UDK 616.831-009.11-036.865-053

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Gender and age related adverse effects of child's hypoxic-ischemic encephalopathy

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Modern Pediatrics. Ukraine. (2022). 1(121): 5-10. doi 10.15574/SP.2022.121.5

For citation: Yablon OS, Bondarenko TV. (2022). Gender and age related adverse effects of child's hypoxic-ischemic encephalopathy. Modern Pediatrics. Ukraine. 1(121): 5-10. doi 10.15574/SP.2022.121.5.

Introduction. Among the causes of childhood disability, the consequences of hypoxic-ischemic encephalopathy (HIE) transmitted in the neonatal period are the most significant. Annually in developed countries, 1–8 neonates per 1,000 are diagnosed with HIE. The incidence rate is twice as high in low- and middle-income countries. Among them, every 4th child with this diagnosis has adverse consequences of the disease sort of severe neurological pathologies such as epilepsy and cerebral palsy (CP). Researchers are particularly interested in the easy course of HIE and the ability to predict its consequences.

Aim of the research. To establish the gender and age characteristics of the adverse effects of HIE in preschool children.

Materials and methods. The study is prospective, carried out on all its stages in the neonatology center and the center of follow-up observation of Vinnytsia Regional Children's Clinical Hospital VOR, 214 children aged 0 to 6 years were examined. The prospective study included 174 children born full-term and in the neonatal period suffered HIE of various severity.

Results. The results of follow-up were analyzed at 1, 3 and 6 years. The formation of disability had gender and age related features. Thus, among 23 children with disabilities, boys predominated — 16 (69.57%). With age, the number of children with disabilities increased from 14 (9.52%) in 1 year to 23 (15.65%) in 3 years and remained unchanged at the age of 6 years. More than half of children had mental and language retardation at the age of 1. Thus, among 23 children with disabilities, boys predominated — 16 (69.57%). With age, the number of children with disabilities increased from 14 (9.52%) at 1 year of age to 23 (15.65%) among 3-agers and remained unchanged among 6-agers. More than half of children had mental and language retardation at the age of 1. As they reached the age of 6, their number decreased to 25% girls and 41.2% boys. Certainly, majority of these children were among patients with severe GIE in the neonatal period. 20 (13.61%) children had episyndrome at the age of 1 year, 11 (55.0%) of them — prevailing boys. For the children aged 3 with slight and moderate HIE, the diagnosis was disaffirmed. Among 6-olders with spasms boys prevailed. At the age of 6 years among children with convulsions significantly prevailed boys 12 (63.16%). Among concomitant pathologies of children with HIE consequences there prevailed anemia at the age of 3 years, found in 1 of 4 girls and 1 of 5 boys severe HIE history, ophthalmic diseases fou nd among 23.5% of boys in this group and bronchial asthma — among 9.52%. Child mortality with HIE in the neonatal period, in the first 6 years of life was 2.72%.

Conclusions. The formation of adverse effects of HIE in children had gender and age characteristics. Boys predominated among children with disabilities, they were more likely to have mental and language retardation and episyndrome. With age, the number of children with adverse effects has decreased, with the exception of the disabled, whose number has increased.

Key words: hypoxic-ischemic encephalopathy, disability, cerebral palsy, episyndrome, gender differences.

Гендерно-вікові особливості несприятливих наслідків гіпоксично-ішемічної енцефалопатії у дітей

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Вступ. Серед причин інвалідності у дитячому віці найбільш значущими є наслідки гіпоксично-ішемічної енцефалопатії (ГІЕ), що передаються в неонатальному періоді. Щорічно в розвинених країнах у 1–8 новонароджених на 1000 діагностується ГІЕ. Рівень захворюваності вдвічі вищий у країнах з низьким і середнім рівнем доходу. Серед них кожна 4-та дитина з таким діагнозом має несприятливі наслідки захворювання у вигляді тяжких неврологічних патологій, таких як епілепсія та дитячий церебральний параліч. Дослідників особливо цікавить легкий перебіг ГІЕ та можливість передбачити його наслідки.

