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CELIAC DISEASE SCREENING IN A LARGE DOWN SYNDROME COHORT: COMPARISON OF DIAGNOSTIC YIELD OF DIFFERENT SEROLOGICAL SCREENING TESTS

GENİŞ BİR DOWN SENDROMU KOHORTUNDA ÇÖLYAK HASTALIĞI TARAMASI: FARKLI SEROLOJİK TARAMA TESTLERİNİN TANISAL VERİMLERİNİN KARŞILAŞTIRILMASI

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ABSTRACT

Objective: Down syndrome (DS) patients have a higher risk of developing Celiac disease (CD) than the general population. This study aimed to estimate the prevalence of CD in DS patients and compare the diagnostic performance of the screening algorithms.

Material and Method: A cohort of 1117 DS patients were included. Patients were grouped according to the initial screening method. Anti-gliadin antibody (AGA)-IgA/IgG were measured in the first, endomysial antibody-IgA (EMA) in the second, and tissue transglutaminase (tTG)-IgA/IgG in the third group. Additionally, EMA was also measured in patients with elevated tTG-IgA or tTG-IgG levels. In the follow-up, 225 patients were re-screened. Intestinal biopsy was planned in patients with positive AGA-IgA/IgG, positive EMA, or more than threefold elevated tTG-IgA levels.

Result: Based on the initial screening, 34.5% of the patients in the first group underwent a biopsy, and 2.3% were diagnosed with CD. In the second and third groups, 1.8% and 1.6% of patients underwent biopsy, and CD was diagnosed in 0.5% and 1.3%, respectively. Among all patients, 1.3% were diagnosed

ÖZET

Amaç: Down sendromlu (DS) hastalarda, Çölyak hastalığı (ÇH) riski yüksektir. Bu çalışmada DS tanılı hastalarda ÇH sıklığının araştırılması ve tarama algoritmalarının tanısal veriminin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 1117 DS tanılı hasta dahil edildi. Hastalar ilk uygulanan tarama yöntemine göre üç gruba ayrıldı. Birinci grup anti-gliadin antikor (AGA)-IgA/IgG, ikinci grup anti-endomisyum IgA antikoru (anti-EMA) ve üçüncü grup doku transglutaminaz (tTG)-IgA/IgG ile tarandı. Üçüncü grupta tTG-IgA veya tTG-IgG düzeyi yüksek saptanan hastalarda ikinci basamak test olarak anti-EMA düzeyi de ölçüldü. Olguların takibinde 225 hastada tarama tekrarlandı. AGA-IgA/IgG yüksekliği, anti-EMA pozitifliği veya 3 kattan fazla tTG-IgA yüksekliği olan hastalarda ince bağırsak biyopsisi planlandı.

Bulgular: İlk taramada birinci gruptaki hastaların %34,5'ine ince bağırsak biyopsisi yapıldı, %2,3'ü ÇH tanısı aldı. İkinci ve üçüncü gruplarda hastaların %1,8'ine ve %1,6'sına ince bağırsak biyopsisi yapıldı ve sırasıyla %0,5 ve %1,3'üne ÇH tanısı konuldu. İlk taramada, tüm hastaların %1,3'ü ÇH tanısı aldı. İzlemde çölyak antikor testi veya bağırsak biyopsisi negatif çıkan 225 hastada ta-

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with CD at initial screening. Two hundred twenty-five patients with negative initial screening tests or intestinal biopsy were re-screened; 8% underwent biopsy and CD was confirmed in 4.9%. Overall, 2.3% of patients were diagnosed with CD. The positive predictive value of AGA-IgA and AGA-IgG was low (13.6% and 7.2%, respectively) compared to EMA (69.6%) and tTG-IgA (66.7%). Gastrointestinal or extraintestinal symptoms were present in 42.3% of CD patients, and none of them had short stature.

Conclusion: Celiac disease was detected in 2.3% of DS patients. The CD detection rate was 1.3% at initial screening but increased to 4.9% at rescreening. Our results strongly suggest that CD screening should be performed regularly in all DS patients, whether they are symptomatic or not.

