DOI: 10.2298/SARH1102006V
UDC: 616.831-005.1-07-053.2:618.43

Neurosensory Outcome of Prematurely Born Children Following Intracranial Haemorrhage

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SUMMARY

Introduction More and more survival of newborns with small or extremely small body mass at birth, as well as increasing percent of prematurely born babies, have emphasized the significance of intracranial haemorrhage problem. Prematurely born infants are under increased risk for strabismus, amblyopia, blinding and hearing loss.

Objective Establishing the frequency of sensory damages (damage of sight and hearing) in prematurely born infants with various degrees of intracranial haemorrhage.

Methods The study is prospective, controlled and included 120 prematurely born infants with diagnosed four different grade intracranial haemorrhage on ultrasonic examination of the central nervous system. The study excluded prematurely born children from twin pregnancies with congenital malformations and stoppage of intrauterine growth. Ophthalmological examination was done at 9, 12, and 36 months of postnatal age. Audilogical examination was done after delivery, at 2 months of age.

Results There are stasistically significant differences ($p<0.01$) related to the presence of strabismus among groups of examinees with vairious haemorrhage degrees. Strabismus was present only in one premature infant with 1st and in 10 children (33.3%) with the 4th degree. Amblyopia occurred only among examinees with 4th degree haemorrhage. There were statistically significant differences ($p<0.01$) related to the finding of transitory otoacoustic emission of the left ear and the right ear among the groups. The finding of the right ear was not usual in 7 examinees from the 4th degree haemorrhage. The finding of the left ear was not usual in 1 examinee from the third and in 7 examinees from the fourth group.

Conclusion Prematurely born children with a higher degree intracranial haemorrhage have a greater risk for the loss of hearing and development of visual handicap.

Keywords: intracranial haemorrhage; prematurely born infant; neurosensory outcome

INTRODUCTION

More and more survival of newborns with low birth weight (under 2500 g) or extremely small body mass at birth (under 1000 g), as well as increasing percent of prematurely born babies have emphasized the significance of intracranial haemorrhage problem. This is one of the most important causes of neonatal morbidity and, sometimes, mortality [1]. Brain damage in prematurely born children results in a series of events more than one specific insult, like ischaemic white matter lesion, cerebral infection, hydrocephalus following intraventricular haemorrhage [2].

The children experience premature birth as a break in normal growth and development, despite the medical care with which they are provided afterwards. Vulnerable immature anatomy, haemodynamic instability and proneness to bleeding as essential factors of premature babies lead to the germinative matrix and intraventricular haemorrhage (GMH-IVH) [3]. The brain of the prematurely born infant contains remains of the germinative matrix that is mostly not seen in infants born in due time. The subependymal germinal matrix is a structure which is the most prominent between 24 and 34 weeks of gestation. It is a good vascularized area between nucelus caudatus and thalamus. The subependymal germinal matrix is the site of vigorous neuroblast and glioblast mitotic activity before the neurons have completed their migration to other parts of the cerebrum. [4]. Today, ultrasound, with improved imaging information, is the method of choice for determination of the localization, size and time of the origin not only of GMH-IVH, but also of hypoxic/ischaemic brain damage, the diagnosis of the central nervous system malformations, the determination of the intracranial relation of certain structures, monitoring the developmental changes of the brain and the determination of the gestation age.

The consequences of premature birth and intracranial haemorrhage may be cerebral paralysis, mental retardation, deafness, blindness, visual damage, diseases of attention, behaviour, learning, communication, perception and minimal cerebral dysfunction. Pre-term children have a significantly higher risk of developing ophthalmological problems and hearing damage than their peers who were born on time. The follow-up of prematurely born infants is a process that is going on for years. This is a progressive re-evaluation of certain organ systems and their functions. According to long-term studies of monitoring, disabilities in prematurely born children are much more frequent than it was thought earlier [5, 6].

Since early signs in children have often been directed towards the development of social

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communication and educational skills, the effects of deafness may have far-reaching consequences. The most important is their early detection and beginning of their aggressive rehabilitation [7].

