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Prenatal and perinatal risk factors for cerebral palsy in children born at term-A review of literature

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Abstract
Background of the Study: The underlying causes of CP are still poorly understood. Several individual risk factors of CP have been identified, but less is known about their interaction and how they might relate to different pathophysiological pathways. The risk factors may be prenatal, perinatal, neonatal, postnatal, or combined. More knowledge regarding risk factors that could be typical for CP in children born at term is needed, because more than half of the children with CP are born at term
Objective of the Study: The objective of the present study was to review and discuss the risk factors for cerebral palsy (CP) in children born at term.
Methodology: We had search articles and abstract which were published from published from 2000 to 2020 were included in this review. Randomized controlled trials and non-randomized controlled trials, systemic review and comparative studies were included in this review of in relation to cerebral palsy risk factors.
Result: From selected 22 relevant research reports Almost studies included in the review shown strong strength of association as causative factor responsible for Cerebral Palsy
Conclusion: From this Review of literature Prenatal, Perinatal and neonatal factors identified as risk factors for cerebral palsy so Preventive strategies for CP in term-born infants are urgently required because infants born at term contribute up to 65% of CP cases and their impairments tend to be more severe than those of children born preterm.

Keywords: Cerebral palsy, risk factors, term infants

Introduction

Cerebral palsy (CP), a non-progressive condition affecting approximately 3 in 1000 new borns, is characterized by acquired brain damage which affects motor and cognitive functions [1, 2, 3, 4, 5]. Cerebral palsy is "A group of permanent disorders of the development of movement and posture causing activity limitation(s) that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication an behavior, by epilepsy and by secondary musculoskeletal problems [6, 7].

Cerebral palsy is not a disease, but a syndrome complex characterized by an aberrant control of movement or posture, which appears early in life and leads to lifelong motor disability Perinatal and neonatal mortality have decreased, maternal and neonatal care have undergone major changes, but the overall prevalence of CP has remained stable over the years, at between 1 and 3 per 1000 live births [8, 9, 10] Children with CP show different clinical patterns, half of them with bilateral spastic type, a third with unilateral spastic type, and the remaining with less common types, such as dyskinetic and ataxic CP

Known Risk Factors Associated with Cerebral Palsy [11]

Prenatal	Perinatal
Hypoxia Metabolic Disorder (HIE) Multiple gestation Intrauterine infection Chorioamnionitis Maternal fever Exposures to toxins	Premature birth<32 weeks or<2500g Infection Blood incompatibility Abnormal fetal presentation Placental abruption Instrument delivery

The underlying causes of CP are still poorly understood. Several individual risk factors of CP have been identified, but less is known about their interaction and how they might relate to different pathophysiological pathways. The risk factors may be antenatal, peri- or neonatal, postneonatal, or combined.
Risk factors vary also by gestational age, and much research has been focused on risk factors in children born preterm. However, the prevalence of CP in children born pre-term is decreasing [12] more knowledge regarding risk factors that could be typical for CP in children born at term is needed, because more than half of the children with CP are born at term.
The purpose of this study is to review the current research of risk factors of CP for children born at term and to hypothesize how the new findings can affect the content of the CP registers across the world.
The research question for this study is 'What Prenatal and Perinatal risk factors for CP have been identified in the literature for infants born at term?'

Objective of the Study

The objective of the present study was to review and discuss the Prenatal and Perinatal risk factors for cerebral palsy (CP) in children born at term.

