UDC 612.8

Raushan Issayeva
MD, Doctor of Medical Sciences, Professor, Director of the
Higher School of Medicine, Faculty of Medicine and Healthcare,
Al-Farabi Kazakh National University, Republic of Kazakhstan

Linas Rovas
MD, PhD, Head of Perinatology Centre
Klaipeda University Hospital, Klaipeda University, Republic of Lithuania

Roza Seisebaeva
MD, Associate Professor, Department of Clinical Diseases,
Higher School of Medicine, Faculty of Medicine and Healthcare,
Al-Farabi Kazakh National University, Republic of Kazakhstan

Aigerim Aliakparova
MD, MSc, 2nd year PhD student, Faculty of Medicine and Healthcare,
Al-Farabi Kazakh National University, Republic of Kazakhstan

Symbat Abzaliyeva
MD, PhD, Deputy Director for Research and Innovation and International Relations,
Higher School of Medicine, Faculty of Medicine and Healthcare,
Al-Farabi Kazakh National University, Republic of Kazakhstan

Gulzhan Kassenova
MD, 2nd year PhD student, senior lecturer at the Department of Fundamental Medicine,
Higher School of Medicine, Faculty of Medicine and Healthcare, Al-Farabi
Kazakh National University, Republic of Kazakhstan

THE MOST SIGNIFICANT RISK FACTORS FOR THE DEVELOPMENT OF THE CEREBRAL PALSY AMONG KIDS OF THE ALMATY CITY, REPUBLIC OF KAZAKHSTAN

Abstract. ***Objective.*** *To identify the most important risk factors related to the development of cerebral palsy in children of the Almaty city, Republic of Kazakhstan.* ***Material and methods.*** *A retrospective case-control study to compare risk factor prevalence among children among children from 6 months to 17 years old living in Almaty with cerebral palsy (CP) and age-matched healthy children. Overall, 300 medical records was analysed.* ***Results and conclusion.*** *The most significant risk factors for CP development in newborns are preterm birth, low birth weight, perinatal infections, metabolic acidosis, hyperbilirubinemia and its consequences. The hyperbilirubinemia among term babies is one of the crucial factors of CP development in the Kazakhstani population.*

Keywords: *Cerebral palsy, term newborn, hyperbilirubinemia, metabolic acidosis.*

Introduction.

Cerebral palsy is a group of disorders that affect the developing foetal or infant brain causing motor dysfunction. Motor disorders in CP are often accompanied by other abnormalities including epilepsy, cognitive impairment, autism, etc. CP is the leading cause of disability among children[1-3].

Many researchers believe that damage to the immature brain happens before birth. However, there is an opinion that different factors could impact the brain up to the age of 3 months causing CP as a consequence. There is some degree of uncertainty regarding the exact etiological factors related to the development of the disease[1-4]. Known reasons for brain damage that may cause CP could entail congenital brain anomalies, trauma, hypoxia, ischemic stroke, genetic disorders or infection. Infants impacted by restricted foetal growth, preterm labour and toxic brain damage in cases of the hyperbilirubinemia of newborns have a greater risk of developing CP[2,3]. The highest risk for CP is registered in babies who were born before 28 weeks of gestation with a low birth weight. Brain damage in the period between 24 and 40 weeks of gestation happens in 50-70% of cases[5]. At the same time, the most critical risk is a

combination of two of the risk factors listed above: low birth weight and preterm labour (5 -8).

The CP incidence varies between 1.5 and 3 per 1,000 live births in different populations[9]. Worldwide the prevalence of CP has remained the same over the last 15 years despite many efforts to improve obstetric and neonatal care. This trend is explained by the fact that the CP risk factors in most of the cases affected babies antenatal. Thus, the measures for obstetric and neonatal care improvement were not effective. In Europe, the CP incidence decreased from 1.90 to 1.77 per 1,000 livebirths, possibly related to the improved obstetric and neonatal care[10,11]. However, in some regions of the World, the incidence of CP is still increasing. In the 2017 data for the Republic of Kazakhstan, the number of CP cases reached 3.6 cases per 1,000 live births; it varied from 0.8 to 6.7 cases per 1,000 live births in different regions of Kazakhstan12. Over recent years, the number of CP diagnoses has demonstrated 10% growth.

To the best of our knowledge, this is the first paper to analyse the available data regarding the significant issue of increasing CP prevalence in the Republic of Kazakhstan. Our aim was to identify risk factors and their impact on CP development in the Kazakhstan population and to promote the importance of managing these risk factors as a measure to decrease the incidence of CP cases.

