Visual and Refractive Status of Children With Down's Syndrome and Nystagmus

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PURPOSE. Children with Down's syndrome (DS) are known to have poorer visual acuity than neurotypical children. One report has shown that children with DS and nystagmus also have poor acuity when compared to typical children with nystagmus. What has not been established is the extent of any acuity deficit due to nystagmus and whether nystagmus affects refractive error within a population with DS.

METHODS. Clinical records from the Cardiff University Down's Syndrome Vision Research Unit were examined retrospectively. Binocular visual acuity and refraction data were available for 50 children who had DS and nystagmus and 176 children who had DS but no nystagmus. Data were compared between the two groups and with published data for neurotypical children with nystagmus.

RESULTS. The study confirms the deficit in acuity in DS, compared to neurotypical children, of approximately 0.2 logMAR and shows a deficit attributable to nystagmus of a further 0.2 logMAR beyond the first year of life. Children with both DS and nystagmus clearly have a significant additional impairment. Children with DS have a wide range of refractive errors, but nystagmus increases the likelihood of myopia. Prevalence and axis direction of astigmatism, on the other hand, appear unaffected by nystagmus.

CONCLUSIONS. Nystagmus confers an additional visual impairment on children with DS and must be recognized as such by families and educators. Children with both DS and nystagmus clearly need targeted support.

Keywords: nystagmus, children's vision, Down's syndrome, refractive error, visual acuity

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Infantile nystagmus (IN) is one of the most frequently seen ocular disorders in children with Down's syndrome (DS) and is estimated to occur in 15% to 30% of the population.[1,2] Among neurotypical children, IN is associated with poorer visual acuity (e.g., Fu et al.[3]) and a wide spectrum of refractive errors associated with failure of emmetropization.[4]

There are little published data on visual acuity (VA) in children with DS and nystagmus (DSN). A study by Felius et al.[5] investigated the VA deficit of 16 children with DSN between the age of 10 months and 14 years using Teller cards. The VA reported was poorer than that of neurotypical children with nystagmus, but no comparison was made with children with DS and no nystagmus. It has been widely reported that children with DS have poorer visual acuity than the neurotypical norm.[6–11] However, in these studies, children with nystagmus or any other visually impairing condition are often excluded.[9–11]

The prevalence of refractive errors has been reported to be much higher in both children and adults with DS compared to the typical population.[12,13] Refractive errors in infants with DS are similar to those of typical infants, but emmetropization does not occur,[14] so the prevalence and degree of refractive errors increase and remain high.[15] To date, there are no published data concerning the refractive status of children with DSN exclusively. Therefore, information on the visual and refractive status of these children is very limited.

The aim of this study was to determine whether there are any differences in the distribution and development of VA and refractive error among children with DSN compared to those of children with DS by analyzing, retrospectively, the clinical records of children participating in the Cardiff University Down's Syndrome Vision Research Unit (CDSVRU) studies.

METHODS

In total, 258 clinical records of children in the CDSVRU between 1992 and 2017 were examined retrospectively. The recruitment procedures were explained in detail in Zahidi et al.[11] Inclusion criterion was a diagnosis of trisomy 21, and there were no exclusion criteria. Qualified optometrists conducted optometric assessments at the children's home, at school, or in the clinic at the School of Optometry and Vision Sciences, Cardiff University.

The method of visual acuity measurement varied, depending on the child's age and cognitive ability, but was confined to preferential looking at 38 cm with Teller Acuity cards (Precision Vision, Woodstock, Illinois, USA)[16] or at 50 cm with the Cardiff Acuity Test,[17] or at 3 m with the

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Kay Picture LogMAR test (singles or crowded)[18] or Keeler LogMAR Crowded test.[19] Depending on the child's cooperation, VA was measured binocularly first and then monocularly. Only binocular data were included in this analysis. Children who had been prescribed eyeglasses wore their corrections during VA measurement. This longitudinal study obtained continual and ongoing approval from NHS Ethics in Wales (National Institute for Social Care and Health Research Ethics Service 08/MRE09/46, amendment 5, July 7, 2016). Study information was given to parents, and written consent was obtained from the parents of all participants involved. This study was conducted in accordance with the Declaration of Helsinki.

