Curr Pediatr Res 2018; 22 (3): 182-184 *ISSN 0971-9032*
www.currentpediatrics.com

Autoimmunity and Vitamin D deficiency in children affected with Trisomy 21.

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Abstract

Background: Individuals with neurodevelopmental disorders and intellectual disabilities such as Trisomy 21 are more likely to experience low vitamin D levels, which has recently been tied to an increased risk of autoimmunity. In addition, Trisomy 21 is associated particularly with an increased incidence in coeliac disease and thyroid dysfunction. The aim of this study was to investigate the prevalence of autoimmune diseases and vitamin D deficiency in children affected with Trisomy 21.

Methodology: This is a retrospective study carried over the period of 12 years and included all children up to the age of 18 years. Data collected included laboratory reports such as profiles of both bone and thyroid, glycosylated haemoglobin A1C, fasting and random serum glucose levels; demographics such as age, gender and nationality; and diagnostic studies such as a tissue Transglutaminase (tTG) test and a duodenal biopsy. Data analysis was using the Statistical Package for Social Sciences v23.

Results: The prevalence of vitamin D deficiency was found to be 65.5% while the prevalence of coeliac disease and type 1 Diabetes Mellitus was found to be respectively 36.8% and 2.1%. Furthermore, 51.1% were found to be hypothyroid and another 22.6% to be hyperthyroid, leaving only 26.3% with a normal thyroid function.

Conclusion: We report a high incidence of vitamin D deficiency and autoimmune disorders, coeliac disease and thyroid dysfunction in particular, in children affected with Trisomy 21.

Keywords: Vitamin D, Trisomy 21, Coeliac, Hypothyroidism, Autoimmune, Diabetes.

Accepted July 27, 2018

Introduction

The prevalence of Trisomy 21 (T-21) has been on the rise as a result of an increasing trend in maternal age coupled with a prolonged life expectancy of affected newborns [1,2]. In addition, the prevalence of autoimmunity in patients particularly affected with T-21 is augmented when compared to the general population [3]. Furthermore, evidence has brought into perspective that vitamin D receptors are now found on several immune cells and that vitamin D metabolites play a role in modulating the function of dendritic cells and the proliferation of T cells, concluding that vitamin D deficiency plays a role in development of autoimmune disorders [4,5]. Individuals with neurodevelopmental disorders and intellectual developmental disabilities, grouped into medically complex developmental disabilities (MCDD), were found to be particularly prone to having low serum concentrations of 1-25-hydroxycholecalciferol, shortly known as Vitamin D [6]. And according to the American Academy of Developmental Medicine and Dentistry, T-21 was classified to be amongst the top most commonly diagnosed neurodevelopmental disorders [7]. Adequate vitamin D levels is found to be protective and is especially encouraged in children born with T-21 due to the aforementioned increased susceptibility to autoimmune dysfunction, encompassing thyroid dysfunction, coeliac disease, and type 1 Diabetes Mellitus, all of which already known to be in association with T-21 [8]. The aim of this study was to investigate the prevalence of Vitamin D deficiency, autoimmune thyroid dysfunction, coeliac disease and type 1 Diabetes Mellitus in the T-21 population.

Methodology

This study is a retrospective study that was carried out through reviewing electronic medical files using the Phoenix online medical records system implemented in KAUH to obtain necessary data. Files of patients from January 2005 till February 2018 were included. The sample size constituted 429 subjects. Inclusion criteria included patients affected with

Trisomy 21 and exclusion criteria ruled out all those above 18 years of age.

Data collected included laboratory reports of bone profile, thyroid and metabolic profiles, thyroglobulin, and thyroid peroxidase, glycosylated haemoglobin A1C, fasting and random serum glucose levels; demographics such as age, gender and nationality; and diagnostic studies such as a tissue Transglutaminase (tTG) test and a duodenal biopsy.

Patients were considered vitamin D deficient/insufficient if levels of 25-Hydroxycholecalciferol were below 20 ng/ml, and normal if more than 20 ng/ml. They were also categorised into four groups based on their thyroid profile: Normal (TSH between 0.27-4.2 UIU/l and FT4 between 12.0-22.0 Pmol/l), Hypothyroid (if TSH>4.2 UIU/l and FT4<12 Pmol/l), Hyperthyroid (if TSH<0.27 UIU/l and FT4>22 Pmol/l), and subclinical hypothyroidism (TSH>4.2 UIU/l and FT4 between 12.0-22.0 Pmol/l). Furthermore, it was considered to be congenital if diagnosed up to 12 months of age in the setting of negative thyroid autoantibodies, whereas those who were older were considered to have an acquired form. Autoimmune thyroiditis was diagnosed in the setting of positive thyroid autoantibodies, thyroid peroxidase and anti-thyroglobulin.

