Screening for Celiac Disease and Thyroid Disease in Pediatric Patients with Down Syndrome

Brian M. Sammon¹, Douglas G. Rogers, M.D.² Sarah Worley, M.S.³
Anne Tang, M.S.³

¹Miami University, Oxford, Ohio; ²Section of Pediatric and Adolescent Endocrinology and ³Division of Biostatistics, Cleveland Clinic, Cleveland, Ohio.

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Corresponding author:

Douglas G. Rogers, M.D.
Cleveland Clinic, A-120
9500 Euclid Ave.
Cleveland OH, 44195

PHONE: 216-445-8048
FAX: 216-445-7792
E-mail: rogersd@ccf.org
ABSTRACT

BACKGROUND: Patients with Down Syndrome (DS) have an increased risk of developing autoimmune diseases such as thyroid disease and celiac disease (CD). The reported prevalence of CD in DS populations varies between 4% and 17%, while the reported prevalence of thyroid disease is about 30%. Recognizing these risks, the growing consensus is that DS patients should be universally screened for both diseases.

OBJECTIVE: To assess the percentage of pediatric patients with DS screened for CD and thyroid disease within the entire Cleveland Clinic Health System, and compare screening rates among provider groups.

DESIGN/METHODS: This retrospective chart review analyzed all 181 patients aged 2 to 20 years seen within the Cleveland Clinic Health System during the years 2005 and 2006 with an ICD-9 diagnosis of DS. A patient was screened for thyroid disease if a thyroid stimulating hormone level was measured and for CD if either endomysial or transglutaminase antibodies were measured.

RESULTS: Two patients were previously diagnosed with CD. Of the remaining 179 patients, 51 (29%) were screened at least once for CD during the years 2005 and 2006, and 4 new cases of CD were discovered. Fifty-three patients were previously diagnosed with thyroid disease. Of the remaining 128 patients, 61 (48%) were screened for thyroid disease during the years 2005 and 2006, resulting in 11 new cases. Chi square test revealed a statistically significant (P value <0.001) difference in the screening rates for both CD and thyroid disease among primary care physicians and 4 pediatric subspecialties. Pediatric endocrinologists screened for CD in 89% of patients. Primary care physicians more commonly screened for thyroid disease (73%) and CD (19%) than the combined pediatric sub-specialists in cardiology, otolaryngology, and neurology (thyroid disease 26%, CD 11%).

CONCLUSIONS: Enhanced education of both primary care physicians and pediatric subspecialists is needed to improve screening of patients with DS for associated CD and thyroid disease.

Key Words:
- Down Syndrome
- Celiac Disease
- Hypothyroidism
- Hyperthyroidism

Abbreviations:
- DS—Down Syndrome
- CD—Celiac Disease
- IgA—Immunoglobulin A
- TTG—Tissue Transglutaminase antibodies
- EMA—Endomysial antibodies
- TSH—Thyroid Stimulating Hormone
- T4—Thyroxin
BACKGROUND

Patients with Down syndrome (DS) have an increased risk of developing autoimmune diseases such as Hashimoto’s thyroiditis, Graves’ disease, type 1-diabetes, and celiac disease (CD)\(^1\)-\(^4\). Celiac disease is an immune-mediated malabsorption disorder of the small intestine caused by ingestion of dietary gluten in genetically susceptible individuals. According to the 2003 study by Fasano et al., the prevalence of CD in the general U.S. population is estimated at about 1:133 (0.75\%).\(^5\) However, the reported prevalence of CD in DS populations varies between 4% and 17% of patients\(^6\)-\(^9\), indicating that patients with DS have an increased risk of developing the disease in their lifetimes.

As a result, the growing consensus is that patients with DS should be screened for CD\(^1\),\(^3\)-\(^4\),\(^7\). But whereas screening for thyroid conditions in these patients is standardized, screening for CD is not. Organizations such as the American Gastroenterological Association recommend screening only symptomatic patients with DS\(^10\). Other organizations and studies, including the National Institutes of Health Consensus Development Conference Statement on CD, recommend universal screening of the DS population\(^1\),\(^11\) starting as early as 2 to 3 years of age\(^3\),\(^12\)-\(^14\). Additional reports together with recommendations from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition have suggested that screening children with DS once in a lifetime is not enough, and routine follow-up testing should be done\(^4\),\(^7\),\(^15\). One study in particular\(^7\) found 3 of 85 new CD cases occurring at least 2 years after patients with DS had first tested negative. However, The American Academy of Pediatrics has not made any recommendations for CD screening. In the Academy’s most recent article “Health Supervision for Children with Down Syndrome,” CD is not even mentioned\(^16\).