Мета дослідження. Встановити гендерно-вікові особливості несприятливих наслідків гіпоксично-ішемічної енцефалопатії у дітей дошкільного віку.

Матеріали і методи. Дослідження є проспективним, етапи якого здійснювалися в неонатологічному центрі та центрі катамнестичного спостереження КНП «Вінницька обласна дитяча клінічна лікарня ВОР». Обстежено 214 дітей віком від 0 до 6 років. Результати катамнестичного спостереження аналізували у 1, 3 та 6 років. В проспективне дослідження включені 174 дитини, які народилися доношеними та в неонатальному періоді перенесли ГІЕ різного ступеня тяжкості.

Результати дослідження. Формування інвалідності мало гендерні та вікові особливості. Так, серед 23 дітей-інвалідів переважали хлопчики — 16 (69,57 %). З віком кількість дітей з встановленою інвалідністю зростала від 14 (9,52 %) у 1 рік до 23 (15,65 %) у 3 роки та залишалася без змін у віці 6 років. Затримку психічного та мовленнєвого розвитку у віці 1 року мали більше половини дітей. З віком їх кількість зменшилася, залишаючись у 6 років у 25 % дівчаток та 41,2 % хлопчиків. Достовірно більше таких дітей було серед пацієнтів-хлопчиків з важкою ГІЕ в неонатальному періоді. Епісиндром у віці 1 року мали 20 дітей (13,61 %), серед них переважали хлопчики – 11 (55,0 %). У віці 3 років діагноз був знятий 3 дітям з легкою і помірною ГІЕ в анамнезі. У віці 6 років серед дітей з судомами достовірно переважали хлопчики – 12 (63,16 %). Серед супутньої патології у дітей з наслідками ГІЕ переважали у віці 3 років анемія, виявлена у кожної четвертої дівчинки та кожного п'ятого хлопчика з тяжкою ГІЕ в анамнезі, офтальмологічні захворювання у 23,5 % хлопчиків цієї групи та бронхіальна астма у 9,52 %. Смертність дітей, що перенесли ГІЕ в неонатальному періоді, у перші 6 років життя становила 2,72 %.

Висновки. Формування несприятливих наслідків ГІЕ у дітей мало гендерні та вікові особливості. Серед дітей-інвалідів переважали хлопчики, у них частіше спостерігалася затримка психічного та мовленнєвого розвитку та епісиндром. З віком кількість дітей з несприятливими наслідками зменшилася, за виключенням інвалідів, кількість яких зросла.

Ключові слова: гіпоксично-ішемічна енцефалопатія, інвалідність, дитячий церебральний параліч, епісиндром, гендерні відмінності.

Introduction

Among the causes of childhood disability, the consequences of hypoxic-ischemic encephalopathy (HIE) transmitted in the neonatal period are the most significant [3,14]. Annually in developed countries, 1–8 neonates per 1,000 are diagnosed with HIE [13,20]. The incidence rate is twice as high in low- and middle-income countries. Among them, every 4th child with this diagnosis has adverse consequences of the disease sort of severe neurological pathologies such as epilepsy and cerebral palsy (CP) [1,5,6]. Researchers are particularly interested in the easy course of HIE and the ability to predict its consequences [16,18]. Children whose central nervous system (CNS) was injured in the perinatal period and avoided a severe disability are at increased risk for long-term intellectual development, speech and motor impairments, and moderately negative impact on the development of behavioral disorders [10,11].

However, nowadays in Ukraine there are no official statistics on the consequences of treatment of full-term infants who have suffered of HIE at birth and the level of their medical and social rehabilitation [26].

The development of a Neonates Post-discharge Follow-ups Department is an important component of medical care for a child with high risk of psycho-neurological disorders in the future [23,24,25]. The approximate results of the pathology or the absence of health problems in early childhood are not enough to assess and predict the health status of high-risk neonates [12]. Long-term Post-discharge Follow-ups will improve your understanding of the links between risk factors, treatment technologies and children's development [4]. It is important to develop a program on providing continuous specialized care for newborns after discharment from anesthesiology and intensive care units with manifestations of CNS injuries and prevention or timely medical and social correction of disabling developmental disorders [15,27].

