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Onset factors in cerebral palsy: A systematic review

Pascal van Lieshout[a,e,f,g,h,*], Hamilton Candundo[b], Rosemary Martino[a,d,g], Sabina Shin[b,c], Caroline Barakat-Haddad[b]

[a] Department of Speech Language Pathology, University of Toronto, Canada
[b] Faculty of Health Sciences, University of Ontario Institute of Technology, Canada
[c] Department of Pediatrics, McMaster University, Canada
[d] Health Care and Outcomes Research, Krembil Research Institute, University Health Network, Canada
[e] Department of Psychology, University of Toronto, Canada
[f] Institute of Biomaterials and Biomedical Engineering, University of Toronto, Canada
[g] Rehabilitation Sciences Institute, University of Toronto, Canada
[h] Toronto Rehabilitation Institute, University Health Network, Canada

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ABSTRACT

Studies have noted several factors associated with the occurrence of Cerebral Palsy (CP), yet considerable uncertainty remains about modifiable factors related to disease onset. A systematic review was performed to identify existing systematic reviews and primary studies pertaining to targeted factors associated with the onset of CP. The following databases were searched: MEDLINE, MEDLINE In Process, EMBASE, PsycINFO, Scopus, Web of Science, Cochrane Database of Systematic Reviews, CINHAL, ProQuest Dissertations & Theses, Huge Navigator, AARP Ageline. Variations of MeSH and keyword search terms were used. Critical appraisal was conducted on selected articles. Data extraction targeted reported factors, risk estimates, and 95% confidence intervals (CI). Findings identified two systematic reviews and three meta- analyses, as well as 83 studies of case control, cohort, and cross-sectional methodological designs. Selected studies indicated that lower gestational age was associated with the onset of CP. Medical diagnoses for the mother, in particular chorioamnionitis, was found to be positively associated with onset of CP. Preeclampsia was reported to be either inconclusive or positively associated with CP onset. Low birth weight predominantly indicated a positive association with the onset of CP, while male gender showed mixed findings. The combination of male gender with pre-term or low birth weight was also found to be positively associated with CP. Evidence was identified in the literature pertaining to specific factors relating to the onset of CP, in particular showing positive associations with lower gestational age and low birth weight.

1. Introduction

Cerebral Palsy (CP) describes a group of heterogeneous non-progressive neurodevelopmental conditions that affect the developing fetal or infant brain (Rosenbaum et al., 2000). A recent meta-analysis, by Oskoui et al. (2013), found a worldwide prevalence rate of 2.11 per 1000 live births. They also reported that the overall prevalence of CP has remained stable over the past 10 years, despite increased survival of preterm infants who are at a high risk of CP. CP is one of the most common physical disabilities occurring in childhood (Novak et al., 2012). However, the definition of CP has varied over the years. Due to the heterogeneity of symptoms in CP patients, it has been challenging to formulate a comprehensive definition. CP is characterized by abnormal development of movement and posture causing activity limitations, often accompanied by secondary impairments in sensation, perception, cognition, communication, and behaviour, and can be accompanied by epilepsy and by secondary musculoskeletal problems (Rosenbaum et al., 2000). Although CP is known as a non-progressive disorder, in terms of its core deficits, many of these secondary impairments can progressively worsen over the lifespan of patients (Novak et al., 2012). CP is caused by injury to the brain, which may occur *in utero* or during the first three years of life when the brain is developing. Even though each individual affected may have unique features, CP patients can be classified into general

* Corresponding author at: Department of Speech Language Pathology, University of Toronto, Canada.
E-mail address: P.vanLieshout@utoronto.ca (P. van Lieshout).

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groups. In traditional classification schemes, categories were based primarily on the distribution pattern of affected limbs, and could be further grouped by the predominant type of tone or movement abnormality. However, other characteristics must be taken into account, such as the age of the child, clinical history, and the extent to which a diagnostic investigation has been performed (Bax et al., 2005). The severity of CP symptoms is typically assessed using the 5-level Gross Motor Functional Classification System (GMFCS) (Russell et al., 1989), which has been shown to be a valid tool for measuring changes in motor function in CP populations (Bjornson et al., 1998; see also (Chrysagis et al., 2014) for a recent comparison among different functional assessment tools). The severity of CP symptoms impacts on quality of life and function, and as shown in a recent study, pain is a very important factor for moderate to severe CP (Houlihan et al., 2004).

A literature review by Odding et al. (2006) reported that a number of studies have noted risk factors associated with the occurrence of CP. Yet, considerable uncertainty remains about modifiable factors related to disease onset and progression of secondary symptoms. The purpose of this study was to systematically review, assess and prioritize factors associated with the onset of CP, including biological, socioeconomic, environmental, psychosocial, comorbid, and genetic factors.

