Non-commercial joint-stock company "West Kazakhstan Marat Ospanov Medical University"

ABSTRACT
OF THE DISSERTATION
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Prognostic value of general movement assessment in the diagnosis of neurological diseases in children

8D10102 - Medicine

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ABSTRACT

of **Zhanna Tulegenovna Zhussupova's** dissertation titled "Prognostic value of general movement assessment in the diagnosis of neurological diseases in children" submitted for the degree of Doctor of Philosophy (PhD) in the field of 8D10102 - "Medicine".

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Research Relevance. According to official data from the Ministry of Labor and Social Protection of the Population of the Republic of Kazakhstan for the year 2021, 83,462 children with disabilities were registered, among which diseases of the nervous system ranked third (Resolution of the Government of the Republic of Kazakhstan 2022). Neurological disorders and disability threaten the full realization of social and economic potential at both family and state levels. One of the factors contributing to this situation is the current level of medical development, which allows for the preservation of life in newborns with unfavorable perinatal events, children with neuroinfections, severe injuries to the nervous system, and congenital developmental defects ("Neonatal mortality 2023" 2023).

One of the common disabling neurological diseases is cerebral palsy (CP). Previously, CP was diagnosed between the ages of 12 and 24 months, but it can now be detected in the first six months of life. Up to the age of 5 months, the most sensitive prognostic tools for risk detection are neonatal magnetic resonance imaging (MRI) of the brain (sensitivity 86-89%), and the qualitative assessment of general movements (General Movement Assessment, GMA) with a detailed evaluation conducted using the Prechtl method at the end of 2 and 5 months of life (sensitivity 98%). Early diagnosis of neurological disorders and interventions are crucial for optimizing motor and cognitive plasticity and preventing secondary complications (Novak et al. 2017). Traditionally used diagnostic methods in our country are less sensitive for this period of life, necessitating the study and implementation of various early diagnostic methods, followed by an approach to early intervention.

Identifying infants at risk of deteriorating motor functions is a complex task. Clear connections between changes in brain structure and potential motor deficits are still insufficiently studied (Einspieler et al. 2019; Crowle, Jackman, and Morgan 2023; Kniaziew-Gomoluch et al. 2023; Mohanty et al. 2023). Research has shown that subtle damages to the brain's matter may be linked to various motor and non-motor issues, for which advanced neuroimaging methods are proposed, typically being invasive and costly (Shepherd et al. 2018; Einspieler et al. 2019). Consequently, the need for functional evaluation of the integrity of the young nervous system remains a pressing issue in pediatric neurology. One reliable and sensitive method for diagnosing central nervous system impairments that does not require

intervention is the General Movement Assessment (GMA) (Michael-Asalu et al. 2019).

General movements are spontaneous movements (involving the entire body) of infants up to five months after full-term birth. These movements vary in sequence, speed, and amplitude. Despite the high reliability of the General Movement Assessment (GMA), a diagnostic method based on the study of various infant movements (Einspieler and Prechtl 2005), it is less frequently used because it requires a specially trained clinician as the evaluator. The nervous system of the fetus and newborn generates numerous motor patterns, among which general movements are paramount. These involve the entire body in a variable sequence of movements of the neck, arms, trunk, and legs (Einspieler and Prechtl 2005), differing across different age periods (Einspieler and Prechtl 2005; Hadders-Algra 2007; Spittle, Doyle, and Boyd 2008). General movements are generated by neural networks and central pattern generators located specifically in those regions of the brain that are more sensitive to adverse factors during the perinatal period (Apaydın et al. 2021; Prechtl et al. 1997; Soleimani et al. 2015). This methodology is predominantly used for predicting motor dysfunctions, particularly cerebral palsy (CP), as evidenced by numerous studies (Einspieler et al. 2019; Tsuji et al. 2020; Caesar et al. 2021). Nevertheless, a more in-depth study of the variability of movement patterns is necessary for predicting other neuromotor disorders not related to CP, as well as for forecasting mental disorders.

