Spectral Domain Optical Coherence Tomography in Detecting Sub-Clinical Retinal Findings in Asian Indian Children with Down Syndrome

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Abstract

Purpose: Trisomy 21, also known as Down syndrome (DS), is the most common trisomy worldwide. Although ocular associations have been reported, retinal anatomy and pathology remain uninvestigated. We evaluate the role of spectral domain optical coherence tomography (SD-OCT) in analyzing foveal morphology of children with DS.

Methods: Nineteen consecutive DS children and eight controls were enrolled under a cross-sectional study in an institutional practice. All subjects underwent SD-OCT imaging on a handheld device. The morphology and thickness of central fovea, inner retinal layers, outer retina, and photoreceptor layers were measured and compared with age-group sub-analysis.

Results: Mean age of the cases was 24 months (3–78 months). All cases and controls had a normal foveal pit. Inner retinal layers were comparable between all eyes (100%) in controls and 100% of cases compared to all eyes (p = 0.01). The outer plexiform layer was normal in 10 eyes of cases (52.6%) compared to all eyes (100%) of the controls. Only 10 eyes of DS (52.6%) had a normal external limiting membrane, compared to all eyes of controls (100%, p = 0.01). The interdigitation zone (outer segment) was normal in one (5.3%) case compared to eight (67%) controls (p = 0.001). On subgroup analysis, in older cohorts, cases had a greater proportion of abnormal layers compared to controls. Visual acuity was found to be lower in cases when compared to controls, although not significant (p = 0.19).

Conclusion: DS babies have abnormal foveal morphology and persistence of inner retinal layers. This may assist our understanding of their visual development.

Introduction

Down syndrome (DS) or Trisomy 21 is the most common chromosomal anomaly reported worldwide. Ocular associations reported with DS predominantly include lid abnormalities like epicanthus, upward slanting palpebral fissure, epiblepharon, blepharitis, entropion, ectropion, ptosis, and chalazion. Other ocular morbidities include refractive errors, strabismus, nystagmus, keratoconus, and Brushfield spots.

Retinal findings are not as commonly reported and include non-specific focal retinal pigment epithelium (RPE) hyperplasia, myopic chorioretinal degeneration associated with their accompanying refractive errors and a higher than normal number of retinal vessel crossing the disc margin. Morton, in his summary on ocular associations and its correlation with visual acuity in DS children, reported that despite appropriate refractive error correction these patients never improved to 20/20. It has long been suspected that unknown retinal findings may help explain this phenomenon.

Recently, spectral domain optical coherence tomography (SD-OCT) has been used to evaluate subclinical pathologies in infants and children and correlating them with visual development. Reports have shown that SD-OCT of infants differs significantly from those of adults by demonstrating a thinner neurosensory retina, persistent inner retinal layers, and attenuated photoreceptors. SD-OCT imaging in DS has so far been reported anecdotally in three children with DS but were neither categorized or detailed.

In this study, we report a cohort of DS children in whom SD-OCT images obtained in the office, were analyzed, and their morphology compared with age-matched children without any systemic or ocular pathologies serving as a control cohort.
Methods

Patients and controls selection

Children with a proven diagnosis of Trisomy 21 referred by the geneticist were enrolled in the study. Patients and controls were included after obtaining a detailed written informed consent from the parents or legal guardians. The study met the approval of the Institute Ethics Committee, and the Institute Research Board and followed the guidelines laid down in the Declaration of Helsinki. We included all consecutive children with Down syndrome regardless of their refractive error.

All patients underwent a comprehensive ophthalmic examination including vision testing using Teller Acuity Cards (TAC), HOTV charts or Snellen’s chart appropriate to the age of the patient. Children who were incapable of performing any of the formal vision tests were subjected to functional vision testing by the early intervention and rehabilitation specialist. In addition, all patients underwent strabismus evaluation, cycloplegic retinoscopy and fundus evaluation by the pediatric ophthalmologist and pediatric retina specialist, respectively. Depending on the patient’s age and cooperation, the anterior and posterior segments were imaged with the Retcam Shuttle (Clarity MSI, CA, USA) or the Topcon Fundus camera (Topcon, NJ, USA). Controls were selected from those presenting to the pediatric ophthalmology clinic for routine evaluation. None of the controls had any ocular or systemic pathology.