Aim of the research — to establish the gender and age characteristics of the adverse effects of HIE in preschool children.

Materials and methods

The study is prospective, carried out on all its stages in the neonatology center and the center of follow-up observation of Vinnytsia Regional Children's Clinical Hospital VOR, being the clinical base of the Department of Pediatrics 1 National Pirogov Memorial Medical University, Vinnytsya, 214 children aged 0 to 6 years were examined. The main group included 174 children born at 37th to 41st gestation weeks and underwent HIE in the neonatal period. According to the classification of severity HIE all patients of main group was divedid into the mild, moderate and severe. The diagnosis of «hypoxic-ischemic encephalopathy» was established in accordance with the Order of the Ministry of Health of Ukraine dated 08.06.2007 No. 312 «On approval of the Clinical Protocol on primary resuscitation and resuscitation of newborns» and the Order of the Ministry of Health of Ukraine dated 28.03.2014 No. 225 «Unified Clinical Protocol, resuscitation and post-resuscitation care for newborns in Ukraine» by the Sarnat scale [17].

Group 1 included 63 children with mild HIE. Group 2 included 65 children with moderate grade HIE. 46 children with severe grade HIE were included in Group 3. The results of the survey were compared with the results of the control group of 40 healthy children. The groups were representative in terms of gender and age.

After completion of the inpatient HIE treatment, all children involved in the study were observed at the follow-up (catamnestic) center. Each patient was observed with an individual approach, defined examination program by specialists (ophthalmologist, otolaryngologist, physiotherapist, neurologist, orthopedist, neurosurgeon) and underwent medical examinations (laboratory tests, neurosonography and magnetic resonance imaging of the brain, ultrasound, internal ultrasound). According to the consultation and examination results, recommendations on the rehabilitation were agreed with parents, the rehabilitation institution was also recommended and a prospective examination and treatment plan was drawn up.

The results of follow-up were analyzed among 1-, 3- and 6-agers. Children who dropped out of the study before the age of 6 were not included in the analysis.

The work was performed in compliance with the basic principles of bioethics: the parents' informational consent to the child's participation in this study was obtained, the principles of the Declaration of Helsinki were observed. The study was approved by the Committee on Bioethics at National Pyrogov Memorial Medical University, Vinnytsya.

Statistical processing of the research results was performed on the licensed statistical package

«Statistica 6.0» using non-parametric evaluation methods.

Results.

103 boys (59.19% of all examined patients) and 71 (40.81%) girls were under observation.

The control group involved 40 healthy children, including 24 (60.00%) boys and 16 (40.00%) girls.

The formed groups, depending on the severity of HIE, included children of both sexes: mild encephalopathy was diagnosed in 33 (52.38%) girls and 30 (47.62%) boys, moderate — in 26 (40.00%) girls and 39 (60.00%) boys, severe encephalopathy — in 12 (26.09%) girls and 34 (73.91%) boys. It was found that if girls slightly prevailed among children with mild HIE, boys significantly prevailed among patients with severe encephalopathy — 73.91%.

Our primary interest was to define what number of children with different severity of CNS injuries during the neonatal period were healthy at these ages and whether these data depended on the children's sex. At the age of 1 year, the lowest number of healthy children was among those who underwent severe encephalopathy in the neonatal period — 16.7% of girls and 26.5% of boys, significantly different from the control goup (p=0.0003) and children with mild and moderate HIE p=0.0006 and 0.0067, respectively).

The number of healthy girls aged 3 in this group increased to 50%, and boys — to 41.2%, significantly different from both control and groups of children with mild and moderate HIE. The number of healthy 6-year old girls remained at the same level — 50%, while the number of healthy boys decreased to 23.5%.

The most serious consequence of HIE is CP. At the age of 1 year, CP had 15 children included in the study, which amounted to 8.62%. Among them 1 (3.8%) girl with moderate HIE, 1 (3.3%) boy with mild HIE and 1 (7.7%) with moderate HIE, 1 (8.3%) girl and 11 (32.4%) boys with severe HIE. The consequences were statistically significant among boys with severe HIE in comparison with both mild and moderate HIE (p=0.0042 and 0.0093, respectively) (Fig. 1).

