Response to correction of refractive errors and hypoaccommodation in children with congenital Zika syndrome

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PURPOSE To describe the immediate response to correction of refractive errors and hypoaccommodation in children with congenital Zika syndrome (CZS).

METHODS Children born between May and December 2015 with a confirmed diagnosis of CZS and enrolled in a multidisciplinary early intervention program were included in this study. All children received a comprehensive ophthalmic examination, including dynamic retinoscopy and cycloplegic refraction. Children were prescribed their full correction if they met the criteria for refractive error, and additional plus 3.00 overcorrection for strabismus, accommodative dysfunction, and/or low vision. Monocular and binocular visual responses to Lea Grating Test at 30 cm, with and without eyeglasses, were measured on day 1 of glasses wear.

RESULTS A total of 60 children were evaluated (mean age at evaluation, 11.5 ± 1.1 months; range, 9.0-16.0 months). Lea Grating Test responses were abnormal in all children prior to spectacle correction. Hypoaccommodation was present in 17 of 21 children (81%). Overcorrection was prescribed for all children. Visual responses were subnormal even with glasses use; however, immediate improvement in binocular vision was found in 37 children (62%) and in 74 of 119 eyes (62.2%). For the monocular visual improvement, 27 of 115 eyes (23.5%) had structural abnormalities, and 44 of 115 eyes (38.3%) were structurally normal. There was a statistical difference between the cycloplegic refraction of the children in August and in November, including emmetropia ($P = 0.001$), hyperopia ($P = 0.000$), myopia ($P = 0.007$), and astigmatism ($P = 0.004$).

CONCLUSIONS Eyeglasses can improve visual acuity in children with CZS. Significant changes in their refractive status over time requires periodic updates. (J AAPOS 2017;21:480-484)

The Zika virus (ZIKV) gained worldwide recognition after October 2015 when Brazil reported an increase in the prevalence of babies born with microcephaly, later proved to be associated with the ZIKV infection during pregnancy.[1,2] The Centers for Disease Control and Prevention (CDC) recognize the term *congenital Zika syndrome* (CZS) to define the broad spectrum of congenital anomalies caused by the vertical transmission of ZIKV and including these five features: severe microcephaly, brain anomalies, neurological impairment, congenital muscle contractures, and ocular findings.[3] The neurological abnormalities include fetal brain disruption sequence, with partially collapsed skull and redundant scalp skin, and other brain anomalies, such as subcortical calcifications, cortical thinning, and ventriculomegaly. Babies with CZS may also present with hypertonia/spasticity, irritability, and epilepsy.[3,4]

The ZIKV manifests a selective tropism for the posterior segment of the eye, including the retina and the optic nerve.[5-10] Recognizable patterns of focal pigment mottling and chorioretinal scarring generally observed in the macular region are considered hallmarks of the disease.[6-8] Ventura and colleagues recently reported that even those children without ocular findings present with visual impairment, suggesting that the brain damage in CZS is a major cause of the visual impairment.[11] This study also showed that 36% of babies with CZS had hypoaccommodation, and 59% had significant refractive errors.

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The role of intervention using glasses and other ophthalmic interventions has not yet been described. The broad spectrum of neurological manifestations as well as the range of ocular clinical presentations may affect the response to optical treatment for children with CZS.

Although other viral infections are associated with neurologic and eye disorders, ZIKV must be considered a distinct clinical entity, with specific adverse outcomes and complications.[3,12,13] Because of the scarcity of data on the short- and long-term effects of congenital ZIKV infection on the overall development in babies, studies addressing these aspects are relevant for public health. The current study aimed to evaluate the immediate visual response to correction of refractive errors, accommodative dysfunction and/or low vision with glasses, in children with CZS.

Subjects and Methods

This cross-sectional study was approved by the Altino Ventura Foundation Institutional Review Board and followed the tenets of the Declaration of Helsinki. Parents or caregivers of subjects provided written informed consent before their children were enrolled.

