

Strabismus in Children of Birth Weight Less Than 1701 g

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Objective: To prospectively study infants of birth weight less than 1701 g in the East Midlands of England in the mid 1980s at 10 to 12 years of age to determine the incidence and risk factors for strabismus in children born preterm.

Methods: Low-birth-weight children (n=572) who had been examined during the neonatal period were invited for a follow-up visit at age 10 to 12 years; 169 eleven-year-old schoolchildren born at full term were also recruited (the school cohort).

Results: Of the original 572 children, 293 consented to further examination. There was no significant difference between children who were examined and those who were not in terms of birth weight, gestational age, retinopathy of prematurity, and cranial ultrasound abnormalities. Compared with the school cohort (n=5 [3.0%];

95% confidence interval, 1.0%-9.1%), the low-birth-weight cohort had a significant increase in the prevalence of strabismus (n=59 [20.1%]; 95% confidence interval, 15.9%-25.0%; $P<.001$). Compared with published data, there was a relative increase in the occurrence of exotropia in the low-birth-weight study cohort. Multivariate analysis, by backward logistic regression, indicated that retinopathy of prematurity, birth weight, cerebral palsy, anisometropia, and refractive error were all independently associated with strabismus ($P<.05$).

Conclusions: The results of this study confirm the increased prevalence of strabismus in a low-birth-weight population. This study also provides more detailed information on risk factors and strabismus types.

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THE INCIDENCE of strabismus is increased in children of low birth weight compared with those who were born at full term.¹⁻¹¹

Despite this research, several issues have not been addressed. First, no study has provided a complete breakdown of the strabismus types, which is pertinent when considering pathogenesis. Because the different types of strabismus vary in etiology, an analysis that includes all cases of strabismus may not identify new risk factors for certain types of strabismus in the low-birth-weight population. Second, although it is known that neonatal factors such as retinopathy of prematurity (ROP), low birth weight, and neurologic abnormalities are associated with strabismus, these factors are all closely interrelated. Therefore, multivariate analysis is required to determine which factors are independently associated with strabismus. This statistical method has only been used in 2 studies,^{1,3} but in one³ the diagnosis of

ROP was made retrospectively. In both of these studies, the age at testing for strabismus was 4 years or younger, before the age by which all strabismus might have developed.

Herein we present findings from long-term follow-up (10-12 years) of infants previously studied prospectively who were born in the East Midlands, England.^{12,13} These infants underwent frequent ophthalmic examinations during the first 12 weeks after birth, with a final examination at corrected age 6 months, which included an assessment of ocular motility.¹⁴

The aims of this follow-up study at 10 to 12 years were to determine the prevalence and types of strabismus in this low-birth-weight cohort and to investigate the relationship between the neonatal ophthalmic findings and the neonatal factors (including birth weight, gestational age, and cranial ultrasound findings) and subsequent strabismus. These findings were compared with those from a cohort of schoolchildren born at full term.

SUBJECTS AND METHODS

SUBJECTS

Between July 1, 1985, and May 31 1987, a prospective study of ROP was undertaken in the 5 neonatal units serving the East Midlands of England (Leicestershire, Nottinghamshire, and the Southern Derbyshire Health Authorities). All infants who survived 3 weeks (n=505), had birth weights of less than 1701 g, and were born to mothers residing in this geographically defined area who were enrolled in the study. In addition, 67 infants born to mothers residing outside the East Midlands but who were transferred to and cared for in 1 of the aforementioned 5 neonatal intensive care units were also assessed. All 572 infants had weekly ophthalmic examinations 3 to 12 weeks after birth,¹² with ROP classified according to the international classification of ROP.¹⁵ In addition, 458 infants had an additional examination at corrected age 6 months,¹⁴ which included an assessment of ocular motility.

TRACING THE INDEX CHILDREN

Extensive efforts were made to trace and gain consent from the children from the original cohort, as described elsewhere.¹⁶ Follow-up involved sending up to 3 letters to each child, telephone contact if possible, and an appeal on local television and radio to encourage parents to consent. Many children had moved during the 10 years since the last contact, so the Office of National Statistics was contacted to identify the child's health authority. From the health authority, the details of the child's general practitioner were obtained, and he or she was then contacted for the child's current address.