Keywords: Celiac disease, Down syndrome, screening

rama tekrarlandı, bu hastaların %8'ine ince bağırsak biyopsisi yapıldı ve %4,9'u ÇH tanısı aldı. Toplamda tüm hastaların %2.3'üne ÇH tanısı konuldu. AGA-IgA ve AGA-IgG'nin pozitif prediktif değeri (sırasıyla %13,6 ve %7,2), anti-EMA (%69,6) ve tTG-IgA'ya (%66,7) göre düşük bulundu. ÇH olanların %42,3'ünde gastrointestinal veya ekstraintestinal semptomlarmevcuttu.

Sonuç: Bu çalışmada DS'lu hastalarda ÇH sıklığı %2,3 saptandı. İlk taramada ÇH saptanma oranı %1,3 iken, tarama tekrarlandığında bu oran %4.,9'a yükseldi. Sonuçlarımız, semptomatik olsun ya da olmasın, tüm DS hastalarında ÇH taramasının düzenli olarak yapılması gerektiğini desteklemektedir.

Anahtar Kelimeler: Çölyak hastalığı, Down sendromu, tarama

INTRODUCTION

Down Syndrome (DS) is the most common chromosomal disorder characterized by facial dysmorphism, intellectual disability, and congenital malformations. Patients with DS are at increased risk of developing autoimmune diseases, including Celiac disease (CD), compared to the general population (1). Celiac disease is an autoimmune disorder of the small intestine triggered by gluten consumption. Classical symptoms include diarrhea, steatorrhea, abdominal distention, weight loss, or failure to thrive (2). In a large meta-analysis, the global prevalence of biopsy-proven CD in a normal population is documented to be 0.7% (3).

The American Academy of Pediatrics (AAP) reported that 1-5% of DS children have CD (4). In different studies, the prevalence varies between 0-19% (5-9). In a recent meta-analysis of 31 studies considering 4383 DS patients, CD was diagnosed in 5.8% of patients (10).

Celiac disease screening in DS patients is important because of the increased risk, the asymptomatic nature of the disease, and the intellectual disability-associated limitations of DS patients in communicating gastrointestinal symptoms. However, there is no consensus on guidelines for CD screening in DS patients (11). The AAP guideline recommends reviewing CD symptoms at each visit and performing serological testing only in symptomatic DS patients (4). In contrast, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guideline recommends CD screening in all DS patients (12).

This study aims to determine the frequency of CD in DS patients, describe clinical and serological findings of the CD, and compare different serologic testing methods in a large cohort of DS patients from a single tertiary center with records collected over 30 years.

MATERIAL and METHODS

Down syndrome patients who were screened for CD between January 1992 and March 2023 were investigated. A total of 1117 patients who had been on a gluten-containing diet for at least one year before screening were included. The male-to-female ratio was 1.12, and the median follow-up duration was 62 months (range:1-281 months). Trisomy 21 was confirmed in all patients by karyotype analysis.

Clinical data was obtained from patient records. Growth patterns were evaluated according to the National Down Syndrome-specific growth charts (13). Celiac disease patients with gastrointestinal (abdominal pain/distension, diarrhea, constipation) and/or extraintestinal symptoms were defined as symptomatic CD, and patients without symptoms were defined as asymptomatic CD. Patients with positive serologic tests but a normal intestinal biopsy were defined as latent CD.

Anti-gliadin antibodies (AGAs) and tissue transglutaminase (tTG) antibodies were investigated by the enzyme-linked immunosorbent assay (ELISA) method. The manufacturer-recommended values were used as cutoff values. Values above 50 AU/ml for AGA-IgA and AGA-IgG and above 18U/ml for tTG-IgA and tTG-IgG were accepted as positive. Endomysial antibody-IgA (EMA) was determined by the indirect immunofluorescent method, and the results were reported as positive or negative. Serum IgA levels were measured in 856 patients, and levels below 0.05 g/L were accepted as selective IgA deficiency.

The CD screening algorithm has been modified over the years with advances in serologic testing. Before the 2000s, AGA-IgA and AGA-IgG were used for screening. Since the 2000s, EMA and tTG antibodies have also been included in CD screening. To compare the diagnostic potency of these screening tests, we divided the DS patient cohort into three groups according to the initial serologic test used for CD screening:

In group 1, AGA-IgA and AGA-IgG were measured in 344 patients. Patients with at least one positive test result were scheduled for intestinal biopsy.

In group 2, EMA was measured in 392 patients. In patients with a positive EMA test, an intestinal biopsy was planned.

