ORIGINAL RESEARCH

VISUAL DEVELOPMENT IN RELATION TO PRETERM BIRTH

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ABSTRACT
Children born before 37 weeks of pregnancy, considered as premature. They are at a greater risk of abnormal visual and neurological development, in comparison to full term. Susceptibility to these long term deficits may manifest during the first 2 yrs of life. A large number of visual deficits are common in preterm born, such as Retinopathy of prematurity, refractive errors , abnormal stereopsis, strabismus, impaired contrast sensitivity, deficits in cortical visual processing and other developmental defects of eye. Routine ophthalmic screening may not detect the problems in initial stages. Hence, these impairments can continue to adolescence and adulthood, contribute to various visual problems, including psychological and educational, which are the main obstacles in life of preterm borns. The most common ailment is Retinopathy of prematurity. The frequency and diversity of visual deficit is inversely proportional to gestational age.

Keywords: preterm, cortical processing, strabismus, refractive error, retinopathy of prematurity

Preterm birth, a live birth before gestational age of 37 weeks,[1] is associated with various developmental deficits. The third trimester of pregnancy is a period of rapid growth for foetus. Younger gestational age at birth is associated with diminished myelinogenesis,[2]synaptogenesis and sprouting. Extrauterine exposure to sensory stimulation in pretem born exposes the neural network to stressors, resulting in increased sensitivity,[3] this marks the neonatal period as a supersensitive period for attention development. Visual development occurs in three steps. First step is anatomical formation of the eye, influenced by genetics, second step is the visual experience related to endogenous stimulation, and third step is the visual experience by exogenous stimulation after birth(Graven2004).[4] Preterm born , before 27 weeks ,are at high risk of visual deficits and associated with psychomotor delay, due to curtailed second step of development and start of third step in immature system.[5](Holmstromet.al2014) During the first year of life, some basic faculties ,as ability to fixate on salienttargetinperipheryofvisualfiel Susceptibity to visual and neurological deficits may manifest during first 2 yrs of life.[7] Children born preterm are at a greater risk of abnormal visual and neurological development in comparison to full term children. Premature birth is very common , with 15 million children born before 37 weeks gestational age annually in the world.[8] In India, incidence 10.5% of total live births.[9] J.Hungerford, A Stewart and P.Hope(1979-1982)[10] revealed, 21% ocular pathology in premature newborns , out of this 14% had retinopathy of prematurity. Giuseppe Mirabela, Patricia K Kjaer (2006),[11] explained the higher amplitude in very low birth weight infants ,visual experience may affect responses to supra threshold stimuli. Hellgren et al (2016) showed 2.1% blindness and 4.8% of visual impairment in infants born before 27 weeks.[12

In 2010 the global prevalence of severe impairment due to retinopathy of prematurity was 20000[13] and out of these 55% had neuro developmental impairment. Preterm birth visual deficits includes reduced visual acuity,[14] strabismus 5-25%, high refractive error- myopia 3-20%,[15] defective stereopsis[16] and loss of peripheral vision.[17] In addition preterm birth can affect the development of brain structures involve in visual pathways. Brain

injury is common in preterm born with low birth weight (less than1500gm) , MRI, revealed 40% white matter injury and 20% extensive injury from conditions like periventricular leukomalacia and intraventricular haemorrrhage.[17] Retinal damage is common in preterm born, due to retinopathy of prematurity In this review the effects of preterm birth and associated conditions including ROP, diversity in form perception, motion perception and visuomotor integration will be analysed. The fact is that the preterm birth affects more dorsal visual system (specialized for motion perception and visuomotor control) than the ventral visual system(responsible for form perception).[18]

PROTOCOL

We reviewed the literature to identify studies, involving visual outcome in preterm borns.

Inclusion criteria –

1. Publication in peer reviewed journal, during past 40 yrs.
2. Inclusion of preterm borns GA< 37 weeks at birth and full term
3. Inclusion of infants aged 2 yrs or less.
4. Reporting of at least 1 visual attention measure that had been attained.

Data collected and analysed in view of basic function as, ability to follow and fixate on visual targets, and complex functions as visual processing, recognition memory and ability to focus attention for learning. Findings revealed that preterm borns were more likely to experience difficulties as per severity and category of manifestation.