The complications of untreated CD include anemia, vitamin and mineral deficiencies, poor growth, osteoporosis, seizures, and rarely, intestinal lymphoma\(^6\),\(^9\). Serological screening is done using Immunoglobulin A (IgA) tissue transglutaminase (TTG) antibody levels or IgA endomysial antibody (EMA) levels, both of which have a high sensitivity and specificity that is useful for diagnosis\(^1\)-\(^2\),\(^11\),\(^13\),\(^17\). In serologically positive patients, endoscopy of the upper gastrointestinal tract with biopsy may show chronic inflammation of the small intestinal mucosa or even atrophy of intestinal villi\(^11\), confirming the diagnosis.

This study’s primary objective was to assess the percentage of pediatric patients with DS screened for CD and thyroid disease within the entire Cleveland Clinic Health System during the years 2005 and 2006. A secondary objective was to compare these screening rates among provider groups.

METHODS

Selection of the Study Population

A list of all children seen within the Cleveland Clinic with an ICD-9 diagnosis code for Down syndrome was generated. All patients diagnosed with DS were included in the study if they were between 2 and 20 years of age and had at least one visit during the years of 2005 and 2006. Children under the age of 2 were excluded since infants typically have low IgA levels and limited exposure time to gluten\(^13\)-\(^14\). Furthermore, 27
additional patients were excluded because their charts lacked sufficient information (i.e. missing visit notes, cancelled appointments, etc) to complete the study. The remaining 181 patients satisfied the criterion and comprised the study population. Information was extracted from patient electronic charts by the authors. Clinical notes, medical histories, and laboratory tests were viewed using a searchable electronic medical records database. The study design was approved by the Cleveland Clinic Institution Review Board.

**Study Variables**

The data were categorized into 2 parts: patient information prior to 2005, and patient information during visits. Patient information prior to 2005 included demographics (i.e. gender and date of birth) and confirmed diagnoses (i.e. CD, type-1 diabetes mellitus, and/or auto-immune thyroiditis). An existing diagnosis was determined by clinical notation; CD was determined by notation and/or positive biopsy results. It was also determined if the patient was screened for CD prior to 2005.

The following categories were included for every visit(s) the patient made to the Cleveland Clinic: date, age, inpatient/outpatient status, whether or not the patient was screened for CD, whether or not the patient was screened for thyroid disease, the service provided, and the location of the visit(s). A patient was screened for CD if blood levels of TTG and/or EMA were tested at a visit. In a serologically positive patient (TTG>30 Units or EMA>1:10 titer), a positive biopsy would confirm the diagnosis. A patient was screened for thyroid disease if blood levels of thyroid stimulating hormone (TSH) and/or thyroxin (T4) were tested at visit. Patients with a previously diagnosed thyroid condition were not included in the study’s final count of patients screened for thyroid disease. The service provided at the visit was the department of pediatrics that treated the subject. The location of the visit was either Cleveland Clinic main campus or its surrounding satellite locations.

**Statistical Methods**

Information was entered into a Microsoft Excel database and organized to the above specifications. Chi-square tests were used to assess the association between selected services and chance of screening. SAS 9.1 (SAS Institute, Cary, NC) was used for all analyses.

**RESULTS**

**CD Screening**

The study population consisted of 181 patients with the diagnosis of DS who had at least one office visit during 2005 or 2006. As noted in Table 1, two patients were previously diagnosed with CD. Of the remaining 179 patients, 51 (29%) were screened at least once for CD during the years 2005 and 2006, and 4 new cases of CD were discovered (Table 1). Generally, the chance of being screened for CD increased with the patient’s number of visits during the study period (Table 2). In addition, 2 more patients had EMA or TTG tests ordered, but the results of those tests were either unavailable in the charts or the tests were never performed.
Forty-seven patients were identified as having negative EMA or TTG tests done prior to the year 2005 (Table 1). Of these 47 patients, 26 (55%) were re-screened during the years 2005 and 2006, and no new cases of CD were discovered in that subgroup.

There was a statistically significant association between service and screening for CD (Table 3). Most notably, pediatric endocrinologists screened 89% of their patients for CD while primary care physicians screened 19% of their patients for CD within the two year study period.

**Thyroid Disease Screening**

Of the 181 study patients, 53 had previously been diagnosed with a thyroid condition (Table 1). Of the remaining 128 patients, 48% (61/128) of the patients were screened at least once during an office visit in 2005 or 2006, resulting in 11 new cases of thyroid disease (Table 1). In addition to the 61 patients screened, 17 more patients had TSH or T4 tests ordered, but the results of those tests were either unavailable in the charts or the tests were never performed. There was a statistically significant association between service and screening for thyroid disease (Table 4). Primary care physicians screened 73% of their patients for thyroid disease within the two year period.

**DISCUSSION**

In our study, patients with DS were screened more frequently for thyroid conditions than for CD. Overall, only 29% of patients were screened for CD during the years 2005 and 2006 while 48% were screened for thyroid conditions. One possible explanation for this difference is the lack of standard guidelines for screening DS populations for CD. Many studies and position statements vary in their recommendations, from screening only symptomatic patients \(^{10}\), to universal screening of children with DS \(^{1,11}\) starting as early as 2 to 3 years of age \(^{3,12-14}\), to having no recommendations at all \(^{16}\).

