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Analysis of Risk Factors for Neurodevelopment and Visual Functions in the Preterm Infant to Establish an Early Detection and Treatment

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Abstract

Objective: By identifying the different risks for neurodevelopmental and visual functions in preterm infants we can establish and early detection and treatment.

Method: A cross-sectional study was conducted in preterm infants to analyze the effect on neuro visual functions related to risk factors, including bronchopulmonary dysplasia (BD), sepsis, ventricular hemorrhage (VH), retinopathy of prematurity (ROP), and the effect on attention, oculomotor defects, Infantile Cerebral Palsy (ICP) and Cortical Visual Impairment (CVI). Fisher Exact Test was used.

Results: 113 children (53 men, 60 women). Gestational age: 30.8+/-3 weeks of pregnancy. Weight: 1586+/-660 g. Strabismus was in 74%, nystagmus in 18.5%, CVI in 14%. Both low weight (0.004) and gestational age (0.0001) were related specifically to BD (0.00001). Hypoxia was associated (50%) with VH (0.0048), ROP (50%, 0.0341), and infections (54.5% 0.00001). CVI was in 16 cases (14%). Epilepsy was present in 47% of cases with CVI, more than double the global rate (0.0022). VH was associated with infections (<0.00001). ICP was related to apneas (0.0154) and VH (0.0112). A relationship was demonstrated between ROP statistically positive with BD (<0.0002).

Oculomotor disorders, strabismus and nystagmus, showed a higher frequency with respiratory defects, sepsis, VH, and optic atrophy. Both, VH and CVI registered a direct statistical relationship with strabismus in premature infants (<0.00001). Nystagmus was related to respiratory failure, BD, apneas (0.0231), and optic nerve atrophy (0.0286).

Conclusions: We found that the oculomotor alterations in premature children are manifestations more related to brain damage, especially hypoxic phenomena and ventricular hemorrhage. The specific detection of strabismus and nystagmus should be considered in the integration of the diagnosis of neurodevelopmental impairment. All this can represent a major risk for neurological developmental in preterm children, knowing this we have to follow them to apply an efficient treatment for better rehabilitation.

Keywords: Amblyopia, Brain damage, Disability, Nystagmus, Retinopathy, Strabismus.

Introduction

The World Health Organization has considered that there are 15 million premature births each year (less than 37th week of gestation), based on 184 countries, the proportion is very diverse and goes from 5% to 18% of live newborns, this could represent a ratio greater than 1 in 10 births, and affecting more to Africa and South Asia, and also related to a low poverty rate, less access to health services and higher disability rate. Disability worldwide covers more than a billion people, with a quality of life affected that will require rehabilitation and health services and who have less access to economic work. In Mexico, an expense of more than 85.6% has been calculated for families with a disabled member, especially compromising health care and medication payments.

More than 70% of disability problems are related to birth, affecting the person from the childhood stages, affecting schooling in childhood up to employment in adulthood, which for example, it has been reported as low as 30.5% for men and 34.7% for women, of which 63.5% do not receive technical aids, 4.6% use Braille and only 1.6% use a computer with an audio system [1-3].

With the increase in the survival of premature infants, there are also higher numbers of people with disabilities. In this study, we have aimed to analyze the different comorbidities that can occur in premature births, as well as their effect on neuro-visual functions; under the hypothesis that knowing the risks that affect the visual development of the premature would allow establishing an intentional search that leads to earlier diagnosis and can establish an effective and timely treatment that allows the reduction in the numbers of visual impairment, including perceptual and attention functions.

Materials and Methods

A retrospective, cross-sectional, and descriptive study was carried out in premature children who attended the retina and strabismus in a private care clinic, from January 1, 2015, to January 1, 2019. The eligibility criteria were based on all the files that concluded both controls and surveillance in the departments of retina and strabismus; the follow-up had to be at least 12 months.