SCHOOL COHORT

A group of 169 children born at term was assessed because there are no published data on the prevalence of strabismus and other visual functions (measured as part of this study, results to be published elsewhere) in children aged 10 to 12 years.

A total of 169 of the 175 children who consented to the examination were tested under identical conditions as the study cohort. Six children were not tested because they were absent from school owing to illness. We were denied access to confidential information on the children who declined to participate. Ten primary schools in one city (Nottingham) took part in the control study, in which every child aged 10 to 11 years was given a letter for their parents asking for consent to an ophthalmic examination. The schools were selected to reflect the social class mix of the areas from which the study cohort was drawn.

OPHTHALMIC INVESTIGATIONS

To minimize disruption, the children were tested in a mobile vision laboratory at home or at school. The testing was carried out by 2 orthoptists (including A.R.O.). Strabismus was detected and classified using a cover test, a prism cover test, and an assessment of ocular movements. Stereopsis was measured using the TNO test. Cycloplegic refraction was measured using an autorefractor (Retinomax K-plus; Nikon Corp, Melville, NY) after instillation of 1% cyclopentolate.

STATISTICAL METHODS

All analysis was performed using a statistical software package (SPSS, Version 8; SPSS Inc, Chicago, Ill). For comparison of categorical variables, χ^2 or Fisher exact tests were used. The only continuous data reported are not normally distributed. Therefore, for comparison between groups, a Mann-Whitney test was used. For multivariate analysis, backward logistic regression was used, at the 10% level of significance.

Permission for this study was obtained from the Nottingham University Hospital Ethics Committee.

RESULTS

From the original cohort of 572 low-birth-weight infants (<1701 g), 33 died after the original study was completed, 7 moved outside the United Kingdom, and 23 could not be traced. At the general practitioner's request, the families of 2 children were not contacted. This reduced the cohort to 507 children. There were 17 refusals and 197 non-responders despite repeated reminders, leaving 293 individuals who consented. From this low-birth-weight cohort, 39 children were born to mothers who resided outside the East Midlands. Therefore, the geographically defined cohort consisted of 254 children.

STRABISMUS

The overall prevalence of strabismus in the entire low-birth-weight cohort was 20.1% (n=59; 95% confidence interval, 15.9%-25.0%) and in the school cohort was 3.0% (n=5; 95% confidence interval, 1.0%-9.1%; $P<.001$). For the geographically defined study cohort, this prevalence was 19.3% (n=49; 95% confidence interval, 14.5%-25.5%) (**Table 1**).

Strabismus types differed between the low-birth-weight and school cohorts. However, the low number of cases in the latter group precluded direct comparison; thus, published data were used. Kvarnstrom et al¹⁹ presented the data from a retrospective study of community visual screening of 3126 children aged 10 years and younger. Four hundred thirteen children were referred to the eye clinic, of whom 84 (2.7%) had strabismus. The subdivision into esotropia, exotropia, microtropia, and symptomatic phorias precludes direct comparison with this and other studies. Therefore, the studies of Graham¹⁷ (4784 children aged 5 years) and Stidwill¹⁸ (60000 adults) were used for comparison of types of strabismus (no birth weight data are available for either study, but low-birth-weight infants represent 7% of all births in the United Kingdom). Table 1 gives the prevalence of strabismus types for the low-birth-weight cohort and the geographically defined cohort and from the published data. Graham¹⁷ reported the re-

Table 1. Prevalence of Strabismus Types in the Study Cohort and in Published Data*

