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Impaired visual fixation at age 2 years in children born before the 28th week of gestation. Antecedents and correlates in the multi-center ELGAN Study

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Abstract

Background—Very little is known about the prevalence, antecedents and correlates of impaired visual fixation in former very preterm newborns.

Methods—In the multi-center ELGAN Study sample of 1057 infants born before the 28th week of gestation who had a developmental assessment at 2 years corrected age, we identified 73 who were unable to follow an object across the midline. We compared them to the 984 infants who could follow an object across the midline.

Results—In this sample of very preterm newborns, those who had impaired visual fixation were much more likely than those without impaired visual fixation to have been born after the shortest of gestations (odds ratio = 3.2; 99% confidence interval = 1.4, 7.5) and exposed to maternal aspirin (OR: 5.2; 99% CI: 2.2, 12). They were also more likely than their peers to have had prethreshold ROP (OR: 4.1; 99% CI: 1.8, 9.0). At age 2 years, the children with impaired fixation were more

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likely than others to be unable to walk (even with assistance) (OR: 7.5; 99% CI: 2.2, 26) and have a Mental Development Index more than 3 standard deviations below the mean of a normative sample (OR:3.6; 99% CI: 1.4, 8.2).

Conclusion—Risk factors for brain and retinal damage, such as very low gestational age, appear to be risk factors for impaired visual fixation. This inference is further supported by the co-occurrence at age 2 years of impaired visual fixation, inability to walk, and a very low Mental Development Index

Keywords

Retinopathy of prematurity; preterm newborn; brain; developmental disabilities

Pursuit eye movements help a child make sense of movement in her environment ¹. Children who have impaired visual pursuit are less able than their peers to do well on assessments of cognition as well as perception. Understanding what contributes to a child's inability to fix on a moving object has the potential to lead to interventions that might reduce the occurrence of such impairments and their consequences.

Little is known about the antecedents of impaired visual fixation in very preterm newborns, other than an association with "brain injuries," including periventricular leukomalacia ^{2,3}. We wanted to correct this deficiency.

ELGAN is the acronym for Extremely Low Gestational Age Newborn. The 14-site ELGAN study, designed to identify characteristics and exposures that increase the risk of structural and functional neurological disorders in ELGANs ⁴, followed 1057 extremely low gestational newborns (i.e. < born before the 28th week of gestation) followed from birth to age 2 years post term equivalent when they underwent visuomotor and neurodevelopmental assessments ⁴. This provided us the opportunity to evaluate the antecedents and correlates of an inability to sustain eye contact long enough to follow the examiner across the midline (N=73).

Methods

Participants

ELGAN is the acronym for Extremely Low Gestational Age Newborn. The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurological disorders in ELGANs ⁴. During the years 2002–2004, women who delivered before 28 weeks gestation were asked to enroll in the study. The enrollment and consent processes were approved by the individual institutional review boards. The sample for this study consists of the 1057 infants who had retinal exams as clinically indicated and had a developmental assessment at 2 years corrected age when the completeness of the visual field could be assessed by confrontation.

Details are presented in the appendix about demographic and pregnancy variables, placenta bacteriology, placenta and umbilical cord morphology, gestational age, birth weight Z scores, extreme blood gas measurements, bacteremia, retinal examinations, procedures for

reading protocol ultrasound scans, developmental assessments, neurological examinations (including assessments of visual fields and dysconjugate gaze). The child was considered to have impaired fixation if s/he could not fixate even briefly (N=18) or could not sustain eye contact long enough to follow the examiner across the midline (N=55).

Data analysis

We evaluated the null hypothesis that infants who had impaired visual fixation at age two years were no more likely than their peers whose visual fixation was not impaired to have an antenatal or early postnatal characteristic or exposure. Because postnatal phenomena can be influenced by antepartum phenomena, we created logistic regression models in which risk factors are ordered in a temporal pattern of sequential epochs, so that the earliest occurring predictors/covariates of impaired fixation are entered first and are NOT displaced by later occurring covariates⁵. For these time-oriented logistic regression risk models, we categorize sets of antecedents/covariates by the time they occur or are identified (*e.g.*, antenatal, early postnatal, and later postnatal). We used a step down procedure seeking a parsimonious solution without interaction terms. These models allowed us to calculate odds ratios and 99% confidence intervals.

