

Original Article

Intrapartum Asphyxia in Relation with the Risk for Developing of Cerebral Palsy

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Abstract

Background and goals

Neonatal hypoxic-ischemic injury defined as: "Asphyxia of the umbilical blood supply to the human fetus occurring at 36 gestational weeks or later", represents still a stable cause of mortality and disability despite the progress in assisted respiratory and intensive care technology. It is thought to be the major cause for developing of Cerebral Palsy (CP). We performed an observational study that included children with cerebral palsy, in order to assess the relation of intrapartum asphyxia and CP.

Methods

Our group included children with diagnosis of CP, age under 5 years with same characteristics regarding sex, families social and educational level. There were excluded children with malformations, brain tumors, neurometabolic and neurodegenerative disorders. We evaluated the relation between the presence of intrapartum asphyxia and type of CP, type of neurological involvement: Spastic, extrapyramidal or mixed and the relation with CP comorbidities as motor and mental retardation and epilepsy.

Results

We evaluated 110 children with CP - 63 females (57 %) and 47 males (43 %); 43 of them (39 %) presented documented intrapartum asphyxia. The type of CP was dominating spastic type (79 %), associated with motor retardation in 102 (92 %), cognitive disability in 81 (73,63 %) and epilepsy in 53 of them (48 %). We found possible relationship for developing dystonic and mixed type of neurological involvement, no relation regarding the type of CP - tetraparesis, diparesis or hemiparesis. In our group, no relationship was found regarding

motor and mental retardation and history of intrapartum asphyxia, instead there was a correlation with epilepsy in this group of children.

Conclusion

CP is a multifactorial disorder. Intrapartum asphyxia could be a factor that determines the type of CP and associated disabilities, but it is not specific. Probably studies on larger groups could better clarify the relation between CP and intrapartum asphyxia.

Keywords: Cerebral palsy; Intrapartum asphyxia

Abbreviations

HI - Hypoxic-Ischemic

HIE - Hypoxic-Ischemic Encephalopathy

EEG - Electroencephalography

CP - Cerebral Palsy

Background

Neonatal Hypoxic-Ischemic (HI) injury is defined as: "Asphyxia of the umbilical blood supply to the human fetus occurring at 36 gestational weeks or later" [1-5]. Neonatal HI is synonymous with Hypoxic-Ischaemic Encephalopathy (HIE) occurring in the term infant (where "term" is defined as 36 gestational weeks or later). The markers for neonatal HI include: 5-min Apgar score of less than 5; need for delivery room intubation or CPR; umbilical cord arterial pH less than 7.00 and abnormal neurological signs, such as hypotonic muscles or lack of sucking reflex. Electroencephalography (EEG) has also proved helpful as a predictor of clinical outcome [6,7].

The watershed zone is susceptible to injury in brain hypoperfusion. There are differences between term and preterm neonates regarding brain reaction to hypoxia, due to anatomical particularities. Preterm have imagerie cerebrale blood flow, the periventricular white matter is the most vulnerable to ischemic insult; autoregulation of cerebral blood flow is limited in preterm infants due to immature vasoregulatory mechanisms and underdevelopment of arteriolar smooth muscles. Hypoxic-ischemic insult results in germinal matrix hemorrhage from rupture of the periventricular capillaries and increased venous pressure due to ischemic tissue reperfusion, cysts formation in periventricular area and finally, periventricular leukomalacia associated with ventriculomegaly and thinning of corpus callosum [8].

In term infants, circulation and autoregulation of cerebral blood flow are similar to that of an adult. Ischemic and hemorrhagic injuries tend to follow similar patterns of those in adults. Infarcts in the parasagittal watershed areas are the most common lesions and they involve territories between anterior cerebral artery and middle cerebral artery, or between middle cerebral artery and posterior cerebral artery; both cortex and subcortical white matter being involved. Severe and diffuse hypoxia results in cerebral edema followed by cortical atrophy, ulegyria or multicystic encephalomalacia [8].

Hypoxic-ischemic cerebral injury during the perinatal period is one of the most commonly recognized causes of severe, long-term

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neurologic deficits in children; it is often related to Cerebral Palsy (CP) [1]. Neonatal HIE occurs in 1.5 / 1000 of the live births [8]. After neonatal HIE, 5-10 % of surviving babies present persistent motor deficits, while 20 - 50 % have sensory or cognitive deficits that persist to adolescence [2,3,5,9,10].