In group 3, tTG-IgA and tTG-IgG were measured in 381 patients. If serum tTG-IgA or tTG-IgG levels were elevated, an EMA test was performed. If the EMA test was negative and the tTG-IgA level was elevated less than threefold, the patient was observed without undergoing an intestinal biopsy. If the EMA test was positive or the tTG-IgA level was elevated more than threefold, an intestinal biopsy was planned.

Among patients who underwent intestinal biopsy, patients with increased intraepithelial lymphocytes and crypt hyperplasia (Marsh II), and villous atrophy (Marsh IIIa: partial villous atrophy, Marsh IIIb: subtotal villous atrophy, Marsh IIIc: total villous atrophy) were diagnosed as CD (14).

Rescreening of patients: In 225 of the patients whose initial screening tests or intestinal biopsy were negative, tTG-IgA and tTG-IgG, and/or EMA were measured during follow-up. If tTG-IgA or tTG-IgG levels were elevated, EMA was performed. If EMA was positive or tTG-IgA was elevated more than threefold, an intestinal biopsy was planned.

Written informed consent was obtained from all patients. The study was approved by the local ethics committee (Date:21.02.2023, No: 626135).

RESULTS

Initial screening for CD

Patients were divided into three groups according to the initial screening algorithm, which changed over time according to recommendations and advancements in screening tests. The initial screening results in the different test groups are shown in Table 1 and Figure 1.

In the first group, 344 patients were screened with AGA-IgA and AGA-IgG. Of these patients, 174 (50.6%) had at least one positive serological test result. AGA-IgA was positive in nine patients, AGA-IgG was positive in 114 patients and both tests were positive in 51 patients. Intestinal biopsy was performed in 119 (34.5%) patients. Fifty-five patients either refused to permit biopsy or were lost to follow-up. Celiac disease was diagnosed in eight patients (Table 1, Figure 1).

In the second group, 392 patients were screened with an EMA test, which was positive in 13 patients. An intestinal biopsy was performed on seven patients, and two were diagnosed with CD. Six patients either refused to permit a biopsy or were lost to follow-up (Table 1, Figure 1).

In the third group, 381 patients were screened by tTG-IgA and tTG-IgG. Eighty-three patients had a positive result in at least one test. tTG-IgA was positive in two patients (tTG-IgA <3X in both), tTG-IgG in 65 patients, and both tTG-IgA and tTG-IgG were positive in 16 patients (tTG-IgA <3X in nine, tTG-IgA ≥ 3X and <10X in four, and tTG-IgA ≥10X in three patients). Endomysial antibody was performed on 76 patients and found positive in six patients. Endomysial antibodies could not be performed in seven patients because they were lost to follow-up. Biopsy was not allowed in three patients; two patients refused intestinal biopsy (one had elevated tTG-IgA <3X, positive tTG-IgG and EMA, second had elevated tTG-IgA ≥10X, positive tTG-IgG and negative EMA) and the third patient who had positive tTG-IgG, positive EMA and negative tTG-IgA was diagnosed with acute leukemia concomitantly. Intestinal biopsy was performed in six patients and CD was diagnosed in five (Table 1, Figure 1).

As a result, 270 (24.2%) patients had at least one positive test result at the initial screening. Among them, 132 (11.8%) patients underwent intestinal biopsy, and 15 were diagnosed with CD. In the entire group, the CD detection rate at initial screening was 1.3%. Selective IgA deficiency was detected in four patients, all with normal tTG-IgG or AGA-IgG levels. Seventy-one patients who had at least one positive serological test either refused to permit further testing or were lost to follow-up.

Rescreening for CD

A total of 225 patients were rescreened for CD by tTG-IgA and tTG-IgG and/or EMA during the follow-up. Thirty-six (16%) patients had at least one positive result (Table 1, Figure 2).