The variables to analyze were selected between the risk factors and conditions related to premature birth. The information was obtained through the parents and the referral of the pediatrician and neuro pediatrician, including the general data and complications events: Weeks of pregnancy (wop), birth weight, days in the Neonatal Intensive Care Unit (NICU), ventricular hemorrhage (VH), hydrocephalus, leukomalacia, bronchopulmonary dysplasia (BD), infantile cerebral palsy (ICP), epilepsy, neonatal infection, apnea. Other variables were added through the examinations indicated for the study: retinopathy of prematurity (ROP), strabismus, nystagmus, cerebral visual impairment (CVI), atrophy of the optical nerve. All patients had a Brain Magnetic Resonance Image.

For retinal examination drops of tropicamide-phenylephrine were applied, and the same Retinologist Doctor performed it. The strabismological examination was performed including cycloplegic refraction using one drop of 1% cyclopentolate and revision 45 minutes later, and the same Strabologist performed it. For the report of refraction alterations, we classified astigmatism as "low" when it was equal or less than 3 diopters and "high" at greater than 3 diopters.

All the data were recorded in the clinical file, which includes the personal data authorization form signed by the responsible family member and which is independent of the medical reports. Medical reports of the Retina and Strabismus department were independent to avoid any potential source of bias. The total size for this

research was completed with these two reports for the unique file.

The quantitative variables were registered from NICU reports wop, weight, NICU days.

The data of the variables were registered in the Excel Windows program and processed with descriptive statistics. Fisher's exact test was applied for 2x2 contingency tables between different variables, with a significance level of 0.05.

Results

Considering the characteristics to be chosen for the study, 113 files were selected. 53 men, 60 women were included. We got the general information of birth, and then the results of the final exploration of retina and strabismus review, to do the cross-sectional analysis late evolution after 12 months was not considered for this research. Average global gestational age: 30.8 +/- 3 wop, ranges 23-38, and median 31. Weight 1586 +/- 660 g, ranges 510-3500, median 1500 g. Multiple pregnancies were reported in 20 cases (17.6%), 18 twin pregnancies, and 2 triplet pregnancies. Average in intensive care: 44 days. The average age at revision: 3.5 +/- 2 years old, ranges from 6 months to 18 years old, median 2 years.

It was diagnosed as a sequel: Infantile cerebral palsy in 22 cases (19.4%), being 90% spastic, 2 cases flaccid. Hemiplegia in 8 cases (7%), hydrocephalus in 6 (5.3%) of which required a bypass valve in 3 cases. Complications close to birth were registered within the first 3 months: Infectious processes 25 (22%) with sepsis in 18 cases (15.9%) and pneumonia in 6 (5.3%), ventricular hemorrhage in 20 cases (17.6%), epilepsy in 20 (17.6%), bronchopulmonary dysplasia 12 (10.6%), apneas 11 (9.7%), persistent cardiac ductus arteriosus 6 (5.3%), leukomalacia 5 cases (4.4%) (Table 1).

Cortical Visual Impairment

CVI was diagnosed in 16 cases (14%). Regarding the CVI, neither weight nor gestational-age was relevant (30.8g, 1642.9 wop), but they did spend more days (59.5) in intensive care. Epilepsy was present in 47% of cases with CVI, being more than double the global rate, demonstrating a positive statistical relationship (0.0022). No relationship was found with ROP, infections, or strabismus than overall, but the percentage (23.5%) was higher in nystagmus (without statistical significance 0.3063), VH (without statistical significance 0.4818), and ICP (without statistical significance 0.7399).

Ventricular Hemorrhage

VH occurred in 18% of premature infants. As a complication associated with risk factors, we found that the pregnancy age and weight in the group of premature infants with hemorrhage were lower (29.6 weeks, 1281 g), with a direct statistical relationship (0.0012), and the days of intensive therapy were more (58 days), compared to the average. VH was directly associated with infectious processes (sepsis, enterocolitis, pneumonia) in 60%, this was practically 3 times more than the global one (with a statistical significance <0.00001). Leukomalacia occurred in 25% of children with VH, and hydrocephalus in 30%, compared to global averages (4.4 and 5.3% respectively). Children with VH were not associated with an increase in the number of cases of strabismus, nystagmus, ROP, epilepsy, ICP, BD, or CVI.

