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Review

Retinopathy of prematurity and neurodevelopmental disabilities in premature infants

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SUMMARY

Prematurity is a major global health issue leading to high mortality and morbidity among the survivors. Neurodevelopmental disability (NDD) and retinopathy of prematurity (ROP) are the most common complications of prematurity. In fact, ROP is the second leading cause of childhood blindness in the world. Although there is much information regarding the occurrence of ROP and of NDD in premature infants, there have been few studies on ROP and its association with NDD. The objectives of this article are to review the current literature on the subject and to publish our own findings concerning the association between ROP and NDD in premature infants. The review suggests that although NDDs are related to degree of prematurity, NDD could also be the result of visual impairments resulting from ROP. Our own study shows a close association between NDD and zonal involvement of ROP: higher NDD if zone 1 is involved and less if zone 3 is involved.

1. Introduction

Retinopathy of prematurity (ROP) is a widespread complication of prematurity. It is the second leading cause of childhood blindness in the world [1]. Infants with ROP are known to develop early and late visual sequelae. Premature infants are also known to develop neurodevelopment disability (NDD) [2]. Both of these morbidities affect quality of life [3,4]. Although there is much information regarding the occurrence of ROP and also of NDD in premature infants, few studies have looked at ROP and its association with NDD. The aim of our study was to determine whether NDD status is worse in premature infants with ROP. We hypothesized that infants with ROP had NDD independent of their gestational age and birth weight. We therefore review the current literature and set out our own findings on the association between ROP and NDD in premature infants.

2. Methods

Children who were being followed at Aravind Eye Care System, a major teaching institution in Southern India, were included in the study. Children born between September 2007 and May 2013 participated in the study. Parental consent was obtained at the time of the visit. Children with congenital malformations or genetic syndromes were excluded. Infants and children whose parents did not consent to participation were excluded from the study. Study visits were conducted from August 6th to 22nd, 2014. The study was approved by the institution review board of the Aravind Eye Care System.

Information regarding maternal and newborn history was gathered from medical records. Additional history was obtained from parents where necessary. Data gathered about the parents/caregiver included maternal age at birth, educational attainment of both parents, both parents' age, pregnancy complications, parity,

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type of conception, and parental knowledge about the child's developmental status. Neonatal history included: route of delivery, gestational age, birth weight, and history of respiratory distress, duration of oxygen therapy, duration of ventilator support, other neonatal complications, final diagnosis, and length of neonatal hospital stay. Information on interim illness, hospitalization and developmental milestones, present activity, and concerns about their children were obtained from interviews with parents/caregivers.

All patients in the study were examined and evaluated for the retinal status by the Vitreo Retinal Surgeons at Eye Care Center, at four weeks to two months of age. At the time of first examination the ophthalmologist coded the ROP staging according to international standards [5]. The follow-up eye examinations and treatments were conducted, as per standard protocol.

Neurodevelopmental assessments were carried out by the developmental specialist (N.B.). Neurodevelopment and behavior of children were assessed using the skills inventory of the Oregon Project for preschool children who are blind or visually impaired (6th edition) [6]. The tool was selected because of the specificity of detecting the functional skills in eight developmental parameters, such as gross motor, fine motor, and cognitive developmental tests of visual motor integration, language, vision, social skills, self-help skills and behavior, for ages one to six years. The Beery–Buktencia, developmental test of visual motor integration [7] was used for children from birth to six years of age for assessing visual perception and motor coordination.

The methodologies for testing the above-mentioned domains are described below.

Gross motor examination consisted of functional ability of children depending upon the age of the child. Functional skills assessed include: crawling, walking, gait, ease of walk in a straight line, or need for assistance. Children who had no difficulty with physical mobility were tested for kick, throw, hop, jump with both or one foot, climb the chair, and catching a ball, balance on one foot and with closed eyes and standing for few seconds (Romeberg sign), and walk with tandem gait. Fine motor coordination was assessed by evaluating writing, scribbling or copying of pictures, circles, squares, and a cross when applicable. In children aged one year or younger, fine motor skills were assessed by evaluating transfer of small cubes from hand to hand, dropping an object into a cup, use of pincer grasp, scribbling, and ability to stack cubes.