Four patients had elevated tTG-IgA less than threefold and negative EMA levels; they were followed up without intestinal biopsy. Fourteen patients had negative tTG-IgA but positive tTG-IgG levels. EMA was positive in one of them who had a normal intestinal biopsy (Figure 2).

tTG-IgA was elevated ≥3X and <10X in six and ≥10X in 11 patients. Endomysial antibody was measured, and an intestinal biopsy was performed in 16 of them. One patient with elevated tTG-IgA≥10X refused further EMA testing and intestinal biopsy. EMA was negative in six patients, and one was diagnosed with CD by intestinal biopsy. Endomysial antibody was positive in ten, and CD was confirmed by intestinal biopsy in nine of them. Normal histopathology was observed in one patient who had elevated tTG-IgA≥ 10X and positive EMA tests. By rescreening, 18 patients underwent intestinal biopsy, and CD was confirmed in 11 patients. The CD detection rate was 4.9% at rescreening (Table 1, Figure 2). While the mean age of these patients

Table 1: Celiac disease screening results of patients

	At least one positive test result n (%)	Biopsy n (%)	CD diagnosis n	CD diagnosis rate of the biopsy (%)	CD diagnosis rate within the group (%)
Initial CD screening (n=1117)	**270 (24.2)**	**132 (11.8)**	**15**	**11.4**	**1.3**
Group 1 (n=344)	174 (50.6)	119 (34.5)	8	6.7	2.3
Group 2 (n=392)	13 (3.3)	7 (1.8)	2	28.6	0.5
Group 3 (n=381)	83 (21.7)	6 (1.6)	5	83.3	1.3
Rescreening (n=225)	**36 (16)**	**18 (8)**	**11**	**61.1**	**4.9**
Total (n=1117)	**304* (27.2)**	**148* (13.3)**	**26**	**17.3**	**2.3**

*Two patients had positive serologic test in the initial screening and rescreening, they were biopsied twice. CD: Celiac disease

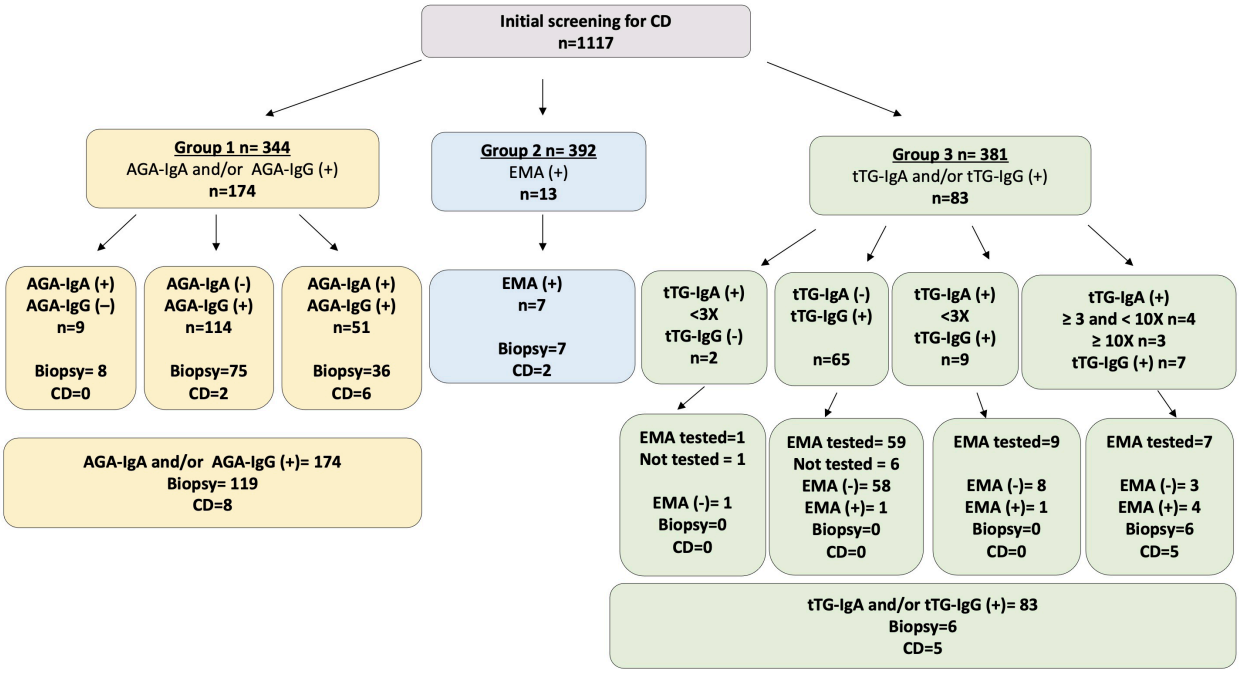

Figure 1: Initial Celiac disease screening in the whole cohort
AGA: Anti gliadin antibody, CD: Celiac disease, EMA: Endomysial antibody, tTG: Tissue transglutaminase antibody

was 3.2 years at initial screening, the mean age at which they were diagnosed with CD was 8.1 years.