	Patients With Strabismus, No. (%)			
	Geographically Defined Cohort (n = 49/254)	LBW Cohort (n = 59/293)	Graham ¹⁷ (n = 339/4784)†	Stidwell ¹⁸ (n = 3075/60 000)‡
Esotropia				
Fully accommodative esotropia	1 (2.0)	1 (1.7)	9.4	313 (10.2)
Convergence excess esotropia (high or low AC:A ratio)	1 (2.0)	3 (5.1)	5.6	36 (1.2)
Constant esotropia with accommodative element (angle greater on near fixation)	6 (12.2)	8 (13.6)	21.5	840 (27.3)
Constant esotropia without accommodative element (angle independent of fixation distance)	13 (26.5)	16 (27.1)	14.5	373 (12.1)
Subtotal	21 (42.9)	28 (47.5)	51.0	1562 (50.8)
Exotropia				
Intermittent distance exotropia (manifest only on distance fixation)	4 (8.2)	4 (6.8)	Unknown	Unknown
Intermittent near exotropia (manifest only on near fixation)	6 (12.2)	6 (10.2)	Unknown	Unknown
Intermittent nonspecific exotropia (independent of fixation distance)	5 (10.2)	6 (10.2)	Unknown	Unknown
Constant exotropia	10 (20.4)	12 (20.3)	1.5	Unknown
Subtotal	25 (51.0)	28 (47.5)	10.9	464 (15.1)
Vertical deviation	1 (2.0)	1 (1.7)	Unknown	Unknown
Manifest strabismus—other	2 (4.1)	2 (3.4)	13.3	Unknown

*LBW indicates low-birth-weight; AC:A, accommodative convergence–accommodation.

†Patients were aged 5 years. Only percentages are given.

‡Patients were adults.

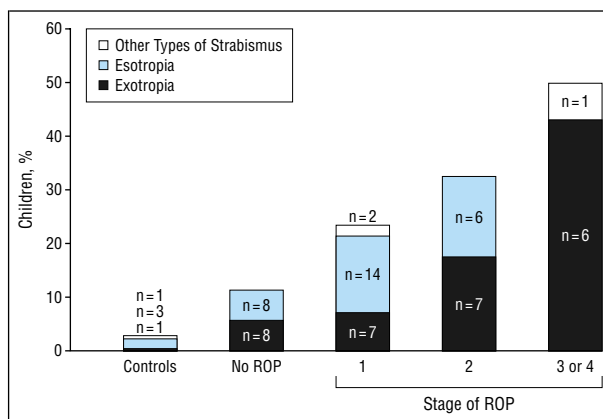
Table 2. Strabismus Types According to Age at Onset*

	Onset by 6 mo	Onset After 6 mo
Esotropia		
Fully accommodative esotropia	Unknown	1
Convergence excess esotropia	Unknown	3
Esotropia with accommodative element	Unknown	5
Esotropia without accommodative element	Unknown	12
Subtotal	10	21
Exotropia		
Intermittent distance exotropia	Unknown	3
Near exotropia	Unknown	5
Nonspecific intermittent exotropia	Unknown	4
Constant exotropia	Unknown	5
Subtotal	5	17
Other manifest strabismus, subtotal	2	1
Total	17	39

*In a number of cases, the diagnosis changed over time; therefore, the numbers do not match up with the data in Table 1. See Table 1 for definitions of strabismus types.

sults of all abnormal cover tests as percentages and did not differentiate phorias and tropias. Stidwell¹⁸ reported all types of binocular anomaly, such as convergence insufficiency, and because some individuals had more than 1 anomaly, the total exceeded 100% (Table 1). Thus, comparison between our study and published studies could only be made with respect to the ratio of esotropia-exotropia, which in our low-birth-weight study cohort was 1:1, in the cohort of Kvarnstrom et al¹⁹ was 2.6:1, in that of Graham was 4.9:1, and in that of Stidwell was 3.4:1.

A total of 263 children were evaluated at corrected age 6 months and at 10 to 12 years. Comparison be-



Strabismus by stage of retinopathy of prematurity (ROP).

tween these 2 periods is shown in **Table 2**. The 6-month data do not give precise details of the classification of strabismus. Therefore, it is not possible to determine whether the diagnosis has changed in the intervening period. Also, in cases in which onset was after 6 months, no data are available on surgical procedures that may have led to a change in diagnosis. However, all children with a manifest deviation at 6 months had a manifest deviation at 10 to 12 years.

The data were summarized into 2 groups—esotropia and exotropia (Table 2)—and strabismus type does not depend on age at onset ($P = .3$). Small numbers in the subgroups precluded direct comparison of the various types of esotropic and exotropic deviations.