A meta-analysis of seven studies, that included 386 infants, analysed the average incidence of mortality and morbidity: 5.9 % of patients across all studies died, 16.3 % presented neonatal seizures, while 17.2 % associated neurological deficits, 14.2 % of them later developed cerebral palsy [5,11].

Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, behaviour, by epilepsy and by secondary musculoskeletal problems” [12].

CP affects approximately 2-2.5 / 1000 live births in the Western world, and more children in the developing world. The sex ratio is 1.4:1 males to females. Perinatal HIE in term infants was evaluated to be responsible for 25 - 30 % of causes of CP in the 80's [13]. In our days, birth asphyxia and complicated labour and delivery are responsible for 10 % of causes of CP [14].

Subjects and Method

We performed an analytical observational study in order to evaluate if HIE is one of the risk and prognosis factors for CP. Target population was formed by children with CP examined in our unit during the year 2008, with or without intrapartum asphyxia. From Demographics point of view, we evaluated children between 2 to 5 years of age, with same characteristics regarding sex, social and educational environment. Inclusion criteria: Children ages from 2 to 5 years with diagnosis of cerebral palsy, with same characteristics regarding sex, social and educational environment. Exclusion criteria: Children presenting disorders of movement and posture of other etiologies were excluded from group: Brain and spine cord malformations, brain tumors, neurometabolic disorder - suspected or confirmed, neurodegenerative disorder - suspected or confirmed, extrapyramidal disorders of unknown etiology.

Statistical analysis was performed using Microsoft Office Excel & Epi Info. We evaluated and quantified the relationship between risk factor and CP. Chi-square test was used: Any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. p -value ≤ 0.05 - indicates strong evidence against the null hypothesis, so you reject the null hypothesis. p -value > 0.05 - indicates weak evidence against the null hypothesis, so you fail to reject the null hypothesis. p -values very close to the cutoff (0.05) are considered to be marginal (could go either way). We used Risk Ratio (Relative Risk) = RR, with confidence intervals of 95 % (upper and lower limit); $RR > 1.2$ - meaning there's a higher risk for children exposed to develop CP; $RR < 0.8$ - significantly lowers the risk of children exposed to develop CP.

Results and Discussions

We evaluated 110 children with CP, 63 girls (57 %) and 47 boys (43 %). Intrapartum asphyxia was documented in 43 of children

(39 %). Cerebral palsy was spastic type in 76 % of children. According to the type of CP: 86 (78 %) were spastic type (tetraplegia - 29 children, diplegia - 30 children, paraplegia - 7 children and hemiplegia - 20 children), 4 with dystonic type and 20 mixed type. Prematurity was present in 34 (30 %) of children from our group. In 43 of the CP children intrapartum HI was documented, the type of CP was spastic type in the majority of them - 34 (14 of them with tetraplegia, 15 with diplegia and 5 with hemiplegia), while the rest of 9 children (21 %) had mixed form of CP.

Spastic Type of CP

Spasticity is defined as hypertonia with resistance „to externally imposed movement that increases with increasing speed of stretch and varies with the direction of joint movement” [15]. There are present brisk deep tendon reflexes, with or without clonus (considered pathological when it does not stop spontaneously), pathological signs as Babinski response and motor deficit that involve lower extremity flexors and upper extremity extensors [15]. There are often associated pathological postures, characterised by internal rotation and adduction of the hips, foot equinus, resulting in a particular 'scissored' position. In our group, spastic CP was 1,01 times more frequent in children with intrapartum asphyxia comparing with those non-exposed: $RR = 1,01$ (95 % CI 0,83-1,24); $P = 0,85$. No clinical relevance was identified.