OCT imaging protocol

A single technician trained in infant OCT imaging used a hand-held SDOCT (Envisu 2300, Bioptigen, Research Triangle, NC, USA) device to image all study participants. Imaging was performed in either supine or upright position depending on the age and co-operation without sedation. Rectangular and radial scans were obtained using the default settings of the device. For analysis, scans of length 8 mm x 8 mm were chosen. The scan parameters were set to 1000 A-scans/B-scan, with three frames acquired for each of the 50 B-scans in a single volume. This resulted in 150 (50 x 3 x 1) frames per eye, per session.

For image analysis, two masked pediatric retina specialists selected appropriate frames from each imaging session. The ‘best frame’ was selected by reviewing the entire session of 150 scans. The aim was to select a frame that best represented the ‘dead center’ of the fovea by identifying the landmarks of the ‘foveal dip’ of the inner retina and the corresponding ‘foveal tenting’ of the photoreceptor layers in the outer retina in the same vertical plane (Supplementary Figure). Where these landmarks were absent or not discernible, the frame with the deepest depression of the fovea and/or the frame with the tallest foveal tent were chosen. Both specialists concurred on the selected frame. In cases where the specialists differed, the scan was selected by mutual consensus. Ten percent of the frames were re-selected two weeks after the initial selection to test for inter-grader variability.

SDOCT analysis of retinal layers

We performed qualitative and quantitative analysis based on published methods by Maldonado et al.35 For quantitative analysis, thickness of the layers was measured using calipers available on the InVivoVue 2.4 OCT Management Software, Bioptigen Inc., Research Triangle Park, North Carolina. These calipers were placed on the borders of the defined layers. Each reading was obtained thrice, and the average was used for statistical analysis. The following previously reported definitions were used for measurements.36,39

- **Central Foveal Thickness (CFT):** Thickness of the entire retina extending from the inner aspect of inner limiting membrane (ILM) to the inner aspect of the retinal pigment epithelium (RPE) at the foveal center.
- **Inner Retina:** Inner retinal layers (IRL) include all the retinal layers from the inner aspect of the ILM to the outer border of the inner nuclear layer (INL).
- **Outer Retina:** The outer retinal layer extends from the inner aspect of the outer plexiform layer (OPL) to the outer border of the RPE which includes the external limiting membrane (ELM).
- **Photoreceptor layer:** The photoreceptor layer (PRL) extends from the outer aspect of the OPL to the inner border of the RPE.
- **Outer plexiform layer (OPL):** This was assessed by subtracting the thickness of the photoreceptor layer (PR) from the outer retina (OR minus PR)
- **Photoreceptor Complex (PRC):** The distance between the inner aspect of the IS-OS or the ellipsoid zone (EZ) to the outer aspect of the RPE.
- **Extent of inner retinal immaturity (IRI):** This is a measure of the inner retinal layers that persist at the foveal center. Normally the foveal center does not have any inner retinal layers in a mature fovea. Persistence is believed to result because of the incomplete centrifugal migration of the inner retinal layers from the foveal center. ‘Fusion’ is the completion of the migration of the inner retinal layers at the foveal center caused by the centrifugal migration of the layers of the inner retina, i.e. ganglion cell layer (GCL), inner plexiform layer (IPL), and INL resulting in the condensation or ‘fusion’ of the OPL and the INL into a single hyperreflective structure visible as a dot or line on SD-OCT. This persistence of the inner retinal layers at the foveal center is a sign of immaturity of the inner retina and has been described in premature infants with and without retinopathy of prematurity36,39,42. It is calculated by combining the thickness of the OPL and the IRL (IR + OPL).
To determine the role of age on the SDOCT layers, we performed a sub-group analysis by dividing the study cohort into three age groups: (1) 0–6 months (2) 6 months to 24 months and (3) older than 24 months. We randomly chose one eye for analysis since we found no difference between the two eyes and based on a previously published study by O’Brien et al. Statistical analysis was performed using IBM-SPSS Version 25.0 (IBM Corp, USA) and JMP Pro 13.1 (SAS, Cary, North Carolina). The distribution of the data was analyzed using the Shapiro–Wilk test. The quantitative measures were analyzed using the Independent sample T-test, and one-way ANOVA and the qualitative variables were analyzed using Chi-square test or the Fischer’s exact test. Two continuous variables were analyzed using Pearson’s correlation coefficient. The inter-grader reproducibility was assessed using interclass correlation coefficient. A multivariate analysis was performed with statistically significant variable to assess their effect on visual acuity throughout the study population.