One hundred fifty-two children (51.9%) in the low-birth-weight cohort had ROP in the neonatal period: 98 in stage 1, 40 in stage 2, and 14 in stage 3 or 4. The prevalence of strabismus increases with increasing severity of acute ROP stage ($\chi^2_{\text{trend}} = 18.70$; $P < .001$) (**Figure**). There

Table 3. Strabismus and the Relationship With Refractive Status*

>+3.00 DS	≥0.0 and <+3.00 DS	<0.0 and >-3.00 DS	≤-3.00 DS
15/27 (55.6)	26/199 (13.1)	10/53 (18.9)	8/14 (57.1)

*Data are given as number of children with strabismus/total number of children (percentage). DS indicates diopter spheres.

is a statistically significant difference between the groups with esotropia and exotropia and the prevalence of ROP (Fisher exact test, $P=.02$). No children with esotropia had severe ROP, whereas 23% of those with exotropia had severe ROP.

OCULAR MOVEMENTS

Ocular movements were assessed in the 9 positions of gaze. Muscle imbalances, that is, underactions and overactions or limitations, were categorized by the direction of action of the individual extraocular muscles and the extent of imbalance, which was graded as very slight, slight, slight +, moderate, and marked. Only muscle imbalances graded greater than slight were classed as an ocular motility disturbance. In the low-birth-weight cohort, 10 children had an ocular muscle imbalance compared with 1 child in the school cohort. Statistical analysis is inappropriate owing to the small numbers.

The most commonly occurring ocular muscle imbalance was overaction of the inferior oblique ($n=9$), which in 6 instances was associated with another type of manifest strabismus. This group includes identical twins with left monocular elevation deficiency.²⁰

STEREOPSIS

The median stereoacuity of the low-birth-weight and school cohorts was 60 seconds of arc (normal), but there was a statistically significant difference between the 2 cohorts ($P<.001$) (interquartile range: low-birth-weight cohort, 60-240; school cohort, 60-60). Because the TNO is limited to measuring a specific range of stereoacuties, some children are outside this scale. Therefore, to allow inclusion of all children in the analysis, those with no demonstrable stereoacuity on TNO were assigned an arbitrary code of 9999. After removal of all cases of strabismus from the analysis, there was no longer a statistical difference between the low-birth-weight and school cohorts ($P=.5$).

ABNORMALITIES IN NEUROIMAGING

Cranial ultrasound was performed during the neonatal period on 325 children in the original cohort,¹⁴ and these data are available for 174 of this low-birth-weight follow-up cohort. Because small numbers preclude analysis of the individual types of cranial ultrasound defect, the data were categorized into normal, mild anomalies (germinal layer or intraventricular hemorrhage, tran-

sient ventricular dilation, or persistent flare), and moderate or severe anomalies (parenchymal hemorrhage, persistent ventricular dilation, or cystic periventricular dilation). There was a significant association between ultrasound defects and strabismus ($\chi^2=21.3$; $P<.001$). The percentages of strabismus in each group were 19.8% (19/96) in the normal group, 19.7% (12/61) in those with mild abnormalities, and 70.6% (12/17) in those with severe abnormalities.

In the most severe group of each neurologic abnormality, there is a large increase in the prevalence of strabismus (cystic periventricular leukomalacia, 70%; parenchymal ventricular hemorrhage, 100%; and persistent ventricular dilation, 71%), suggesting that no single ultrasound finding is responsible for the increase in strabismus in this subgroup of the low-birth-weight population. Esotropia and exotropia occurred equally in association with cranial ultrasound abnormalities diagnosed in the neonatal period ($\chi^2=2.29$; $P=.3$).

REFRACTIVE ERROR

To compare refractive error with the presence of strabismus, the spherical equivalent, measured in diopter spheres (DS), was calculated, and the more ametropic eye was used. The prevalence of strabismus was statistically associated with refractive error ($\chi^2_3=39.2$; $P<.001$) (**Table 3**). Hypermetropia is frequently associated with strabismus, and because it has been shown that hypermetropia greater than 3.00 DS is a risk factor for amblyopia, we used 3.00 DS as the cutoff value for low hypermetropia and low myopia.²¹⁻²⁵ There was no difference in the prevalence of refractive errors between the esotropia and exotropia groups. However, there was a statistically significant increase in the prevalence of anisometropia in the exotropia group ($\chi^2_1=9.85$; $P=.002$). Only 3.8% of the esotropia group had anisometropia greater than 1.00 DS, whereas 40% of the exotropia group had anisometropia.

