The Assessment of General Movements in Term and Late-Preterm Infants Diagnosed with Neonatal Encephalopathy, As a Predictive Tool of Cerebral Palsy by Two Years of Age - A Scoping Review.

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Research

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Abstract

BACKGROUND The General Movements Assessment is a non-invasive and cost-effective tool with demonstrated reliability for identifying infants at risk for cerebral palsy. Early detection of cerebral palsy allows for implementation of early intervention, and is associated with better functional outcomes. No review to date has summarized the utility of the General Movements Assessment to predict cerebral palsy in term and late-preterm infants diagnosed with neonatal encephalopathy and so detect the research gaps.

METHODS We conducted a systematic scoping review for data on sensitivity, specificity, positive and negative predictive value and described the strengths and limitations of the results. We searched five databases (MEDLINE, Embase, PsychINFO, Scopus and CINAHL). Two reviewers conducted all screening and data extraction independently. The articles were categorized according key findings and a critical appraisal performed.

RESULTS From the electronic database search, only two studies, case series, met all of the inclusion criteria. The total number of participants were 60. Neither of the final eligible studies included late-preterm neonates. Both studies reported on sensitivity, specificity, positive predictive and negative predictive value. The newer study reported that in the time period between term and 4-5 months post-term, that any cramped synchronized movements in this time period had results of 100% sensitivity and variable results for specificity, positive predictive value and negative predictive value. Neither of the studies had infants that received therapeutic hypothermia for Neonatal Encephalopathy.

CONCLUSIONS The finding of cramped synchronized General Movements is a strong predictor of cerebral palsy by two years of age in the term population. Neonatal encephalopathy has an effect on spontaneous movements in term infants, be it transient or persistent. The predictive ability of spontaneous movements is very accurate when assessed early but improves when done later (at 15-22 weeks of age). A deficit of research exists with regards to cerebral palsy prediction using general movements in term and late-preterm infant with encephalopathy, especially when therapeutic hypothermia is instituted.

Systematic review registration

Title registration with Joanna Briggs Institute. URL: http://joannabriggs-webdev.org/research/registered_titles.aspx

Background

Prediction of long-term neurodevelopmental outcomes remains an elusive goal for neonatology. Clinical and socioeconomic markers have not proven to be as reliable as we have hoped [1,2]. The limitation in prognostication is particularly challenging for those term and late-preterm infants born with neonatal encephalopathy (NE).

NE describes those infants born with an atypical neurological exam and is by definition heterogeneous in etiology[3]. The specific etiology may not be clear for months to years later but the presentation is characterized by central nervous system disruption[4] and is associated with an increased risk for long-term neurodevelopmental challenges including cerebral palsy (CP). Infants presenting with NE are managed now with therapeutic hypothermia as the standard of care; this is presumptive management, and is time sensitive should the etiology be hypoxia/ischemia (Hypoxic Ischemic Encephalopathy (HIE)), in term and late-preterm infants[4,5]. Therapeutic hypothermia reduces the likelihood of challenging outcomes by containing any potential ongoing neurological injury. It does not, however, completely eradicate the possibility of long-term neurodevelopmental disability[6].

For parents of infants affected by NE, the desire for accurate prognostication is of tantamount importance[6,7]. This information can guide decisions around early intervention and, in severe cases, withdrawal of care for those infants with severe involvement. For those infants that survive NE and are at increased risk for CP, recent international recommendations now call for early detection and intervention of CP in order to improve functional outcomes[1,8,9]. These recommendations are based on mounting evidence for better detection tools as well as the benefits of early intervention.

Historically, clinical and radiological predictors of neurological outcomes were used to classify the degree of NE. Severity scoring systems include the classical grading by Sarnat and Sarnat[10] in 1976, to the newer scores by Miller et al.[11] in 2004, with added parameters such as oral feeding difficulties and the presence of seizures. Radiologically, specific findings of diffusion restriction on magnetic resonance imaging (MRI) have been linked to later development of CP[4]. These predictors, however, were not sufficiently accurate[1,2] and the high costs of imaging as well as shortages in access further restricts the utility. Neurological examinations have historically been limited in predictive value but recent emerging evidence with an observational tool, the General Movements Assessment (GMA) developed by Dr. Heinz Prechtl has demonstrated strong predictive value[12, 13].