At the age of 3, the diagnosis CP was disaffirmed for 1 girl with moderate HIE and 1 boy with a history of mild HIE. At the same time, another 2 boys with severe HIE were diagnosed with CP, thus, the total number of children with CP in this group increased to 13 (38.2%), significantly exceeding the rate of boys in other groups (p=0.0003 and 0.0024, respectively).

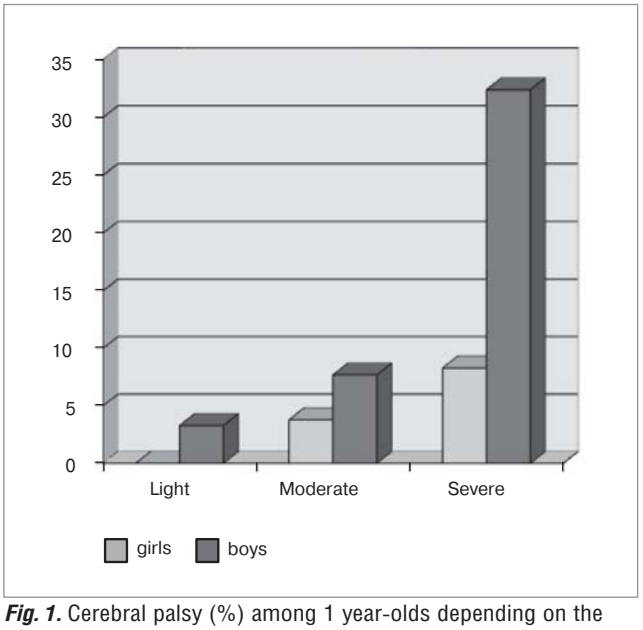

Fig. 1. Cerebral palsy (%) among 1 year-olds depending on the sex and severity of HIE in the neonatal period

At the age of 6, one boy from the group of severe HIE diagnosed with CP died, while severe pathology remained in 14 (8.05%) children.

One of the consequences of HIE is a delay in mental and language development. It was found out that 46 (26.44%) children had such violations. The largest number of such patients at the age of 1 year was among 7 (58.3%) girls and 18 (52.9%) boys with severe HIE. At the age of 3, the number of children with mental and language retardation decreased in all groups, remaining the maximum in children with severe HIE — 2 (16.7%) of girls and 15 (44.1%) of boys.

At the age of 6, girls with a delay in this group made up 3 (25.0%), and boys — 14 (41.2%). The data significantly differ from all groups with lower HIE (p=0.0266 and 0.0551 in girls and p=0.0004 and 0.0032 in boys).

Neurological disorders manifested by delayed motor development were detected among 1-year-olds in all groups, except for girls with a history of mild HIE. At the age of 3, the number of children with delays decreased, most — twice in children with severe HIE. At the age of 6, the delay remained in 3 (25.0%) of girls and 14 (41.2%) of boys in this group. Statistical differences are significant for all groups with a lower severity of HIE in the anamnesis.

Another serious consequence of HIE is episyndrome. At the age of 1, seizures occurred to 3 (9.1%) girls with a history of mild HIE, 4 (15.4%) with moderate and 2 (16.7%) with severe HIE. Among the boys who experienced mild HIE,

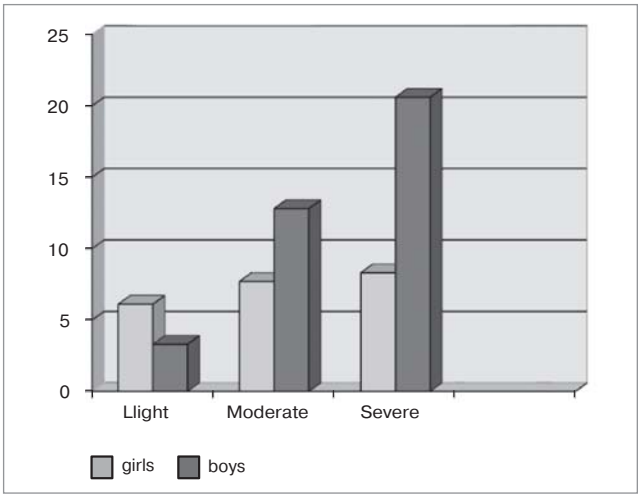

Fig. 2. Epilepsy at the age of 6 depending on the sex and HIE severity in the neonatal period (%)