Review of Literature

Table 1: Prenatal and perinatal risk factor

No	Author name and title	Study	Risk factor	Conclusion
1	Yvonne W. Wu, MD, MPH Gabriel J. Escobar, MD.et.al ;(2003)	Chorioamnionitis and Cerebral Palsy in Term and Near-Term Infants	Choriomnionitis, intrauterine growth restriction, maternal black ethnicity; maternal age older than 25 years and nulliparity.	From their data they have concluded that chorioamnionitis is an independent risk factor for CP among term and near-term infants. Independent risk factors identified in multiple logistic regression included chorioamnionitis, intrauterine growth restriction, maternal black ethnicity; maternal age older than 25 years and nulliparity [13]
2	Michael D. Neufeld, MD, MPH, Chantal Frigon, MD, MS Alan S. Graham, et.al; (2004)	Maternal Infection and Risk of Cerebral Palsy in Term and Preterm Infants	Maternal infection	In their study the results suggest that maternal infection is a risk factor for CP in both term and preterm infants. [14].
3	Janet Walstab, Robin Bell, et, ai; (2004)	Antenatal and intrapartum antecedents of cerebral palsy: a case-control study	Cigarette smoking, antenatal.	In their study they have concluded that the number of previously identified risk factors for CP were confirmed in their data. New observations were (in specific sub groups): protective effects of mother's negative Rhesus status, cigarette smoking at the first visit and episiotomy and an increased risk of CP associated with an abnormal antenatal cardiotocograph [15].
4	CGreenwood1,P Yudkin2, et.al;(200ss5)	Why is there a modifying effect of gestational age on risk factors for cerebral palsy?	Pre-eclampsia	In their study they have concluded that the inflammatory processes, including pre-eclampsia, are important in the aetiology of cerebral palsy. The apparent reduced risk of cerebral palsy associated with pre-eclampsia in very preterm infants is driven by the characteristics of the gestation matched control group. Use of the term “protective” in this context should be abandoned [16].
5	Dr Ayse Gurbuz, Ates Karateke, Ufuk Yilmaz & Canan Kabaca (2006)	The role of perinatal and intrapartum risk factors in the etiology of cerebral palsy in term deliveries in a Turkish population	Extreme low birth weight, low apgar score, and NICU admission	This Result of the study shows Perinatal risk factor was neonatal wt <2500 gm, decrease electronic fetal monitoring, an apgar score <7 at 1 and 5 minutes and necessity of niu admission so they concluded that Intrapartum risk factors were significantly more frequent in the CP group ($p < 0.01$). An increased cesarean section rate could not prevent CP, suggesting that the hypoxic insult that causes CP might be of chronic onset. The development of diagnostic tests to detect non-reassuring fetal status in its intrauterine life and interventions at appropriate times may decrease the CP rate [17].
6	Kristina Thorngren-Jerneck, MD, PhD, and Andreas Herbst.et.al; (2006)	Perinatal Factors Associated with Cerebral Palsy in Children Born in Sweden	Small or large for gestational age, abruption placental diabetes mellitus type 1, maternal age, preeclampsia, instrumental delivery, smoking, c-section, primiparity, breech presentatio n at vaginal birth	In their study they have concluded that factors associated with CP were being small or large for gestational age at birth, abruption placental, insulin-dependent diabetes mellitus type 1, preeclampsia, maternal age older than 40 years or 35–39 years al birth, instrumental delivery, and emergency, cesarean delivery primiparity, and smoking. In term infants, low Apgar scores were associated with a high risk for CP; Other factors associated with CP in term infants were breech presentation at vagina birth, instrumental delivery and emergency cesarean delivery [18]
7	A. Drougia[a] V. Giapros[a] et. Al (2006)	Incidence and risk factors for cerebral palsy in infants with perinatal problems: A 15-year review	Gestational age, PDA, SGA, neonatal transfer and sepsis/ meningitis	In their study they have concluded that PVL, PROM and PDA were the most powerful independent predictors of CP in children of GA < 34 weeks and SGA, neonatal transfer and sepsis/meningitis in children of GA > 34 weeks [19].
8	Savas Menticoglou (2008)	How Often Do Perinatal Events at Full Term Cause Cerebral Palsy?	Perinatal event	In their study they concluded that in their hospital, perinatal events are an important cause of cerebral palsy in children born at full term, but few cases are potentially preventable [20].
9	LF Nielsen, D Schendel, J Grove, et.al; (2008)	Asphyxia-related risk factors and their timing in spastic	Cord around neck, abnormal fetal growth	In their study they have concluded that Placental and cord complications accounted for the majority of asphyxia conditions. In multivariate analysis, placental infarction was

		cerebral palsy	SGA	significantly associated with a four-fold increased risk for spastic quadriplegia and cord around the neck was significantly associated with a three-fold increased risk for spastic CP overall. The combination of placental infarction and being small for gestational age (SGA) afforded an especially high risk for spastic quadriplegia. The risk for spastic quadriplegia from placental infarction may be linked in some cases with abnormal fetal growth [21]
10	Guro L Andersen Md, Lorentz M Irgens Md Phd, Et. Al (2009)	Is breech presentation a risk factor for cerebral palsy? A Norwegian birth cohort study	Breech presentation	In their study they found that breech presentation is a significant risk factor for cp the most striking finding was a fourfold increased risk for cp in singletons in breech born vaginally at term [22].
11	Kate Himmelmann1, Kristina Ahlin2, et. Al (2011)	Risk factors for cerebral palsy in children born at term	Infection,	In their study they have concluded that Information on maternal and neonatal infections, umbilical cord blood gases at birth, mode of delivery and placental status should be collected in a standardized way [23].
12	Kristina Ahlin, MD, Kate Himmelmann, MD, PhD, et.all;(2013)	Cerebral Palsy and Perinatal Infection in Children Born at Term	Infection, urinary tract infection.	In their study they concluded that the infection-related risk factors were shown to be independent risk factors for spastic cerebral palsy in the adjusted analyses. This was especially pronounced in the subgroup with spastic hemiplegia in which bacterial growth in urine during pregnancy, any infectious [24]
13	Farin Soleimani MD[1], Roshanak Vameghi MD MPH•[1], Akbar Biglarian PhD[2] (2013)	Antenatal and Intrapartum Risk Factors for Cerebral Palsy in Term and Near-term Newborns	Perinatal asphyxia, mother's age age, High risk pregnancy	This study shows that perinatal asphyxia, mother's age, and any pathology during pregnancy are independent factors associated with CP in term newborns. Previous studies have suggested that improving maternal care improves neonatal outcome. However the extent to which preventing or treating these and other risk factors would reduce the incidence of CP in newborns is unknown and merits further study [25]
14	Jonas H Ellenberg | Karin B Nelson (2013) s	The association of cerebral palsy with birth asphyxia: a definitional-Quagmire	Birth asphyxia	They have concluded that their data do not support the belief, widely held in the medical and legal communities, that birth asphyxia can be recognized reliably and specifically, or that much of CP is due to birth asphyxia. The very high case exposure rates linking birth asphyxia to CP can probably be attributed to several factors: the fact that the clinical picture at birth cannot specifically identify birth asphyxia; the definition of CP employed; and confusion of proximal effects – results – with causes. an Further research is needed [26]

Methodology

Search duration

Article published from 2000-2020 were included in this review.