2. Methods

The methods utilized have been provided in detail (Hersi et al., 2016), and are only briefly described here.

2.1. Locating systematic reviews and meta-analyses: stage one

2.1.1. Search for identification of studies

To identify eligible studies, searches of the following electronic databases were executed: MEDLINE (1946 to October Week 1 2012), MEDLINE In-Process (1946 to October 15, 2012), Embase (1980 to 2012 Week 41), PsycINFO (1806 to October Week 2 2012), Scopus (1960 to October 16, 2012), Web of Science (1899 to October 16, 2012), Cochrane Database of Systematic Reviews (up to October 2012), and CINAHL (1981 to October 2012). Appropriate modifications were made to the search strategy used by the central research office in Ottawa following extensive consultation with local library staff at the University of Toronto, including variations of MeSH and keywords related to CP, risk factors, and study type, such as systematic review and meta-analysis. For further details on the search strategies, refer to Supplementary Material I.

2.1.2. Inclusion criteria

To be included, eligible studies had to meet all of the following inclusion criteria: be published in English or French; involve human subjects only; be a systematic review or meta-analysis; have a definition of CP that is explicitly specified; evaluate at least one onset factor; and report a measure of risk.

2.1.3. Study selection

Two raters independently screened all unique citations, titles and abstracts, for eligibility using Distiller SR software (Distiller SR, Evidence Partners, Ottawa, Canada). Full articles for all eligible citations were then assessed for inclusion by the same two independent raters. Discrepancies between raters were resolved by consensus.

2.1.4. Quality assessment

Two raters independently evaluated the quality of selected systematic reviews and meta-analyses using the validated Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) tool (Shea et al., 2007) in the Distiller SR software. Reviews that had low scores, three or less, were excluded, while reviews that had moderate scores, between four and seven, or high scores, greater than eight, were included. AMSTAR score discrepancies were resolved by consensus, using a third rater. For further details on the AMSTAR tool, see Hersi et al. (2016).

2.1.5. Data extraction

Two raters independently extracted the data from the systematic reviews and meta-analyses included using Distiller SR software. The data collected included methodological design details, such as years of capture, databases utilized, risk factors, risk estimates, whether or not publication bias was addressed by the authors, and whether or not a heterogeneity test had been performed for pooled data.

2.2. Locating observational studies: stage two

2.2.1. Search for identification of studies

To identify eligible studies, searches of the following electronic databases were executed: MEDLINE (1946 to April Week 2 2012), MEDLINE In-Process (1946 to April 18, 2012), EMBASE (1980 to 2012 Week 16), PsycINFO (1806 to April Week 3 2012), Scopus (1960 to April 19, 2012), Web of Science (1899 to April 19, 2012), Cochrane Library (up to April 2012), CINAHL (1981 to April 2012), HuGE Navigator (2001 to April 2012), ProQuest Dissertations & Theses (1997 to April 2012), and AARP Ageline (1978 to April 2012). Again, appropriate modifications were made to the search strategy that was used by the central research office in Ottawa, following extensive consultation with local library staff at the University of Toronto. Variations were used for MeSH and keyword search terms relating to CP and CP type (including spastic monoplegia; diplegia; tetraplegia; quadriplegia; hemeplegia; dyskinesia; and athetoid); risk factors; observational and epidemiologic studies; biological; lifestyle; socioeconomic; comorbid; environmental; genetic; and psychosocial factors. For further details on the search strategies; see Supplementary material I.

2.2.2. Inclusion criteria

To be included, eligible studies had to meet all of these inclusion criteria—published in English or French; involve human subjects only; have a definition of CP that is explicitly specified; evaluate at least one onset factor; be a case-control or cohort or cross-sectional study; and provide risk estimates.

2.2.3. Study selection

The liberal accelerated method was utilized to select studies (Hersi et al., 2016). One reviewer screened all citations and rated all full articles, for accepted citations, using Distiller SR. A second reviewer screened only the excluded citations and articles rejected by the primary reviewer. Citations and articles originally excluded, but accepted by the second rater, were selected based on consensus between the two reviewers.

2.2.4. Quality assessment

The quality of studies was assessed using the Downs and Black Checklist (Downs and Black, 1998) in Distiller SR. The primary reviewer evaluated all studies included, while the secondary reviewer randomly assessed a sample consisting of five percent of the studies included.

2.2.5. Data extraction

The primary reviewer extracted the data from all articles included, while the secondary reviewer randomly extracted data from a sample consisting of five percent of the studies included. Data capture was compared and discrepancies were resolved by consensus. Data extraction was completed using the Distiller SR.