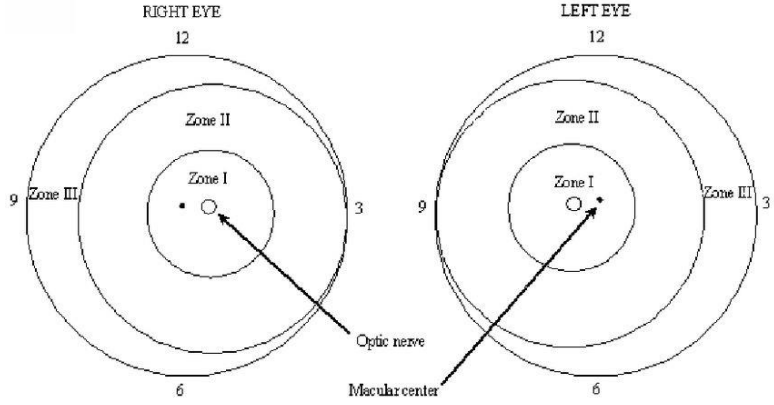
The manifestations of preterm birth deficits are as follows

RETINOPATHY OF PREMATURITY: Since 1940,[19]ROP has been recognized as a major cause of visual impairment in preterm born . It is a proliferative retinal vascular disorder affecting premature, low birth weight neonates. Incidence of ROP in different regions across India has been reported to range from 38% to 47% of low birth weight preterm birth.[20] The prevalence of childhood blindness is very high in countries with an infant mortality rate greater than 60 per 1000 births, but low incidence of ROP,is recorded, because of low survival rate due to non availability of intensive care set up.[21]However in countries , like India, with IMR between 10- 60 per 1000 birth, ROP accounts for a major cause of childhood blindness, depending on the level of post natal care.[22] In 1951 Campbell [23] noticed toxic effect of uncontrolled oxygen therapy to preterm born is responsible for ROP, as it obliterates the blood vessels in neonatal retina. The peripheral retina is only fully vascularised near full term, hence in preterm born peripheral retina remain vascular.[24] After birth, the baby is exposed to hyperoxic environment and this suppressed VEGF production and stop the growth of peripheral retinal blood vessels.[25] As the metabolic activity of retina increases after 31 weeks GA, oxygen supply is not sufficient to ,existing blood vessels ,which upregulates VEGF , production, resulting uncontrolled proliferation of blood vessels.[26]These new vessels extend from retina into vitreous and may cause retinal detachment.

The international classification of ROP,[26]describes the location relative to optic nerve, the extent of developing vasculature and progress of the disease. Stage 1 is the less severe , with stages 4&5 referring to partial and total retinal detachment respectively. The term plus disease is active ROP, may be in any stage. Threshold ROP indicates 5 contiguous or 8 cumulative clock hours of stage 3 in zones 1or2 in the presence of plus disease, may progress to detachment of retina. This process of ROP, has been categorized in different zones (locations on the retina), stages (severity) and extent (retinal area affected in clock hours).[27] This figure showing the posterior zone I ,the intermediate zone II and the peripheral zone III

PREDISPOSING FACTORS

GESTATIONAL AGE AND BIRTH WEIGHT:Along with Gestational Age and Low Birth Weight, supplemental oxygen therapy following delivery is associated with disease, Palmer EA (1997)[28] reported that infants of less than 1000 gm , 81.6% developed ROP, while 46.9% incidence seen in infants of 1200 gm birth weight.



OXYGEN SATURATION LEVELS: ROP, develop between 32- 34 weeks after conception ,has two phases. During first acute phase, the vasculogenesis of retina is disturbed by hyperoxia of extrauterine environment, causes vaso- obliteration and nonvascularisation of anterior retina, in second phase occurs gliosis, arteriovenous shunt formation, cicatrisation and visual impairment.[29]The significance of oxygen level lies in choroidal circulation, which does not autoregulate in change of oxygen tension. Under hyperoxic conditions, excess oxygen moves from choroidal to retinal circulation, constricting the retinal vessels which leads to obstruction.[30]

GENETIC FACTORS: Genetic factors in addition to prematurity or environmental factors play major role in the development and progression of ROP. ROP, involves multiple genes, each gene has small contribution but additive effect resulting in final phenotype. Molecular genetic studies of FEVR have identified four causative genes (NDP, FZD4, LRP5 andTSPAN12) which when mutated cause x- linked, AD and AR FEVR. All these genes control the development of the retinal vasculature,[31] these are mutated in ROP.