Bronchopulmonary Dysplasia

Children, whit respiratory difficulties, BD and pneumonia, had low weight (1248.9g), 28.9 wop, and more days of intensive therapy than the average (66 days). Both low weight (0.004) and gestational age (0.0001) were statistically related to increased respiratory stress, and specifically to BD (0.00001). Ventilation and oxygenation problems were more frequently associated (50%) with VH (statistically positive 0.0048), with ROP (50% and statistically positive 0.0341), with infectious processes (54.5% and statistically positive (0.00001) with sepsis (33.3%), followed by pneumonia (15.1%), enterocolitis (6%), and hepatitis (3%). Likewise, oxygenation defects and respiratory problems were statistically associated with CVI (50%, positive Fisher value 0.0125). Despite the increase in the percentage of presentation in the following damages, a statistical relationship was not demonstrated: epilepsy (27%, 0.1063), ICP (30%, 0.072), leukomalacia (10%, 0.1693), nystagmus (27.2%, 0.1063), strabismus (69.6%, 0.2964), and atrophy of the optical nerve (27.2%, 0.3223).

Infantile Cerebral Palsy

Children with ICP weighted 1497 g, which is less than the global average (not significant 0.239), 30.4 wop, and 58.6 days in intensive care. It was not related to higher CVI or ROP. When analyzing the ICP with other risk factors, a higher frequency of apneas was found, which was three times that of the global apnea (36%),

Table 1

	GENERAL GROUP	WITHOUT VENTRICULAR HEMORRHAGE	WITH VENTRICULAR HEMORRHAGE
TOTAL	113 (100%)	93 (82%)	20 (18%)
AGE	3.5 +/- 2 years old	3.7 +/-4 years old	2.4+/-1 years old
SEX	53 Male: 60 female	43 male: 50 female	10 male: 10 female
WEEKS OF PREGNANCY (wop)	30.8 +/- 3 wop ranges 23-38 median 31	31+/-3 wop ranges 24-38 median 31	29.6+/- 3 wop ranges 25-37 median 29.5
WEIGHT	1586 +/- 660 g median 1500	1652+/-668 g median 1650	1281 +/-536 g median1082
DAYS IN THERAPY	44 days	37 days	58 days
INFANTILE CEREBRAL PALSY	22 cases (19.4%)	13 cases (11.5%)	9 cases (7.9%)
HEMIPLEGIA	8 cases (7%)	5 cases (4.4%)	3 cases (2.6%)
HYDROCEPHALUS	6 cases (5.3%)	0 cases	6 cases (5.3%)
SEPSIS	18 cases (15.9%)	9 cases (7.9%)	9 cases (7.9%)
BRONCHOPULMONARY DYSPLASIA	12 cases (10.6%)	8 cases (7%)	4 cases (3.5%)
EPILEPSY	20 cases (17.6%)	15 cases (13.2%)	5 cases (4.4%)
RETHINOPATY OF PREMATURITY	22 cases (19.4%)	18 cases (15.9%)	4 cases (3.5%)
NYSTAGMUS	22 cases (19.4%)	20 cases (17.6%)	2 cases (1.7%)
STRABISMUS	74 cases (65.4%) (58% ESOTROPIA)	57 cases (50%) (56% ESOTROPIA) 1 SKEW DEVIATION	17 cases (15%) (58% ESOTROPIA) 1 SKEW DEVIATION
OPTIC NERVE ATROPHY	24 cases (21%)	15 cases (13.2%)	9 cases (7.9%)
MYOPIA	25 cases (22%) -4.2	23 cases (20.3%) -4.7	2 cases (1.7%) -4.5
HYPERMETROPIA	36 cases (31.8%) +4.7	26 cases (23%) +4.5	10 cases (8.8%) +5.2
MULTIPLE PREGNANCY	20 cases (17.6%)	16 cases (14.1%)	4 cases (3.5%)
CORTICAL VISUAL IMPAIRMENT	17 cases (15%)	12 cases (10.6%)	4 cases (3.5%)
LEUKOMALACIA	5 cases (4.4%)	0 cases	5 cases (4.4%)
CORTICAL ATROPHY	8 cases (7%)	5 cases (4.4%)	3 cases (2.6%)
PATENT DUCTUS ARTERIOSUS	6 cases (5.3%)	5 cases (4.4%)	1 case (0.8%)
PNEUMONIA	6 cases (5.3%)	3 cases (2.6%)	3 cases (2.6%)
APNEA	11 cases (9.7%)	6 cases (5.3%)	5 cases (4.4%)
MACULAR ECTOPIA	5 cases (4.4%)	4 cases (3.5%)	1 case (0.8%)
INFECTIONS	25 cases (22%)	9 cases (12.3%)	11 cases (9.7%)