Results

Sample description

Compared to the 984 children whose visual fixation was not impaired, the 73 children who had impaired fixation were much more likely to have exotropia (15% v. 2%), reduced visual field size (40% v. 4%), quadriparetic CP (33% v. 4%), and an inability to walk even with assistance (34% v. 3%) (Table 1). They were also more likely than their peers to have esotropia (26% v. 10%), prethreshold retinopathy of prematurity (ROP) (42% v. 11%), brain ultrasound findings of ventriculomegaly (25% v. 9%), a hypoechoic lesion (18% v. 6%), very low Mental Development Index (MDI) (48 v. 13%), very low Motor Development Index (PDI) (45% v. 14%), a positive screen for an autism spectrum disorder (46% v. 15%), and microcephaly (20% v. 10%).

Maternal and pregnancy characteristics

By and large, socio-demographic characteristics of the mother were not associated with impaired fixation in the child (Data not shown in any table). Mothers of infants with impaired fixation were a bit more likely than other mothers to be married and to have sought conception assistance.

Fully 21% of the mothers of fixation-impaired children consumed aspirin during the pregnancy while only 5% of other mothers did so. Mothers of children who had impaired fixation were also more likely to have consumed non-steroidal anti-inflammatory agents (NSAIDs) (13% v. 7%) and acetaminophen (57% v. 51%).

Placenta, delivery, and newborn characteristic

The placentas of children who had impaired fixation were less likely to have had umbilical cord vasculitis (11% v. 17%), and also less likely to have had increased syncytial knots

(14% v. 21%) (Table 2). Their placentas, however, were more likely to have harbored an organism considered part of normal skin flora (*i.e.*, *Corynebacterium sp*, *Propionibacterium sp*, *Staphylococcus sp*) (27% v. 18%).

Fever within the interval from shortly before delivery to 48 hours was experienced by more mothers of children who had impaired fixation than by the mothers of other children (10% v. 6%). Children who had impaired fixation were more likely than others to be a boy (67% v. 51%), to have been born during the 23rd and 24th weeks of gestation (41% v. 19%), and to have had a birth weight ≥ 750 (53% v. 35%). Children who had impaired fixation, however, were no more likely than others to have had severe fetal growth restriction (birth weight Z-score < -2) (5% v. 5%).

Early post-natal characteristics

Children who later developed impaired fixation were more likely than their peers to have had a Score for Acute Physiology (SNAP) ≥ 30 (29% v. 22%), persistently or recurrently low measurements of PaO₂ (28% v. 20%), and pH (32% v. 20%), and to be ventilated on day 14 (78% v. 57%), day 21 (74% v. 56%), and day 28 (62% v. 47%) (Table 3). They were less likely to have received a methylxanthine for 15 or more days (45% v. 61%), and more likely to have received an analgesic during the first 28 days (86% v. 69%), a sedative (33% v. 26%), treatment for a patent ductus arteriosus (70% v. 60%), a transfusion during three of the first 4 weeks (81% v. 55%), and an antibiotic during the second through fourth postnatal weeks (95% v. 77%).

Diagnoses

Children who later developed impaired fixation were more likely than others to have been given a diagnosis of a patent ductus arteriosus (78% v. 67%), pulmonary interstitial emphysema (26% v. 15%), pulmonary hemorrhage (8% v. 3%), early and persistent pulmonary dysfunction (50% v. 41%), isolated intestinal perforation (7% v. 3%), prethreshold ROP (42% v. 11%), and bronchopulmonary dysplasia (on a ventilator: 14% v. 8%; and not on a ventilator: (61% v. 41%) (Data not shown in any table).

Time-oriented risk models

Of the five variables in the antenatal epoch, only two were associated with prominently increased risk of impaired fixation: maternal ingestion of aspirin (OR=5.2; 2.2, 12) and gestational age between 23 and 24 weeks (OR=3.2; 1.4, 7.5) (Table 4). Prethreshold ROP (OR=4.1; 1.8, 9.0) was the only one of 17 postnatal variables that added significant information to the model that had the antenatal variables.

Adding two variables from the two-year assessment, inability to walk Gross Motor Function Classification System (GMFCS) level of 5: OR=7.5; 2.2, 26) and mental development index more than 3 standard deviations below the expected mean (MDI < 55 : OR=3.6; 1.4, 8.2) added statistically significant information about the risk of impaired fixation. In this final model only low gestational age lost its statistical significance.

Discussion

We place most reliance on our time-oriented risk models because they introduce the earliest occurring variables and only subsequently introduce variables that first occur later. In the final model, one prenatal variable, maternal ingestion of aspirin, one early postnatal variable, prethreshold ROP, and two late postnatal variables, an inability to walk and a mental development index more than 3 standard deviations below the mean of a normative sample each provided statistically significant ($p < .01$) information about the risk of impaired fixation.