OBJECTIVE

Establishing the frequency of sensory damages (damage of sight and hearing) in prematurely born infants with various degrees of intracranial haemorrhage.

METHODS

The examination was implemented at the Institute for the Health Protection of Children and Youth of Vojvodina in Novi Sad. The examination included prematurely born infants hospitalized at the premature infant ward of the Department of Neonatology, Intensive Care and Therapy of the Institute.

The study excluded prematurely born children from twin pregnancies with congenital malformations and stoppage of intrauterine growth.

The study is prospective, controlled and included 120 prematurely born infants with the diagnosed intracranial haemorrhage on ultrasonic examination of the central nervous system. Ultrasound examinations were done during hospitalization on the first, thirth, seventh and fourtheenth day of age. Echosonographic examinations of the central nervous system were done on the ultrasonic device Siemens Adara with 3 and 5 MHz frequency convex probes and 5 and 7.5 MHz frequency linear probes. Standardization of echogram evaluation of the central nervous system of infants was made according to Papilleu classification [8] (Table 1). The prematurely born children were regularly controlled at the neonatology ward until the age of three.

Based on the findings of the ophthalmologist and audiologist, the sensory damages were assessed.

The ophthalmological examination of prematurely born children was carried out during hospitalization aiming at prevention of premature retinopathy, and after fully developed blood network in the period of 9, 12 and 36 months of postnatal age. By ophthalmological examination, the existence of binocular vision was assessed, as well as the existence of strabismus and amblyopia (lazy eye) by cover test. Cover test is a test for objective determination of ocular deviation. The test is developed as follows: the child is focusing at a nearby object. The cover is put over the eye for a short time and then removed. During this time, the examiner is watching the movements of both eyes. The "lazy eye" will move either towards the field or towards the inner side since it stops using its perceptive visual advantage. This process is repeated on both eyes and then the child is examined while focusing at a distant object.

The audiological examination is based on transitory otoacoustic emission (TEOAE). All hearing examinations of prematurely born children were done after they had been discharged from the ward with no pre-medication.

Table 1. Papille classification of intracranial haemorrhage

Grade	Expanding haemorrhage
I	GMH
II	GMH + IVH – VD
III	GMH + IVH + VD
IV	GMH + IVH + PI

GMH – germinal matrix haemorrhage; IVH – intraventricular haemorrhage; VD – ventricular dilatation; PI – parenchymal involvement

Transitory otoacoustic emission was measured on both ears with known directions for the technical procedure [9]. The results were analyzed by the audiologist who did not know anything about the origin of the children, nor about their clinical data. They were interpreted as "pass". Recording without emission was graded as "non-pass" through the test, either one-sided or both-sided.

Statistical data processing was made by using appropriate modules within the programme packages SPSS 12.0 for Windows, Pearson χ^2 test, variant analysis (ANOVA).

RESULTS

In the examined prematurely born infants with various haemorrhage degrees, comparisons were made of their body masses at birth (Table 2). The value of F-test was statistically significant at the level p<0.01, and it makes F=4.29 (df=119; p=0.01).

The representation of genders among the examinees with various haemorrhage degrees is presented on Table 3. The value of chi-squared test is statistically not significant and it makes χ^2=3.35 (df=3; p=0.34). The results of the examination suggest that there are no differences related to the gender of the examinees with various intracranial haemorrhage degrees. The medium value of Apgar score at birth of premature newborns with various haemorrhage degrees is presented on Table 4. The level of F-test is statistically significant at the level p<0.01, and it makes F=10.74 (df=118; p=0.00). The average Agpar scores at birth are higher in the examinees from the first and the second groups of damages, and they continue to decrease with the increase of the level of damage.