statistically significant (0.0154), with 4 cases suffering cardiorespiratory arrest, and 1 case with dextrocardia, as well as the increased frequency of VH that was statistically significant (36%, 0.0112). On the other hand, the following, despite their higher percentage of presentation, were not statistically significant: hydrocephalus 13.6% (0.0869), sepsis 31% (0.133), nystagmus 27% (0.3682), and optic atrophy 36% (0.0787). Epilepsy (18%) and strabismus (63%) results were similar to the global.

Retinopathy of Prematurity

These children with ROP had an average of 26 +/- 1 wop, with ranges from 23 to 30 wop, mode 25 wop; birth weight 900 +/- 170

g, ranges 510 to 1230 g, and they were in the intensive care unit for an average of 68 days. The children who developed ROP had a much lower gestation age and weight compared to the global average (26 vs. 30.8 wop and weight: 900 vs. 1586 g); and they required more days of hospitalization (68 vs 44 days). ROP was more frequent in women (63.6%).

Despite this low weight and prematurity, ROP was not associated with more frequency of VH, nor was it demonstrated that there was a greater presence of ROP due to infectious processes including sepsis (Fisher value: 1.0), or a relationship with a higher frequency of ICP. (0.5585).

In general, retinal damage was demonstrated in 36 cases (31.8%) of which vascular tortuosity were observed in 3 cases, macular ectopia in 5 cases. There was ROP in 22 children (19.4%), being: ROP grade II: 3 cases, ROP III: 16 cases, ROP with plus disease: 2, ROP IV: 1, ROP V: 3 cases, none of these were bilateral, being the best eye in ROP II, II and III. Twelve cases were treated: 5 with an application of intravitreal antiangiogenic (Ranibizumab) plus laser and 7 with an application of laser, all of them under inhalation anesthesia.

Regarding refractive errors in children with ROP, myopia predominated with 54.5% (average -4.2) and hyperopia was 18% (average +6.00), which was a number greater than the global average.

The albinotic retina was observed in 2 cases; peripheral retinal degeneration white without pressure in 1 case, lattice degeneration in a 5-year-old boy who had previously received laser for ROP.

There was atrophy of the optical nerve in 24 cases (21%), coloboma of the optic nerve in 2 cases; bilateral (1 was Morning glory syndrome), congenital retinal folds in 1 case.

A relationship was demonstrated between the children with ROP that was statistically positive with BD (<0.0002). It was not significant with strabismus (0.6268) or nystagmus (1.0) compared to children without ROP.

Strabismus and Nystagmus

Refractive defects were: Low myopic astigmatism in 9 cases, high myopic astigmatism in 3. Low hypermetropic astigmatism in 20 cases, high hypermetropic astigmatism in 1; myopia in 25 (22%) with average -4.2, the highest -14.00 dioptres, hyperopia in 36 cases (31.8%) with average +4.7, the highest +8.00 dioptres.