As a result, a total of 26 patients were diagnosed with CD (2.3%). Of the patients with CD, 15 were diagnosed at the initial screening. Rescreening for CD was performed in 225 patients, and 11 patients who had normal at initial screening were diagnosed with CD during the follow-up. Biopsy could not be performed in 72 patients who refused further testing or lost to follow-up.

Clinical and laboratory features of patients with CD

The diagnosis of CD was confirmed by intestinal biopsy in 26 patients. Gastrointestinal or extraintestinal symptoms were only present in 42.3% of patients with CD. Gastrointestinal symptoms were present in three and extraintestinal symptoms were present in seven patients. One patient had both gastrointestinal and extraintestinal symptoms (Table 2). None of the patients had short stature. Fifteen patients who had no gastrointestinal or extraintestinal symptoms were classified as asymptomatic patients. Intestinal biopsy revealed Marsh IIIa and Marsh IIIc lesions in 11 and 15 patients, respectively (Table 2).

Diagnostic accuracy of serological tests

Intestinal biopsy was performed in 148 patients due to positive screening tests in our cohort. Among the patients who underwent biopsy, 119 of them had elevated

Table 2: The serological tests, clinical and pathological findings of patients with Celiac disease

No	AGA-IgA (AU/ml)	AGA-IgG (AU ml)	tTG-IgA (U/ml)	tTG-IgG (U/ml)	EMA	Clinical findings	Pathology (Marsh modified)	Initial screening test
1	16	74				Diarrhea	Type 3c	
2	184	420				Asymptomatic	Type 3a	
3	Positive	Positive				Autoimmune thyroiditis	Type 3c	
4	Negative	Positive				Diarrhea	Type 3c	
5	Positive	Positive				Asymptomatic	Type 3a	
6	131	144				Asymptomatic	Type 3a	
7	82	51				Asymptomatic	Type 3a	
8	11.3	142				Asymptomatic	Type 3a	
9					Positive	Asymptomatic	Type 3c	
10					Positive	Autoimmune thyroiditis	Type 3c	tTG-IgA (-), tTG-IgG (-)
11					Positive	Asymptomatic	Type 3a	
12			300	82	Positive	Iron deficiency anemia	Type 3c	EMA (-)
13			300	193	Positive	Iron deficiency anemia	Type 3a	tTG-IgA (-), tTG-IgG (-)
14			170	29.3	Positive	Diarrhea,iron deficiency anemia	Type 3c	tTG-IgA (-), tTG-IgG (-)
15			300	41	Positive	Asymptomatic	Type 3a	
16			57.7	19	Positive	Autoimmune thyroiditis	Type 3a	AGA-IgA (-),AGA-IgG (-)
17			192	6.2	Positive	Diarrhea	Type 3c	EMA (-)
18			300	59	Positive	Asymptomatic	Type 3c	
19			300	187	Positive	Asymptomatic	Type 3c	tTG-IgA (-), tTG-IgG (-)
20			277	300	Positive	Asymptomatic	Type 3a	AGA-IgA(-), AGA-IgG (-)
21			91	14.6	Positive	Asymptomatic	Type 3a	tTG-IgA (-), tTG-IgG (-)
22			166	187	Negative	Asymptomatic	Type 3a	
23			158	12.5	Positive	Autoimmune thyroiditis	Type 3a	AGA-IgA (-),AGA-IgG (-)
24			300	123	Positive	Asymptomatic	Type 3c	
25			300	12	Negative	Autoimmune thyroiditis	Type 3a	tTG-IgA (-), tTG-IgG (-)
26			300	98	Positive	Asymptomatic	Type 3a	

AGA: Anti gliadin antibody, CD: Celiac disease, EMA: Endomysial antibody, tTG: Tissue transglutaminase antibody

AGA-IgA and/or, AGA-IgG levels. Celiac disease was confirmed in six of 44 patients with elevated AGA-IgA and eight out of 111 patients with elevated AGA-IgG levels. The positive predictive value (PPV) of AGA-IgA and AGA-IgG were 13.6% and 7.2%, respectively.