MULTIVARIATE ANALYSIS

The first stage was to perform univariate analysis to determine which factors are associated with strabismus in the low-birth-weight cohort (**Table 4**). Also, from a review of the literature, several other risk factors for strabismus were identified²⁶ and, where possible, were included in the analysis: birth weight, gestational age, and cerebral palsy (data from parent questionnaires). However, although maternal age, maternal smoking, and ethnic origin have also been shown to be risk factors for strabismus, they were not significantly associated on univariate analysis in this low-birth-weight cohort.

To determine which factors are associated with strabismus after controlling for potential confounders, a backward logistic regression analysis was performed that included the variables that were significant on univariate analysis. The final model showed that ROP (any stage), refractive error (greatest risk >+3.00 DS), birth weight (<1500 and ≤1000 g), anisometropia, and cerebral palsy were all independently associated with the

Table 4. Univariate Analysis for Strabismus*

Variable	Odds Ratio (95% CI)	P Value (Wald Test)	P Value (LRT)
Cerebral palsy (n = 271)			
No	1.0		
Yes	6.82 (2.46-18.89)	<.001	<.001
Cranial ultrasound abnormalities (n = 293)			
Normal	1.0		
Mild	0.99 (0.44-2.22)	.98	<.001
Moderate/severe	9.73 (3.06-30.96)	<.001	
Unknown	0.63 (0.30-1.30)	.21	
Birth weight, g (n = 292)			
≥1500	1.0		
1000-1499	2.81 (1.11-7.13)	.03	.03
<1000	2.26 (1.13-4.52)	.02	
Gestational age, wk (n = 293)			
<28	1.0		
28-32	0.45 (0.24-0.86)	.02	<.001
>32	0.20 (0.08-0.47)	<.001	
Refractive error (n = 293)			
Low hypermetropia	1.0		
High hypermetropia	8.32 (3.51-19.73)	<.001	<.001
Low myopia	1.55 (0.69-3.45)	.29	
High myopia	8.87 (2.85-27.63)	<.001	
ROP stage (n = 293)			
No ROP	1.0		
Stage 1	2.40 (1.19-4.82)	.01	<.001
Stage 2	3.76 (1.62-8.73)	.002	
Stage 3 or 4	7.81 (2.42-25.17)	<.001	
Anisometropia (n = 291)			
None	1.0		
>1 DS	8.14 (3.31-19.99)	<.001	<.001
Ethnic origin (n = 293)			
White	1.0		
Asian	0.63 (0.18-2.22)	.48	.77
African Caribbean	0.48 (0.06-3.88)	.49	
Mixed	1.08 (0.22-5.37)	.92	
Cigarettes, No. (n = 293)			
<10	1.0		
10-19	1.69 (0.39-7.2)	.48	.27
≥20	1.22 (0.24-6.23)	.81	
Unknown	0.79 (0.21-2.95)	.72	
Maternal age, y (n = 293)			
<20	1.0		
20-24	0.53 (0.18-1.58)	.25	.35
25-29	0.51 (0.17-1.52)	.23	
30-34	1.01 (0.34-2.99)	.99	
≥35	1.56 (0.42-5.81)	.51	
Unknown	0.68 (0.24-1.92)	.46	

*LRT indicates the likelihood ratio test, which tests the overall association between strabismus and each variable; CI, confidence interval; ROP, retinopathy of prematurity; and DS, diopter spheres.

presence of strabismus at age 10 to 12 years ($\chi^2_5=32.31$; $P<.001$) (**Table 5**). The results of the backward logistic regression were confirmed by a forward stepwise logistic regression. Using the risk factors shown in Table 5 to predict strabismus, the sensitivity of this model was 65.3% and the specificity was 86.0%.

COMMENT

The results of this study confirm the increased prevalence of strabismus in this low-birth-weight population of children with a birth weight less than 1701 g. It is the first study, to our knowledge, to report specific types and

prevalence of strabismus on an epidemiologic basis at age 10 to 12 years.