GMA is fast, non-invasive, unobtrusive, and cost-effective. It has high reliability and validity for predicting neurological anomalies that indicate cerebral palsy (CP) and developmental disorders in later life. There is compelling evidence that early intervention improves functional outcomes in infants with neurological disorders and is cost-effective as it reduces the frequency and severity of subsequent disorders (Hadders-Algra 2014; Morgan et al. 2014; Einspieler, Freilinger, and Marschik 2016; Novak et al. 2017; Shepherd et al. 2018).

Currently, in the Republic of Kazakhstan, there are no early detection and intervention programs, making it crucial to be able to recognize early markers of neurological disorders and identify infants in need of neurological assessments. This underscores the necessity for detailed and in-depth study of the variability of general movements. Based on the above, the objectives and goals of the study were formulated.

Aim of research

To formulate key aspects of the development of neurological disorders in infants based on the study of the variability of general movements.

Research Objectives

1. To study the impact of adverse perinatal factors on the variability of general movements in infants.
2. To identify early predictors of neurological disorders based on the assessment of the variability of general movement patterns.
3. To evaluate the effectiveness of early intervention on neurological outcomes.

Scientific Novelty of the Study

A combined assessment of general movements with a detailed evaluation of motor development has been conducted;

For the first time, based on the analysis of the assessment of the optimality of detailed movements, new reference values for developmental optimality have been obtained;

Early predictors in the form of pathological movements have been identified not only in predicting CP but also in determining the severity in conjunction with a combined assessment with perinatal factors;

The type and extent of early intervention at predetermined times for a specific type of pathological movement allow for influencing the severity of CP in the long-term outcome.

Research Objectives Theoretical and Practical Significance

The prognostic value of general movements in children has clinical significance, both for early diagnosis and early intervention in cerebral palsy. A comprehensive study of neurological disorders based on general movements and perinatal factors will serve as a tool for predicting neurological outcomes, and also allows for a targeted approach when choosing the type and timing of early intervention.

Based on the identified predictors of early diagnosis of neurological disorders in children, the developed nomogram with the proposed formula will serve as a basis for the diagnosis, management, and prognosis of CP, providing significant information in the early stages for the application of early intervention.

At the initial consultation of patients suspected of having CP, it is recommended that neurologists and pediatricians (neonatologists) in the outpatient setting use a "decision tree" diagram for the indicator "CP present" based on a combination of three influencing factors: "Adverse perinatal factors (present/which)", "Character of movements by GMA", and "Age at the time of pathological movements".

The results of the dissertation work have been implemented in the educational process of the Department of Neurology with a course in psychiatry and narcology at the Non-commercial joint-stock company "West Kazakhstan Marat Ospanov Medical University", as well as in practical healthcare.

Theses for Defense

Clinically significant adverse perinatal factors were asphyxia and prematurity, which influenced the variability of CS and Fidgety movements, allowing for the identification of a high-risk group for cerebral palsy at early stages for the initiation of specific early intervention. The incidence of neurological disorders in preterm infants was 30 times higher compared to full-term infants.

The predictive power of the quantitative analysis of general movements is high, where CS movements predict both the occurrence and severity of cerebral palsy in 100% of cases; PR movements, in combination with perinatal factors, predict cerebral palsy in 67.4% of cases. The early detection method for "high risk" of CP was

GMOS, conducted at 42 weeks PMA, which achieved 100% sensitivity and specificity, allowing for new reference values in the range of <29 (as opposed to <25), while the prognostic value of the MOS method, conducted at 52 weeks PMA, is higher in terms of cerebral palsy and its severity.

Early intervention, started from birth, influenced the outcome by reducing the risk of severe disability by half, through changes in the variability of pathological movements at early stages.

Validation of the Work. The results of the conducted research were presented at:

Oral presentation at the International Conference celebrating the 11th anniversary of the "School of Young Neurologists," Tashkent, Uzbekistan, March 24-25, 2021.

Oral presentation at the International Scientific Conference of Students and Young Scientists "FARABI ALEMİ," Almaty, Kazakhstan, April 6-8, 2021.

Oral presentation at the International Conference of Young Scientists LXI "SCIENCE: YESTERDAY, TODAY, TOMORROW," Aktobe, Kazakhstan, April 27, 2022.