The GMA is a non-invasive, cost-effective tool with demonstrated reliability for identifying infants at risk for neuromotor impairment[14]. General movements (GMs) are complex, highly variable, whole-body movements which emerge in the fetus and progress through an age-specific developmental trajectory, dissipating by the end of the first four to five months of life[13]. Developmental progression and variety, or lack thereof, are indicators of nervous system integrity and can reflect neurodevelopmental outcomes[15]. Cramped synchronized (CS) and absent fidgety movements are considered abnormal GMAs, demonstrating developmental stereotypy[13]. Additionally, the Motor Optimality Score (MOS) represents a more detailed quantitative analysis of the general movements motor repertoire of infants between 11 and 17 weeks post-term. The MOS has been shown to be predictive of the severity and type of Cerebral Palsy[16, 17].

Several researchers have looked at the GMA from different aspects. We were interested in term and late-term preterm infants with NE and how the GMA may be useful in predicting CP. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports was conducted to assess this research. There were two current systematic reviews on GMA, one in 2018[18] and the other in 2017[9]. In addition, eight older reviews were identified: seven systematic reviews[13,19-24] and one literature review[25] done between 2001 to 2013. The search also revealed three pending reviews identified around the topic of the predictive value of GMA[26-28]. These pending reviews were all systematic reviews.

The key characteristics and main findings of the above reviews on GMA are detailed in the protocol for this systematic review[29] and is included in Table 1, Additional file 1. The two latest reviews were by Kwong et al. 2018[18] and Novak et al. 2017[9]. In general, these reviews did not look specifically at the population we were interested in for this scoping review, that is, term and late-preterm infants with NE. Additionally, the other systematic reviews and literature review were all more than five years ago with the latest in 2013[13]. Thus, a gap exists in the literature to clearly identify the evidence for our population of interest.

The objective of this review is therefore, to identify the scope of the research with regards to the GMA and its ability to predict CP, in term and late-preterm infants with a diagnosis of NE, and to identify the gaps in the literature.

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Objectives

The primary research question for this review is: What is the published data on the predictive value of the GMA for the diagnosis of CP by two years of age in infants born at term or late-preterm presenting with NE?

The secondary research question is: What is the gap in the literature when the GMA is used to predict CP by two years of age in infants born at term or late-preterm presenting with NE?

Methods

Study Design

A scoping method was chosen for this type of review as to fulfilling of the objective of the review it required searching and assessing a wide range of research methodologies involving the use of the GMA in CP prediction. A scoping review captured all types of relevant research on the topic in a systematic, transparent, rigorous and reproducible manner. This scoping review was conducted in accordance with the JBI methodology for scoping reviews[30]. The objectives, inclusion criteria and methods for this scoping review were detailed in advance and documented in a proposal (included as Additional file 2). The title of our review was registered with JBI. The protocol was published prior to this review[29] (Additional file 1).

Inherent in the nature of the scoping review is the inclusiveness of a wide range of literature, and so we anticipated differences in the data quality. Critical appraisal and data synthesis therefore were challenging in terms of conclusive evidence as opposed to in a systematic review. The scoping review methodology was however especially advantageous to our question as these types of reviews target areas that have not been comprehensively assessed before.

Eligibility Criteria

The participant, concept, context (PCC) framework for scoping reviews was used to define the review focus and can be found summarized in Table 2 in the protocol[29] in Additional file 1.

Participants

This review considered studies that included infants ≥ 34+0 weeks GA diagnosed with NE with a GMA done between birth to six months of life and an assessment for CP by at least two years of age (Table 2, Additional file 1).

Those studies without a GMA or with any automated application of the GMA were excluded.

