Tear Function Abnormalities in Down Syndrome

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Abstract

Background: Down syndrome is a common chromosomal anomaly, characterized by specific facial features, eye anomalies with repeated ophthalmic infections. The integrity of the ocular surface is maintained by the tear film.

Objective: To determine the presence of tear function changes in children with Down syndrome and their relation with the development of ophthalmic diseases.

Patients and Methods: Tear film was evaluated by the ferning test and breakup time (BUT) measurement in 23 patients (46 eyes) confirmed as having Down syndrome by cytogenetic analysis and 20 normal control children (40 eyes) with matched age and sex.

Results: There was an alteration in both ferning and BUT tests in children with Down syndrome compared to controls. Abnormal ferning test was found in 28 out of 46 tear samples from the patient’s eyes compared to 2 out of 40 normal control eyes. BUT test results showed that the precorneal tear film stability was poor in 65.2% of patients’ eyes, average in 26.1% and good in only 8.7% of their eyes; while controls had good and average tear film stability each representing 50% of eye’s number.

Conclusion: These tear function abnormalities may have a role in the frequent infectious pathologies found in the anterior eye segment in patients with Down syndrome which necessitates applying new stringent strategies for ophthalmologic care and management of these patients.

Key Words: Down syndrome – Tear function abnormalities – Tear function tests – Ferning test – Breakup time test.

Introduction

DOWN syndrome (MIM 190685) is the most common viable autosomal trisomy. It occurs at a frequency of approximately 1 in 600 – 800 live births; the risk increases with advancing maternal age. Classic phenotypic facial features include upslanting palpebral fissures, epicanthus and flat nasal bridge. Reported ocular abnormalities included nasolacrimal outflow drainage anomalies and repeated infections [1].

The integrity of the ocular surface in humans is maintained by the tear film, which is an organized liquid structure covering the bulbar and palpebral conjunctiva and the cornea. In normal conditions it is made up of three main components: The superficial lipidic layer, the middle aqueous layer and the deep mucinous layer. The lipidic layer is secreted mostly from Meibomian glands present along the eyelid border, the watery component is produced from the main and accessory lacrimal glands and the mucous component from goblet cells (that lay in the fornix) and from epithelial non goblet glands. The three layers act as one unit to maintain the integrity of the ocular surface and are considered a functional unit. Failure of one of these layers causes tear film instability [2]. The lipidic layer acts mainly to retard evaporation and ensures optimal spreading and stability of the tear film. The middle watery or aqueous layer helps to wet the conjunctival and corneal epithelial cells, causes mechanical flushing of debris and organisms, and its constituents help to inhibit the growth of microorganisms on the ocular surface. The mucous component forms a hydrophilic layer between the corneal and the conjunctival epithelium and the watery layer that constitutes the intermediate area of the tear film. Ocular mucins are thought to play integral roles in ocular surface lubrication, anchoring of the aqueous, stabilizing the lipid components of the tear film and eliminating foreign bodies and pathogens. It is also characterized by potential involvement in cell cycle mediation and apoptotic activity of ocular surface epithelia [3]. From the physiopathological point of view, alteration of the mucous layer causes abnormal distribution of the tear film on the eye surface, with a formation of
significant dry spots. The mucous component of the tear film is characterized by crystallization, forming ferning structures if left to evaporate at room temperature [4].

Many tests can be applied in either the clinical or the laboratory setting, to determine whether the tears of the individual patient exert their physiological and antimicrobial functions at the normal level [5]. Tear breakup time (BUT) is the time elapsed from the blink to appearance of the first corneal dry spot. It is a clinical test measuring the tear film instability that maintained by the three layers of the tear film. The ferning test is a laboratory test evaluating the mucous component of the tear film [6].

The aim of this study was to determine the presence of tear function abnormalities in children with Down syndrome and their relation to the development of ophthalmic diseases.

Subjects and Methods

All patients with Down syndrome were referred from Clinical Genetics Clinic, National Research Centre to the Ophthalmogenic Clinic, Research Institute of Ophthalmology. The study included twenty three children with Down syndrome (group 1) and 20 control normal subjects (group 2) with matched age and sex. Patients’ ages ranged from 1-9 years, with mean age 3.04 ± 2.488 years. They were subjected to full personal, past and family history with special emphasis to history for dryness, watering, grittiness, discharge and the use of ocular medications. Full clinical examination was carried out and ocular evaluation included examination of the lacrimal drainage system. Tear film function was evaluated by applying mucus fern test and breakup time test in both eyes of patients and controls.