Results

Nineteen consecutive patients with a clinical and genetically confirmed diagnosis of Trisomy 21 were enrolled as cases in the study. All patients were of Asian Indian ethnicity and ranged from 3 to 78 months. The mean age of the cohort was 24 months. There were 11 males and 8 females. The 12 controls enrolled from the pediatric ophthalmology clinic ranged from 4 to 82 months, of which 7 were male. The mean age of the controls was 29 months (Table 1, Figure 1).

Table 1. Demographic distribution of Down syndrome and Control groups.

|                      | Down Syndrome (N = 19) | Controls (N = 12) | P-value  |
|----------------------|------------------------|-------------------|----------|
| Gender               |                        |                   |          |
| Male n (%)           | 11 (58)                | 7 (58)            |          |
| Female n (%)         | 8 (42)                 | 5 (42)            |          |
| Age (in months) Mean (SD) | 24 ± 26             | 29 ± 30           |          |
| Range                | 3–78                   | 4–82              |          |
| Visual acuity (in logMAR) | 0.4–2.13          | 0.1–2             |          |

Ophthalmic evaluation

Visual acuity testing was possible for 17 of the 19 patients. The corrected distance visual acuity (CDVA) ranged from 20/60 to 20/2700. Two patients could not be assessed for visual acuity due to subnormal intelligence and unreliable test results. The visual acuity of the DS cases was found to be lower when compared to that of controls, although not significant (Figure 2). However, we found no correlation between morphological abnormalities in each of the layers versus visual acuity. Anterior segment evaluation revealed diagnoses of epicanthus in all cases and congenital nasolacrimal duct obstruction in four patients. All 19 cases had a clinically normal fundus. None of the controls had any ophthalmic abnormality.

Spectral domain OCT imaging

For analysis, 19 eyes from 19 cases were included. The mean CFT was comparable between DS and controls (p = 0.718). The layers were qualitatively (Table 2, Figure 3) and quantitatively (Table 3) compared between the cases and controls and are summarized below.

Inner retinal layers:

The ILM, NFL, and GCL were seen in all the eyes of both cases and controls. Inner retinal fusion was complete in the foveal center (Figure 3a) in only three eyes (15.8%) of cases.
compared to all eyes (100%) of controls (p < 0.001). This immaturity of the inner retina, with persistence of the inner retinal layers was one of the most striking differences between the cases and the controls (Figure 3b).

The foveal contour was assessed based on the following factors: the foveal crest-to-crest distance, the pit surface and foveal inner retinal area (FIRA), and deemed them as either shallow or deep based on Tick S et al.\textsuperscript{44}, deep considered to be the normal contour (Figure 3c,d). A shallow foveal contour (Figure 3d) was seen in 13 of 19 cases (68.4%) when compared to one control (12.5%), p = 0.008. The other inner retinal layers, namely the IPL and the INL were predominantly normal in all cases and controls.

Outer retinal layers:

The OPL was uniform and normal in contour in nine cases (47.4%). In the remaining eyes, the OPL was irregularly jagged. Comparatively, all 12 eyes (100%) of the controls had normal OPLs. The ONL was normal in eyes of all cases (100%) and controls (100%).

The ELM showed considerable variation between the cases and controls. Only 10 eyes of DS cases (52.6%) had a normal ELM (Figure 3e) compared to all 12 eyes of controls (100%, p = 0.01). In the remaining nine eyes of the DS cases, the ELM was attenuated or absent (Figure 3f).

Photoreceptor layer:

Table 3. Quantitative analysis of the difference in thickness between the layers in Down syndrome versus controls.

| Parameters                          | Cases (n = 19) | Controls (n = 12) | p-value |
|-------------------------------------|---------------|------------------|---------|
| Central foveal thickness            | 198 ± 39      | 191 ± 65         | 0.718   |
| Non-fusion of inner retinal layers  | 40 ± 21       | -                | -       |
| Outer retina                        | 157 ± 34      | 191 ± 65         | 0.06    |
| Photoreceptor layer                 | 133 ± 34      | 191 ± 65         | 0.002*  |
| Outer plexiform layer               | 24 ± 8        | -                | -       |
| Non-fusion                          | 64 ± 25       | -                | -       |
| Photoreceptor complex               | 58 ± 33       | 93 ± 42          | 0.01*   |
| Choroid                             | 203 ± 46      | 229 ± 84         | 0.276   |

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Photoreceptor layer:
The foveal tent, caused by the elevation of the IS-OS or the EZ was another important layer that differed between the cases and controls. A normal elevation of the foveal tent (Figure 3g) was observed in two eyes (10.5%). In the remaining nine eyes, the elevation was absent with the EZ layer maintaining a straight contour (Figure 3h). In contrast, 8 eyes out of 12 (67%) of controls had a normal foveal tent elevation, with one eye having no elevation (p < 0.001). The EZ was continuous at the foveal center in 15 eyes (78.9%) of the cases compared to 11 eyes of controls (92%, p = 0.634).