Refraction was performed using the Mohindra technique in a completely dark room or light-proof tent using a dim retinoscope light following the procedure outlined by Elliot.[20] This technique has been shown to obtain results not significantly different from cycloplegic refraction in children with DS.[14] Refractive error was recorded in sphere, minus cylinder (cyl) form, and axis. Significant refractive error was defined as spherical equivalent refractive error (SER) of <-0.50 diopter (D) (myopia) or $\geq+2.50$D (hypermetropia).[21] Significant astigmatism was defined as <-0.50 Diopter cyl (DC). Data for the right eye (RE) were used for analysis for all participants except for those with anisometropia (a difference in SER ≥1.00D between right and left eyes) when the data of the least ametropic eye was used.[22] Axis of astigmatism was recorded as with the rule (WTR: minus cyl axis $180° \pm 15°$), against the rule (minus cyl axis $90° \pm 15°$), or oblique (minus cyl axis greater than $\pm15°$ from the horizontal and vertical meridian).[21]

Children with either manifest or latent nystagmus during two or more visits were identified and grouped into the DSN group, with the remainder in the non-nystagmus group (DS). Nystagmus in all children was assessed clinically by observation, including cover test and ocular motility. In addition, parents of two children in the DSN group provided a report from their child's ophthalmologist, and letters were sent to the ophthalmologists of a further 18 children in the DSN group who joined the study from 2016, requesting confirmation of a diagnosis of nystagmus. Nine responses with the details of the participant's diagnosis were received. Therefore, information on the diagnosis of nystagmus was available for 11 children. Eye movement recording was carried out on 28 children with DSN to investigate the characteristics of nystagmus; these data will be described in a separate publication.

Records from 32 children were excluded from analysis for the following reasons: (1) there were no visits in which binocular acuity data were obtained ($n = 8$), (2) the age when entering the study was over 12 years ($n = 13$), (3) ocular condition such as cataract ($n = 2$), and (4) not fully corrected during visual acuity measurement ($n = 9$).

To prevent any bias, the database was inspected without names (codes were used), acuity, or refractive error data. The children were allocated to seven age groups to enable meaningful comparison of the findings with that of typically developing children with nystagmus[3,4,23,24]: 1 to 11.9 months, 12 to 23.9 months, 2 to 3.9 years, 4 to 5.9 years, 6 to 7.9 years, 8 to 9.9 years, and 10 to 11.9 years. Participants were limited to inclusion in one age group only.

Statistical analysis was performed using the IBM SPSS version 23 statistical package (SPSS, Inc., Chicago, IL, USA). Descriptive analysis was performed on both VA and refractive error data to determine the mean, standard deviation (SD), median, 95% confidence intervals, and frequency of each age group for both the DSN and DS groups. The distribution of binocular VA, SER, and astigmatism data for each group of children at each age group was tested for normality using the Shapiro–Wilk test. Data that were normally distributed ($P > 0.05$) were analyzed using parametric statistical tests; otherwise, non-parametric statistical tests were used.

RESULTS

After exclusions, 226 children were included in the cross-sectional study, which consisted of children with DSN ($n = 50$) and DS ($n = 176$). Of these, 91 (40%) were female and 135 (60%) were male. Note that the acuity of 159 children in the DS group has already been reported.[11] The database was updated for the current analysis and age groups modified. The distribution of children in each age group is presented in Table 1.