Table 2. Body mass (g) of prematurely born children at birth with various haemorrhage degrees

Group	N	$\bar{X}$	SD	Min	Max
I	30	1915.67	666.678	960	3620
II	30	1581	444.292	900	3100
III	30	1497	429.684	790	2400
IV	30	1442.17	658.784	710	3640
Total	120	1608.96	584.176	710	3640

N – number of examinees; $\bar{X}$ – arythmetic medium; SD – standard deviation; Min – lowest score; Max – highest score

Table 3. The gender of examinees with various haemorrhage degrees

Gender	Haemorrhage degree				Total
	I	II	III	IV	
Male	19	19	13	16	67
Female	11	11	17	14	53
Total	30	30	30	30	120

Table 4. Average values of Apgar scores at birth in examinees with various haemorrhage degrees

Group	N	$\overline{X}$	SD	Min	Max
I	30	6.43	1.695	4	10
II	30	6.27	1.68	3	9
III	30	5.13	2.315	1	9
IV	29	3.9	2.024	1	8
Total	119	5.45	2.173	1	10

Table 5. Average values of Apgar score 5 minutes after birth in examinees with various haemorrhage degrees

Group	N	$\overline{X}$	SD	Min	Max
I	30	7.77	1.278	5	10
II	30	7.83	1.234	5	10
III	30	6.77	1.995	2	10
IV	29	5.97	1.842	2	10
Total	119	7.09	1.775	2	10

Table 6. Average gestation age (days) of examinees with various haemorrhage degrees

Group	N	$\overline{X}$	SD	Min	Max
I	30	235.53	16.718	196	258
II	30	225.2	18.567	189	257
III	30	217.43	19.609	170	252
IV	30	208.4	25.945	172	259
Total	120	221.64	22.592	170	259

Table 7. Average gestation age (weeks) of examinees with various haemorrhage degrees

Group	N	$\overline{X}$	SD	Min	Max
I	30	33+4.53/7	16.718	28	36+6/7
II	30	32+1.20/7	18.567	27	36+5/7
III	30	31+0.43/7	19.609	24+2/7	36
IV	30	29+5.40/7	25.945	24+4/7	37
Total	120	31+4.64/7	22.592	24+2/7	37

The medium value of Apgar score in the fifth minute of premature newborns with various haemorrhage degrees is presented on Table 5. The level of F-test is statistically significant at the level $p<0.01$, and it makes $F=8.90$ ($df=118$; $p=0.00$).

The average gestation age of prematurely born infants with 1st degree haemorrhage was 33 weeks and 4 days, in the examinees with the most severe, 4th degree haemorrhage, was 29 weeks and 5 days. The medium values of gestation age of premature newborns for all the examined groups are presented on Tables 6 and 7. The level of F-test is statistically significant at the level $p<0.01$, and it makes $F=9.48$ ($df=119$; $p=0.00$). The values of average gestation age decrease with the increase of a more expressed degree of intracranial haemorrhage.

Prematurely born infants with various haemorrhage degrees were monitored related to neurosensory outcome until the age of 3. Strabismus was present only in one premature infant (3.33%) with 1st degree haemorrhage and in 10 children (33.33%) with the 4th, the most severe degree of intracranial haemorrhage. The frequency of strabismus in prematurely born infants with various haemorrhage levels is presented on Table 8.

The value of chi-squared test is statistically significant at the level $p<0.01$ and it makes $\chi^2=12.69$ ($df=3$; $p=0.00$). The results of the examination suggest that there are differences related to the presence of strabismus among groups of examinees with various haemorrhage degrees. The frequency of strabismus increases with the increase of haemorrhage degree.

The frequency of amblyopia in prematurely born infants with various haemorrhage degrees is presented on Table 9. In premature infants with 1st, 2nd and 3rd haemorrhage degree, amblyopia was not recorded. It occurred in 3 premature babies (10%) with the 4th, the most severe haemorrhage degree.

The value of chi-squared test is statistically significant at the level $p<0.05$ and it makes $\chi^2=9.23$ ($df=3$; $p=0.03$). The results of the examination suggest that there are differences related to the presence of amblyopia among groups of the examinees with various haemorrhage degrees. As it can be seen in Table 9, amblyopia occurs among the examinees with 4th degree haemorrhage. However, these results should be interpreted with great care since amblyopia has been registered only in 3 examinees.