Oral presentation at the International Congress on Pediatric Neurology: "Prognostic value of the Hammersmith neurological examination and general movement assessment in children with neurological disorders," Antalya, Turkey, October 3-7, 2022.

Publications on the Dissertation Topic

Six scientific papers have been published on the topic of the dissertation research: two articles in the international peer-reviewed journal Early Human Development, indexed in the Web of Science Core Collection with a JCR, JCI Q2, IF 2.5, and having a percentile rank of 76 in the Scopus Q1 database; one article in a scientific publication recommended by the Committee for Control in the Field of Education and Science of the Republic of Kazakhstan; four in the proceedings of international scientific conferences (including two international ones).

The materials from the scientific research have been implemented in practical healthcare:

- Implementation Act No. 202 from January 5, 2022, at the Public Health Center for Mother and Child Health: Use of the "Hammersmith Infant Neurological Examination" scale in neurological examinations of children from 3 months to 2 years old.
- Implementation Act No. 203 from January 5, 2022, at the Public Health Center for Mother and Child Health: Use of the "General Movements Assessment" scale.
- Implementation Act No. 18 from March 28, 2024, in the educational process: "Use of GMA in the early diagnosis of cerebral palsy" for fifth-year students of the "General Medicine" faculty in the discipline of "Neurology".
- Certificate of entry into the state register of rights for objects protected by copyright No. 21011 from October 19, 2021: "Hammersmith neurological examination of children"

Dissertation Research Funding

The dissertation research was conducted under funded scientific projects: NTP Order No. 13/2-18-222-N/Қ from April 15, 2021, "Clinical-functional characteristics of neurological diseases in early childhood," funded by the Marat Ospanov ZKMU.

Author's Personal Contribution

Within the framework of this study, the author personally developed the objectives and goals for a comprehensive analysis of the problem at hand. Data collection and interpretation were carried out. A significant personal contribution was made to the process of statistical analysis of the results, which achieved objectivity and reliability of conclusions. Scientifically substantiated conclusions were formulated and practical recommendations were developed, contributing to the further development of the scientific field of study. The author took direct part in conducting the experimental part of the work, in organizing and implementing early intervention in the form of movement simulations, analyzing the obtained data, interpreting and summarizing the results in the form of publications, which makes a significant contribution to the theoretical and practical significance of the conducted research.

The author has completed both basic and advanced levels of training in "GM Trust."

Volume and Structure of the Dissertation

The dissertation is presented on 86 pages of computer text and includes sections on introduction, literature review, materials and methods, research results, discussion, conclusion, findings, practical recommendations, references, and appendices. It is illustrated with 10 tables and 24 figures. The bibliography includes 150 sources.

MATERIALS AND METHODS OF RESEARCH

General Characteristics of the Work

This work was conducted at the OPC in Aktobe. The study was carried out within the framework of funded scientific projects: NTP Order No. 13/2-18-222-N/Q from April 15, 2021, "Clinical-functional characteristics of neurological diseases in early childhood" funded by Marat Ospanov ZKMU, 2021-2022.

A consecutive sampling method was used. Combined estimates from epidemiological studies on neurological diseases in children indicate that between 5.7% to 9.2% of children may have neurological disorders in various areas of neurological development (Einspieler and Prechtl 2005; Michael-Asalu A., et al., 2019; Einspieler and Prechtl 2005). The population of children in the Aktobe region is 77,360. According to the statistical report, the birth rate in the Aktobe region for 2019 and 2020 varied from 18.7 to 21.3 per 1000 (STATISTICS 2021), meaning an expected birth rate at the OPC of 7000-7500 newborns in 2021. With an alpha error adjustment of 5% and a beta threshold of 20% (power 80%), aimed at achieving a predictive power of 0.95 and in line with our selection criteria, we expected to

identify 155 children with neurological disorders. In our sample, the study group consisted of 327 children.

The study design was developed according to the objectives and tasks of the dissertation, defining the selection of patients and research methods.

The research adhered to the principles of the Helsinki Declaration of the World Medical Association (World Medical Association of Helsinki, 1964, updated in October 2013 at the 64th WMA General Assembly, Fortaleza, Brazil).

The dissertation research was reviewed by the local ethics committee at Marat Ospanov ZKMU in Aktobe on December 11, 2020, protocol number 10.