Children born between May and December 2015 with confirmed diagnosis of CZS and with the diagnosis of significant refractive error, anisometropia, strabismus with a refractive etiology, accommodation deficit, and/or atypical visual responses that according to the study protocol had glasses prescribed in a prior evaluation were included. The diagnosis of CZS was based on positive immunoglobulin M antibody capture enzyme-linked immunosorbent assay for ZIKV in the cerebrospinal fluid, as described in previous publications.[7] Infants with positive serology for other congenital infections, such as toxoplasmosis, rubella, cytomegalovirus, syphilis, herpes, and human immunodeficiency virus, were excluded from the study. All children recruited were taking part in a standardized multidisciplinary early intervention protocol at the Altino Ventura Foundation in Brazil.

Ophthalmologic and Visual Function Assessment

Pediatric ophthalmologists using a standardized protocol performed comprehensive ophthalmic examination in August 2016 including dynamic retinoscopy, cycloplegic refraction, indirect ophthalmoscopy, and retinal imaging. Dynamic retinoscopy was based on the method described by Hunter.[14] A near fixation target was held 60 cm from the examiner's retinoscope and brought to a distance of 30 cm then to 10 cm. If there was no fixation at 30 cm, the child was considered untestable. The retinoscopic reflex was noted. If with motion and fixation were noted at 60 cm, the object was brought to 30 cm, observed, and accommodation was determined using the retinoscope. If there was no change, the test object was brought closer to 10 cm, neutralization was a positive response. Static cycloplegic refraction was performed in all infants 30 minutes after instillation of 0.5% cyclopentolate hydrochloride and tropicamide 1% diluted 1:1 with artificial tears. One drop with punctal occlusion in each eye was placed to minimize potential systemic side effects in these medically fragile infants.

Bilateral retinal imaging was performed in all babies after pupil dilatation using the RetCam wide-angle digital fundus camera (Clarity Medical Systems, Pleasanton, CA). The infants' retinal and optic nerve characteristics at baseline have been reported previously and are summarized here.[5,6] For this study, fundus examination was considered performed when assessed in both eyes by both indirect ophthalmoscopy and RetCam. Glasses were prescribed by a protocol established prior to the evaluations. Significant refractive error, strabismus (with refractive etiology), accommodative dysfunction and/or low vision were indicators for glasses prescription. Significant refractive error was defined as spherical correction of $> +3$ D or < -1 D and/or cylindrical correction of >1 D and anisometropia of >1 D. In children with accommodative dysfunction, lack of visual attention, or low vision, a $+3$ D was prescribed over cycloplegic refraction for magnification in the focal plane of the infant's communication distance of around 33 cm.

Children received the eyeglasses 90 days after the initial evaluation and were reassessed on the same day. The testing delay was due to challenging socioeconomic conditions of patients' families; most could not afford to buy the eyeglasses, and the rehabilitation center raised funds to provide eyeglasses at no cost to these families.

This evaluation included light perception, pupil reaction, ocular alignment at near (using Krimsky test), and evaluation for nystagmus. An ophthalmologist experienced in pediatric neurologic vision impairment who was masked to the ocular pathology and refractive status measured responses to the Lea Gratings Test (Good-Lite, Elgin, IL) at 30 cm, first without, then with the glasses prescription in place. The test was performed in standard testing conditions and room illumination, free from distractions. Visual responses were measured both binocularly and monocularly. Results were recorded as the spatial frequency of the finest grating to which the infant showed a consistent fixation response. Testing was kept within the child's sphere of vision, which in all cases was 30 cm.[15]

After vision response assessment, the cycloplegic refraction in all infants was repeated to determine whether there was change in the 90-day interim. In cases of significant refractive change the prescription was updated.

Individualized verbal and written instruction was given to each family regarding the infant's ocular findings, the reason for the glasses prescription, and treatment of amblyopia with eyeglasses and patching if indicated at the time of glasses prescription. Glasses with a $+3$ D overcorrection incorporated were only to be used for near activity (within 30 cm) while the child was under supervision.

Refractive status was defined in spherical equivalent (SE), calculated as the numerical sum of the sphere and half of the cylinder. The negative cylinder method was used. Emmetropia was defined as SE > -0.50 D or $< +2.00$ D, myopia as SE of ≥ -0.50 D, and hyperopia as SE of $\geq +2.00$. The prevalence of astigmatism was assessed at two levels: ≤ -0.75 to > -2.00 cylinder, and ≤ -2.00 cylinder in the greatest meridian.