Distonik - Dyskinetic Type of CP

Distonia is a movement disorder characterised by sustained involuntary movements and intermittent muscle contractions that induce repetitive movements and / or abnormal postures [15]. Clinical signs and symptoms are characterised by involuntary, uncontrolled, stereotyped movements. The primitive reflex patterns are preserved and predominate, and the muscle tone varies from hypotonia to rigidity. Dystonic CP is dominated by abnormal postures (they may appear hypokinetic) and hypertonia (muscle tone is fluctuating, but easily elicitable tone increase). Statistical analysis in this group, related to intrapartum Hypoxic-Ischemic revealed: $RR = 0$ (95 % CI 0,83 - 1,24). $p = 0,13$; meaning it could be a possible clinical relevance, but larger sample is needed.

Mixed Type of CP

As the name says means a mixed CP form, associating spasticity and ataxia and / or dyskinesia. The child should be classified according to the dominant clinical feature. In our group, statistical analysis revealed that mixed CP is 1,27 times more frequent in children with intrapartum asphyxia comparing with those non-exposed: $RR = 1,27$ (95% CI 0,57-2,81); there is a possible clinical relevance, but larger sample is needed ($p = 0,54$).

Relation with Topographical Distribution of the CP Hemiplegia

Appears secondary to a focal cerebrovascular insult, most often in the territory of the middle cerebral artery. It was related to gestational diabetes, preeclampsia, fetal bradycardia and heart decelerations, prolonged rupture of membranes, or prolonged second stage of labor, vacuum delivery, emergency Caesarian section, also Apgar score of < 7 at 5 minutes, maternal fever $> 38^{\circ}\text{C}$ and hypoglycemia have been identified as independent risk factors for perinatal stroke [16]. In our

group, hemiplegia was 0.51 times more frequent in children with CP and intrapartum asphyxia comparing with non-exposed; RR = 0,51 (95 % CI 0,2-1,32), with possible clinical relevance but, larger sample is needed ($p = 0,15$).

Diplegia

It appears secondary to white matter lesions, Periventricular Leu-komalacia (PVL) or Periventricular Haemorrhagic Infarction (PVH) are consequences of insults operating mainly between 23 - 30 weeks gestation. After the 24th week of gestation, axon and dendrite formation appears, synaptogenesis and myelination and synaptic pruning and development of circuitry, process that continue up to the age of 2 years. Any injury at this age is associated with severe developmental disorders (Volpe cited by [17]). In our group, diplegia was 1.26 times more frequent in children with CP and intrapartum asphyxia comparing with non-exposed; RR = 1,26 (95 % CI 0,67-2,36), with possible clinical relevance but, larger sample is needed ($p = 0,46$).

In the group of paraplegia

Statistical analysis revealed: RR = 0 (undefined) and $p = 0,02$, meaning there is clinical relevance for developing paraplegia in relation with intrapartum asphyxia.

Tetraplegia

Appears more often when the brain reaches maturity close to term, when grey matter is more sensitive to injury than white matter. Acute severe hypoxia results in selective neuronal necrosis that involved especially the basal ganglia, thalamus and bilateral; the extent of insults depends on the severity and duration of the hypoxic-ischemic event [18,19]. In our group, tetraplegia appeared 1,55 more frequently in children with CP and intrapartum asphyxia comparing with non-exposed RR = 1,55 (95 % CI 0,82 - 2,93), with possible clinical relevance but larger sample is needed ($p = 0,17$).

We further analyzed the relation of intrapartum asphyxia in our CP group and associated impairments

Motor impairment is defined as: Partial or total loss of function of a body part, usually a limb or limbs that results in muscle weakness, poor stamina, lack of muscle control, or total body paralysis [20]. Impaired motor control (both gross and fine movements and oral coordination) represents one of the major symptoms of CP beside impaired coordination and poor muscle tone, balance and posture [21]. From all 110 children with CP in our group, 8 were considered to have normal motor development, the rest of 102 had motor disability. Statistical analysis revealed that motor impairment was 1,13 times more frequent in children with CP and intrapartum asphyxia comparing with non-exposed; RR = 1,13 (95 % CI 1,03 - 1,24), with clinical relevance between intrapartum asphyxia and the appearance of motor impairment ($p = 0,01$).

Intellectual disability

Was defined by WHO as: "Significantly reduced ability to understand new or complex information and to learn and apply new skills (impaired intelligence). This results in a reduced ability to cope independently (impaired social functioning), and begins before adulthood, with a lasting effect on development" (<http://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/news/news/2010/15/childrens-right-to-family-life/definition-intellectu->

al-disability); it represents associate condition in children with cerebral palsy, beside learning disabilities and epilepsy [21].