When globally analyzing the oculomotor alterations including nystagmus, strabismus, and apraxias, there were a total of 85 cases with predominance in the female sex (47 vs 38), more hyperopia was observed (35%) with an average of +4.7 diopters, compared with the 20% of myopias with an average of -5.3%; taking into account that in children without strabismus, myopia appeared in 35.7% with an average of -2.1 and with hyperopia in 7% with an average of +5.5. The percentage of hyperopia in the group of children without strabismus is significantly lower than in the global group, and the relationship as a risk factor between hyperopia in premature children and strabismus was statistically significant (0.0051). Low-weight children presented more strabismus (1574g in children with strabismus vs. 1623g children without strabismus), but neither the lower weight nor the weeks of pregnancy as variables recorded a statistical relationship with strabismus (0.6638, 0.8276), nor the longest time in the NICU (46 days vs 31.5 in children without strabismus) (0.5526).

The study among the group of premature infants with oculomotor disorders, strabismus and nystagmus, compared with the group without them, showed a higher frequency with respiratory defects (40 vs. 25%), higher frequency of sepsis (23.7 vs. 10.5%), more children with ventricular hemorrhage (21% vs. 10.7%), and optic atrophy (21 vs. 14%), although the latter was not a risk marker for strabismus unless it had generated visual loss (0.5868).

In both groups, with and without strabismus, ROP damage was identified (20 vs. 17.8%) whose relationship with the global number was not statistically significant.

Both the VH and the CVI registered a direct statistical relationship with the presence of strabismus in premature infants (Fisher's exact test <0.00001), and not so with leukomalacia, epilepsy, or ICP, which in children with strabismus was found to be 22.3%, a percentage higher than the global percentage, and compared with children without strabismus 17.8% (0.7914); and although sepsis was percentage higher, we did not find statistical significance compared to children without strabismus (0.1184).

To better identify whether nystagmus contributed the greatest risk, they were exposed to the group of children without nystagmus, finding a higher statistical correlation between respiratory failure,

especially BD and apneas (0.0231), and the presence of atrophy of the optical nerve (0.0286), not so with ICP, VH, hydrocephalus, ROP, or CVI. When studying only the children with nystagmus, they had more days in intensive care (57), lower gestational age (31.1 wop), but not in weight (1648.9 g); compared to children with strabismus without nystagmus (weight: 1550.4g, 41.8 wop, 41.8 days in NICU).

About the type of strabismus, which was diagnosed in 74 cases (65.4%), were: Esotropia in 42 cases (56.7%), exotropia in 28 (37.8%), convergence spasm 2, skew deviation in 2; all the esotropia cases were congenital esotropia, of which they had a cross fixation pattern and a big angle in 4 cases, microstrabism in 5, associated with Dissociated Vertical Deviation in 5. Exotropia: constant exotropia in 15 cases, intermittent exotropia in 11, and exophoria in 2. They required treatment for amblyopia in 20 cases of strabismus, chemodenervation with botulinum toxin was indicated in 5 cases, and strabismus surgery was required in 7 cases. Nystagmus was diagnosed in 22 cases (19.4%), and 3 cases required nystagmus surgery.

Discussion

Achieving good visual maturation, adequate image transmission, image perception, and then a consistent response depends on the efficiency of brain structures at different levels. The adequate image capture in both retinas will be transformed from light stimuli to neural codes that by various brain pathways will stimulate perception, understanding, and response in a complex and individualized way, and then be stored in the memory functions that they will favor the subsequent strategies for learning and intelligence of the person.

CVI

When there is an interruption at any of these levels, these visual sensorineural processes can be damaged and the manifestations are usually multiple, of great variability, and have their characteristics, and with diverse combinations. They can be characterized, for example, from common and easily identifiable patterns, to other patterns with signs so slight that they can go unnoticed, and this does not mean that they are mild or less harmful. The various alterations in the integration of the images are contained in the concept of CVI, and generally do not necessarily correspond to an eye injury.

