SUJMS
Sana'a University Journal of Medical Sciences

Original Article

Patterns of autoimmune diseases among Yemeni children with Down syndrome

Waled A. Al-Dubai [1*], Jameel A. Al-Ghazaly[2], Sami S. Al-Dubai[3], Najlaa Z. Amer[1]

1 Department of Biochemistry and Molecular Biology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen

2 Department of Internal Medicine, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen

3 Aulaqui Specialized Medical Laboratories, Sana'a, Yemen.

Abstract

Background: Down syndrome can be associated with autoimmune diseases such as Celiac disease, autoimmune Thyroiditis, Type 1 DM and other diseases.
Aim: The aim of this study was to determine the prevalence of hypothyroidism, Type 1 DM, and Celiac disease in Yemeni children with Down syndrome as well as the most common mother's age for the occurrence of this syndrome.
Method: This study was cross-sectional study involving one hundred and six Yemeni children with Down syndrome selected by simple random sampling from Special Needs Centers for Down syndrome in Sana'a city, Yemen, during 2019. These children were investigated for the presence of anti-thyroid peroxidase antibodies, TSH, and T4 for hypothyroidism; random blood sugar, anti-glutamic acid decarboxylase antibodies for Type 1 DM; and anti-transglutaminase immunoglobulin A, and G antibodies for Celiac disease.
Results: The prevalence of autoimmune diseases in the 106 Yemeni children with Down syndrome was 5.77% hypothyroidism, 2.8% Type 1 DM, and 0.94% Celiac disease. The highest number of Down syndrome babies were born at 41 to 50 years of mother's age.
Conclusion: Hypothyroidism was the most prevalent autoimmune disease in Yemeni children with Down syndrome and Celiac disease was the least prevalent. Down syndrome can occur at any maternal age, but may increase with age. Children suffering from Down syndrome should be monitored periodically for autoimmune diseases to make early diagnosis, start early treatment, and decrease the occurrence of complications.

Keywords: Autoimmune diseases; Down syndrome, Hypothyroidism, Type 1 DM, Celiac disease, Yemeni children.

Introduction:

Down syndrome (DS), or trisomy 21, represents the most common chromosomal abnormality associated with intellectual impairment [1]. Down syndrome is the most common chromosomal disorder with prevalence estimates ranging from 6.1 to 13.1 per 10,000 people [2,3]. Most often DS results from complete trisomy of chromosome 21, due to non-disjunction during gamete formation (about 95%), while the remaining ones are due to either complete or partial translocation of chromosome 21 to another chromosome, typically in the D (13–15) or G (21–22) group [4]. Down syndrome is the most common recognizable genetic syndrome associated with abnormal immune function and immune defects. Individuals with DS have a higher incidence of autoimmune disorders [5]. The increased susceptibility to infections has been associated with atypical immune function in conjunction with various non-immune related medical and anatomical comorbidities [6]. Among those, endocrinopathies are the most common [7]. The physiopathological bases for these changes are not fully understood, and studies suggest that endocrine dysfunction in DS may be multifactorial,

Corresponding Author: *Waled A. Al-Dubai Associate Professor of Biochemistry Sana'a University, Sana'a, Yemen. E-mail: walidw2001@yahoo.com*

explained not only by autoimmunity but also by cellular mechanisms [8]. To the best of our knowledge, there is no previous study in Yemen about prevalence of autoimmune diseases among Down syndrome individuals, also there is a wide variation in reported prevalence rates of autoimmune diseases in other countries among Down syndrome individuals compared to general population, so the aim of this study was to determine the prevalence of hypothyroidism, Type 1 DM, and Celiac disease in Yemeni children with Down syndrome as well as the most common mother's age for the occurrence of this syndrome.

Subjects and Methods

The present study was a cross-sectional study, carried out on 106 Yemeni children with Down syndrome (60 male and 46 female), aged 5 to 18 years, selected mainly from Special Needs Centers for Down's syndrome in Sana'a city, Yemen, during 2019. Sample size was calculated by using OpenEpi program (Version 2.3.1) using 95% confident level, expected frequency of Down syndrome is 13.1% according to De Graaf [2], target children number 220, design effect 1 and sampling was done by simple random sampling. The study was approved by the committee of Postgraduate Studies and Scientific Research of the Faculty of Medicine and Health Sciences, Sana'a University. Written informed consent was obtained from parents of participant prior to enrolling them in the study.