Concept

GMA as a predictor of CP by two years of age is the main concept. Studies that reported on sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were considered for inclusion. Detailed definition of concepts can be found in Table 3 in the study protocol[29] (Additional file 1).

Context

This review considered studies that reported on infants with an existing diagnosis of NE managed in hospitals and diagnosed by the standard of care assessment of a neurological history and examination. Studies were considered from all countries that have outcomes reported in the acute neonatal and in the follow-up period by two years of age. Studies in the English language only were considered as there is no team member with adequate language skills to translate from any other language.

Search strategy and databases searched

A range of electronic databases were searched to include medicine, nursing, allied health professions, sociology, psychology, education and social work. This scoping review considered both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. Case reports, case series, case control and cross-sectional studies and systematic reviews that met the inclusion criteria were included. Text and opinion papers were not considered for inclusion in this scoping review as this is a highly specific and medical topic. Animal studies were not included. Studies published from at least 1970 were included as this is around the time when the GMA was first introduced in neonatology as a potential predictor of neuromotor outcomes[9]. The reference lists of articles were scanned and experts in the infant developmental field were consulted to identify studies relevant to our topic.

The search strategy was phased, firstly created in Ovid Medline using a combination of index terms and keywords around general movements, Prechtl, brain disease, HIE and perinatal asphyxia. An initial limited search of Ovid Medline, Embase and PsychINFO was undertaken to identify articles on the topic (See Additional file 3). There were no previous similar reviews. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles from this limited search were then used to develop a more refined full search strategy in the second phase, for MEDLINE, Embase, PsychINFO, Scopus and CINAHL (Additional file 4). The search strategy, including all identified keywords and index terms, were adapted for each included information source.

Results

Study selection

EndNote X9 was used for citation collation. Duplicates were removed manually. Covidence was used for screening by two independent reviewers (JS and ML). Disagreements were resolved through a third reviewer (RB). The results of the search were reported in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews.

Ethical approval was not required as this was a scoping review and did not contain information directly identifying patients or content requiring patient consent.

We conducted our bibliographic database searches between April 30th and March 30th, 2020. The reference lists of all full-text relevant studies that were identified were hand-searched for additional relevant studies. Citations were identified, duplicates removed and screened by two independent reviewers (JS, ML). Relevant studies were identified for full text review and searched for via Google Scholar, institutional journal access, e-Resources and databases sites.

Any disagreements that arose between the reviewers at each stage of the study selection process was resolved through discussion. A third reviewer (RB), was the final arbitrator for any unresolved disagreements. From the full text articles, articles were selected for further review that met most of the inclusion and exclusion criteria. From these, articles were identified that fully met all the criteria. The results of the search were reported in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-ScR) flow diagram[31].

Each article was independently reviewed and assessed by two of the authors (JS, ML). The data was extracted from articles using a data extraction tool developed by the reviewers. The distribution of the studies was determined by year of publication, as well as countries of origin. These were important contextual factors to consider as the older studies and the country of origin's physical and human resources may be limiting factors in the studies coverage of a representative portion of the population. These factors affect the generalizability of the results.

The study characteristics included information such as gender, GA, birth weight, numbers of term and late-preterm neonates in the sample as well as the overall sample size, number of neonates diagnosed with NE and the number of cases of CP.

Following the searches, 883 citations were identified. Removal of duplicates yielded 537 titles and abstracts. Studies excluded by title and abstract were 428. In total, 109 articles were deemed as eligible for assessment by full text, 71 full texts were reviewed, but only 20 met most of the inclusion criteria.

There were 18 studies[32,33,36,39,41,43,44,46,47,49,50,52,54,56,58-61] that included late-preterm and term infants but did not delineate them as a specific group as it relates to their diagnosis of NE and their CP outcomes and when using GMA as a predictive tool. Table 4 (Additional file 4) presents the summary of the characteristics of the excluded studies. There was a wide variety in their key characteristics. We summarize these characteristics here. These studies had a wide date range from 1997 to 2019. They were mainly prospective studies (13 of the 18) and the majority used clinical assessments only to identify infants at high risk (10 of the 18). The Pretchl GMA was almost exclusively the assessment used (17 of the 18). In our study question we looked at a CP diagnosis by 2 years of age and 11 of the excluded studies met this criteria variety of Standardized assessments were used for the

CP diagnosis, with the most frequent being by Amiel-Tison and Grenier[37]. Eight studies either used non-standardized methods or did not clearly state their method.