Materials and methods

The study included 150 children (main group) with cerebral palsy (CP) aged between 6 months and 17 years who were born in Almaty and 150 children (control group) of the same age who lived in Almaty city.

The data is a collection of clinical, functional, and laboratory information from their medical records that has been put in a structured questionnaire: it includes the discharge note from obstetrics, the history of the newborn's development (the birth record, the pregnancy card or individual card of a pregnant woman), and the hospital discharge note.

Statistical analysis was performed using IBM SPSS Statistics, version 22.0. The differences between categorical variables were analysed using Pearson's chi-squared

test and Fisher's exact test. And the differences between continuous variables were analysed using Tukey's range test and Student's t-test. The difference was considered statistically significant if the P value was <0.05. The primary statistical analysis was performed by calculating the prevalence of the CP risk factors in the general population, with the stratification of the clinical diagnoses in the subgroups of the pregnancy term during the time of the CP's development.

The study was approved by the Local Ethical Committee of the Kazakh Medical University of Continuous Education. The investigators obtained informed consent from the parents or guardians of the children. Protocol №1 from 20.09.2017.

Results

In the group of children with CP, 85 (56.7%) were boys and 65 (43.4%) were girls; in the control group, there were 61 (40.7%) boys and 89 (59.3%) girls.

The gestational age of below 37 w. (22-37 w.) was registered for 78 babies (52.3%) with a diagnosis of CP. The gestational age of 28-34 w. was registered for 40 (26.7%) babies. In the control group, preterm babies (10 babies, 6.7%) were born at 34-37 weeks ($p<0.001$).

Preterm newborns in the main group had an increased risk of CP development: OR 99.4 (95% CI 6.0 to 163.8, $p<0.0013$) at the gestational age of 28 w + 0 d to 33 w + 6 d, and OR 5.0 (2.4 to 10.6, $p<0.0001$) at the gestational age of 34 w + 0 d do 36 w + 7 d.

In the main group, the vast majority of babies (45%) were born with the very low body weight (1000g. – 1499g). Meanwhile, in the control group, the majority (78.6%) comprised babies with a body weight of between 3,999g. and 4,999 g.

Babies with a low birth weight in the main group had an increased risk of CP development: OR 40.6 (95% CI 12.3 to 133.0, $p<0.0001$) in the group with a birth weight of 1,000g. –1,499 g and OR 1.3 (95% CI 0.7 to 2.6, $p = 0.3288$) in newborns with a birth weight of 1,500g.-2,499 g.

Severe metabolic acidosis (pH<7.0; BE>12 mmol/l) was registered in 38 (25.3%) newborns with CP and none in the control group.

Hyperbilirubinemia among full-term newborns with cerebral palsy was observed in 58 (94.7%) newborns, and in the control group it was observed in 9 (6.0%) full-term newborns OR 12.6 (95% CI 5.9 to 26.9, p<0.0001). Hyperbilirubinemia among preterm infants was detected in all newborns in the main group and in the control group. Kernicterus (bilirubin level over 425 μmol / L) was detected in 55 (36.7%) newborns with cerebral palsy and none in the control group (p<0.001). Haemolytic disease of newborns was detected in 57 (38.0%) newborns with cerebral palsy.

Intrauterine infections with sepsis were detected in 38.0% of newborns with cerebral palsy (p <0.0001).

Discussion

The present study has shown that the main risk factors for the development of cerebral palsy in newborns of the studied population are prematurity: OR 99.4 (95% CI 6.0 to 163.8, p<0.0013) at the gestational age of 28 w. + 0 d. to 33 w. + 6 d, low (1.000g. -1.499g) birth weight OR 40.6 (95% CI 12.3 to 133.0, p<0.0001), perinatal infections with sepsis OR 28.8 (95% CI 10 to 82.7, p< 0.0001) and hyperbilirubinemia with obvious consequences. All these risk factor are well known and well documented by other researchers[13-15].

The most interesting fact in our study was that hyperbilirubinemia in the CP group occurred in almost 97% of term babies vs. 6.0% of babies in the control group, and it was one of the highest risk factors for CP development in term newborns OR 12.6 (95% CI 5.9-26.9, p<0.0001). According to the data in the literature, hyperbilirubinemia in newborns is diagnosed in approximately 2-4%[16]. Thus, the risk factors for hyperbilirubinemia are a low gestational age (<38 weeks), intraventricular haemorrhage, cephalohaematoma, and low birth weight[17].