However, most healthcare guidelines for patients with DS agree that thyroid screening should be done regularly in the primary care setting \(^{12-13,16,18}\). Our results indicated that primary care physicians do typically screen for thyroid disease but not for CD. During the years 2005 and 2006, primary care physicians screened 73% of their patients with DS for thyroid disease (Table 4) whereas only 19% were screened for CD (Table 3).

Data from our study indicates that thyroid screening is done far less frequently by pediatric sub-specialties when compared to primary care physicians. For instance, cardiology was the most visited sub-specialty for these patients, because congenital heart disorders are one of the leading complications of DS \(^{1-4}\). Yet, only 24% of their patients were screened for thyroid disease (Table 4) and only 11% for CD (Table 3). Our study shows a statistically significant difference among the screening rates of specialties for both CD and thyroid disease, indicating that there is no overall conformity with screening practices.

Of the 181 pediatric patients with DS who visited the Cleveland Clinic Health System during the study period, 51 were screened for CD. This number can be broken down into 25 patients screened for the first time and 26 patients who had been screened for CD.
before 2005 and were re-screened during the study period. Four new cases were discovered and this 8% prevalence of CD in patients with DS is consistent with previously reported ranges of 4% to 17%.6-9

Finally, repeat screening for CD within 2 years may not be necessary since no new cases of CD were discovered in the 26 previously screened subjects. This data supports the Csizmadia et al. study in which no new CD cases occurred until more than 2 years after patients with DS had first tested negative7.

CONCLUSION
Since pediatric patients with Down syndrome are at a higher risk for celiac disease, it is important to universally screen these patients. Although untreated celiac disease is rarely fatal (some cases have linked untreated celiac disease with intestinal lymphoma), there are many serious complications including anemia, vitamin deficiencies, poor growth, osteoporosis, and seizures that subtract from quality of life. Furthermore, children with Down syndrome may be unable to accurately describe ailments due to varying degrees of associated mental retardation, and universal screening would prevent a delayed diagnosis.

The findings of this study suggest that pediatric patients with DS are not being screened for CD consistently. Therefore, enhanced education of both primary care physicians and pediatric sub-specialists is needed to improve screening rates for CD and thyroid disease. The authors also recommend developing a Best Practice Alert within the electronic medical record for children with DS. This would remind physicians to screen patients with DS for thyroid disease and CD.

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REFERENCES
TABLES

Table 1. Demographics of study population (n=181).

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
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<tbody>
<tr>
<td><strong>Age (Mean)</strong></td>
<td>2-20 years (8.42)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>92 (51)</td>
</tr>
<tr>
<td>Female</td>
<td>89 (49)</td>
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<tr>
<td><strong>Diagnosis before 2005</strong></td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>2 (1)</td>
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<tr>
<td>Thyroid Disease</td>
<td>53 (29)</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Screened before 2005</strong></td>
<td></td>
</tr>
<tr>
<td>CD, Negative</td>
<td>47 (26)</td>
</tr>
<tr>
<td><strong>Screened during study</strong></td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>51 (29)</td>
</tr>
<tr>
<td>Positive</td>
<td>4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>61 (48)</td>
</tr>
<tr>
<td>Positive</td>
<td>11</td>
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Table 2. Comparison of patient visits vs. CD screening

<table>
<thead>
<tr>
<th>Number of Visits</th>
<th>Total Number of Patients</th>
<th>Screened at least once n (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>9 (21.4)</td>
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<tr>
<td>2</td>
<td>72</td>
<td>25 (34.7)</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>8 (17.8)</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>9 (45)</td>
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<tr>
<td>Totals</td>
<td>179</td>
<td>51 (29)</td>
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Table 3. Screening rates for CD in previously undiagnosed patients *(n=179)*

<table>
<thead>
<tr>
<th>Service</th>
<th>Total Visits*</th>
<th>Screened n (%)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Pediatrics</td>
<td>135</td>
<td>26 (19.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>64</td>
<td>57 (89.1)</td>
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<tr>
<td>Cardiology</td>
<td>56</td>
<td>6 (10.7)</td>
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</tr>
<tr>
<td>ENT</td>
<td>31</td>
<td>5 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td>22</td>
<td>1 (4.6)</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>20</td>
<td>16 (80.0)</td>
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</tbody>
</table>

*Includes patients with multiple visits
†Chi-Squared test
Table 4. Screening rates for thyroid disease in previously unscreened patients (*n*=128)

<table>
<thead>
<tr>
<th>Service</th>
<th>Total Visits</th>
<th>Screened n (%)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Pediatrics</td>
<td>112</td>
<td>82 (73.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Cardiology</td>
<td>50</td>
<td>12 (24.0)</td>
<td></td>
</tr>
<tr>
<td>ENT</td>
<td>25</td>
<td>9 (36.0)</td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td>22</td>
<td>4 (18.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Includes patients with multiple visits  †Chi-square test