Table 5 (Additional file 4) presents the summary of the key findings of these excluded studies and reasons for their exclusion. These findings showed that in high-risk infants, including those with NE, GMA is a strong predictor of CP[32], especially when used in the fidgety period[33,47,49,56,59,61] . Absent fidgety[50] and CS GM[39] are highly predictive of CP. The trajectory of the GMA is more important as a predictor of CP[33]. The GMA is more sensitive than the traditional neurological examination[34,39,44] and the sensitivity increases with combined use of other modalities such as electroencephalogram (EEG)[44], neuroimaging[58], Hammersmith Infant Neurological Examination (HINE) and neuroimaging[50].

For these excluded studies, sensitivity values were as high as 100%[32,33,39,46,49] and specificity similar close to[32,50] or at 100%[56]. We contacted the authors of the study closest to our inclusion criteria, Solemani et al.[56], as they delineated their populations by NE and by GA but their outcome was reported as “neurodevelopmental outcomes” and not CP. They reported to us that did not specifically report CP and so could not be included for us. PPV and NPV was reported for seven of the excluded studies[44, 46, 47, 50, 54, 56, 58] with some studies reporting PPV as high as 98% when used in combination with HINE and neuroimaging[50] and NPV as high as 100%[46]. Themes for the limitations identified by the authors can be summarized as limited external validity due to small population size[39,41, 50, 59, 60], selection bias related to recruitment from high–risk populations[43, 49,50] and practice variation between sites[32,46,49,]. The most common reasons for exclusion of these studies were failure to delineate their participants for the diagnosis of NE, most quoting their participants as high-risk infants, or not delineating their GA into the groups relevant to our questions (late-preterm and term).

Only two articles therefore, one by Ferrari et al.[62] and the other by Prechtl et al.[63], were identified as meeting selection criteria and were included in the final review. The results of the search were reported here in a flow diagram (Figure 1), adapted from the PRISMA-ScR[25] structure.

The final two studies included were case series[62, 63] from Italy. The total number of participants were only 60 term neonate (34 and 26 participants respectively); neither included late-preterm neonates. NE was reported as a single group by Ferrari et al. [62] but divided into mild-moderate and severe by Prechtl et al. [63]. The high-risk groups in both studies were identified by history only. The GMA used by both studies was Prechtl. Table 6 (Additional file 4) presents the characteristics of these two studies. Both were published more than five years ago and reported on sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). A variety of standardized tools were used for CP diagnosis between the two studies. Table 7 (Additional file 4) details the key findings and the outcomes evaluated, with the limitations identified by the authors. In the more recent study, Ferrari et al. [62] reported that the presence of any CS movements between term and four to five months post-term had a sensitivity of 100%, specificity of 68.7%, with a PPV 100% and a NPV of 78.3% for predicting CP. In the older study by Prechtl et al. [63], the predictive ability in terms of the timing of the GMA was determined, that is, if done early, in the first two weeks of life versus late assessments between 15-22 weeks of life. Their findings were: sensitivity 100%, specificity 46.2%, with PPV 65.0% and NPV 100% for the early assessments, compared to late assessments with 84.6% across the board for sensitivity, specificity, PPV and NPV. Neither of the studies included infants receiving therapeutic hypothermia for NE which was not yet the standard of care. Ferrari et al.[62] identified selection bias as a limitation, where mild HIE as a contributor to NE may have been underrepresented due to these infants not being referred for evaluation. Prechtl et al.[63] did not state their limitations.

Risk of Bias

Even though this was a scoping review and did not require the critical appraisal of the two included articles, the critical appraisal tool for JBI[64] helped to identify differences and similarities between these two case studies. These main points are summarized here and details are presented in Table 8 (Additional file 5).