However, we did not find any literature that mentioned this high percentage of hyperbilirubinemia among the term babies akin to the one we registered for term babies

in our study. Hyperbilirubinemia is described as one of the risk factors for the development of newborn encephalopathy and inadequate treatment of hyperbilirubinemia in the newborn could lead to brain damage (kernicterus) and CP as a consequence[18].

Sabena Setia at al. were the first to point out that East Asian neonates had more significant total serum bilirubin means and a higher risk for hyperbilirubinemia and its consequences[19]. It is difficult to say what the main reason for this fact was. We could consider a gene mutation associated with hyperbilirubinemia among some of the Asian race subgroups[19]. However, we cannot ignore the fact that the diagnosis of hyperbilirubinemia is often missed. The reasons for this could be a specific phenotype due to which hyperbilirubinemia is ignored and babies are discharged from hospitals without adequate treatment of their hyperbilirubinemia[20]. This limits the chances of detecting the hyperbilirubinemia's progression to more serious complications. This feature is specific to countries with moderate levels of neonatal care[21]. It is difficult to say, but this probably explains the fact that, in some regions of Kazakhstan, where European races were predominant, CP was registered in 0.6 per 1,000 live births, and, in the other regions (Southern Kazakhstan), where the Asian race was more predominant, there were 6 CP incidents per 1,000 newborns[14].

It could be concluded that, in the main group of children of the Almaty region in the Republic of Kazakhstan, many risk factors for CP development did not differ from those already detected. However, among the risk factors, the most significant in the Kazakhstani population was hyperbilirubinemia with its consequences. Another significant risk factor was perinatal infection. In the Kazakhstani population, more than 50 % of pregnant women suffer from pregnancy anaemia. It is likely, that pregnancy anemia interferes with immune system functioning therefore increasing the risk of perinatal infections. We plan to investigate this assumption in more detail in the future.

A group of researchers from Norway showed that the incidence of CP could be changed by improving obstetric and neonatal care, and one of the ways to achieve this was to reduce the number of preterm births[11]. According to 2017 data, the number of

preterm births in Kazakhstan reached 8%[22]. Thus, reducing the number of preterm births, perinatal infection, pregnancy anaemia and particularly giving more attention to the problems associated with hyperbilirubinemia (early diagnosis, treatment protocols, training of neonatologists, preterm neonatal care) could reduce the incidence of CP in the Republic of Kazakhstan, which is the main conclusion of this study.

The limitations of this study include its reliance on the mentioned medical records: some important objective factors, such as the resuscitation of newborns and others, were not described in detail. We also did not have many important factors in the control group, which was the reason why some of the risk factors lost their statistical significance. Moreover, we did not analyse factors associated with the mother, which might have indicated factors for the development of CP.

Therefore, to confirm the theory that hyperbilirubinemia is an important risk factor for CP development in Kazakhstan, the analysis of the forms of CP in children should be performed. Toxic brain damage in cases of hyperbilirubinemia mainly manifests in damage to the basal ganglia and thalamus, which leads to the dyskinetic form of CP. Toxic damage to the basal ganglia and thalamus has a bigger impact on term babies than on preterm babies. This is why we can suggest that children born in term who have the dyskinetic form of CP experienced hyperbilirubinemia during their postnatal period[23]. Thus, the investigation of the forms of CP in the children who participated in our study could answer the question regarding the influence of hyperbilirubinemia on this pathology.

Acknowledgments

The authors would like to thank the Public fund The volunteer Society “Miloserdiye”, the administration, the paediatricians and specialist doctors of the obstetrics, outpatient clinics of Almaty City, OS “Association of parents of the disabled children “ARDI” for support and collaboration. **Conflict of interests**

The authors report no conflicts of interest in this work.