Diagnosis of Nystagmus

On the basis of the responses of the ophthalmologists, five children with DSN were diagnosed with INS, two with latent nystagmus and two of unknown type. Only one child with DSN (out of nine) had a thorough investigation of nystagmus, which consisted of electroretinogram, visual evoked potential, and orthoptic assessment. The nystagmus of all five children with DSN who were diagnosed with INS was reported to be "associated with the DS" and no other ocular conditions. Although there are no reports of children with DSN presenting with any ocular abnormalities, equally, there are no reports of specific investigations performed to confirm those claims. The following is a typical quote from a referral letter:

"Horizontal nystagmus is a reasonably common association of Down's syndrome, so I have not advised any investigation" (ophthalmologist of P82 2018, response letter).
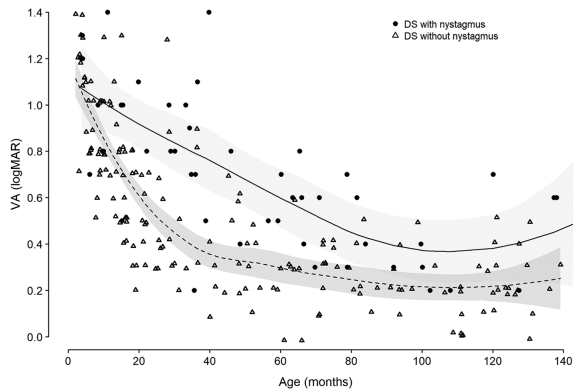
TABLE 1. Distribution and Mean ± SD Age of Children With DS and Nystagmus (DSN) and Without Nystagmus (DS) in Each Age Group

| Characteristic	1–11.9 Months	12–23.9 Months	2–3.9 Years	4–5.9 Years	6–7.9 Years	8–9.9 Years	10–11.9 Years
DSN							
Number	8	9	9	9	5	5	5
Age, mean ± SD, y	0.59 ± 0.25	1.48 ± 0.30	2.88 ± 0.47	5.15 ± 0.56	6.92 ± 0.46	8.44 ± 0.35	11.11 ± 0.79
DS							
Number	38	35	25	23	23	14	18
Age, mean ± SD, y	0.56 ± 0.23	1.45 ± 0.28	2.78 ± 0.58	4.95 ± 1.05	6.81 ± 0.69	8.86 ± 1.21	10.53 ± 0.47

Visual Acuity

The mean binocular acuity (BVA) of children with DS and DSN is shown for age groups in Figure 1. In both groups, because the older age groups had fewer participants (only five in the case of DSN; see Table 1), the acuity results showing an increase should be treated with caution. BVA ranged from 0.2 and 1.4 logMAR for the children in the DSN group and 0.0 and 1.4 logMAR for the children in the DS group. In the first year of life, the median BVA of the children in the DSN group was 0.1 logMAR poorer than that of children in the DS group and worsened to approximately 0.2 logMAR (two lines) poorer beyond the first year of life. Analysis of covariance (ANCOVA) performed on all data with age as a covariant showed a significant difference ($F = 28.42$, $P < 0.05$), with the DSN group having poorer BVA than the DS group.