With regards to coeliac disease, patients were considered latent if they had a high tTG in the setting of a normal biopsy and were positively diagnosed if they had a high tTG in the setting of positive biopsy. Fasting glucose 126 mg/dl random 200 mg/dl, HbA1C 6.5.

Informed consent was attained from the ethical committee at King AbdulAziz University Hospital prior to accessing patient files.

Data analysis

Data was interpreted using the 23rd version of the Statistical Package for Social Sciences (SPSS). Categorical data is presented in the form of numbers and percentages and continuous data in the form of mean ± standard deviation. Chi square test is used to compare the percentages between the groups and a p-value of <0.05 was chosen to represent statistical significance.

Results

Regarding demographics, 47.8% of the children were of the female gender. Means included current age and age at diagnosis, which were 6.55 years (SD ± 4.41) and 1.7 years (SD ± 2.9), respectively. The prevalence of vitamin D deficiency was found to be 65.5% while the prevalence of coeliac disease and type 1 Diabetes Mellitus were found to be respectively 36.8% and 2.1%. On the other hand, a thyroid profile was available for only 350 patients of our total sample size, of which 51.1% were found to be hypothyroid and another 22.6% to be hyperthyroid, leaving only 26.3% with a normal thyroid function. Regarding age at diagnosis, 72.3% cases of thyroid dysfunction belonged to the congenital category. Significance of gender played no role in autoimmunity for either disorder, with a respective p value of 0.92 and 0.89 for both coeliac and thyroid dysfunction.

Discussion

Trisomy 21 is considered to be yet the most common genetic cause of mental subnormality with an incidence of 1 in every 700-1000 live births [9]. Alongside general determinants of low vitamin D levels such as dietary factors and vitamin D supplements, which vary upon individual basis, is the high incidence of hypotonia amongst children affected with T-21. This is achieved by limiting their activity and exercise, which in turn leads to a shorter duration of outdoor time and consequent sun exposure [10]. Mental submentality is a known consequence of early onset thyroid dysfunction if not diagnosed and treated promptly, and therefore timely recognition and especially in the T-21 population cannot be stressed upon enough in order to prevent further deterioration in this already mentally impaired group. The lifetime prevalence of autoimmune thyroid dysfunction alone has reached up to 63% in the T-21 population, with up to 28 times the risk of development during the neonatal period, and a prevalence of up to 85% during infancy [11]. Similarly, our study showed that 72.3% of those who suffered thyroid dysfunction were diagnosed in the infancy period, with a total incidence of congenital hypothyroidism at 37%. This is matched by another study that concluded a 39% incidence of hypothyroidism within the first year of life [3]. However, in contrast, no cases of hyperthyroidism were found, while in our study, 22.6% of the patients were diagnosed with hyperthyroidism. Even then, we still conclude that hypothyroidism is more common in T-21 patients than hyperthyroidism as the prevalence was 51.1% of our total sample size. On the other hand, another study showed that all of the cases of hypothyroidism were acquired, occurring beyond the first year of life [12]. Although the majority of thyroid dysfunction encountered by our cases was of the congenital form, approximately 28% of them suffered the acquired form associated with autoimmunity. And while the female gender has been considered as an independent risk factor to the development of thyroid dysfunction, the role of gender in the onset of thyroid disease in the T-21 population was found to be not significant (p=0.89).

Children affected with T-21 are vulnerable to the delayed diagnosis of coeliac disease due to classical symptoms such as abdominal distention and discomfort, alteration in bowel habit, anaemia, and growth failure being attributed to the baseline disorder [13]. The prevalence of coeliac disease found by European studies amounted up to 17% in the T-21 population [14], while in American studies, was found up to 96 times more the risk encountered by the general population [15]. One study had shown that the prevalence of coeliac disease in the T-21 population was 5%, which reflected the general prevalence presumed by the United States [16]. Further European studies have shown a considerably higher increase in prevalence ranging from 7% up to 16% [14]. However, in either case, this is strongly contrasted by the prevalence estimated by our study, which approximated 37%. With regards to autoimmune insulin dependent Diabetes Mellitus, the prevalence in the T-21 population is thought to

be around 1% [17]. The results shown by our study was not too far ahead as the prevalence was estimated to be at 2.1%.

Conclusion

In conclusion, we report a high incidence of both vitamin D deficiency and autoimmune disorders in children born with Trisomy 21 and recommend the screening and early diagnosis of both coeliac and thyroid disease in order to minimise the potential growth failure and mental submentality already anticipated with the syndrome alone. With regards to Diabetes Mellitus, while it is not as common as thyroid and coeliac disease, it is still a possibility and is seen in the T-21 population.

Consent for Publication

Consent was obtained from the patients' legal guardian for this publication.

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