Table 1. Refractive errors in August and November 2016 in 60 infants with serologic evidence of CZV infection

Cycloplegic refraction[a]	No. eyes (%)[b] August	November
Emmetropia, SE (>−0.50 D or < +2.00 D)	52 (43.7)	55 (46.6)
Hyperopia, SE (≥+2.00)	46 (38.7)	43 (36.4)
Myopia, SE (≤−0.50 D)	21 (17.6)	20 (16.9)
Astigmatism[c]		
≤ −0.75 D to > −2.00 D	44 (37.0)	55 (46.6)
≤ −2.00 D	19 (16.0)	14 (11.9)

D, diopter; *SE*, spherical equivalent.
[a]Anisometropia was present in 11/57 eyes (19.3%) in August and 12/58 (20.7%) in November.
[b]In eyes for which values were known: 119 eyes of 60 patients in August and 118 eyes of 60 patients in November.
[c]Interocular difference of ≥1.00 D (spherical equivalent).

Anisometropia was defined as difference of SE of 1.00 D or more between the two eyes in the greatest (most discrepant) meridian.[16]

Statistical Analysis

Statistical analysis was performed (version 16.0; SPSS Inc, Chicago, IL). Continuous data were expressed as mean with standard deviation and range of values. Statistical analyses were performed using the Wilcoxon test, with a significance level set at or below 5%.

Results

A total of 60 children with CZS were included. Mean age at evaluation was 11.5 ± 1.1 months (range, 9.0-16 months). Microcephaly was present in 51 children (85%). See eTable 1.

Dynamic retinoscopy proved practicable in 21 of the 60 children (35%). Hypo-accommodation was present in 17 of 21 children (81%). Cycloplegic refractive errors were assessed in all 60 children, 119 of 120 eyes (99.2%). Significant refractive error meriting spectacle prescription was found in 52 of 119 eyes (43.7%) in 29 children (48%). Lea Gratings test responses were impaired in all children. Full cycloplegic correction with a +3 D overcorrection (for magnification and optimal clarity at 33 cm) was prescribed for all cases, based on assessments made in August 2016 (eTable 1 and Table 1).

During assessments in November 2016, all children had light perception. The direct (afferent) pupillary reflex was abnormal in 1 child (2%). Unilateral cataract, microcornea, and microphthalmia were observed in 1 case (2%). Without spectacles, all children (100%) demonstrated binocular and monocular visual responses below nomal for age and published standards.[15] Of 60 children, 55 (92%) had strabismus: exotropia in 28 children (51%), with a mean deviation of $27.4^{\Delta} \pm 11.5^{\Delta}$ (range, 10^{Δ} to 45^{Δ}), and esotropia in 24 (44%), with a mean deviation of $31.2^{\Delta} \pm 10.0^{\Delta}$ (range, 10^{Δ}-50^{Δ}). Nystagmus was present in 28 of 60 children (47%).

Cycloplegic refractive errors were assessed in all 60 children, 119 of 120 eyes (99.2%) There was statistical significant difference of refractive errors status comparing the data of cycloplegic refraction of the children in August with November assessments concerning emmetropia ($P = 0.001$), hyperopia ($P = 0.000$), myopia ($P = 0.007$), and astigmatism of ≤ −2.00 D ($P = 0.004$). See Table 2.

Dilated fundus examination was possible in 58 children, or 115 of 120 eyes (95.8%). Two children (3%) were excluded due to poor fundus evaluation; in another case fundus examination was not possible in one eye due to dense monocular cataract. Structural ocular findings (retina and/or optic nerve) were detected in 48 of 115 eyes (41.7%) of 30 infants, of whom 18 (60%) were affected binocularly and 12 (40%) monocularly. Retinal abnormalities were identified in 35 of 115 eyes (30.4%) in 22 of 58 infants (40%). Optic nerve abnormalities were seen in 26 of 115 eyes (22.6%) in 16 of 58 patients (27.6%), and retinal vessel attenuation in 2 of 115 eyes (1.7%), both eyes of the same patient (Table 3).