The OS-RPE layer (interdigitation zone, ID) was normal (Figure 3i) in one (5.3%) case compared to eight (67%) controls (p = 0.001). In the remaining 18 eyes of DS cases with abnormal OS-RPE (Figure 3j), it was either absent at the foveal center or altogether absent throughout the scan volume. This layer had considerable similarities in the controls as well. Of the four control eyes, which did not have a normal OS-RPE, four were absent at the foveal center (50%). The RPE was present and appeared normal in all the DS cases and in all the control eyes.

The intraclass correlation coefficient (95% confidence interval) for intergrader reproducibility for choosing the foveal frame, qualitative and quantitative assessments were 0.98 (0.97–0.98), 0.98 (0.97–0.98), and 0.95 (0.88–0.98), based on analysis at the same imaging session, respectively.

In a multivariate model, when considering mean visual acuity across the entire study population, we found PRL thickness (p < 0.001) and photoreceptor complex measurements (p = 0.03) contributed to visual acuity (R2 = 0.42, p = 0.01).

Subgroup analysis

The sub-group analysis based on age distribution was divided into three groups, namely 0–6 months (Cases = 5, Controls = 3), 6–24 months (Cases = 7, Controls = 4) and >24 months (Cases = 7, Controls = 5). Our aim was to compare the layers between the cases and the controls within each age group to determine if the older ages had any difference in their layers. We report the findings of the inner retinal fusion and foveal tent in Figure 4.

To summarize this analysis, we were unable to compare DS cases and controls in the 0–6 months age cohort due to the lack of controls in this cohort. In the older cohorts, a significantly large proportion of DS cases had abnormal layers whereas the controls had fewer eyes with abnormal layers. For example, in the 6–24 months cohort, 100% of eyes of the controls demonstrated inner retinal fusion, compared to no eyes in the DS cases. In the oldest cohort of >24 months, all control eyes (100%) had IRL fusion whereas only 28.6% of the DS cases showed this occurrence. A similar distribution was observed with the foveal tent morphology as well.

Discussion

Down syndrome was first described in 1866 by John Langdon Down39 in his monograph which reported that a group of more than 10% of his cognitively delayed patients looked ‘similar to one another’ and shared many physical characteristics as well. He described them as a very large number of ‘congenital idiots’, typical ‘Mongols’. Ocular findings in DS has been described by several groups; however, no study has studied the OCT features in DS. Anecdotally, Gail V Morton42 in his paper reported the SDOCT findings of three older children with DS, with 20/40 vision. He described them as lacking dense foveal packing and the IS-OS layer being less reflective.

Recently, with the availability of hand-held SDOCT devices, infant imaging on the OCT has become popular.39 Clinically normal looking fundi of preterm infants have been reported to have structurally abnormal foveae, which despite spontaneous resolution,44,45 have influenced visual acuity and refractive status several months after the defect resolved.38 Furthermore, certain foveal layers were responsible for positively or negatively influencing visual acuity in infants.

We have reported that visual acuity positively correlated with the presence of IRL fusion, ELM, EZ, and OS-RPE between the third and sixth corrected month. Subsequently, during the sixth and ninth month, the IRL fusion was significantly associated with visual acuity and during the 9 months and completion of the corrected first year, the IRL fusion and the presence of the EZ correlated with visual acuity.42

Our current study describes the SDOCT findings in Asian Indian children with DS. We imaged 19 children between 3 and 78 months with karyotype confirmed DS and compared them to controls. Interestingly, we observed that infants and