This CVI with shortcomings in visuospatial processing and learning can impact the development of the child in both motor and mental skills and can be limiting for the development of independence and quality of life. The difficulty in identifying all the manifestations that can add to CVI can delay the possibility of early rehabilitation. The frequency with which the CVI can appear in the child with premature birth is one of the reasons to anticipate the directed search for these alterations.

One of the most important causes of CVI is perinatal hypoxic-ischemic encephalopathy, especially affecting gray matter, hippocampus, thalamus, and brainstem; as well as the periventricular leukomalacia lesions that occur in the premature associated with ventricular hemorrhage. In both situations, there will be damage associated with both sensory and motor areas with the consequent symptom of cognitive injury with ICP. Other causes of CVI are traumatic brain injuries, infectious processes, and seizure events [4].

In the present work, we have evaluated the different risks associated with prematurity. Some are very evident and already known, but the statistical relationship made it possible to better identify these correspondences.

CVI in premature infants had a direct relationship specifically with the presence of epilepsy, which has significant destabilizing significance, making it necessary to keep the seizure symptoms as stable as possible. There is the possibility of seizures in children who have suffered a ventricular hemorrhage, for which reason we analyze this risk, which has already been associated with low weight and a few weeks of pregnancy, and sepsis; and later, taking the risk of leukomalacia, which in turn can impair proper axonal communication and be a factor in the development of ICP. Also, the higher frequency of nystagmus and its relationship with strabismus should be taken into account since the CVI would then add the phenomena of amblyopia, worsening the attention processes in the child.

VH, BD, Leukomalacia, Sepsis and ICP

Children under 28 wop are approximately three times more likely to experience severe ventricular hemorrhage than the 28-31 wop group. It appears that vasodilation resulting from hypoxia or hy-

percapnia initiates the event, and intravascular pressure may exceed interstitial pressure, with subsequent rupture of the germinal matrix capillaries, stasis, thrombosis, and ventricular hemorrhage.

The subependymal germ matrix contains the stem cells of the neurons and the glia, which migrate from the 26th week of gestation. This is a gelatinous layer located between the caudate nucleus and the thalamus. It is notorious between weeks 26 to 34 and disappears towards the 40th week of pregnancy. The germinal matrix is highly vascularized and receives irrigation from branches of the middle cerebral artery, the anterior cerebral artery, and the carotid artery, and the venous drainage goes to Galen's vein. From week 26 to 34 the vessels are made up of a thin layer of endothelium with no muscle layer, elastin, or collagen. Endothelial cells contain a large number of mitochondria and appear to have a high oxidative metabolism requirement.

When a hemorrhage in the Subependymal Germinal Matrix happens, the bleeding can be originated in the vascular zone of the layer of the germinal matrix, which in term infants and 10% of premature infants occurs in the choroid plexus or on the roof of the fourth ventricle; and in children younger than 28 weeks of pregnancy, bleeding may occur in the germinal matrix of the body or head of the Caudate nucleus. Chronic neuropathological changes seen after germinal matrix bleeding can leave a subependymal cystic lesion.

VH can spread and extravasated blood can cause arachnoiditis and acute dilation of the ventricular system, which occurs in 50% of cases, causing compression damage and hydrocephalus, which can be communicating or non-communicating. In the communicant, there is obstruction at the level of the Foramen of Monro, Sylvius's cerebral aqueduct, or the Luschka or Magendie foramen. Ventricular dilation is usually rapid, and clinical hydrocephalus is evident within two weeks of bleeding.