The mean BVA of neurotypical children with idiopathic IN and IN associated with albinism reported by Fu et al.[3] was plotted in Figure 2 along with the mean BVA of children with DS with and without nystagmus from the present study. The BVA of children with DSN appears more similar to that of neurotypical children with albinism than neurotypical children with IN. The progression of BVA with age of
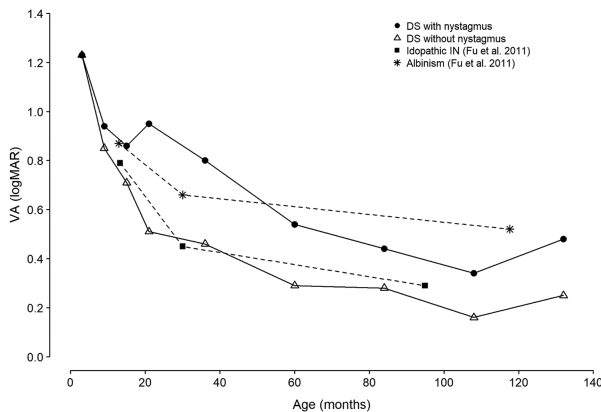
children in the DS group is not markedly different from that of typically developing children with idiopathic IN.
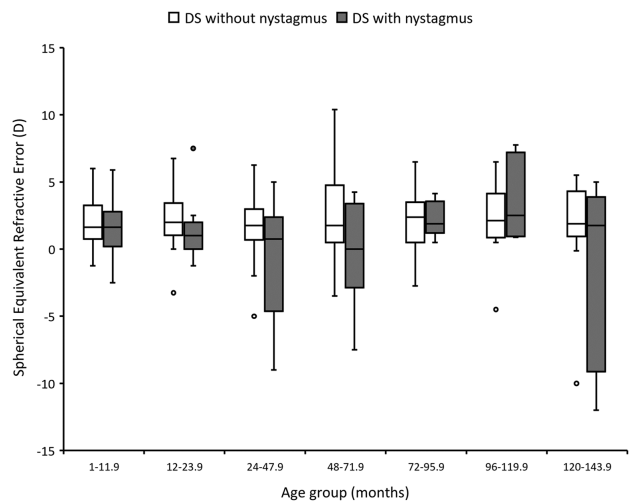
SER

Seven (14%) and 18 (10.2%) of the children in the DSN and DS groups, respectively, were anisometropic. Data of the left eye were used for five children in the DSN group and eight children in DS group; otherwise, RE data were used. SER data of both groups of children were normally distributed ($P > 0.05$) for all age groups except those 12 to 23.9 months and 10 to 11.9 years in the DSN group and children 12 to 23.9 months in the DS group ($P < 0.05$ in all cases). SER was between −12.00 D and +7.75 D in the DSN group and between −10.00 D and +10.38 D in the DS group.

Figure 3 shows the median SER of both groups of children for each age group. Data for children under 1 year were removed because refractive error is likely to change in early infancy.[25] Although the data were normally distributed, medians and interquartile ranges were used to enable comparisons of the results with those reported by Al-Bagdady et al.,[22] whose data were not normally distributed. Children in the DSN group showed more variability in the SER compared to the DS group. Regression analysis showed no significant change in SER with age for both groups of children (DSN, $P = 0.936$; DS, $P = 0.889$). ANCOVA showed a significant difference in the SER between children in the DSN and DS group when age was taken into account ($F = 8.30$, $P < 0.05$).

The SER distribution of children in the DSN group was plotted alongside SER data of typically developing children with idiopathic infantile nystagmus (IIN) reported by Healey et al.[4] As shown in Figure 4, only eight (16%) of the children in the DSN group fell outside the 95% confidence limits of the SER of children with DS and IIN; seven of these were more myopic and only one more hypermetropic.

Table 2 shows the frequency of type of refractive error for each group of children with DS. Children in the DSN group showed a significantly higher prevalence of myopia (40.7%) than the DS group (11.2%) ($\chi^2 = 13.790$, $P < 0.05$).

FIGURE 1. Distribution of binocular VA with age of both groups of children with DS, with and without nystagmus. *Solid and dashed lines*: Best-fit line for BVA of children with DS and nystagmus and DS without nystagmus, respectively. *Shaded areas* indicate 95% confidence intervals.

FIGURE 2. Mean binocular VA of children with DS, with and without nystagmus, compared to published data of idiopathic IN and IN associated with albinism (Fu et al.[3]).

