, while the incidence in the general population was one in 3800.[24] In the UAE, the incidence of hypothyroidism in newborns was one in 1557 newborns in two hospitals in Al Ain after screening 32 698 newborns between 1998–2004.[26] The incidence of hypothyroidism in DS in the present study was one in 4 patients (23.9%), which is a significantly more frequent occurrence than that found in the above study (12%).[26] In Kuwait an even higher percentage of patients (55%) with DS had thyroid dysfunction.[27] While we believe that over-diagnosis of hypothyroidism should not be made, the evidence from the present study is compelling enough for the performance of annual screening for hypothyroidism in all patients with DS. However, even if there was screening, some rapidly progressive Hashimoto's thyroiditis might be missed. Therefore, it is important to have a national register of all patients with DS so that timely screening for hypothyroidism can be performed.

It is good to know that all patients found to be hypothyroid in this study were already on treatment. Anti-TPO antibodies were measured in 303 patients with either thyroiditis or Graves' disease, and the highest frequency of positive anti-TPO test occurred in those with autoimmune thyroiditis (88%) followed by patients with Graves' disease (53%). A sensitivity of 96% was obtained for

Hashimoto's thyroiditis and 59% for Graves' disease with a specificity of 100% (50 cases).[28] Before any treatment is given the presence of TPO antibody shows a sensitivity of 20%, a specificity of 95% and a predictive value of 66.6% for the development of thyroid dysfunction.[25] In the present study, the sensitivity of the anti-TPO test was only 37.0% with a PPV of 47.0%. This means that this test produces many false positive values, but the specificity (89.0%) and NPV (84.0%) were acceptable. Similarly, the thyroglobulin test also had low sensitivity and PPV, but acceptable specificity and NPV. When the two tests were taken together to determine whether the sensitivity improved, it was found that the sensitivity and specificity altered only slightly. The reason could be that the hypothyroidism may not all have been due to autoimmune causes and treatment may have somehow attenuated the antibody response.

The prevalence of type 1 DM in children with DS was shown to be significantly increased in studies of 20 362 patients with DS.[7] Some studies have shown up to four-times increase in type 1 DM in patients with DS.[29] A recent study from Denmark has also shown a four-fold increase in the occurrence of type 1 DM in patients with DS.[30] Generally in DS, type 1 DM develops early. It was previously thought to develop at the age of eight years, but is now known to develop a bit later at 14 years old. The distribution of type 1 DM in patients with autoimmune thyroid disease and DS was no different than in those without DS in a study of 832 children.[31]

A study from the UK investigated the immunogenic characteristics of diabetes in children with DS and found that the autoantibodies GAD were present in eight children, IA-2A (islet antigen-2 antibody) in five children, and insulin autoantibodies in nine of the 109 children tested.[32] Two or more islet autoantibodies were present in six of 106 children with DS compared with 13 of 2860 healthy schoolchildren ($p = 0.001$).[32] We only measured anti-GAD antibodies, which might result in underestimation of the prevalence of diabetes predisposition in our cohort. We found seven patients with DS (7.6%) had high GAD antibody levels. This is significantly more than that found in the normal population (1.7%).[33]

One of the limitations of the study was the fact that genetic testing was not performed in three patients (the diagnosis was made by the presence of typical features of the condition). None of these patients had evidence of celiac disease, DM, or hypothyroidism. Therefore, the fact that genetic testing was not done in these patients did not affect the results. Another limitation of the study was that the patients did not undergo measurement of total IgA antibody. IgA deficiency is known to be associated with celiac disease. However, that was not the objective of the study, the objective of the study was to determine the occurrence of autoimmune disorders like celiac disease, hypothyroidism, and DM in patients with DS in the UAE population.

CONCLUSION

Markers for type 1 DM and hypothyroidism were commonly seen in UAE patients with DS, but the markers for celiac disease were not found to be as common.

Disclosure

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