Figure 4. Bar graphs representing the presence of inner retinal layer (IRL) fusion and foveal tent in Down syndrome and Control groups at different time periods. Left panel bar graph shows absence of IRL fusion in all cases at 6–24 months and >24 months, IRL fusion is seen in 20% of the cases at 0–6 months and in 28.6% >24 months when compared to 100% of controls at 0–6, 6–24 months and in the >24 months sub-groups. Right panel bar graph shows absence of a normal foveal tent in all cases at 0–6 months and 6–24 months. All controls (100%) in the 0–6 months, 6–24 months and >24 months groups show the presence of a normal foveal tent when compare to 66.7% of cases with normal tent seen only in the >24 months sub-group.
children with DS have underdeveloped retinal layers when compared to the controls. A larger proportion of DS cases had abnormal layers compared to fewer eyes with abnormal layers amongst controls. This is in conjunction with the study published by O’Brien et al. in 2015 that observed the macular structure in children with Down’s syndrome using Fourier domain OCT.43 However, in contrast to O’Brien et al., we found a thinner macula in DS when compared to the normal controls.43

Inner retinal immaturity, which was seen in 84.2% of DS cases, is characterized by persistent inner retinal layers at the foveal center. With the centrifugal migration of these layers, the OPL moves closer to the ILM and eventually “fuses”. This event is termed as IRL fusion. The GCL, IPL, and INL were distinctly measurable layers at the foveal center in cases of DS as in other immature retinas. As the infant grows older, although not known exactly when, there is a centrifugal growth and the IPL and INL condense into a single band with the ILM. There is some evidence to suggest that progressive centrifugal migration of these layers at the fovea begins as early as 26–28 weeks PMA and has been observed on SDOCT at 31 weeks PMA and continues to a variable end point beyond 45 weeks.36,46 The outward migration of these layers corresponds to the formation of the “foveal pit” and hence represents a more mature version of the growing fovea. A positive correlation with vision is therefore biologically plausible.

A lesser proportion of DS eyes had a normal ELM compared to controls. The ELM is a series of intermediate junctions known as zonulae adherentiae between the rod and cone inner segments and the apical processes of the Müller cells. The inner segment of the photoreceptor cells is linked to the Müller cells by this junctional membrane which precedes the photoreceptor layer’s centripetal growth and maturation.

Fifteen eyes of cases and one eye from the control group had an abnormal OS-RPE layer. Previous studies have shown a positive correlation of the OS-RPE layer with visual acuity in babies between 3 and 6 months of corrected age. The OS-RPE layer represents the growth of the apical microvilli of the RPE. It occurs at a time frame after the central fusion of the IS–OS layer at the foveal center and is likely to represent the maturation of foveal cones.36,47,48 However, we found no association between OS-RPE and visual acuity in either of our groups.

The normal foveal development of term babies or those in early infancy is still not known. However, we can draw parallels from studies of brain development in a similar cohort. Becker et al.49 in 1986 compared dendrites from the visual cortex of eight DS patients and control infants aged between 4 months and 7 years. Becker compared the number of intersections, and total dendritic length and found the infantile group, aged 4 to 6 months, to be above normal in the DS group; this then dropped steadily in infants between 6 months to 2 years and was found to be below normal in 2 to 4-year-old age group. The inference of Becker’s report is that children with DS behave closer to normal age-matched children early on and grow further apart and ‘more abnormal’ compared to their age controls in older children.

We made an eyeball comparison of the quantitative measurements of our dataset to Lee et al.’s.43 available quantitative measurements in normal children of the same age as our cohort. We found that most of the quantitative measurements fell into the range of Lee et al.’s measurements.

In our sub-group analysis, we found in the older subgroup, the difference became larger, with the DS babies being more abnormal than their controls (Figure 4). This interestingly resembles the differences in the age groups reported by Becker in brain tissue. It is currently a matter of conjecture if these findings have a true correlation or is an interesting coincidence.

The limitation of this study is that it is a single session, observational study. Secondly, it is a study that comprises of homogenous Asian Indian children and has not been tested in any other population setting. Another limitation of this study was the lack of axial measurements on these children due to which were unable to comment about the variation of certain structural parameters with eye length. Our controls were not age or gender matched due to the limited sample size. Despite these limitations, this study establishes that SDOCT is a useful tool in assessing the fovea in children with DS, many of whom may have subnormal intelligence and are not cooperative in the office for visual assessment. This new method of assessing abnormal layers could help us understand why despite having clinically normal-looking fundi some of these children never have 20/20 vision.32

It is possible that with further studies correlating vision with these layers, we would be able to predict and monitor improvement of vision in these and other syndromic children. Longitudinal studies correlating visual acuity with the development of layers may provide better evidence to understand the functional outcomes in children with DS and other chromosomal abnormalities.

Disclosure Statement
None of the authors have financial disclosures. No authors have a proprietary interest in the current study.

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