FIGURE 3. SER for each age group of children with DSN and DS. *Box* represents median and interquartile range (IQR). *Whiskers* represent minimum and maximum values excluding outliers. *Circles* represent outliers.
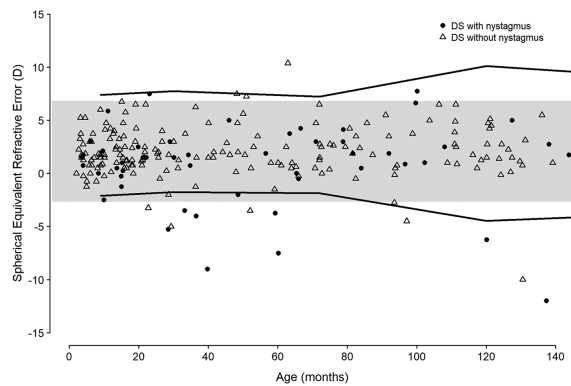
FIGURE 4. SER for both groups of children with DS, with and without nystagmus, alongside. *Shaded area* depicts 95% confidence interval of overall mean SER of children with DS without nystagmus. *Solid lines* depict upper and lower limit of mean SER in children with idiopathic infantile nystagmus at different age groups published by Healy et al[4].

TABLE 2. Frequency of Refractive Error Type in Each Group of Children With DS

Characteristic	Frequency of Refractive Error Type, No. (%)		
	Myopia	**Hyperopia**	**Emmetropia**
DSN ($n = 50$)	12 (24.0)	14 (32.0)	24 (48.0)
DS ($n = 176$)	12 (6.82)	62 (35.23)	102 (57.95)

Astigmatism

Mean ± SD astigmatism was -0.76 ± 0.62 DC for the children in the DSN group and -0.74 ± 0.81 DC for the children in the DS group, which were not significantly different (ANCOVA $F = 0.16$, $P = 0.68$), with age as a covariant. Twenty-seven (54%) children in the DSN group and 102 (58%) children in the DS group had significant astigmatism, a difference that was also not significant ($\chi^2 = 1.65$, $P = 0.69$). Furthermore, when the children were divided into three age groups, including infancy (up to 23.9 months), early childhood (2–5.9 years), and later childhood (6–11.9 years), the prevalence of significant astigmatism increased (50%–67.3% for DS and 47.1%–73.3% for DSN), but the difference between DS and DSN was not significant at any age ($\chi^2 = 0.48$, 1.21, and 0.20 and $P = 0.83$, 0.27, and 0.65, respectively). Moreover, there was no significant difference in the axis of astigmatism between children with DS and DSN ($\chi^2 = 1.46$, $P = 0.48$). The most common type of astigmatism seen in both groups of children was WTR (DS = 61.76% and DSN = 74.07%), followed by oblique astigmatism (DS = 19.61% and DSN = 18.51%). The average age of children with WTR astigmatism in the DS and DSN groups was 3.49 years and 5.04 years, respectively. The average age of children with oblique astigmatism in both the DS and DSN groups was 6.38 years and 7.28 years, respectively.

DISCUSSION

To our knowledge, this retrospective study is the first to specifically describe the visual and refractive status of children with DSN, who comprise over 20% of our study cohort. The current analysis shows that children with DSN have significantly poorer VA compared to that of children with DS. A recent retrospective analysis of VA data by Zahidi et al.[11] confirms that children with DS have poorer corrected acuity compared to typically developing children by approximately 0.2 logMAR. The additional deficit in the median acuity of children with DSN was a further 0.2 logMAR. Felius et al.[5] also reported a VA deficit of 0.4 logMAR in children with DSN compared to typical norms and suggested that nystagmus is not the sole cause of poor vision in children with DSN. The current study confirms this, as children with DS and no nystagmus appear to have VA on par with neurotypical children with nystagmus. The difference in VA between neurotypical children and those with DS is not yet fully explained.

Self et al.[26] emphasize the importance of a full clinical examination (possibly including electrophysiology) to differentiate between idiopathic IN and nystagmus with an underlying cause. Since children with DS presumably also carry a risk for an underlying cause for their nystagmus, it is clear that a full investigation is called for. Our small sample (nine children) suggests that some ophthalmologists might assume that an additional category of nystagmus exclusive to DS exists, and no other cause of the condition can apply to children with DS.