Search database

Studies were identified from following database.
Google scholar, The Cochrane Library, PubMed, Wikipedia, Physiopedia

Study design

Randomized controlled trials and non-randomized controlled trials, systemic review and comparative studies were included in this review of in relation to cerebral palsy Prenatal and Perinatal risk factors

Key words

Cerebral palsy, Prenatal and Perinatal Risk factors

Inclusion criteria:

- Articles published in English language
- Articles between 2000 to 2020
- CP was the primary outcome (using a known definition appropriate for the time of the original study
- The primary aim of the study was to identify Prenatal and Perinatal risk factors for CP in (a) all births or (b) infants born at term;
- The publication had been peer reviewed.

Exclusion criteria:

- Articles published in languages other than English
- Case reports
- Comments and letters or report information
- Study includes Neonatal and Post natal factors
- Study includes the primary to identify risk factors in those born preterm or to identify risk factors for a broader definition of adverse outcome that may include neurodevelopmental impairment, learning disability, etc., from which the risk factors specific to CP cannot be identified
- to identify genetic risk factors, as systematic reviews dedicated entirely to genetic risk factors

Result

We selected 14 relevant research reports in the period of 2000 to 2020 of which few are full-text articles; few are abstracts and 3 review articles. Almost studies included in the review shown strong strength of association as causative factor responsible for Cerebral Palsy and in few studies, they mention that further research is needed. There were several research areas of interest. Studies regarding one or a few Prenatal and perinatal risk factors are listed in Table1.

Discussion

In our review almost all studies show most risk factors and their strength of association with term CP and all CP was

different. However, risk factors such as older maternal age at delivery, prior maternal disease, pre- eclampsia, and birth defects were not associated with different risk, and thus may be on causal paths to CP irrespective of gestational age at birth. In fact, these factors may work together, as high maternal age is also associated with a higher incidence of birth defects, pre-eclampsia, vascular disease, and pre-existing maternal diseases such as thyroid disorders [27, 28]. There are several and heterogeneous risk factors at focus in current research regarding cerebral palsy. In the present review, we found several areas with intense research. Perinatal events, including asphyxia and perinatal stroke, had attracted the largest number of publications, followed by genetic studies [29, 30, 31, 32, 33, 34, 35, 36].

In our study two of the study shows that chorioamnionitis is one of the cause of cp. in their study they found that chorioamnionitis is independently associated with a 4-fold increased risk of cp in term infants. a history of birth asphyxia was also strongly predictive of cp, a finding that is supported by recent reports.the diagnosis of birth asphyxia often was made in the setting of clinical chorioamnionitis [22]. Three articles shows that maternal infection and UTI (Urinary Tract Infection) is one of the cause of cp The major finding of this study is that maternal infection was associated with an approximately two-fold increased risk of CP in both term and preterm infants. The effect of maternal infection on CP risk appears to be greater in preterm than in term infants. Chorioamnionitis and UTI were also associated with an increased risk of CP in preterm infants but not in term infants. Maternal fever was not associated with CP in either term or preterm infants and may not be a good proxy for infection [23].

More than 5 articles shows that birth asphyxia is one of the cause of cp According to the results of the present study, perinatal asphyxia, maternal age >35 years and high risk pregnancy were independent factors that correlated with CP in term and near-term newborns. In developing countries, 4 to 9 million infants experience birth asphyxia annually.12 There are 1 million neonatal deaths attributed to birth asphyxia each year, which comprises 20%–40% of all neonatal deaths [24].

Few of articles shows that gestational age and pre-eclampsia are cause of cp Gestational age appears to modify the effect of risk factors for CP, particularly pre-eclampsia and SGA; these appear protective before 33 weeks gestation, but are associated with an apparent increased risk of CP in term babies. Several explanations have previously been put forward to explain this counterintuitive phenomenon. Firstly, babies with cerebral damage delivered very preterm to mothers with preeclampsia may be particularly likely to die. With current management, however, most babies delivered preterm because of severe pre-eclampsia survive.16 Secondly, magnesium sulphate, used in many centres for the prevention or treatment of eclamptic seizures, may be neuroprotective.17 This has been examined in trials [25].

Conclusion

From this Review of literature Prenatal and Perinatal identified as risk factors for cerebral palsy so Preventive strategies for CP in term-born infants are urgently required because infants born at term contribute up to 65% of CP cases and their impairments tend to be more severe than those of children born preterm.

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