Ferning test:

Ferning test was done, for both eyes of patients and normal control children, by obtaining the conjunctival fluid from the inferior fornix with a capillary tube 1mm diameter that was able to remove 4 µl liquid. This fluid was deposited on a glass slide and left to dry at room temperature. After 6-7 minutes, the glass slide was examined and the crystallization was analyzed by two separate researchers, using an Olympus phase contrast microscope equipped with a x40 objective and a camera. With a green filter in front of the objective lens, photographs were taken by means of the camera using Ford 400 ASA film. Evaluation of results was done according to Rolando et al. [7] who classified conjunctival mucous ferning into 4 types:

Type I: The ferning phenomenon is evenly present without any free spots between different ferns.

Type II: Crystallization in ferning structures still abundant but every single fern appears smaller in dimensions with empty spots between the ferns.

Type III: Ferning is present, although partial ferns are small and mixed to spaces with no signs of the ferning phenomenon, including shapeless mucin.

Type IV: Total ferning absence with filamentous material and exfoliate cells.

Type I and II represented the normal ferning while types III and IV were considered abnormal.

Breakup time (BUT) test:

Non invasive tear breakup time was measured with a hand held tearscope-plus (2413-P-2003, Keeler, UK). The lids were blinked manually to distribute the tear film and then the eye was held open. The time taken for distortion of the reflected image of the tearscope grid was recorded for each eye. Two timed tear breakup measurements were taken in succession then averaged [8]. Tear film stability in patients and controls were classified according to the manual of the tearscope-plus instrument into good stability (breakup time = 18.6-20.7 seconds), average stability (14.8-18.5 seconds) and poor stability (breakup time = 7.9-14.7 seconds).

Chromosomal analysis: Was performed for all examined patients by using Giemsa Trypsin banding technique [9].

Statistical analysis was performed using SPSS v.10 software. Ages of the children with Down syndrome (group 1) and controls (group 2) were compared with Student’s t test. Odd ratio was used to compare difference in gender between the two groups. Statistical analysis by X² test was used to compare ferning test and breakup time test results between patients and controls.

Results

The demographic data of patients and controls were shown in (Table 1). The two groups were not significantly different with respect to age (t=0.34, p>0.05) and gender (OR=0.96, p>0.05). General examination revealed that 9 Down syndrome patients (39.1%) had different forms of congenital
heart diseases. Chromosomal analysis by G-banding technique revealed non-disjunction trisomy 21 in all studied patients, which confirmed the diagnosis of Down syndrome.

Ophthalmic examination revealed that 5 (21.7%) patients had bilateral positive lacrimal regurge. Mucopurulent conjunctivitis was diagnosed and managed in 4 patients (17.4%), while 3 (13%) patients had alternating esotropia and 2 (8.7%) children were diagnosed with congenital cataract. Evaluation of ferning test revealed that most of tear samples from eyes of normal subjects (95%) represented type I and II and only 5% (2 eyes) were diagnosed as type III, while Down syndrome children were evaluated as type II, III, and IV but none of them presented ferning test type I. Comparing the results of ferning test between the two groups revealed high statistical significance \[X^2 = 49.749, p < 0.001 \text{ with } D.f=3\] (Table 2 and Fig. 1). Ferning test type I, II, III, and IV of patients and controls were shown in Figs. (2-5).

The breakup time results were shown in Table (3). Tear film stability was good in 50% of the control eyes and average in the other 50%, while Down syndrome patients’ tear film stability was poor in 65.2% of patients’ eyes; average in 26.1% and good in only 8.7% of their eyes. The difference between the two groups was statistically significant \[X^2 = 46.95, p < 0.001 \text{ with } D.f=2\].
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Table (1): Demographic data of Down syndrome patients and controls.

<table>
<thead>
<tr>
<th>Item</th>
<th>Down syndrome patients</th>
<th>Controls</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>23</td>
<td>20</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male n (%)</td>
<td>9 (39.1%)</td>
<td>8 (40%)</td>
<td>0.96</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>14 (60.9%)</td>
<td>12 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(1-9)</td>
<td>(1.5-10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.04±2.488</td>
<td>3.27±2.486</td>
<td>–</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table (2): Ferning test results in Down syndrome children and controls.