OTHER PRESUMED RISK FACTORS: Infants conceived through fertility programmes have tendency of pretem birth, raising risk of ROP.[32] Children with cerebral palsy, blood transfusion, PDA, bronchopulmonary dysplasia, sepsis, may contribute for ROP. Improved surveillance and treatment programmes may reduce the blindness due to ROP. Two multi centre studies, cryotherapy for ROP (CRYO-ROP) study [33] and the Early treatment ROP (ETROP) study,[34] investigated the efficacy of avascular retina ablation for preventing blindness in severe ROP by reducing uncontrolled neovascularisation and preventing retinal detachment. In CRYO-ROP study, patients with threshold ROP, were received transcleral cryotherapy applied to avascular retina revealed severe visual impairment compared to untreated patients. This indicates poor vision due to preterm related factors other than retinal damage.[30] After the CRYO-ROP study, the ETROP study initiated the treatment at a prê-threshold stage of active ROP, which significantly reduced the rate of visual acuity impairment and retinal detachment in long term follow-up [35] After cryotherapy, ablation treatment was taken over LASER photocoagulation, which have contributed to the improvement in ocular structural and visual outcome of children with severe ROP.[36] Due to improvement of neonatal care, survival rate has increased, hence incidence of ROP has also raised. Recently with the advent of anti VEGF intravitreal injection, the visual outcome has improved.

CORTICAL PROCESSING OF VISUAL INFORMATION: Prematurity is among the leading risk factors for poor neurocognitive outcomes, brains of preterm borns show alterations in structure, connectivity and electrical activity. EEG in preterm borns accelerates the maturation of a periodic EEG components including decreased spectral power in the theta and alpha bands and flattened I/f slope.Preterm birth continues to be associated with numerous visual deficits due to abnormal cortical development or cerebral injury.[37] Visual impairments vary from mild visual diminution , refractive errors, to strabismus, defective stereopsis, reduced field of vision, defective contrast sensitivity. Cortical processing deficits may lead to difficulties in learning, impaired behavior, attention and cognition.

DORSAL AND VENTRAL PROCESSING COURSE: Two cortical pathways exist for visual processing, one pathway involve inferior temporal cortex and responsible for recognition while other involve posterior parietal cortex and supports object localization.[38] The ventral stream is responsible for form perceptionand the dorsal stream supports motion perception, object localization and vasomotor control. Both streams are interconnected. Impaired performance of global motion task in preterm born is due to atypical brain development and other neuro developmental disorders.

DORSAL AND VENTRAL PROCESSING IN PRETERM BORNS: Dorsal streams deals with spatial location of objects and informations required for action, while the ventral stream deals with shape, color and other identifying features required for object recognition.[39] Motion perception revealed is impaired in preterm born but form sense is spared, on psychophysical testing performed.[40] 60% of preterm borns has reduced stereoacuity, (to pass the titmus test of stereoacuity, at least 100 seconds of arc for 5yrs and 40 seconds of arc for six years of age & older.[41] The preterm borns has higher coherence thresholds for global motion than full term births. 50% of preterm borns are unable to detect motion defined form correctly 75 % of the time. Sensitivity to biological motion is also impaired in preterm born.[42] There is a relative sparing of global form perception(ventral stream) compared to global motion(dorsal stream) Preterm birth has a negative effect on the dorsal and ventral streams and other white matter pathways. Damage to these microstructures affects language comprehension, visual cognition, visuospatial working memory and visually guided actions. Jakobson and colleagues found that the children born preterm and had no ROP had motion defined form perception in comparison to full term borns, while the preterm borns with ROP had impaired motion- defined form sense.

Williamson and colleagues found that preterm borns performed worse on biological motion task and displayed more autistic traits. The combined effect of globe motion and biological motion deficits may be associated with the lower education and poorer social relations. Hence motion processing may be improved through perpetual learning in preterm borns , along with improvement in visuomotor integration.

PSYCHOPHYSICAL TESTS OF GLOBAL MOTION AND FORM PERCEPTION: Motion perception is an important aspect of daily visual experience. It involves a network of regions that contribute to different functions such as perceiving object motion, self motion, the guidance of eye and hand movements and the perception of the form of moving two to three dimensional objects. Global motion perception involve the ability to extract the central direction tendency from an extended area of visual space containing different local directions. Global motion perception may be a sensitive measure of neurologic and visual cortex development. Psychological testing includes intelligence tests, vocational tests, aptitude tests and personality tests. Random dot kinematogram (RDK) stimuli are used to measure motion coherence threshold in preterm children with analysis of eye movements to grade the direction of optico kinetic reflex (OKR). Tzu-Ying, Robert j jacobs ,Nabin Paudel (2013), stated that Global perception emerges at 1-3 months of age and continue to develop though out childhood . [43] N.M AYLOR,l.s Jakobson, D. Maurer, (2009) , revealed preterm borns show elevated threshold for global motion and global form, reduced sensitivity to all three types of stimuli, but as expected, these deficits were not comparable in magnitude. This deficit score analysis revealed that problems with the processing of dynamic cues- particularly those signaling coherent. Deficits in the ability to process global motion , affect 40% of preterm borns. Preterm borns have an increased risk of isolated and combined motion perception problems, independent of their performance IQ.[44] But may be associated with autism and developmental dyslexia.(Gunn et al 2002)