Not all children with impaired visual fixation were unable to walk or were severely cognitively limited. Similarly, all children who were unable to walk and those who had severe cognitive limitation did not have impaired visual fixation. Thus, it seems reasonable to infer that the pathways involved in visual pursuit and fixation are not the same that involve walking or cognition. Thus, impaired visual fixation should be seen as indicative of brain damage beyond that expected with walking and cognitive impairments. This is in contrast to those who feel that cognitive limitations account for much of “impaired visual orienting behavior in children with intellectual disabilities”⁶. As significant variables were added from the later time points, the large odds initially associated with low gestational age diminished. This is expected in this sample because the least mature were at increased risk of two variables in the model, retinopathy of prematurity⁷ and severe quadriparetic cerebral palsy (which accounts for the inability to walk variable indicated by GMFCS = 2)⁸. Compared to low gestational age, however, these indicators of brain damage are more powerful predictors of the consequences and correlates of brain damage, such as impaired visual fixation.

Maternal ingestion of aspirin during pregnancy was associated with an increased risk of impaired fixation in the child years later. This is not surprising given our observation that infants whose mother consumed aspirin during the pregnancy were at increased risk of quadriparetic cerebral palsy (and a GMFCS = 5), even after adjustment for the potential confounding of disorders for which aspirin might have been indicated⁸. Perhaps that is why both aspirin and an inability to walk were associated with impaired visual fixation. The observation that both of these variables contribute independent information about the risk of impaired fixation leads us to infer that the more severe the brain damage, the higher the risk of impaired fixation. In light of what we know about the contribution of inflammatory disorders to brain damage in preterm newborns⁹, and the evidence that confounding by indication is almost impossible to eliminate¹⁰, the illness that prompted the pregnant woman to take aspirin might be more likely than the aspirin itself to contribute to impaired fixation¹¹.

ROP and impaired fixation can be seen in the same child when the ROP contributes to the impaired fixation². For example, changes in foveal architecture that reduce central acuity and thereby result in eccentric fixation have been reported in children who developed severe ROP, especially those who had a vitrectomy or retinal re-attachment surgery¹².

On the other hand, some of the fixation impairments associated with severe ROP might be more appropriately attributed to the brain damage that appears to occur more commonly among children with severe ROP than among very preterm infants who do not have severe ROP². The co-occurrence of severe ROP and brain damage might reflect nothing other than the antecedents they share including immaturity^{13,14}, illness severity indicators^{15,16}, hyperoxemia^{7,17}, bacteremia^{18,19}, fetal and postnatal growth restriction^{20,21}, and need for or receipt of (prolonged) ventilator assistance^{22,23}.

In our sample, ventriculomegaly on a brain scan while the child was in the intensive care nursery, an inability to walk even with assistance at age 2 years, and very low score then on the mental development index of the Bayley Scales, each contributed independent information about the risk of impaired fixation. As above, since each contributed non-redundant information, we draw the inference that the more severe the brain damage, the higher the risk of impaired fixation.

Visual motion information is processed via the dorsal stream from the optic nerve via the lateral geniculate nucleus and the primary visual cortex of the occipital lobe to the associative visual cortex in the parietal lobe²⁴. Motion is also processed in the subcortical stream that goes from the optic nerve via the superior colliculus and pulvinar nucleus of the thalamus to the medial temporal complex area, bypassing occipital lobe primary visual cortex²⁵. Disturb either the dorsal or subcortical stream and visual pursuit/fixation can be impaired²⁴.

Lesions such as periventricular leukomalacia can be followed by visual fixation impairment² and impaired motion perception²⁶. Some of this has been attributed to thalamic atrophy²⁶, which is expected in light of the role that the pulvinar nucleus of the thalamus plays in the subcortical stream²⁵, while some has been attributed to peritrogonal damage²⁷. Early “poor visual fixation scores for age” among preterm infants were associated with MRI microstructural indicators of delay in maturation of the optic radiation²⁸.

Limitations and strengths

The limitations of our study are those of all observational studies. We are unable to distinguish between causation and association as explanations for what we found. In addition, the sickest infants were more likely to be treated aggressively than others who were not quite so sick, making our study prone to confounding by indication¹¹.