The research protocol was registered at ClinicalTrials.gov under the protocol number 10.04.12.2020. Clinical Trials.gov is managed by the U.S. National Library of Medicine (NLM) at the National Institutes of Health and is the largest database of clinical studies. Identification number: ID NCT05262088.

Research Design and Key Characteristics of Materials and Methods

Inclusion Criteria:

Newborns with adverse perinatal history (changes in consciousness, seizures, muscle tone abnormalities, altered motor activity and reflexes, respiratory and feeding difficulties, metabolic changes).

Exclusion Criteria:

Genetic diseases

Major congenital malformations

Fatal outcomes

Task 1: Investigate the influence of adverse perinatal factors on the variability of generalized movements in infants. A prospective study was conducted. All children underwent both qualitative and quantitative assessments of generalized movements at 42 weeks postmenstrual age (PMA), and again at 52 weeks PMA in line with adverse perinatal factors. This led to the identification of a group of children at high risk for cerebral palsy. Early interventions were implemented for these children from birth to 60 weeks PMA. Neurological outcomes with motor impairments were assessed at 5 months of age, and cognitive impairments and the severity of motor impairments were evaluated at 18 months of age.

Task 2: Identify early predictors of neurological disorders based on the assessment of the variability of patterns of generalized movements. Analytical work was conducted. Statistical correlations were explored to identify predictors of high risk for cerebral palsy and its severity through the qualitative and quantitative evaluation of generalized movements at 42 and 52 weeks PMA, enabling the assessment of the prognostic value of movement variability.

Task 3: Evaluating the Effectiveness of Early Intervention on Neurological Outcomes

To assess the impact of early intervention (EI) on neurological outcomes and the severity of conditions, a specific research design was developed. An open-label controlled clinical trial was conducted. The selection criteria for starting EI among full-term infants included those with CS movements and those with PR-type

movements scoring below 25 on the GMOS at 42 weeks postmenstrual age (PMA). The effectiveness was evaluated based on the variability of Fidgety movements at 52 weeks PMA. For preterm infants, the selection criteria for starting EI were pathological movements of the CS and PR types (EI initiated no later than one week after the appearance of pathological movements). At 52 weeks PMA, infants who did not exhibit Fidgety movements formed an additional group for EI, which continued until 60 weeks PMA. The sample was formed from groups that received EI starting at 42 weeks (main group) and 52 weeks (control group). The sampling criterion was based on the quantitative analysis of movements using MOS at 52 weeks, where infants were grouped by scores ranging from 9-19 points (moderate severity level of suboptimality). After the EI period ended at 60 weeks PMA, MOS scores were assessed for comparison.

Statistical Data Analysis Methods

Data management and bibliometric analysis were conducted using the bibliometric data package (version 3.1.4) and the Biblioshiny web application in RStudio.

Descriptive statistics were used to analyze demographic, obstetric, and perinatal factors. Continuous variables were presented as mean ± standard deviation (SD) or median (range), while categorical variables were presented as frequencies. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. The distribution of categorical or continuous variables was evaluated using the Mann-Whitney U test or the U-test, respectively. The chi-square test was used to study the relationship between types of movements and other categorical variables, where applicable. Given the categorical nature of the data (normal movements like Wr, PR, and CS), nonparametric tests were used for this analysis. One-way analysis of variance (ANOVA) was used to assess differences between groups for quantitative variables. Post-hoc tests, typically the Tukey test, were conducted to clarify which specific groups differed after finding significant differences with ANOVA. This method helps to determine if there are statistically significant differences between the mean values of three or more independent groups.