Six ml of venous blood was collected from each participant into labeled plain test tubes for determination of random blood sugar for diagnosis diabetes mellitus by using Cobas Integra 400 plus auto-analyzer (Roche, Germany), serum thyroid-stimulating hormone (TSH), Free thyroxin (FT4) using Cobas E411 auto-analyzer (Roche, Germany), anti-thyroid peroxidase antibodies for diagnosis of thyroid disorders, anti-transglutaminase IgA, IgG for diagnosis of Celiac disease, and anti-glutamic acid decarboxylase (anti-GAD) for diagnosis of Type 1 DM by Snibe Maglumi 4000 plus Immunoassay Analyzer (Snibe Diagnostic, China).

2.1 Statistical analysis

The results were analyzed by Social Package of Statistical Science (SPSS) version 21 (LEAD Technologies; Inc. USA) to get frequencies, percentage, mean and standard deviation.

Results

The mean age of participants was 10.5±3.4 years and mean body mass index (BMI) was 17.6±4.8 kg/m2. The prevalence of autoimmune diseases in Down syndrome children is shown in table 1. Among all children with Down syndrome only six children, 3 males and 3 females (5.66%) had positive antibodies against thyroid peroxidase (TPO), and high TSH with low T4, three children, 1 male & 2 females (2.8%) had positive antibodies against anti-glutamic acid decarboxylase (anti-GAD) with a random blood sugar >200 mg/dl. Positive anti-transglutaminase of IgG class was found in one child (0.94%).

Table (1): Clinical characteristics of Down syndrome individuals

Variables	Prevalence
Hashimoto Thyroiditis	5.66 %
Type 1 DM	2.8 %
Celiac disease	0.94 %

Table 2 shows the distribution of Down syndrome babies according to maternal age at birth. Although Down syndrome can occur at any maternal age, but the highest number of down syndrome babies were born to women at the age of 41 to 50.

Table (2): Distribution of Down syndrome baby numbers according to maternal age at birth

Maternal age	*Number of Children*	*Percentage*
20 - 30 (years)	8	7.6%
31 - 40 (years)	33	31.4%
41 - 50 (years)	50	47.7%
51 - 60 (years)	14	13.3%

Discussion

Down syndrome can be associated with autoimmune diseases such as Celiac disease, autoimmune thyroiditis, and Type I DM [9-12], because Down syndrome individuals have abnormal expression of the autoimmune regulator (AIRE) gene that is located on chromosome 21 (21q22.3 region) and has been identified as a likely cause for increased autoimmunity in Down syndrome, because the AIRE gene regulates T-cell function and self-recognition, so abnormal AIRE expression in children with Down syndrome may increase autoimmunity [13,14]. This study reported that female children with Down syndrome had higher prevalence of Type 1 DM compared to males (66.7% vs. 33.3%). In general, the increased susceptibility of female to autoimmune diseases may be attributed to chromosomal factors, such as skewed X-chromosome inactivation [15] or to female sex steroids [16]. The overall prevalence of Type 1 DM in Yemeni children with Down syndrome was 2.77%, which is less than the prevalence of Type 1 DM in Emirati children with Down syndrome (4.3%) [17]. The prevalence of hypothyroidism (Hashimoto Thyroiditis) in Yemeni children with Down syndrome was 5.77%, which is less than the prevalence of hypothyroidism in Emirati children with Down syndrome (19.6%) [17]. The prevalence of Celiac disease in this study was 0.94%, which is less than that in the Arab world that lies between 2% and 3.8% [18,19].

The highest number of Down syndrome babies were born at 41 to 50 years of mother's age because nondisjunction of chromosomes can occur during either meiosis I or meiosis II of oocytes and increases with increased maternal age that lead to increase chromosomal abnormalities [20,21].

Conclusion

Hypothyroidism was the most prevalent autoimmune disease in Yemeni children with Down syndrome, followed by Type 1 DM and then Celiac disease being the least prevalent autoimmune disease. Down syndrome can occur at any maternal age, but may increase with maternal age. Children suffering from Down syndrome should be monitored periodically for autoimmune diseases for early diagnosis, start early treatment, and decrease the occurrence of complications.

Acknowledgments

The authors would like to thank Lab staff of Aulaqi Specialized Medical Laboratories especially Dr. Nedal Noman, Dr. Basem Al-Subahe and Dr. Adeeb Al-Salahe for their help in laboratory work of this research, as well as the participating children and their parents.

Declarations

No conflict of interest is associated with this work.

References

1. Macho V, Coelho A, Areias C, Macedo P, Andrade D. Craniofacial features and specific oral characteristics of Down syndrome children. Oral Health Dent Manag 2014; 13: 408-11.