Thirty-one patients with EMA testing underwent intestinal biopsy. Of these patients, EMA was negative in eight patients (tTG-IgA≥3X in all these patients) and positive in 23 patients. Two of eight EMA-negative patients and 16 of 23 EMA-positive patients were diagnosed with CD.

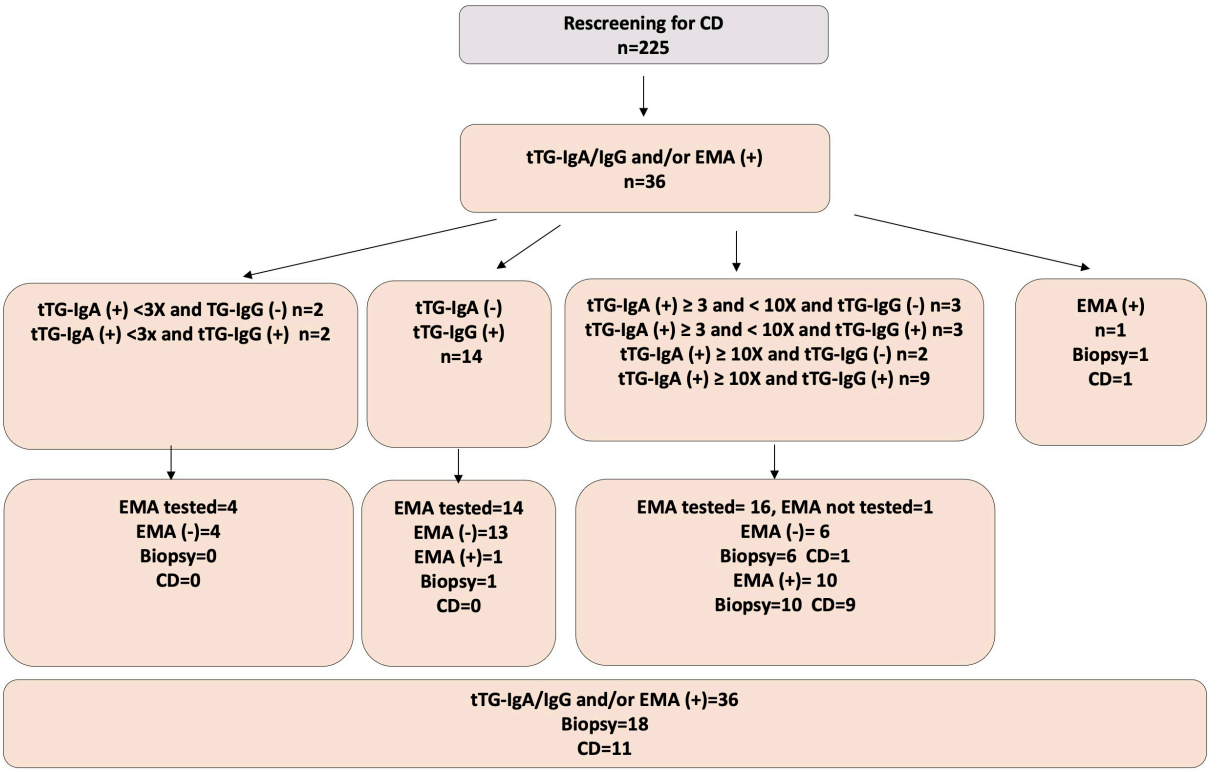

Figure 2: Celiac disease rescreening in patients who had normal serology or biopsy at initial screening
AGA: Anti gliadin antibody, CD: Celiac disease, EMA: Endomysial antibody, tTG: Tissue transglutaminase antibody

The PPV of EMA was 69.6%. A total of 21 patients with elevated tTG-IgA underwent intestinal biopsy and CD was confirmed in 14 of them. The PPV of tTG-IgA was 66.7%.