Some factors that may cause VH are: fluctuations in cerebral blood flow due to respiratory distress, increased blood pressure, maximum vasodilation associated with hypercapnia or hypoxemia, or both, increased central venous pressure, more use of a mechanical ventilator, pneumothorax, tracheal aspiration, coagulation disorders, the rapid expansion of blood volume, seizures, patent ductus arteriosus, painful procedures, use of dexamethasone, vasopressors, caffeine, among others. It can occur more frequently between 24-48 hours after birth and is more common in very young mothers with a low weight of the child <1500 g, and lower gestational age, occurring up to 90% in children younger than 32 weeks of pregnancy.

Periventricular leukomalacia is a complication that occurs due to necrosis of the periventricular white matter, dorsal, and lateral to the external angles of the lateral ventricles. Generally, there is the participation of the region adjacent to the trigones and occipital body, frontal horn, and ventricular body (centrum semiovale). It is associated with maternal infection, chorioamnionitis, hypocarbia (<CO2), among others. Depending on the degree of injury, it can be associated with spastic diplegia and ICP, sensorial and neural injuries, both visual and auditory, somesthetic, and cognitive problems. In a review of 2,113 premature infants, it was possible to analyze the impact on neurodevelopment associated with different risk factors [5,6].

Sepsis significantly increases the morbidity of premature infants and is inversely proportional to gestational age, related to low weight and associated with the effects of hypotension and decreased brain flow, which can have important effects on the white matter and therefore with cognitive and motor damage, memory functions, attention mechanisms, and ICP; therefore it should be considered as a possible risk factor for long-term neurodevelopmental disorders in premature infants [7].

We can observe that the most important factor for the presence of VH and CVI was BD, which are frankly associated with hypoxic phenomena, therefore it will also be related to a higher frequency of ROP, and is especially found in low-weight and very premature babies.

The effects on saturation levels between 85-89% compared to 91-95% showed less possibility of ROP, but it must be considered that they have also been associated with an increase in mortality in extremely preterm children. When faced with BD, oxygen therapy sometimes requires greater aggressiveness and, consequently, greater ROP, which although it can be considered multifactorial, the presence of ROP can, therefore, result in a marker, consequently, of neurological and sensory damage [8].

ROP, Strabismus and Nystagmus

Several publications have mentioned as risk factors in the development of ROP: hyperoxia, long-term oxygenation therapy, artificial ventilation especially longer than 7 days, episodes of hypoxemia, BD, apneas, blood transfusions, anemia, sepsis, enterocolitis, metabolic acidosis, low Apgar, asphyxia, VH, heart disease, glucose disturbances, hypotension, pneumothorax, use of pre and postnatal steroids, use of antibiotics and xanthines such as aminophylline and theophylline, patent ductus persistence treatments such as indomethacin, phototherapy, and parenteral nutrition requirements.

About strabismus, although the abnormality associated with macular ectopia, optic atrophy, or retinal detachment alone may be a cause of strabismus, there was no statistically significant relationship among children who had ROP, so there was no-showed a global tendency to strabismus and nystagmus compared to the universe of premature children or children without ROP (children with ROP: 54.5% of strabismus and 18% of nystagmus, vs. global strabismus 65.4% and 19.4% of nystagmus). But a change was observed since while the most frequent strabismus in this paper was esotropia, in children with ROP there was a higher percentage of exotropia (66%); Strabismus was related to visual loss due to atrophy of the optical nerve or total retinal detachment in 50%, being only by ectopia in 16.6%, this would explain the greater frequency of exotropias.

We can identify strabismus as a risk factor associated with VH and for CVI; and nystagmus to BD, hypoxia, apneas, and atrophy of the optical nerve. This difference could be caused, the first with neural changes due to the phenomena of amblyopia; and probably nystagmus from a more diffuse hypoxic and metabolic injury.