The VA deficit of children with IN has been associated with the onset of binocular visual deprivation and the change in the nystagmus waveform.[27] Typically developing children with IN usually have a triangular waveform during infancy, which transforms into pendular and then to jerk waveforms.[28–30] This change in the waveform type results in, or perhaps is a consequence of, changes in the foveation strategy, which has an impact on the visual performance in IN.[27] Reinecke et al.[28] speculate that children with IN adopt new foveation strategies as they try to focus on the objects that interest them, hence producing the observed change in the nystagmus waveform type. Therefore, the onset of change from pendular to jerk nystagmus is crucial to the visual development of children with nystagmus. Longitudinal data from infancy were available for only four children with DSN, so it is difficult to estimate the timing of the onset of nystagmus for this group of children. Longitudinal eye movement recording data would be needed to determine any changes in the nystagmus waveforms.

One of the limitations of the current study is that VA was measured with current eyeglasses and not necessarily with the children's best correction, as testing acuity while wearing a trial frame can distract the children, perhaps affecting their performance during the test. This would apply, of course, to both groups. Although there could have been some change in refractive error since their last clinical correction, this is likely to be small because the children were seen at regular intervals. The visual acuity of the typically developing children with INS in the study by Fu et al.[3] was also measured using "habitual optical correction" as well as with age-appropriate tests. Children with DS have been reported to have poorer VA than the expected norm,[6,8–10] despite refractive errors being corrected. None of the reported studies measured acuity with the children's best correction. In the current study, more than 85% of VA in DSN fell below the 95% confidence limits of typically developing children with INS and children in the DS group.

Neurotypical children with IN have been shown to have unconventional refractive development.[4] Refractive error of children with DSN differs significantly from that of children with DS who do not have nystagmus over the age of 1 year.

Although both groups of children were hypermetropic since early infancy, children with DSN were more likely to be myopic compared to the DS group and showed a larger variability in refractive error. Previous studies of children with DS have shown an association between congenital heart defect and nystagmus,[31,32] as well as between congenital heart defect and myopia.[31] Therefore, it may not be surprising that children with DSN are more myopic than those who do not have nystagmus.

Astigmatism is common in children with DS[21,22] and, in this study, equally common in children with DSN. Weiss et al.[33] reported a prevalence of 66% in their small cohort of 18 children with DSN. The pattern of the development of astigmatism in children with DS has been reported to differ significantly from typically developing children with no ocular conditions.[21,22] In both DS and DSN groups, significant astigmatism increased with age, as expected. Children with DS present with WTR astigmatism from an early age, which then develops into oblique astigmatism later during their childhood,[22] and this pattern was also observed in the group of children with DSN. Weiss et al.[33] also recorded WTR and oblique astigmatism in their group of children with DSN (one child's data had no axis recorded). On the other hand, neurotypical children with IIN have been reported to have WTR astigmatism throughout their childhood.[23,34] Our analysis showed that nystagmus had no effect on the prevalence or type of astigmatism in children with DS.

CONCLUSIONS

The results of this study have shown that children with DSN have poorer VA than children with DS, in a similar manner to neurotypical children with nystagmus having poorer acuity than children without nystagmus. However, it is quite clear that there is a significant baseline deficit in acuity attributable to DS and an additional deficit associated with nystagmus. There was no difference in astigmatism between children with DSN and DS, which contrasts with typically developing children who have a higher prevalence of astigmatism compared to their counterparts without nystagmus. Finally, the findings of this study show that myopia is associated with nystagmus in children with DS.

It is clear that children with DSN have an increased visual impairment. It is essential, therefore, that nystagmus in DS receives the same level of attention as it does among typical children (i.e., with definitive diagnosis, appropriate advice for parents, and targeted educational support for children).

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