Lea Gratings Test responses, both monocular and binocular, with and without eyeglasses use, was testable in 60 children (119 eyes). Lea Grating Test binocular responses improved with glasses in 37 children (62%). In children with improved binocular responses, visual responses improved in 74 of 119 eyes (62.2%): 33 right eyes and 42 left eyes. In 23 of 60 children (38%), no immediate improvement in binocular vision was seen with glasses. However, in this no-change group, 6 right eyes and 10 left eyes improved monocularly. Seven children had no response to the gratings without glasses but manifested measurable vision with glasses. Optic nerve and/or retinal pathology was present in 27/115 eyes (23.5%) that showed monocular visual response improvement with glasses (Table 4).

Discussion

The current study evaluated the effectiveness of immediate correction of refractive error and management of poor accommodation in 60 children with CZS. Visual acuity responses to treatment were measured using the Lea Grating test at the distance of 30 cm, which is considered an objective and accurate test for quantifying visual responses to gratings in preliterate children.[15]

Although funduscopic change was detected in 42% of children, visual impairment was found in all (100%). Children with structural ocular abnormalities, such as retinal and/or optic nerve findings, presented with grating responses consistent with the severity of the findings. Nevertheless, children with no evidence of structural abnormalities presented with subnormal visual responses. Similar findings were described by our group previously and suggests a neurological basis for the visual impairment.[11] This hypothesis is also supported by Van der Pol and colleagues,[17] who demonstrated in a mice model

Table 2. Statistical difference between cycloplegic refraction in August and November 2016 in 60 infants with serologic evidence of CZS infection

Cycloplegic refraction[a]	D, mean ± SD (range)		*P* value[c]
	August[b]	November	
Emmetropia, SE (>−0.50 D or < +2.00 D)	+0.63 ± 0.49 (−0.25 to +1.50)	+0.87 ± 0.49 (−0.25 to +1.75)	0.001
Hyperopia, SE (≥+2.00)	+3.27 ± 1.04 (+2.00 to +6.50)	+3.05 ± 0.78 (+2.00 to +5.00)	0.000
Myopia, SE (≤−0.50 D)	−1.48 ± 1.28 (−5.25 to −0.50)	−1.49 ± 1.01 (−4.00 to −0.50)	0.007
Astigmatism			
≤ −0.75 D to > −2.00 D	−1.13 ± 0.22 (−1.50 to −1.00)	−1.10 ± 0.20 (−1.50 to −1.00)	0.392
≤ −2.00 D	−2.47 ± 0.68 (−4.00 to −2.00)	−2.18 ± 0.25 (−2.50 to −2.00)	0.004

D, diopter; *SE*, spherical equivalent.
[a]In eyes for which values were known: 119 eyes of 60 patients in August and 118 eyes of 60 patients in November.
[b]Prescription of eye glasses were based on refraction of August.
[c]Wilcoxon test.

Table 3. Funduscopic findings of infants with serologic evidence of congenital Zika virus infection (n = 58 infants, 115 eyes)[a]

Characteristic	Eyes, no. (%) n = 115
Retina findings	35 (30.4)
Pigment mottling	17 (14.8)
Chorioretinal scars	26 (22.6)
Optic Nerve findings	26 (22.6)
Hypoplasia	7 (6.1)
Increased cup:disk ratio	19 (16.5)
Optic nerve pallor	9 (7.8)
Vessel attenuation	2 (1.7)

[a]Funduscopy was considered performed when assessed by both indirect ophthalmoscopy and RetCam imaging (Clarity Medical Systems, Pleasanton, CA).

Table 4. Lea Gratings test monocular response with use of glasses with cycloplegic refraction and +3 D overcorrection, according to presence of funduscopic findings in 115 eyes of 58 infants with CZV[a]

Findings	Optic nerve and/or retinal pathology, no. eyes (%)	No ocular pathology, no. eyes (%)	Total no. eyes (%)
Improved	27 (23.5)	44 (38.3)	71 (61.7)
Not improved	21 (18.3.6)	23 (20.0)	44 (38.3)
Total	48 (41.7)	67 (58.3)	115 (100.0)

[a]Funduscopy was considered performed when assessed by both indirect ophthalmoscopy and RetCam imaging.

experiment that CZS may affect the anterior parts of the visual system (eye globe and visual pathways, anterior to the lateral geniculate body), and also parts of the posterior visual processing areas of the brain.