The number of children consenting to be assessed was 293 (51.2%) of the 572 in the original cohort. This follow-up was not planned at the time of the original investigation, family contact was not maintained, and this long gap without communication probably accounts for some of the response failure. Also, at a test age of 10 to 12 years the child is also involved in the decision to participate, which may also have affected the consent rate. However, we¹⁶ discussed elsewhere that there was no significant difference between children assessed at follow-up and those not assessed in terms of birth weight,

Table 5. Multivariate Analysis to Predict Strabismus*

	Odds Ratio (95% CI)	P Value†
ROP stage		
No ROP	1.0	.08
1	2.6 (1.13-5.99)	
2	3.0 (1.07-8.42)	
3 or 4	2.9 (0.42-20.35)	
Refractive error		
Low hypermetropia (≥ 0.0 and $< +3.00$ DS)	1.0	.03
Higher hypermetropia ($> +3.00$ DS)	4.6 (1.67-12.71)	
Low myopia (< 0.0 and > -3.00 DS)	1.6 (0.63-3.97)	
High myopia (≤ -3.00 DS)	2.6 (0.53-12.36)	
Anisometropia		
None	1.0	.02
> 1 DS	4.0 (1.23-13.29)	
Birth weight, g		
≥ 1500	1.0	.07
< 1500 and ≥ 1000	2.5 (1.02-5.94)	
< 1000	1.1 (0.28-4.40)	
Cerebral palsy		
No	1.0	.02
Yes	5.0 (1.36-18.20)	

*CI indicates confidence interval; ROP, retinopathy of prematurity; and DS, diopter spheres.

†The P value is from the likelihood ratio test, which tests the association between each variable and strabismus while controlling for the other variables in the model.

gestational age, ROP, or cranial ultrasound abnormalities. Sensitivity analysis shows that even if there were no cases of strabismus in the 246 children not assessed (children known to be alive at age 10 to 12 years), there would still be a significant difference in the prevalence of strabismus between the low-birth-weight cohort and the school cohort.

Previous studies have attributed the increase in strabismus in children born prematurely either wholly or in part to ROP,^{7,27} the increase in refractive error,² and neurologic impairment.¹ These factors are interrelated, and, therefore, univariate analysis may simply be detecting confounding variables. Only Pennefather et al³ and Holmstrom et al¹ addressed this issue, showing that cicatricial ROP, refractive error, family history, and general development quotient were each independently associated with strabismus. Other studies have shown that maternal age, smoking, and ethnic origin are risk factors for strabismus.²⁶ These factors may be responsible for the differing results we found in that ROP, birth weight, cerebral palsy, anisometropia, and refractive error were independently related to strabismus. However, a weakness of our study is the lack of detailed data on family history, which has a well-known association with strabismus. Amblyopia in this cohort will be the topic of another article.

Extremely low-birth-weight children (< 1000 g) have the greatest risk for ophthalmic morbidity.¹⁶ However, although birth weight is a risk factor for strabismus, there is no increased risk associated with the lowest birth weight category, emphasizing that all low-birth-weight children are at risk of strabismus, irrespective of birth weight.

It is known that constant exotropia, compared with esotropia, is more likely to be associated with a coexist-

ing ocular or systemic condition, including ROP and prematurity.²⁸ With the high prevalence of ocular and systemic problems in the low-birth-weight population, it may be predicted that there would be an increase in the occurrence of exotropia. This hypothesis is supported by the findings of our study with a high prevalence of exotropia, which is reflected in the 1:1 exotropia-esotropia ratio. Although we identified several risk factors for strabismus in general, only anisometropia and ROP are specific for exotropia. In the low-birth-weight cohort, there was an especially high prevalence of intermittent near exotropia (10%).

For 75% of children in our study, the onset of non-accommodative esotropia was after corrected age 6 months. However, the precise age at onset is unknown, as the children were not examined between corrected age 6 months and age 10 years.

In summary, this study confirms the increased prevalence of strabismus in a low-birth-weight population and provides information on strabismus types. Analysis has shown that ROP, birth weight, cerebral palsy, and refractive error are all independently associated with strabismus. However, it is not possible to use this model to predict the occurrence of strabismus. This study highlights the importance of screening for strabismus in low-birth-weight children with and without ROP and demonstrates the impact on ophthalmic services. However, because age at onset is not known, further research is required to determine precise screening guidelines.

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