The quality of evidence derived from a review is largely dependent on the quality of the studies included. Neither study scored 100% on all ten questions. The two studies scored 100% for six of the ten questions on the checklist. These questions assess the two included studies as being moderate quality case series as there were limitations. They had good scores for using valid methods for identification of the condition for all participants, having clear reporting of the demographics of the participants in the study, as well as, having clear clinical information of the participants. The outcomes of the cases were clearly reported for both studies. They also had clear reporting of the presenting sites demographic information and used appropriate statistical analysis.

According to the JBI method, for the study participants, the authors should provide clear and exclusion criteria. These inclusion and exclusion criteria should be specified with sufficient detail and all the necessary information critical to the study. While Ferrari et al.62 did fulfil this criteria, of note, Prechtl et al.63 did not state their exclusion criteria and so this may limit the generalizability of the results. For good quality case series, the study should clearly describe the method of measurement of the condition. This should be done in a standard (i.e. same way for all patients) and reliable (i.e. repeatable and reproducible results) way. The clinical condition for our study is NE. Both studies listed a number of criteria for possible inclusion for NE but did not state the number or combination of these criteria required for the diagnosis and so scored 0.0% for this question. They did use a standard, albeit different, method for NE severity, with Ferrari et al.62 use the Sarnat staging10 while Prechtl et al.63 used the Levine method65. With regards to consecutive inclusion, studies that indicate a consecutive inclusion are more reliable than those that do not. Neither of our included studies

stated clearly if they did consecutive inclusion of every neonate meeting the inclusion criteria, at their institutions, during the identified periods. Thus they both scored 0.0% for this. Along a similar vein, the completeness of a case series contributes to its reliability. Studies that indicate a complete inclusion are more reliable than those that do not. Neither Ferrari et al.62 nor Prechtl et al. 63clearly stated that they included all the patients in their studies and scored 0.0% for this question.

The biases include selection, information and sampling variation. Selection bias is typical of case series as it is a choice of a series of patients with a particular illness (NE), and a suspected linked outcome (CP)[66]. Selection bias limits the generalizability of results. Information bias is less in retrospectively collected data as it is determined by what is already documented in the medical chart. These two studies both were prospectively collected data making them susceptible to information bias. With regards to sampling variation, the precise determination of the rate of a disease, other than by chance, requires a large sample size. Both studies can be described as employing small sample sizes, Ferrari et al.[62] had 34 cases and Prechtl et al.[63] had 26 cases with a follow up period of over three to four years. Sample size may have been limited by the collection method as neither study stated if they were inclusive of every neonate meeting the inclusion criteria, at their institutions, during the identified periods.

Discussion

The finding of a CS movement pattern on the GMA has a strong predictive value for CP by two years of age in the term population. Prechtl et al.[63] noted that NE has an effect on spontaneous movements in term neonates, be it transient or persistent. Early assessments may be unable to differentiate between abnormal spontaneous movements that may be transient from those that will persist and eventually be associated with CP. Early assessments do not give as good predictive values as later assessments as the very high sensitivity (100%) for early assessments equates to a high rate of false positives. Late assessments at 15-22 weeks still maintain a relatively high sensitivity with improved specificity (84.6% from 46.2%). As elucidated by Brogna et al.[33], the trajectory of the GMA may be more significant an indicator of outcomes than a solitary assessment.

Limitations

Our findings support the role of the GMA as a good tool for prediction of CP for those infants born at term with NE. There are however limitations to consider including: both publications were case series, the variability in the NE definitions, the date of the publications identified and neither study contained neonates treated with the now standard of care, therapeutic hypothermia. Another important limitation is the low number of studies meeting our inclusion criteria.

Firstly, internal validity is likely to be low, as occurs in case series, since there are no comparator groups exposed to a similar array of variables. External validity would similarly be limited. Despite this scoping review therefore only representing Level IV evidence[67] it allows the hypothesis to be formulated that neonates with NE at term or late-preterm may benefit from follow-up assessments with the GMA to help with earlier identification of CP.