2. De Graaf G, Vis JC, Haveman M, Van Hove G, De Graaf EA, Tijssen JG, et al. Assessment of prevalence of persons with Down syndrome: A theory-based demographic model. J Appl Res Intellectual Disabilities 2011; 24: 247-62.

3. Persson S, Dahlquist G, Gerdtham U-G, Carlsson KS. Impact of childhood-onset type 1 diabetes on schooling: A population-based register study. Diabetologia 2013; 56: 1254-62.

4. De Asua DR, Quero M, Moldenhauer F, Suarez C. Clinical profile and main comorbidities of Spanish adults with Down syndrome. Eur J Internal Med 2015; 26: 385-91.

5. Aitken RJ, Mehers KL, Williams AJ, et al. Early-onset, coexisting autoimmunity and decreased HLA-mediated susceptibility are the characteristics of diabetes in Down syndrome. Diabetes Care 2013; 36(5): 1181-5.

6. Huggard D, Mcgrane F, Lagan N, Roche E, Balfe J, Leahy TR, et al. Altered endotoxin responsiveness in healthy children with Down syndrome. BMC Immunology 2018; 19: 1-10.

7. Carroll KN, Arbogast PG, Dudley JA, Cooper WO. Increase in incidence of medically treated thyroid disease in children with Down syndrome after rerelease of American Academy of Pediatrics Health Supervision guidelines. Pediatrics 2008; 122: e493-8.

8. American Academy of Pediatrics. Committee on Genetics, American Academy of Pediatrics: Health supervision for children with Down syndrome. Pediatrics 2001; 107(2): 442-9.

9. Wouters J, Weijerman ME, van Furth AM, et al. Prospective human leukocyte antigen, endomysium immunoglobulin A antibodies, and transglutaminase antibodies testing for celiac disease in children with Down Syndrome. J Pediatr 2009; 154(2): 239-42.

10. Shamaly H, Hartman C, Pollack S, Hujerat M, Katz R, Gideoni O, et al. Tissue transglutaminase antibodies are a useful serological marker for the diagnosis of celiac disease in patients with Down syndrome. J Pediatrc Gastroenterol Nutr 2007; 44(5): 583-6.

11. Alanay Y, Buduro A, Ergül T. Celiac screening in 100 Down syndrome Turkish patients. Turk J Pediatr 2005; 47(2): 138-40.

12. Kurrpa K, Collin P, Vilijamaa M, Haimila K, Saavalanainen P, Partanen J, et al. Diagnosing mild enteropathy celiac disease: A randomized, controlled clinical study. Gastroenterology 2009; 136(3): 816-23.

13. Skogberg G, Lundberg V, Lindgren S, et al. Altered expression of autoimmune regulator in infant Down syndrome thymus, a possible contributor to an autoimmune phenotype. J Immunol 2014; 193: 2187-95.

14. Gimenez-Barcons M, Casteras A, Armengol Mdel P, et al. Autoimmune predisposition in Down syndrome may result from a partial central tolerance failure due to insufficient intrathymic expression of AIRE and peripheral antigens. J Immunol 2014; 193: 3872-9.

15. Ozcelik T, Uz E, Akyerli CB, Bagislar S, Mustafa CA, Gursoy A, et al. Evidence from autoimmune thyroiditis of skewed X-chromosome inactivation in female predisposition to autoimmunity. Eur J Hum Genet 2006; 14: 791-7.

16. Ansar Ahmed S, Young PR, Penhale WJ. The effects of female sex steroids on the development of autoimmune thyroiditisim thymectomized and irradiated rats. Clin Exp Immunol 1983; 54: 351-8.

17. Abdulrazzaq Y, El-Azzabi T, Al Hamad S, Attia S, Deeb A, Aburawi H. Occurrence of hypothyroidism, diabetes mellitus, and celiac disease in Emirati children with Down's syndrome. Oman Med J 2018; 33(5): 387.

18. Saadah OI, Al-Aama JY, Alaifan MA, Bin Talib YY, AlMughales JA. Prevalence of celiac disease in children with Down syndrome screened by anti-tissue transglutaminase antibodies. Saudi Med J 2012; 33(2): 208-10.

19. Rawashdeh MO, Khalil B, Raweily E. Celiac disease in Arabs. J Pediatr Gastroenterol Nutr 1996; 23(4): 415-8.

20. Sandalinas M, Márquez C, Munné S. Spectral karyotyping of fresh, non-inseminated oöcytes. Mol Hum Reprod 2002; 8: 580-5.

21. Sherman SL, Freeman SB, Allen EG, Lamb NE. Risk factors for nondisjunction of trisomy 21. Cytogenet Genome Res 2005; 111: 273-80.