Our study has several strengths. First, we included a large number of infants, making it unlikely that we have missed important associations due to lack of statistical power, or claimed associations that might reflect the instability of small numbers. Second, we selected infants based on gestational age, not birth weight, in order to minimize confounding due to factors related to fetal growth restriction. Third, we collected all of our data prospectively. Fourth, examiners were not aware of the medical histories of the children they examined, thereby minimizing “diagnostic suspicion bias.” Fifth, we have minimized observer variability as best we can in the interpretation of ultrasound scans and assessments of

neurodevelopmental functions. Sixth, attrition in the first two years was modest, with information about the two-year assessment available from 85% of all infants.

Conclusion

In light of the observation that impaired visual fixation shares risk factors with cerebral palsy and very low Mental Development Indices, and that impaired visual fixation co-occurs with an inability to walk and with very low Mental Development Indices, severely impaired visual fixation is most likely an indicator of brain damage, and that efforts to reduce the occurrence of impaired fixation are likely to be most rewarding if they are directed to preventing brain damage. How much retinopathy actually contributes to impaired fixation remains uncertain.

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Table 1

Visual, retinal, and brain disorders associated with impaired fixation. These are column percents and row and column total numbers.

		Impaired fixation		Row N
		Yes	No	
Esotropia	Yes	26	10	114
Exotropia	Yes	15	2	30
Visual field deficit	Yes	40	4	64
Threshold ^T retinopathy of prematurity	Yes	13	2	26
Pre-threshold ^P retinopathy of prematurity	Yes	42	11	141
Retinopathy of prematurity stage	4-5	10	1	18
	3	50	25	278
Ventriculomegaly [*]	Yes	25	9	105
Hypoechoic lesion [*]	Yes	18	6	74
Cerebral palsy diagnosis	Quadriplegia	33	4	64
	Diparesis	5	3	37
	Hemiparesis	7	1	18
GMFCS	2	34	3	55
MDI [§]	< 55	48	13	153
PDI ^{§§}	< 55	45	14	160
M-CHAT [‡] screen	positive	46	15	152
2 year head circumference Z-score ^{‡‡}	< -2	20	10	107
2 year body weight Z-score ^{‡‡}	< -2	4	3	30
Maximum column N		73	984	1057

^T Satisfied CRYO-ROP criteria for ablative surgery.

^P Satisfied ET-ROP criteria for ablative surgery.

^{*} On ultrasound in the NICU

[§] Mental Development Index of the Bayley Scales for Infant Development II

^{§§} Motor Development Index of the Bayley Scales for Infant Development II

[‡] among those with GMFCS < 1 and no vision or hearing abnormality

^{‡‡} CDC standard

Table 2

The percent of children with or without impaired fixation who had the placenta, delivery, and newborn characteristic listed on the left. These are column percents and row and column total numbers.

Characteristics of the placenta and delivery		Impaired fixation		N
		Yes	No	
Inflammation chorionic plate [§]	Yes	17	20	190
Inflammation chorion/decidua ^{§§}	Yes	36	36	352
Neut infiltration fetal stem vessels	Yes	26	26	245
Umbilical cord vasculitis ^{§§§}	Yes	11	17	159
Thrombosis of fetal stem vessels	Yes	6	5	49
Infarct	Yes	15	17	166
Increased syncytial knots	Yes	14	21	198
Decidual hem/fibrin deposition	Yes	14	16	156
Number of species isolated	1	27	24	230
	2	28	24	235
Aerobe	Yes	31	32	304
Anaerobe	Yes	31	28	266
Mycoplasma	Yes	8	10	95
Skin organisms [†]	Yes	27	18	182
Vaginal organisms ^{††}	Yes	17	16	151
Antenatal steroid course	Complete	60	65	681
	Partial	26	25	261
Pregnancy disorder leading to preterm delivery	PTL	51	45	476
	pPROM	15	22	231
	PE	12	13	138
	Abruption	10	11	114
	Cervical insufficiency	7	5	55
	Fetal Indication	5	4	43
Duration of labor	0 hours	27	24	256
	> 12 hours	56	54	568
Duration of ROM	< 1 hour	66	58	617
	> 24 hours	19	26	271
Magnesium	Tocolysis	51	55	571
	Seizure prophylaxis	11	13	134
Cesarean delivery	Yes	66	67	705
Fever [*]	Yes	10	6	68
Sex	Male	67	51	549
Type of gestation	Multiple	34	34	699
Gestational age (weeks)	23–24	41	19	212

Characteristics of the placenta and delivery		Impaired fixation		N
		Yes	No	
	25–26	37	47	488
Birth weight (grams)	750	53	35	383
	750–1000	37	45	469
Birth weight Z-score **	< -2	5	5	55
	-2, < -1	15	13	141

§ Stage 3 and severity 3

§§ Grades 3 and 4

§§§ Grades 3, 4 and 5

† *Corynebacterium* sp, *Propionibacterium* sp, *Staphylococcus* sp

†† *Prevotella bivia*, *Lactobacillus* sp, *Peptostrep magnus*, *Gardnerella vaginalis*

* within the interval from before delivery to 48 hours post delivery

** defined with external standards

Table 3

The percent of children with or without impaired fixation who had the neonatal characteristic listed on the left who had impaired fixation. These are column percents and row and column total numbers.