Prematurely born infants with various haemorrhage degrees were monitored in the direction of neurosensory outcome. After they had been discharged, they were referred to screening of hearing by transitory otoacoustic emission (TEOAE). The findings of the emission for the right ear in premature infants with various haemorrhage degrees are presented on Table 10.

Table 8. Frequency of strabismus in examinees with various haemorrhage degrees

Strabismus	Haemorrhage degree				Total
	I	II	III	IV	
Yes	1	2	6	10	19
No	29	28	24	20	101
Total	30	30	30	30	120

Table 9. Frequency of amblyopia in examinees with various haemorrhage degrees

Amblyopia	Haemorrhage degree				Total
	I	II	III	IV	
Yes	0	0	0	3	3
No	30	30	30	27	117
Total	30	30	30	30	120

Table 10. TEOAE finding of the right ear in premature infants with various haemorrhage degrees

TEOAE of the right ear	Haemorrhage degree				Total
	I	II	III	IV	
Not usual	0	0	0	7	7
Usual	30	30	30	22	112
Total	30	30	30	29	119

Table 11. TEOAE finding of the left ear in examinees with various haemorrhage degrees

TEOAE of the left ear	Haemorrhage degree				Total
	I	II	III	IV	
Not usual	0	0	1	7	8
Usual	30	30	29	22	111
Total	30	30	30	29	119

doi: 10.2298/SARH1102006V

The value of chi-squared test is statistically significant at the level p<0.01 and it makes χ^2=23.08 (df=3; p=0.00). The results of the examination suggest that there are differences related to the TEOAE finding of the right ear among the groups of the examinees with various levels of damage. As it can be seen on the Graph, among the examinees from the first, second and third group of damage, the TEOAE finding of the right ear is usual, while in 7 examinees, from the fourth group of damage, the TEOAE finding of the right ear is not usual.

The transitory otoacoustic finding of the left ear in premature infants with various haemorrhage degrees is presented on Table 11.

The value of chi-squared test is statistically significant at the level p<0.01 and it makes χ^2=18.90 (df=3; p=0.00). The results of the examination suggest that there are differences related to the TEOAE finding of the left ear among the groups of the examinees with various levels of damage. The TEOAE finding of the left ear, among the examinees from the first and second group of damage is usual, while the finding is not usual in 1 examinee from the third and in 7 examinees from the fourth group of damage.

DISCUSSION

The incidence of long-term neurological sequels depends on the weight of germinative matrix-intraventricular haemorrhage. Mild GMH-IVH (1st degree) has the incidence of neurological sequels about 5% related to 15% in the 2nd degree, 35% in the 3rd degree and 90% in severe cases with periventricular infarctions (4th degree) [10].

Neurosensory follow-up of prematurely born infants with intracranial haemorrhage is a part of all follow-up studies of high-risk children. The possible sequels which occurred from intracranial haemorrhage may vary from mild to very severe with the loss of hearing and vision. The risk of visual disability of very low body weight (VLBW) children is reversely proportional with gestation age. Vohr and associates found visual damages in 9% of new-borns with extremely low body mass at birth that were monitored until the age of 18 months. They found unilateral blindness in 1% and bilateral blindness in 2% of these children [11]. The results of this study found amblyopia in 3 children with the most severe form of haemorrhage, which was 10% within the group of 4th degree haemorrhage, or 2.5% of all children in the study. High association of periventricular leucomalacia and the presence of bilateral porencephalic cysts in the group of children of the 4th haemorrhage degree may explain this frequency.