DISCUSSION

Overall, among the 1117 DS patients considered in this study, 26 patients were diagnosed with CD. The prevalence of CD in our DS patients was 2.3%, lower than previous large-cohort studies; one of which included 1317 patients and reported CD in 9.8%, and the second included 1202 patients and reported CD in 4.6% (6,15). A recent meta-analysis that included studies from European countries and the United States reported that the prevalence of CD was 6% and 5.7%, respectively, in DS patients (10). Studies on the prevalence of CD in DS patients from Turkiye were limited. In one study, CD screening was performed based on EMA in 100 DS patients. One patient was found to be EMA positive, but an intestinal biopsy could not be performed because the patient refused the biopsy (16). The prevalence of CD in DS was reported to be 6.4% and 3.1% in two studies from Turkiye, including 47 and 98 patients, respectively (17,18). In a previous study of our center which included 164 patients, CD was reported in 3% of DS patients (19). In this study, we performed an intestinal biopsy on 148 DS patients; however, 72 patients with positive serologic tests refused further testing or were lost to follow-up. If we could also perform a biopsy on these patients, the prevalence of CD in our cohort would increase even more.

Celiac disease can develop at any age, from infancy to adulthood. Therefore, it is crucial to repeat CD screening regularly in high-risk patients whose serologic tests or biopsies are initially negative. In our cohort, 225 patients were rescreened, and CD was diagnosed in 11 of them. The CD detection rate was 1.3% at initial screening and increased to 4.9% at rescreening. Similarly, Ostermaier et al. emphasized that CD screening in DS should not be limited to one time as the frequency of CD increases with age (7).

The classical gastrointestinal presentation of CD has been observed less frequently in recent years, and many CD patients are diagnosed with mild gastrointestinal or extraintestinal findings or are asymptomatic (20). In our cohort, 57.7% of CD patients were asymptomatic, and only 15.4% had gastrointestinal symptoms.

According to the AAP, CD testing was recommended for symptomatic DS patients (2). However, if only symptomatic patients were tested, and a significant number of CD patients would be missed. Liu et al. reported that almost half of CD patients detected by routine screening had no symptoms, and if routine screening had not

been performed, 82% of CD patients would have been undiagnosed (15). In addition, the complaints of symptomatic patients overlap with the symptoms commonly seen in DS patients. Sharr et al. reported that gastrointestinal problems were present in 30.7% of patients, whereas the new CD was diagnosed in <1% (21). In our cohort, more than half of CD patients were asymptomatic, and 42.3% of CD patients had normal initial screening. While the mean age of these patients was 3.2 years at initial screening, the mean age at which they were diagnosed with CD was 8.1 years. Therefore, we recommend regular screening for CD in the management of DS patients.

Serologic tests offered in the screening have changed over the years due to advances in technology. In the early 1980s, AGA was the only serologic test available. It was widely used until the discovery of EMA and tTG antibodies. Both tTG antibodies and EMA have high sensitivity and specificity. The endomysial antibody is more expensive and labor-intensive than tTG antibodies. Therefore, tTG-IgA, along with serum IgA, has been a first-line test in the screening of CD worldwide (22). Toftedal et al. investigated the PPV of CD screening methods in a large cohort of patients (23). They reported the PPV of AGA-IgA, AGA-IgG, EMA, and tTG-IgA was 79.6%, 39.5%, 80.7%, and 60.2%, respectively. In our study, the PPV of AGA-IgA and AGA-IgG were relatively low (13.6% and 7.2%, respectively). We found PPV of EMA was 69.6%, and tTG-IgA was 66.7%. Only one patient with normal tTG-IgA underwent intestinal biopsy, and it was found normal. Celiac disease diagnosis without biopsy is possible in patients with elevated tTG-IgA ≥10X and positive EMA (10). In our cohort, CD could not be confirmed with biopsy in one patient that had elevated tTG-IgA ≥10X and positive EMA. Therefore, in patients diagnosed without biopsy, the risk of a false-positive diagnosis should be considered, and if possible, the CD diagnosis should be confirmed by intestinal biopsy.

CONCLUSION

In conclusion, we demonstrated the prevalence of CD in a large cohort of DS patients from a single tertiary center as 2.3%. The CD detection rate was 1.3% at initial screening, whereas it increased to 4.9% at rescreening. More than half of the patients were asymptomatic, and only 15.4% of them had gastrointestinal symptoms. Due to the increased risk of CD and the presence of asymptomatic patients, we strongly recommend CD screening in DS. In our cohort, 42.3% of CD patients were diagnosed at rescreening, which supports that rescreening should also be performed regularly.

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