<table>
<thead>
<tr>
<th>Item</th>
<th>Type I N (%)</th>
<th>Type II N (%)</th>
<th>Type III N (%)</th>
<th>Type IV N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome (46 eyes)</td>
<td>0.0</td>
<td>18 (39.1%)</td>
<td>20 (43.5%)</td>
<td>8 (17.4%)</td>
</tr>
<tr>
<td>Controls (40 eyes)</td>
<td>26 (65%)</td>
<td>12 (30%)</td>
<td>2 (5%)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table (3): Breakup time (BUT) test results in Down syndrome children and controls.

<table>
<thead>
<tr>
<th>Item</th>
<th>Breakup time (BUT)</th>
<th>Down syndrome (46 eyes)</th>
<th>Controls (40 eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good stability (18.6-20.7)</td>
<td>4 (8.7%)</td>
<td>20 (50%)</td>
<td></td>
</tr>
<tr>
<td>Average stability (14.8-18.5)</td>
<td>12 (26.1%)</td>
<td>20 (50%)</td>
<td></td>
</tr>
<tr>
<td>Poor stability (7.9-14.7)</td>
<td>30 (65.2%)</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Down syndrome is by far the most common and best known chromosomal disorder in humans. The extra chromosome 21 affects almost every organ system and results in a wide spectrum of phenotypic consequences. Congenital heart defects occur frequently in patients with Down syndrome. They are one of the common causes of death in this aneuploidy in the first two years of life [10]. This study revealed that 9 patients had congenital heart diseases which represented 39.1% of cases. Azman et al. [11] reported that congenital heart disease was diagnosed in 49.3% in a retrospective analysis performed on the case records of 149 children with Down syndrome in Malaysia. Meguid et al. [12] diagnosed congenital heart diseases among 23% of 200 Down syndrome patients whose ages ranged from 1-10 years. Our results Lies in the range of the previous Egyptian and Malaysian studies.

Ferning test results of this study denoted alterations in the tear structure in patients with Down syndrome. Some authors [7,13] suggested that the crystallization phenomenon of the tear film in ferning structure depends on the concentration of electrolytes in the conjunctival fluid, which interact with proteins of high molecular weight. The presence of ferning type I and II represents the normal ratio, on the contrary, type III and IV indicates an altered phenomenon of the interaction between the two components. Our study showed a high percentage of ferning type I and II (95%) in normal subjects, while pathological forms in type III (5%) were few and even absent type IV. This phenomenon was inverted in our studied Down syndrome patients where crystallization of type I, which is considered to be normal, was absent and only type II was present (39.1%); while pathological forms of types III and IV were equal to 60.9% of the whole sample. This percentage of abnormal types in our study was similar to percentage found in other disorders affecting the eye such as dry keratoconjunctivitis and cystic fibrosis [14,15,16]. The ferning test results of our study was in accordance with the data published by many researchers [14,17,18]. Filipello et al. [18] suggested an altered conjunctival fluid secretion that causes the presence of numerous dry areas on the external eye surface. The formation of these areas is responsible for frequent irritating and infectious states often found in Down syndrome patients. Frequent attacks of blepharo-conjunctivitis was reported by many authors in Down syndrome cases [19,20].

Tear mucus ferning alteration in Down syndrome might be related to an alteration of the amount of mucin produced by the conjunctival goblet cells. Filipello and his colleagues, [21] reported marked reduction of goblet cells in the bulbar conjunctival epithelium of 15 patients with Down syndrome relative to normal control subjects using impression cytology method. They also, suggested that the detection of significant reduction of goblet cells in patients with Down syndrome represented an evidence of the involvement of the mucin layer in the different tear structure. A significant reduction in the level of mucin implies a consequential rapid degeneration of the tear film and the creation of hydrophobic areas on the cornea and conjunctiva, which in turn can give rise to increased risk of infection. They further hypothesized that the alteration of the conjunctival epithelium in Down syndrome may be due to an altered metabolism of some elements such as vitamin A which is involved in both the formation of glycoproteins as mucin and the maturation of epithelial cells, including those in the corneal and conjunctiva.
The results of this study indicated that Down syndrome is associated with disturbance of tear function and these anomalies could be responsible for frequent infectious pathologies found in the anterior eye segment in these subjects.

In conclusion, these tear function abnormalities necessitates applying a new stringent strategies for ophthalmologic care and management of patients with Down syndrome.

References


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