References:

1. Smithers-Sheedy H, Badawi N, Blair E, et al; What constitutes cerebral palsy in the twenty-first century? Dev Med Child Neurol. 2014; 56(4):323-328. doi: 10.1111/dmcn.12262.
2. Alastair H. MacLennan, MD, Suzanna C. Thompson, Jozef Gecz. Cerebral palsy: causes, pathways, and the role of genetic variants. American Journal of Obstetrics & Gynecology. 2015;12:779-788. https://doi.org/10.1016/j.ajog.2015.05.034
3. Fairhurst C. Cerebral palsy: the whys and hows. Arch Dis Child Educ Pract Ed. 2012; 97(4):122231. doi: 10.1136/edpract-2011-300593.
4. Blair E1, Watson L. Epidemiology of cerebral palsy. Semin Fetal Neonatal Med. 2006;11(2):117125. doi:10.1016/j.siny.2005.10.010.
5. Hadders-Algra M. Early diagnosis and early intervention in cerebral palsy. Front Neurol. 2014; 245:255. doi: 10.3389/fneur.2014.00185.
6. Beanom G, Khoshnood S, Kaminski M, Pierrat V. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. Developmental Medicine & Child Neurology. 2010;52:119-125. doi: 10.1111/j.1469-8749.2010.03612.x.
7. De Jesus L. C., Pappas A., Shankaran S. et al. Outcomes of small for gestational age infants born at < 27 weeks' gestation. J Pediatr. 2013;163 (1):55–60.doi: https://doi.org/10.1016/j.ajog.2015.05.034.
8. Moster D., Wilcox A. J., Vollset S. E., Markestad T., Lie R. T. Cerebral palsy among term and postterm births. JAMA. 2010; 304 (9):976–982. doi: 10.1001/jama.2010.1271.
9. Oskoui M, Coutinho F, Dykeman J,et al. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol 2013;55(6):509-519. doi: 10.1111/dmcn.12080.
10. Sellier E, Platt MJ, Andersen GL, et al. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. Dev Med Child Neurol. 2016; 58(1):85-92. doi: 10.1111/dmcn.12865.
11. Hollung SJ, Vik T, Lydersen S, et al. Decreasing prevalence and severity of cerebral palsy in Norway among children born 1999 to 2010 concomitant with improvements in perinatal health. European journal of pediatric neurology. 2018;22:814-821. doi: 10.1016/j.ejpn.2018.05.001.
12. Children of Kazakhstan Statistical Yearbook Available at: https://www.unicef.org/kazakhstan/en/reports/children-kazakhstan-statistical-yearbook. [accesed 20.10.2019].

13. Blair E, Stanley F, Hockey A. Intrapartum asphyxia and cerebral palsy. J Pediatr. 1992;121:170171. doi:10.1016/s0022-3476(05)82585-5.
14. Oskoui M1, Coutinho F, Dykeman J, et al. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013;55:509-519. doi: 10.1111/dmcn.12080.
15. Smithers-Sheedy H, Badawi N, Blair E, et al. What constitutes cerebral palsy in the twenty-first century?. Dev Med Child Neurol. 2014;56(4):323-328. doi: 10.1111/dmcn.12262.
16. Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn Available at: http://www.uptodate.com/contents/pathogenesis-and-etiology-of-unconjugatedhyperbilirubinemia-inthe-newborn. [accessed 1/09/2019].
17. Norman M, Aberg K, Holmsten K, et al. Predicting Nonhemolytic Neonatal Hyperbilirubinemia. Pediatrics 2015;136(6):1087-1094. doi: 10.1542/peds.2015-2001.
18. Usman F, Diala U, Shapiro S et al. Acute bilirubin encephalopathy and its progression to kernicterus: current perspectives. Research and Reports in Neonatology 2018;8:33–44. https://doi.org/10.2147/RRN.S125758.
19. Setia S, Villaveces A, et al. Neonatal Jaundice in Asian, White, and Mixed –Race Infants. Arch Pediatr Adolesc Med. 2002;156:276-279. doi:10.1001/archpedi.156.3.276.
20. Lain SJ, Roberts CL, Bowen JR, et al. Early discharge of infants and risk of readmission for jaundice. Pediatrics. 2015;135(2):314-321. doi: 10.1542/peds.2014-2388.
21. Olusanya BO, Osibanjo FB, Slusher TM. Risk factors for severe neonatal hyperbilirubinemia in low and middle-income countries: a systematic review and meta-analysis. PLoS One. 2015;12;10(2): e0117229. doi: 10.1371/journal.pone.0117229.
22. Статистический сборник "Здоровье населения Республики Казахстан и деятельность организаций здравоохранения в 2017 году" Available at: http://dsm.gov.kz/ru/kategorii/statistika-0. [accessed 1.09.2019].
23. Rosea J,Vassar R. Movement disorders due to bilirubin toxicity. Semin Fetal Neonatal Med. 2015;20(1): 20–25. doi: 10.1016/j.siny.2014.11.002.