Language was assessed for receptive skills, follow-up of directions and commands in performing activities. Expressive language was assessed with utterance of sounds, words and utterance of two- or three-word sentences or long sentences. Fluency of words or stuttering depending upon the age of the child was also noted.

Cognitive skills were measured by the child's ability to recognize and identify the object. Recall memory was tested using picture identification and story-telling, counting numbers, matching colors, and shapes and sizes. In children one year of age or younger, cognitive ability was assessed by evaluating for their ability to follow the objects with eyes, matching color, recognizing the shapes, sizes, stripes, and crosses. Block designs were used to assess for visual acuity and cognition. Children older than one year were observed for attention span and concentration. Children were observed and documented for their ability to adapt to examiners, their comfort in the environment, for any unusual behavior, and their cooperation.

The degree of NDD was classified according to Oregon Project skills assessment. Scores were recorded and converted as a percentage of skills attained. These scores were used as mild, moderate and severe for uniformity. When the scores were <30% in any one domain, the disability was considered as mild, requiring only parental education. When more than one domain was affected by >30% they were classified as moderate, and required early intervention. When one or more domains were affected by >50%, they were grouped as severe, requiring early intervention and other services.

Data were analyzed using STATA 11.1 (College Station, TX, USA) software. Chi-square testing and Fisher's exact test were used to assess the association between categorical variables and NDD.

3. Results

One hundred families were invited to participate. Seventy-four patients were included in the study. All seventy-four children were assessed for NDD.

Maternal data are shown in Table 1. All mothers had prenatal care either by a private physician or at a general hospital. Mean paternal age was 34.2 (SD: 5.5) years; mean maternal age was 28.0 (SD: 5.3) years. Pregnancy complications were reported in 55% of mothers, including in-vitro fertilization (IVF), first trimester bleeding, diabetes, gestational diabetes, high blood pressure, anemia, abruptio placentae, eclampsia, and premature rupture of membranes. Infants were either delivered at freestanding clinics or at government institutions. Thirty-eight infants (51.3%) were delivered by normal spontaneous vaginal route, and 36 (48.7%) were delivered by cesarean section. Forty-one (55%) children were males and 33 (44.6%) were females. Thirty-nine (53%) were singletons and 35 (47%) were multiple births. Among the multiple births, 32.4% (24/74) were twins, 14.9% (11/74) were triplets; 34% (25/74) of the multiple births were conceived by IVF.

The gestational age and birth weight distribution are shown in Table 2. The gestational age (GA) ranged between 25 and 40 weeks. A total of 51.3% (38/74) of infants were <32 weeks GA and 48.6% (36/74) were >32 weeks GA. There were 12 infants (16%) with GA >35–40 weeks. The birth weight of infants in this study ranged from 600 to 3500 g; 58% of the babies were <1500 g, 38% between 1501 and 2500 g, and 0.4% >2500 g.

In terms of diagnosis, neonatal respiratory distress syndrome (RDS) was the major diagnosis accounting for 84% (62/74) of the population. A large proportion of infants (87.8%, 67/74) received oxygen; of these, 63.5% (47) were ventilated: 42% (20/47) required

Table 1
Characteristics of maternal and neonatal population as maternal variables.

Maternal variables	No. (%)
Parental age (years)	
Maternal (range)	19–45
Paternal (range)	25–47
Type of conception	
In-vitro fertilization	25 (34%)
Normal	49 (66%)
Pregnancy complications	
All	55 (74%)
Eclampsia	17 (23%)
PROM	6 (8%)
Others	22 (43%)
Route of delivery	
NSVD	38 (51%)
Cesarean section	36 (49%)
No. of births	
Singletons	39 (53%)
Twins	24 (32%)
Triplets	11 (15%)
Parental education	
Higher secondary and college	74 (100%)

PROM, premature rupture of membranes; NSVD, normal spontaneous vaginal delivery.