Infants with neurological visual impairment may have limited power of accommodation, poor visual acuity, high refractive errors, and strabismus.[18-20] The prevalence of strabismus in this cohort of children with CZS was 92%; similarly high rates have been observed in previous cohort studies of children with neurological conditions.[21-23] Jacobson and colleagues[21] studied 48 children with periventricular leukomalacia and detected strabismus in 91.7% cases, 50.9% exotropia, and 43.6% esotropia. In their study of 48 children with cerebral palsy, Erkkilä and colleagues[22] reported that 64.8% presented with esotropia. In addition to strabismus, nystagmus was observed in 47% of the cases in our sample, comparable to the 33% reported by Guzzetta and colleagues[23] in their study of children with brain lesions. These ocular motility findings underscore the need for early and intensive treatment to prevent amblyopia.[18]

The most common refractive errors found in our sample of children with CZS in August and November were hyperopia (39% and 36%, resp.) and astigmatism of ≤ −0.75 to > −2.00 CD (37% and 46.6%, resp.). The studied sample presented statistically significant change in their refractive status over 3 months (emmetropia, hyperopia, myopia, and astigmatism ≤ −2.00 CD. The significant change in the refractive error suggests that these children must be assessed routinely and periodically.

As hypothesized by McClelland and colleagues,[20] in children with neurologic impairment typical accommodation may not develop normally. Poor accommodation can cause difficulty with near vision and negatively affect the child's development.[23,24] For these cases, the prescription of +3 D overcorrected spectacles for near appears to facilitate the child's focus within their immediate sphere of interest (30 cm); however, this supposition is corroborated only by anecdotal and clinical reports. In our study, hypo-accommodation was detected in 81% of the 21 children with CZS that could have accommodation assessed, of whom 58% had improvement in the binocular responses to the Lea Gratings Test at the time of the examination by wearing glasses with +3 D greater than cycloplegic refraction determined at a distance of 30 cm.

In the current study 62% of the children prescribed glasses had immediate improvement in the binocular responses to the Lea Gratings Test at 30 cm. When analyzing the monocular improvement, 24% of structurally affected eyes improved with treatment compared to 38% of the apparently unaffected eyes. Though preliminary, this result suggests a positive response to early treatment in children with CZS.

In 3% of children responses to gratings were less in the binocular condition. Fatigue from many factors, including

multiple testing may have contributed to the findings in all categories. Visual response and refraction in children with neurologic visual impairment must be followed closely; as the sphere of visual attention increases from 30 cm, the use of bifocals for poor accommodation should be considered as an option instead of single-vision glasses, overplussed by +3 D glasses for 30 cm. Additionally, assessments for children with CZS should include a visual function testing battery, because visual responses to gratings do not necessarily indicate useful visual function.[16]

This study has several limitations, one of the most important being the delay in starting the treatment. Due to the difficulty with travel, expenses, and the actual making of the glasses in this social setting, the refractions were 90 days old when the child first received the glasses. The delay in use of updated prescriptions in infants <1 year of age may have affected the visual response, and in this case, there was a statistically significant change in their refractive status. Another limitation is the variations in attention that were common in this cohort; dynamic retinoscopy to measure accommodative effort was not possible in most children. In addition, measurement of accommodative and refractive errors in eyes with central retinal lesions and abnormal motor functions was challenging. Finally, compliance with glasses wear was not considered, because patients were receiving their glasses on the day of the second assessment; this topic should be assessed in future studies with short and long-term follow-up.