VISUOSPATIAL PERCEPTION: Visuospatial perception is the ability to perceive the physical location of an object in relation to the own body and to identify the physical relationship between different objects.It is vulnerable to the disruption in development associated with preterm births. The deficit may be due to depressed intellectual skill or may be combined effect with perpetual skill. Preterm borns have difficulty with attentional control. It is assessed using four verbal (VIQ) subtests (similarities, arithmetic, vocabulary, comprehension) and three performance (PIQ) subtests (picture arrangement, block design, object Assembly) [45] Children born preterm, perform poorly than full-term control four visuospatial perceptual tasks. Intelligence and parental education are associated with performance, preterm birth contribute independently of these factors on three of four tasks. Hence preterm borns have deficit on visuospatial tasks, the lower IQ scores and parental education levels increase the deficit. Phillipa R. Butcher, Anke Bouma (2012) revealed children born preterm perform less accurately and slowly on all the tasks. Children born preterm scores lower VIQ (verbal intelligence quotient) and PIQ (performance intelligence quotient).[44],[45],[46],[47]

NEURO PSYCHOLOGICAL TESTS: These tests are done to differentiate between different pictures, reaction times and processing speeds. These tests shows poor performance of preterm borns , in tasks involving motor skills, aspects of visual perception such as discriminating line orientations, naming shapes or matching block patterns and visuomotor integration. These deficits continue into childhood and even in adult life.[48] Performance of motor, visual perception and vasomotor integration tasks appears to be correlated with gestational age and birth weight and preterm borns have poor performance. The incidence of strabismus and impaired stereopsis is noted in preterm borns. Inspite of the advances in neonatal care, the preterm borns had minor motor skill deficits. Chaminade and colleagues [49]noticed that the adults who were born preterm are unable to perform action recognition tasks. Low birth weight preterm borns has low visuomotor integration are associated with structural changes of brain , including thinning in lateral areas of temporal and parietal lobes along with thickening of frontal lobe, reduced cortical surface area primarily in the frontal, temporal and parietal lobes and reduced white matter integrity with in associated tracts. Ventricular dilatation, corpus callosum thinning and reduced white matter integrity are associated with impaired visuomotor and visual perceptual performance in low birth weight , preterm born adolescents.[51] Influence of visuomotor and visual perception the abnormalities on brain may help in management of neuropsychological deficits in preterm born. O'Connor and colleagues found a statistically lower score on fine motor skill tasks in children with zone 1 ROP compared to those with zone2 ROP(zone 1 is closer to the macula, the centre of vision and likely to indicate more severe ROP).[50] Children with severe ROP, have reduced vision, strabismus, amblyopia, which affect visuomotor development.

IMPLICATIONS OF DEFICITS IN VISUAL PERCEPTION AND VISUOMOTOR INTEGRATION: Visual perception, motor skill and visuomotor integration are associated with educational outcomes, learning, behaviour and attention. Visuospatial perception, visuomotor co-ordination, attention executive function and performance of preterm children were poor, particularly in mathematics, which is associated with visuospatial memory.

DISCUSSION

This systemic review revealed that individual born preterm has attention difficulties as early as during 2 yrs of life. Reflexive functions as visual following, latency to fixate are impaired. Present findings are similar to previous studies. Preterm borns showed the deficit of visual following and latency to fixate. The review suggests that the increased risk for deficits in volitional control is associated with prematurity. It was found that very low birth weight infants with no IVH or PVL and only mild ROP are largely spared from major disruptions in visual functions, hence it is evident that visual system in preterm borns is disrupted by severe retinopathy or significant cerebral abnormalities. Therefore, a single point measurement may not be responsible impairment of entire spectrum of visual development and this needs a religious follow up of premature infants during early childhood.

Searle et al showed that acquity of vision depends on post conceptional age. The neurological pathways of retina are active between 22 & 40 weeks GA, their organization occurs during sleep in dark (Graven). However total darkness is bad for visual development.

CONCLUSION

It may be concluded that the present analysis revealed the visual efficacy, visual perpetual skills and visuomotor skills in preterm borns, is impaired, more if associated with severe retinopathy or gross cerebral mal development.

Children born preterm are at risk of reduced performance on tasks targeting higher level visual function .These may be related to the conditions associated with preterm birth as intraventicular haemorrhage, PVL and ROP.

It is evident that preterm children present visual efficacy problems and are at risk of delays in perpetual motor abilities. Early evaluation should be considered for accurate diagnosis and treatment in order to improve their cognitive functioning.

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