Optimal cutoff values, where sensitivity and specificity were maximized, were determined for children with cerebral palsy, and an analysis of sensitivity and specificity values for different GMOS scores compared to MOS and HINE was conducted. Categorical variables were compared using either Pearson's chi-square test or Fisher's two-sided criterion. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for motor regularities that significantly differentiated outcome variables. The Mann-Whitney U test or the Kruskal-Wallis test was used to assess whether independent samples had the same distribution in MOS and/or GMFCS-E&R. The relationship between GMOS or MOS and GMFCS-E&R levels was examined using Spearman's rank-order correlation method. Receiver operating characteristic (ROC) analysis was performed to determine optimal thresholds for motor disorders using GMOS, MOS, and GMFCS-E&R. A binary logistic regression analysis was conducted to test the predictive power of MOS or GMOS subcategories relative to CP results. For this purpose, MOS data were categorized into three groups:

5 to 9 as Cat1, 9 to 19 as Cat2, and 20 to 28 as Cat3, and GMOS data were categorized into three groups: 9 to 19 as Cat1, 20 to 27 as Cat2, and 28 to 42 as Cat3.

All statistical tests were considered significant at a p-value of less than 0.05. Data analysis was performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, Illinois, USA), and GraphPad software (Version 9.5.1, San Diego, California, USA) was used for graphical representation. RStudio (version 2023.09.0+463, PBC, Boston, Massachusetts) was used for graphical representation.

RESULTS OF OWN RESEARCH

During the analysis of all births at the Regional Perinatal Center during the study period, the total number of births was 8249. Full-term infants accounted for 7809 (94.7%) births, while 440 (5.3%) infants were born prematurely. Among the full-term infants, 120 (1.5%) were identified with perinatal adverse factors, whereas among the 440 premature infants, 207 (47%) had adverse perinatal factors. Common adverse perinatal factors included: hypoxia-ischemia, altered muscle tone, impaired consciousness, suppression of reflexes, seizures, signs of respiratory insufficiency, hyperbilirubinemia, hypoglycemia, hypocalcemia, and signs of toxic encephalopathy. These factors led to pathological conditions, which were grouped into 9 categories: Hypoxic-Ischemic Encephalopathy (HIE) of 1st, 2nd, and 3rd degrees; Neonatal Jaundice; Hypoglycemia; Toxic-Metabolic Encephalopathy; Infants with Perinatal Asphyxia and Hypoglycemia; Infants with Neonatal Seizures; and Infants with Neonatal Respiratory Distress. Generalized movements were evaluated within each of these nosological groups.

Results of qualitative assessment of general movements:

Qualitative analysis of general movements using the GMA method revealed normal movements of type Wr in 111 (33.9%) children, pathological movements in the form of PR in 201 (61.5%) children, and pathological movements in the form of CS in 15 (4.6%) children. The sensitivity of qualitative assessment was 100%, and the specificity was 83.5%.

Clinically significant perinatal factors included severe hypoxic-ischemic encephalopathy (11%) and premature infants with perinatal asphyxia (14%), among whom at 42 weeks PMA, pathological movements in the form of CS were observed in 80% of cases, pathological movements in the form of PR in 23.9% of cases, while normal movements in the form of Wr were not observed ($p<0.05$). At 52 weeks PMA, pathological movements, characterized by the absence of Fidgety, were observed in 67.7% and 80% of cases in infants with HIE of grades 2 and 3, respectively, and in 34.5% of cases in premature infants with perinatal asphyxia ($p<0.05$).

Evaluation of variability showed that in 100% of cases, children with CS movements did not change to physiological movements, while in children with PR movements, this occurred in 15.4% of cases.

Results of quantitative (detailed) assessment of general movements:

According to the GMOS assessment at 42 weeks post-menstrual age (PMA), suboptimal scores (<25) were observed in 50 (15.3%) out of 327 children, 35 (70%) of whom had PR movements, and 15 (30%) had CS movements ($p<0.05$). These 50 children constituted a high-risk group for cerebral palsy (CP), and early intervention was initiated at 42 weeks PMA.

Regarding the MOS assessment at 52 weeks PMA, suboptimal scores (<25) were observed in children with HIE of grades 2 and 3, and in premature infants with perinatal asphyxia, with scores of 17.9, 17.8, and 19.1, respectively ($p<0.05$). At 52 weeks PMA, in 19 (6.9%) out of 277 children who had optimal scores (>25) according to GMOS at 42 weeks PMA, normal physiological movements of Fidgety did not develop, prompting early intervention initiation at 52 weeks PMA based on this criterion.

The sensitivity and specificity of the quantitative detailed assessment were both 100%.