References

1. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med 2016;374:1552-63.
2. Calvet G, Aguiar RS, Melo AS, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect Dis 2016;16:653-60.
3. Moore CA, Staples JE, Dobyns WB, et al. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. JAMA Pediatr 2017;171:288-95.
4. de Fatima Vasco Aragao M, van der Linden V, Brainer-Lima AM, et al. Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study. BMJ 2016;353:i1901.
5. Ventura CV, Maia M, Ventura BV, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. Arq Bras Oftalmol 2016;79:1-3.
6. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed zika virus congenital infection in Salvador. Brazil. JAMA Ophthalmol 2016;134:529-35.
7. Ventura CV, Maia M, Travassos SB, et al. Risk factors associated with the ophthalmoscopic findings identified in infants with presumed Zika virus congenital infection. JAMA Ophthalmol 2016;134:912-18.
8. Miranda HA 2nd, Costa MC, Frazão MA, Simão N, Franchischini S, Moshfeghi DM. Expanded spectrum of congenital ocular findings in microcephaly with presumed Zika infection. Ophthalmology 2016;123:1788-94.
9. de Paula Freitas B, Ko AI, Khouri R, et al. Glaucoma and congenital Zika syndrome. Ophthalmology 2017;124:407-8.
10. Ventura CV, Ventura LO, Bravo-Filho V, et al. Optical coherence tomography of retinal lesions in infants with congenital Zika syndrome. JAMA Ophthalmol 2016;134:1420-27.
11. Ventura LO, Ventura CV, Lawrence L, et al. Visual impairment in children with congenital Zika syndrome. J AAPOS 2017;21:295-299.e2.
12. Corona-Rivera JR, Corona-Rivera E, Romero-Velarde E, Hernández-Rocha J, Bobadilla-Morales L, Corona-Rivera A. Report and review of the fetal brain disruption sequence. Eur J Pediatr 2001;160:664-7.
13. Bale JF Jr. Fetal infections and brain development. Clin Perinatol 2009;36:639-53.
14. Hunter DG. Dynamic retinoscopy: the missing data. Surv Ophthalmol 2001;46:269-74.
15. Mody KH, Kothari MT, Sil A, Doshi P, Walinjkar JA, Chatterjee D. Comparison of lea gratings with cardiff acuity cards for vision testing of preverbal children. Indian J Ophthalmol 2012;60:541-3.
16. Salomão SR, Cinoto RW, Berezovsky A, et al. Prevalence and causes of visual impairment in low-middle income school children in São Paulo, Brazil. Invest Ophthalmol Vis Sci 2008;49:4308-13.
17. Van der Pol AN, Mao G, Yang Y, Ornaghi S, Davis JN. Zika virus targeting in the developing brain. J Neurosci 2017;37:2161-75.
18. Hyvärinen L, Walthes R, Jacob N, Chaplin KN, Leonhardt M. Current understanding of what infants see. Curr Ophthalmol Rep 2014;2:142-9.
19. Good WV, Jan JE, Burden SK, Skoczenski A, Candy R. Recent advances in cortical visual impairment. Dev Med Child Neurol 2001;43:56-60.
20. McClelland JF, Parkes J, Hill J, Jackson AJ, Saunders KJ. Accommodative dysfunction in children with cerebral palsy: a population-based study. Invest Ophthalmol Vis Sci 2006;47:1824-30.
21. Jacobson L, Ygge J, Flodmark O, Ek U. Visual and perceptual characteristics, ocular motility and strabismus in children with periventricular leukomalacia. Strabismus 2002;10:179-83.
22. Erkkilä H, Lindberg L, Kallio AK. Strabismus in children with cerebral palsy. Acta Ophthalmol Scand 1996;74:636-8.
23. Guzzetta A, Mercuri E, Cioni G. Visual disorders in children with brain lesions: 2. Visual impairment associated with cerebral palsy. Eur J Paediatr Neurol 2001;5:115-19.
24. Dale N, Sonksen P. Developmental outcome, including setback, in young children with severe visual impairment. Dev Med Child Neurol 2002;44:613-22.

eTable 1. Demographic and clinical features of 60 infants with serologic evidence of congenital Zika syndrome (CZS)

Characteristic	Study group
Sex, no. (%)	
Female	36 (60.0)
Male	24 (40.0)
Age at examination, mos, mean ± SD (range)	11.5 ± 1.1 (9.0-16.0)
Microcephaly,[a] no. (%)	51/60 (85.0)
Mild[b]	14/51 (27.5)
Severe[b]	37/51 (72.5)
Strabismus, no. (%)[b,c]	55/60 (91.7)
Exotropia	28/55 (50.9)
Esotropia	24/55 (43.6)
Dyskinetic	1/55 (1.8)
Nystagmus[c]	28/60 (46.7)

SD, standard deviation.
[a]Newborn head circumference measurements 2 (mild) or 3 (severe) standard deviations below the mean for gestational age and sex.
[b]Number of children for whom the values were known if <60.
[c]Clinical features of November 2016 assessments.