Secondly, in terms of the definition of NE, for the study by Ferrari et al.[62] there were some differences in the way NE was defined. In general, the standard accepted criteria that defines NE was used, but they stated that study participants had different combinations of the NE criteria. Evidence shows that the etiology[7] of encephalopathy as well as its severity[11] may influence outcomes. Although the severity of NE (that is, mild, moderate or severe reflected by the Sarnat stage) was assessed in the study, no further differentiation of severity as it related to the predictive ability for CP was done. This may have been due to the small sample size of the study (n=34) and the inevitable decreased power that would have resulted from subdivisions. Prechtl[32] also subdivided the NE diagnosis into mild to moderate (n=13) and severe (n=13) NE. Similar to Ferrari, outcomes were not reported according to these NE subdivisions.

Thirdly, in terms of the timing of the publications, both were more than five years old. Management has changed over time and updated data in this evolving area would be beneficial. It is however interesting that the older study by Prechtl et al. [63] in 1993 supports the same later findings of the Ferrari et al.[62] study in 2011 with respect to the predictive ability of the GMA. This lends support to the reliable role of the GMA in the identification of children at risk for CP.

Fourthly, neither of the studies seemed to have been done in neonates treated with therapeutic hypothermia, which is the current standard of care[4,5]. We are therefore uncertain if therapeutic hypothermia changes the quality of the GM and if it does change, how long might this persist. Information like this is important to inform the timing of the early GMA- post therapeutic hypothermia intervention. Similar consideration had to be done for identifying the optimal window for cranial MRI in neonates treated with therapeutic hypothermia[68]. This lends credence to the gap in research in this area of NE and its association with CP.

Conclusion

The findings of this scoping review suggest that the GMA is a reliable tool to be used in the assessment of term and late-preterm neonates with NE in order to earlier predict those at higher risk for CP. GMA done early should be interpreted with caution and not be used as the basis for counselling. The higher specificity of the later assessment provides a better prediction for CP. The GMA trajectory in NE treated with therapeutic hypothermia needs further elucidation.

The GMA should not be used in isolation as a definitive test for CP prediction. The use of the GMA along with neurological examination, electroencephalogram and neuroimaging increases the overall predictive ability for long-term motor challenges, mainly CP. Furthermore, of possibly greater potential applicability is the evolution of the GMA as a predictor of CP in high-risk neonates between term to four to five months of GA when treated with therapeutic hypothermia, than single evaluations that capture only a moment in time.

Suggestions for further research

Studies that address a few but key areas in neonates with NE are needed, especially with respect to NE severity and etiology when therapeutic hypothermia is used. Additionally, prediction ability of the GMA and its optimality score for the degree of functionality in CP, such as that determined by the Gross Motor Function Classification System (GMFCS)[42] scoring system would be beneficial for early intervention.

Abbreviations

BW, birth weight; CI, confidence interval; CP, cerebral palsy; CS, cramped synchronized; EEG, electroencephalogram; ELBW, extremely low birth weight; FM, fidgety movements; GMs, general movements; GA, gestational age; GMA, general movements assessment; GMFCS, Gross Motor Function Classification System; HIE, hypoxic ischemic encephalopathy; HINE, Hammersmith Infant Neurological Examination; JBI, Joanna Briggs Institute; LR, likelihood ratio; LBW, low birth weight; MOS Motor Optimality Score; MRI, magnetic resonance imaging; NBW, normal birth weight; NE, Neonatal encephalopathy; NPV, negative predictive value; n.s., not stated; PCC, participant, concept, context; PR, poor repertoire; PPV, positive predictive value; PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review; SD, standard deviation; US, ultrasound; VLBW, very low birth weight; wks, weeks.

Declarations

Ethics approval and consent to participate

Ethical approval was not required as this is a scoping review of the literature and did not contain

information directly identifying patients or content requiring patient consent.

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the

current study. Materials during the current study are available from the corresponding author on

reasonable request.

Competing interests

The authors declare that they have no competing interests.

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