Results of prognostic assessment of predictors:

Out of 69 high-risk children, 54 (78.3%) developed CP. The prognostic power was evaluated based on pathological movements: for CS movements, it was 100%, for PR movements – 67.4%, and for Fidgety – 100%, with a correlation coefficient of 0.989 at $p<0.001$.

New reference values for suboptimality were obtained for GMOS, with a threshold of <29 points ($p<0.01$).

Strong negative correlations were found between the predictive severity values of CP according to the GMFCS scale for GMOS and MOS: -0.812 and -0.947, respectively ($p<0.001$).

Regression analysis for predictive values regarding the development of CP based on detailed assessments showed an odds ratio (OR) of 0.86 (0.63; 1.17) for GMOS and an OR of 0.26 (0.16; 0.43) for MOS, with $p<0.33$ and $p<0.001$, respectively.

Results of early intervention assessment on neurological outcomes:

In the main group of children receiving early intervention from 42 weeks post-menstrual age (PMA), cerebral palsy (CP) was realized in 35 (97.2%) out of 36 children, while in the control group of 18 children, CP was realized in all 18 (100%) children.

Scores on the MOS scale before and after early intervention were 14.19±0.83 and 17.28±0.13, respectively, in the main group ($p<0.001$), indicating a trend towards improvement. In contrast, in the control group, these indicators were 16.61±0.145 and 16.83±0.143.

The influence of early intervention on the severity of children's condition with CP according to the GMFCS-E&R scale showed that the ratio of mild, moderate, and severe degrees in the main and control groups was 21 (60%)/1 (5.6%); 5 (14.3%)/5 (27.8%); 9 (25.7%)/12 (66.6%) respectively ($p<0.05$). Based on the obtained prognostic predictor data, a nomogram for the prognostic model has been developed. This model utilizes the formula for predicting cerebral palsy (CP) based on the

variables: X = 1.7512951 - (0.075677214 * MOS) + (0.0044921396 * GMOS) + (0.10982359 * EI). Where, if the value of X is ≥0.5, CP is probable; whereas if X is <0.5, CP risk is minimal or absent

CONCLUSION

In our study, the prognostic value of assessing general movements, including GMOS and MOS, in predicting the development of neurological disorders in children based on the variability of these movements was investigated.

Thus, based on the results of our study, the following conclusions were drawn: Clinically significant adverse perinatal factors include asphyxia and prematurity, which affect the variability of CS and Fidgety movements, allowing for the identification of a high-risk group for cerebral palsy at an early stage to initiate specific early intervention. The frequency of neurological disorders in preterm infants is 30 times higher compared to full-term infants.

The predictive power of quantitative analysis of general movements is high, where CS movements predict cerebral palsy and its severity in 100% of cases; PR movements in combination with perinatal factors predict cerebral palsy in 67.4% of cases. The GMOS method, conducted at 42 weeks post-menstrual age, served as an "early risk" detection method for CP, with sensitivity and specificity reaching 100%, providing new reference values in the range of <29 (opposite to <25), while the prognostic value of the MOS method, conducted at 52 weeks PMA, is higher for cerebral palsy and its severity.

Early intervention, started from birth, influenced the outcome by reducing the risk of severe manifestation by 2 times through changing the variability of pathological movements at early stages.

PRACTICAL RECOMMENDATIONS

The prognostic value of general movements in children is clinically significant for both early diagnosis and early intervention in cerebral palsy.

A comprehensive study of neurological disorders based on general movements and perinatal factors will serve as a tool for predicting neurological outcomes and provide the opportunity for a targeted approach in selecting the type and timing of early intervention.

Based on the identified predictors of early diagnosis of neurological disorders in children, a nomogram with a proposed formula has been developed, which will serve as the basis for the diagnosis, management, and prognosis of cerebral palsy, providing the most information in the early stages for the application of early intervention.

When initially assessing patients suspected of cerebral palsy, neurologists and pediatricians (neonatologists) in outpatient settings are recommended to use a "decision tree" diagram for the indicator "CP, present" based on a combination of three influencing factors: "Adverse perinatal factors (present/which ones)," "Character of movements per GMA," and "PMA age at the time of pathological movements."

The scientifically based conclusions and values obtained can be used for educational purposes at the university level.