Analyzing statistical correlation between intrapartum asphyxia and association of cognitive impairment in our group of CP children, we found that cognitive impairment was 1,07 times more frequent in children with CP and intrapartum asphyxia comparing with non-exposed; RR = 1,07 (95 % CI 0,85 - 1,33), but no clinical relevance was found ($p = 0,55$).

According to DSM 5, intellectual disability (term that replace the old term of "mental retardation") is classified as: Mild (IQ = 50-55 to 70), moderate (IQ = 35-40 to 50-55), severe (IQ = 20-25 to 35-40) and profound (IQ below 20-25) [22].

Intellectual disability was present in 84 (76 %) of our CP children; 17 of them (15 %) presented mild intellectual disability, 18 (16 %) presented moderate intellectual disability, while the others 46 presented severe and profound intellectual disability. In the group of mild intellectual disability, statistical data showed that mild cognitive impairment was 1,38 times more frequent in children with CP and intrapartum asphyxia comparing with non-exposed, RR = 1,38 (95 % CI 0,57 - 3,31), it could be possible clinical relevance but, larger sample is needed ($p = 0,46$). As about moderate intellectual impairment, statistical analysis revealed that it was 1,24 times more frequent in children with CP and intrapartum asphyxia comparing with non-exposed; RR = 1,24 (95 % CI 0,53 - 2,9), there is possible clinical relevance, but larger sample is needed ($p = 0,61$).

Regarding the group of profound intellectual disability, it was 0,91 times more frequent in children with CP and intrapartum asphyxia comparing with non-exposed; RR = 0,91 (95 % CI 0,57 - 1,44), no clinical relevance was found ($p = 0,69$).

Epilepsy

Is another comorbidity of CP; 15 to 60 % of children with CP have been reported of having epilepsy [23]. It has been proved that hypoxic-ischemic insult induce neurotrophic factors release, with activation of multipotential progenitor cells in subventricular area and secondary proliferation and differentiation into neuronal and glial cells with migration and colonization of damaged cerebral structures [24]. Abnormal, excessive migration of neurons represents a high risk to develop epilepsy in these children. In our group, 53 children presented associated epilepsy (48 %). Epilepsy associated with CP was 1,39 times more frequent in children with CP and intrapartum asphyxia, comparing to non-exposed; RR = 1,39 (95 % CI 0,95 - 2,03), there is a possible clinical relevance ($p = 0,09$) but larger sample is needed. Other behaviour disorders could be associated in children with CP, including psychiatric or behavioural problems such as autistic spectrum disorders, ADHD, sleep disturbances, mood disorders and anxiety disorders. Four children (4 %) in our group presented autistic spectrum features. Statistical analysis showed that autistic spectrum features were 1,55 times more frequent in children with CP and intrapartum asphyxia comparing to non-exposed; RR = 1,55 (95 % CI 0,22 - 10,65), there is possible clinical relevance but larger sample is needed ($p = 0,51$).

Also, 12 children (11 %) presented hyperanxiety documented by psychological evaluation. Statistical analysis showed that anxiety is 0,14 times more frequent in children with CP and intrapartum

asphyxia comparing to non-exposed; RR = 0,14 (95 % CI 0,01 - 1,05), there was definite clinical relevance (p = 0,01).

Limitations of the study: As statistical analysis showed, larger samples are needed to identify relationship between intrapartum asphyxia and CP type and associated imparments. The observation was conducted when intrapartum and perinatal monitoring was still under development, observational studies in more recent years could show if the parameters remain the same or if they have improved.

Conclusion

It could not be established a straight relationship between intrapartum asphyxia and the risk of CP developing, that confirms, once again the multifactorial etiology of CP. Our results showed that intrapartum asphyxia could have a role in developing dyskinetic and mixed forms of CP.

We identified an obvious relationship between intrapartum asphyxia and paraplegia ('mild') form of CP.

Our results showed that intrapartum asphyxia could be involved in the development of associated imparments such as: Epilepsy, behavior disorders and cognitive impairment in children with CP, but larger groups and more recent observations are needed.

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Conflict of Interest

No conflict of interests.

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