Amblyopia, as a sequel of intracranial haemorrhage, was not noted in children with the 1st, 2nd and 3rd haemorrhage level. The results of the examination suggest that there are differences as far as the presence of strabismus is concerned among the groups of the examinees with various haemorrhage degrees. The frequency of the occurrence of strabismus grows with the growth of the haemorrhage degree. Based on ultrasonic finding in neonatal period, it was found that the children diagnosed with a more severe haemorrhage level had significantly more pathological visual functions and lower scores on visual motor tests than children without this morbidity [12]. In relation to visual and hearing impairment and retinopathy of premature baby, it is important to know that the same aetiological factors which lead to visual and hearing impairment and retiopathy lead to intracranial haemorrhage. The visual and hearing impairment of premature infants could be due to cortical visual and auditory impairment, structural damage or impairment of optical radiation and it could be found to be more frequent in prematurely born infants with severe grades of intracranial haemorrhage. The visual damage level is in correlation with the level of neurodevelopmental damage.

Premature new-borns with very low body mass at birth (lower than 1500 g) and/or very prematurely born infants are at risk for the development of strabismus. In the study that examined strabismus at the age of 5 in prematurely born children, strabismus was found in 14.4% [13]. Three percent of these children were not referred to, or treated by ophthalmologist. Only 2% of children at risk were treated for strabismus before the end of their first year of life. According to longitudinal studies, the frequency of strabismus looks constant and stable in the first 2.5 years and ranges from 14% to 18%. Only small percentage of children that were diagnosed for strabismus with 6 weeks of life were still having it at the age of 2.5 years. Screening programmes for children at risk have to focus on diagnosing strabismus with 9 months of corrected age. Due to the known fact that strabismus may also occur after this age, it is important to repeat the examinations of visual functions after this age in children at risk.

The incidence of the loss of hearing is more frequent in children who were at neonatal intensive units compared with the general population of healthy infants. All children hospitalized in intensive care units must undergo evaluation of hearing before or immediately after discharge from hospital. Parents must be informed whether the children passed the test of hearing. If not, they must be referred to the audiologist. Vohr and associates found hearing damage in 11% of VLBW infants at birth who were monitored until the age of 18 months. The percentage of children who required hearing aids was significantly lower, that is 3% [11]. The incidence of significant hearing impairment was higher (4% hearing aid were provided) in the study of high-risk follow-up group in Hong-Kong [14] . The findings of neurosensory examinations in this study indicate that transitory otoacoustic emission was not registered in 7 children from the 4th haemorrhage group, which is 23.3% within the observed group of children, or 5.83% of all observed children in the study. Transitory otoacoustic emission was not registered only in 1 child with the 3rd haemorrhage degree, or 10% of children with the same haemorrhage degree, where dilatation of the chamber system is present.

In literature, there is an agreement that the risk of cerebral paralysis and large neurosensory and/or neurological disabilities are reversely proportional with the level of immaturity, no matter whether it is measured as per gestation age or body weight at birth [15, 16]. In addition, neurologic and neurosensory impairments are more frequent in premature infants with GMH-IVH grades III and IV than GMH-IVH grades I and II. In multivariate analyses, GMH-IVH grades III and IV were an independent risk factor for adverse outcomes [17]. Professor Cooke from the neonatal ward of the hospital in Liverpool found that children born before due term and without large neurodevelopmental sequels had the increased prevalence of ophthalmological damages. The damages are diagnosed at the beginning of school age, which is rather late. They are associated with visual perception, motor and cognitive defects [18]. The cause may also be generalized abnormality of cortical development rather than perinatally acquired focal lesions of the brain.

The eye achieves its largest part of development in the first three years of life. The peripheral retina is relatively well developed at birth. The macular region continues its development until the age of 4 [19]. The maturation of vision and posterior visual pattern is continuing to develop several years after birth [20]. The visual sharpness reaches adult level with the age of 4-5 [21]. While the eye is growing, the refractory status of the eye is changing. During the neonatal and early infant period, transitory refractory deviations occur. Most infants are mildly hypermetropic though premature infants are transitory myopic. The development of visual functions have to be evaluated in time with prematurely born children, because the application of rehabilitation programme in due time may reduce the consequences of visual handicap. Prematurely born children must undergo testing, that is examination of the eye at the age of two and a half years in order to prevent the development of visual disease [20].