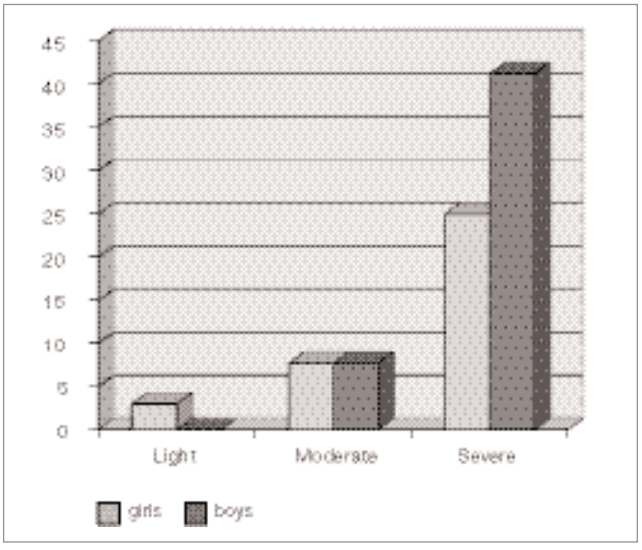

Fig. 3. Disability at the age of 3 years depending on the gender and severity of HIE in the neonatal period (%)

3 (10.0%) presented episyndrom, those who had moderate HIE — 3 (7.7%) and severe HIE — 5 (14.7%). In total, 20 (13.61%) children had seizures at the age of 1.

At age of 3, episyndrome diagnosis was disaffirmed for 1 (3.85%) girl with moderate HIE and 2 (6.67%) boys with mild HIE, while other 2 (5.88%) boys with severe HIE were diagnosed with episyndrome. In total, 7 (20.6%) boys in this group had seizures, which significantly exceeds the number of children with mild HIE (p=0.0408). At the age of 6, the number of girls with episyndrome decreased — twice in the group with severe HIE, while the number of boys remained unchanged compared to 3 years of age (Fig. 2).

At the age of 1 year, disability was issued to 14 (9.52%) children: 1 (8.3%) girl with CP due to severe HIE, 1 (3.3%) boy with mild HIE and 1 (2.6%) boy with moderate HIE and 11 (32.4%) boys who experienced severe HIE. The latter was significantly higher than in the groups with mild and moderate HIE (p=0.0042 and 0.0010, respectively).

At the age of 3, the number of children with HIE associated disabilities among girls — 1 (3.0%) with mild HIE, 2 (7.7%) with moderate HIE and 4 (33.3%) with severe HIE in the anamnesis. Among boys — 2 (5.13%) with moderate and 14 (41.2%) with severe HIE. In total 23 (15.65%) children got disability. Differences are significant for girls with severe HIE (p=0.0266) and boys with mild and moderate HIE (p=0.0002 and 0.0012, respectively) (Fig. 3). At the age of 6, the number of children with disabilities decreased by 1 (2.9%) boy in the severe HIE group, since he died.

It is known, that among children with HIE effects, a significant number have visual impairments like nearsightedness and farsightedness, strabismus, optic nerve damage. The children of the main group at the age of 3 presented ophthalmological problems: 1 (3.3%) boy with mild HIE, 2 (7.7%) girls and 1 (5.1%) boy with moderate brain damage, 1 (8.3%) girl and 8 (23.5%) boys with severe HIE. The incidence of visual impairment in boys with severe HIE in the anamnesis significantly exceeded not only the control group, but also those of children with mild (p=0.0235) and moderate HIE (p=0.0254).