Amblyopia is one of the most important causes of visual damage worldwide. Neurological alterations in amblyopia begin before the establishment of binocular integration of thalamocortical impulses, with "Long-term Depression" (LTD) changes at the synapses of the visual cortex with acute activation of NMDA receptors mediated by AMPA receptors. These changes that occur in various brain areas, for example in the CA1 region of the hippocampus, and they are similar to what occurs in layers 2-4 of the visual cortex (unlike layer 6 that requires activation of the glutamate receptor 5, mGluR5); and that it finally shares two characteristics: the impact on visual damage due to the failure of an adequate visual stimulus occurs very early, and second: that the structural alterations of the synaptic connections are secondary to LTD. Both changes can be closely correlated with a cerebral dysfunction observed in the CVI, and amblyopia can impede the adequate binocular stimulus and affect the attention mechanisms, learning, and development of the different types of intelligence in the child [9,10].

This is one of the most urgent factors in the rehabilitation of the premature baby and its possible negative effect when delayed. The possibility that binocular injuries due to damage in retinotopic reception in the Primary Visual Cortex could achieve a reorganization through axonal recovery with a remodeling in the interconnectivity and even recovery of originally damaged connectivity from non-deprived areas suggest that the plasticity dependent on experience and activity can be stimulated to favor and consolidate the dynamic changes necessary for visual perceptual abilities [11].

The concept of "Perceptual Learning" (PL) has been referred to as the acquisition of long-term visual skills as a capacity obtained by plasticity mechanisms in visual perception. These processes occur most important during childhood and require the participation of multiple circuits, early changes in them, and adequate interconnectivity. Multiple studies have shown activity in the Primary Visual Cortex, in the medial cortex and lateral intraparietal area that has been known in perceptual decision making, frontoparietal, temporomedial areas, among others; whose varied responses may be subject to the type of stimulation, orientation, speed, the direction of movement, contrast, etc., that could stimulate brain circuits by different neural mechanisms and the interconnection between them, responding both to discrimination and detection and then understanding of visual stimuli. The attention mechanisms will allow the child, from the first months of life, to categorize the most relevant information about the not important of all the transmitted signals, so that attention is essential for PL. These selective attention mechanisms achieve their maturation by more effective connectivity between neuronal groups that transport relevant information with selective synchronization patterns, that at the same time are capable of modulating selective interaction patterns towards other neuronal groups to improve more complex visuomotor responses [12].

The function of selective attention mechanisms not only improves the synchronization of the neuronal zone coherent to the stimulus

but also manages to suppress the neuronal group that responds to non-relevant distracting stimuli, in addition to maintaining an interaction towards distant cortical regions; selective attention synchronization is active even before the arrival of the stimuli, followed by an accurate and individual reading to process the information in time and quality [13].

The brain structures activated during the attention mechanisms operate at various levels of processing and are required both for spatial perception, preparation, approach, and sensorimotor activities, as well as for identity and social functions, for example in the temporoparietal junction that includes the self-reference and social cognition in which the person can discern the mental state of others or feel empathy [14].

We take into account the limitations of the present study that may be contributed by the lack of information, lost information, or failure in diagnostic imaging methods, for example, especially when premature infants did not receive more comprehensive hospital care. In the present study, files that did not have complete studies were not included and therefore this same bias may modify the assessment results. For this reason, we left open the possibility that although some variables resulted in a lower significant risk value, they continue to be considered as a probable factor of greater brain damage.

Conclusions

The neurovisual effects happening in the premature baby can be multiple, diverse, and dangerous. The current concepts of CVI include various alterations in the perception understanding and responsiveness of the child. Risks such as VH, BD, hydrocephalus, epilepsy, leukomalacia, strabismus, nystagmus, ROP, may be factors that can increase the ICP indices, and difficulties in learning, in attention mechanisms, and different types intelligence, including emotional. Early detection of risk factors and timely establishment of disability diagnoses can help establish treatment more effectively by installing it promptly. Proper management of strabismus, nystagmus, and amblyopia phenomena, considering the effects on multiple brain interconnectivity, would improve the conditions of attention functions, memory, psychosocial and visuomotor skills, impacting all this on a better quality of life.

Conflict of Interest

The author(s) declare that they have no competing interests.

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