Postnatal factors		Impaired fixation		N
		Yes	No	
SNAP-II (0–12 hrs)	< 20	44	53	543
	20–29	27	25	262
	30	29	22	234
Lowest quartile P _a O ₂ *	Yes	28	20	185
highest quartile P _a O ₂ *	Yes	23	21	189
Lowest quartile PCO ₂ *	Yes	27	22	197
highest quartile PCO ₂ *	Yes	25	21	192
Lowest quartile pH *	Yes	32	20	183
Early bacteremia	Presumed	37	36	378
	Definite	10	6	64
Late bacteremia	Presumed	16	15	156
	Definite	32	25	268
Mech/hi freq vent, day 14	Yes	78	57	615
Mech/hi freq vent, day 21	Yes	74	56	598
Mech/hi freq vent, day 28	Yes	62	47	498
Mech/hi freq vent, 36 weeks	Yes	14	8	93
Surfactant (first week)	Yes	92	89	941
Methylxanthine, 15 days	Yes	45	61	636
Any hydrocortisone	Yes	14	13	138
Any dexamethasone	Yes	8	8	82
Any analgesics, 0–28 days	Yes	86	69	737
Any sedative, 0–28 days	Yes	33	26	282
PDA treatment	Yes	70	60	645
Transfusion [†] in 3–4 weeks	Yes	81	55	597
Antibiotic, week 1	Yes	99	98	1037
Antibiotic, weeks 2–4	Yes	95	77	825

* extreme quartile for gestational age on two of the first three postnatal days

[†] packed cells or whole blood

Table 4

Odds ratios (and 99% confidence intervals) of impaired fixation at age 2 years associated with antecedents and correlates. These are calculated from time-oriented logistic risk models. Variables were retained in the model if the p value when they first entered the model was < 0.01. Bold numbers are statistically significant at p < 0.01.

Epoch	Variable	Odds ratios (99% confidence intervals)		
		Antenatal	Early postnatal	2-year exam
Antenatal ^A	Maternal aspirin	5.2 (2.2, 12)	4.8 (1.8, 13)	4.0 (1.2, 13)
	Gest age: 23–24	3.2 (1.4, 7.5)	1.4 (0.5, 4.2)	1.0 (0.3, 3.3)
Postnatal ^E	ROP – prethreshold*		4.1 (1.8, 9.0)	5.2 (2.0, 13)
2-yr exam ^X	GMFCS 2 [‡]			7.5 (2.2, 26)
	MDI < 55 [§]			3.6 (1.4, 8.2)

Epoch Candidates

^A Antenatal: mother ingested aspirin, perinatal fever; skin organism isolated from the placenta; gestational age categories; birth weight < 750 grams.

^E Early postnatal: SNAP-II: < 30; lowest quartile of P_aO₂ on 2 of the first 3 postnatal days; highest quartile of P_aO₂ on 2 of the first 3 postnatal days; lowest quartile of pH on 2 of the first 3 postnatal days; early definite bacteremia; late definite bacteremia; ventilation on day 14; a transfusion of any blood product during 3 of the first 4 weeks; antibiotic during weeks 2–4, any of pneumothorax, pulmonary interstitial emphysema, or pulmonary hemorrhage, surgery for necrotizing enterocolitis or isolated intestinal perforation; ventriculomegaly, echolucent lesion on brain ultrasound scan; prethreshold retinopathy of prematurity, bronchopulmonary dysplasia (oxygen dependent at 36 weeks post-menstrual age)

^X Gross Motor Functional Classification System < 2, Bayley Scales of Infant Development II Mental Development Index < 55; Bayley Scales of Infant Development II Motor Development Index < 55; head circumference Z-score < -2

* Prethreshold retinopathy of prematurity

[‡] Gross Motor Functional Classification System

[§] Bayley Scales of Infant Development II Mental Development Index < 55