At the age of 6, the number of children with ophthalmic problems among girls increased by another 2, while boys remained at the same level. It should be noted that in preschool, vision diseases were diagnosed in boys of the control group — in 2 (8.3%) children myopia was detected.

Children of all groups at the age of 1 presented anemia, not significantly different from children in the control group, while among patients with severe HIE, one of three suffered from anemia, which significantly exceeded the rates of children with mild HIE in both girls (p=0.0065) and boys (p=0.075). At the age of 3 and 6, the number of cases of anemia decreased. Among the pathologies found in patients with a history of HIE, asthma had a significant proportion. At the age of 6 there were 14 (9.52%) such children, with predominance of boys: 11 (78.57%) boys and 3 (21.48%) girls. Children of the control group were not diagnosed with asthma.

All children up to 1 year, included in the study survived. One (8.3%) girl with severe HIE died

before the age of 3. By the age of 6, another 2 girls with a history of mild and severe HIE (3.0% and 8.3%, respectively) and 1 (2.9%) boy with severe HIE died. Thus, the mortality among children who experienced HIE in the neonatal period, in the first 6 years of life was 2.72%. No child died in the control group.

Discussion

Neonatal encephalopathy, caused by acute perinatal hypoxia, is a major cause of brain damage and adverse events [21,22,28]. Moderate to severe neonatal encephalopathy is associated with high mortality and morbidity. However, the results of neurodevelopment in neonates with mild neonatal encephalopathy are unclear. Thus, a number of studies have shown that newborns with mild HIE later developed a disability [7]. Our data (15.63% people with HIE associated disability) coincide with the published results, where out of 43 babies with HIE, 7 (16%) were diagnosed with disability, including 1 cerebral palsy and 2 cases of autism [3].

In a study [1] abnormal short-term effect was the following: convulsions or abnormal electroencephalogram, abnormal magnetic resonance imaging of the brain obtained during the first 4 weeks of life, and abnormal results of neurological examination at discharge. 18% of neonates involved in this study had adverse short-term effects, which is slightly higher than in our study — 9.52%. According to the literature, the introduction of craniocerebral hypothermia had a significant impact on improving the consequences of HIE [19]. But the patients in our study did not receive such treatment because it was introduced later in Ukraine.

Conclusions

1. The analysis of HIE asscociated adverse effects among children in the first 6 years of life showed that the formation of disability had gender and age peculiarities. Thus, among 23 (15.65%) children with disabilities, boys predominated — 16 (69.57%). With growth, the number of children with disabilities increased from 14 (9.52%) in 1 year to 23 (15.65%) in 3 years and remained unchanged at the age of 6 years.

2. More than half of the children had mental and language development delays at the age of 1 year. As they grew older, their number decreased, remaining at the age of 6–3 (25%) of girls and 14 (41.2%) of boys. Boys who had severe HIE in the neonatal period made up a larger number of such patients.

3. Episyndrome at the age of 1 year was diagnosed among 20 (13.61%) children with prevalent boys: 11 (55.0%). At the age of 3, this diagnosis was set for 1 (3.85%) girl with moderate HIE and 2 (6.67%) boys with a history of mild HIE. At the age of 6 years among children with convulsions, boys significantly prevailed — 12 (63.16%).

4. Among concomitant pathologies of children with HIE effects anemia was prevalent at the age of 3 years, diagnosed in 1 of 4 girls and 1 of 5 boys with a history of severe HIE, ophthalmic diseases in 23.5% of boys in this group and bronchial asthma in 9.52%.

5. The mortality among children who experienced HIE in the neonatal period, made up 2.72% in the first 6 years of life. Girls prevailed among the mortal cases — 3 (75%), but the mortality causes are not HIE associated.

Ethical Clearance: The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of all the institutions mentioned in the work. Informed consent of parents of children (or their guardians) was obtained for the research. The study was approved by the Committee on Bioethics at National Pirogov Memorial Medical University, Vinnytsya.

Source of Funding: Self

Conflict of Interest: The authors declare no conflict of interest.

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Стаття надійшла до редакції 09.11.2021 р., прийнята до друку 06.02.2022 р.