Hearing is essential for the development of speech, therefore early diagnoses of its damage are essential. It must be known that out of 100 newborns hospitalized in the intensive care units, 2-4 newborns have hearing damage [22]. Before the screening period of hearing of newborns, there was a several-year delay in the recognition of the loss of hearing, when the side-effects on the speech and language development became obvious. In case the congenital perinatal loss of hearing is diagnosed before the 3rd month, and treatment of amplification and communication therapy begins before the 6th month, the chances for the development of speech and language are better. In children with normal hearing, the essential component – speech – is formed at the age of 3-4 years. Concerning the far-reaching consequences of delayed diagnosed loss of hearing in newborns, the American Pediatric Academy gave recommendation as early as 1999 for system screening of hearing for all newborn children. The expenses of accommodation of handicapped children, application of therapeutic and rehabilitation measures are high both for their families and the society. All efforts should be invested in the prevention of premature births, by which the percentage of children with intracranial haemorrhage and percentage of children with possible handicaps may be reduced.

CONCLUSION

Related to the existence of strabismus among groups of the examinees with various levels of damage, there are statistically significant differences at the level $p<0.01$. The frequency of strabismus is growing with the increase of the degree of intracranial haemorrhage.

There are differences related to the presence of amblyopia among the groups of the examinees with various levels of damage.

There are statistically significant differences at the level $p<0.01$ related to the finding of transitory otoacoustic emission (TEOAE) of the left and the right ear among the groups of the examinees with various haemorrhage degrees.

Prematurely born children with a higher degree of intracranial haemorrhage have a greater risk for the loss of hearing and development of visual handicap.

NOTE

The study is a part of the author's doctoral thesis titled "Intracranial Haemorrhage and Neuropsychological Outcome of Premature Infants", which was defended at the Faculty of Medicine, University of Novi Sad, in 2010.

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Неуросензорни исход превремено рођене деце после интракранијалног крварења

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КРАТАК САДРЖАЈ

Увод Све веће преживљавање новорођенчади мале и веома мале телесне масе на рођењу и све већи проценат превремено рођених беба повећали су значај проблема интракранијалног крварења (ИК). Деца рођена пре термина под повећаним су ризиком за развој страбизма, слабовидости, губитак вида и губитак слуха.

Циљ рада Циљ рада је био да се утврди учесталост сензорних оштећења (вида и слуха) код превремено рођене деце с различитим степеном ИК.

Методе рада Студија је била проспективна и контролисана, а обухватила је 120 превремено рођене деце са ИК различитог степена дијагностикованим током ултразвучног прегледа централног нервног система. Из истраживања су искључена превремено рођена деца из близаначких трудноћа, са конгениталним аномалијама и застојем интраутерусног раста. Офталмолошки преглед обављен је у деветом, 12. и 36. месецу постнатално. Аудиолошки преглед вршен је након отпуста недоношчета с одељења, у узрасту од два месеца.

Резултати Утврђена је статистички значајна разлика ($p<0,01$) у погледу постојања страбизма међу групама новорођенчади с различитим степеном ИК. Страбизам је дијагностикован само код једног детета с првим и код десеторо деце са четвртим степеном ИК. Амблиопија се појавила само код новорођенчади са четвртим степеном ИК. Утврђена је и статистички значајна разлика ($p<0,01$) у односу на налазе пролазне отоакустичке емисије на левом и десном уву међу испитиваним групама. Налаз на десном уву није био нормалан код седморо деце са четвртим степеном ИК, а на левом код једног новорођенчета са трећим и седморо новорођенчади са четвртим степеном ИК.

Закључак Код превремено рођене деце са већим степеном ИК постоји већа могућност за губитак слуха и развој визуелног хендикепа.

Кључне речи: интракранијално крварење; превремено рођено дете; неуросензорни исход

Примљен • Received: 16/10/2009 **Прихваћен • Accepted:** 12/01/2010