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Clinical Plus Ultrasonographic Prediction After Hypoxic-Ischaemic Encephalopathy

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Summary

Aim: To compare the predictive value of ultrasonography (US) with that of the clinical examination for the outcome after hypoxic-ischaemic encephalopathy (HIE). *Methods:* A follow-up cohort study of 64 full-term infants investigated in the first month, in 4 age periods through the first year, in the second and fifth year. *Results:* HIE grade showed the best association with the outcome after the first year ($R=0.78$), followed by neonatal brain hyperechogenicity ($R=0.66$), postneonatal clinical status ($R=0.63$) and postneonatal US results ($R=0.56$). The association between simultaneous postneonatal clinical and US studies was $R=0.36$. Atrophic lesions visualized by US in the first three months were associated significantly with poorer outcome despite their extent. *Conclusions:* Brain US is most predictive in the first trimester after birth. Its results are complementary to the neurological status.

Key words: hypoxic-ischaemic encephalopathy, brain ultrasound, follow-up, prediction.

Introduction

Hypoxic-ischaemic encephalopathy (HIE) is the most common neurological disease in full-term neonates and an important cause of

neurological sequelae in infancy and childhood [12]. The introduction of brain imaging by transfontanel ultrasonography (US) enhanced diagnostics and prognostication in child neurology [1], although being still underestimated for the postneonatal period. An investigation of the prognostic properties of the clinical and US examination results in the neonatal and postneonatal periods and a comparison among them is needed for the pediatric neurology practice.

Materials and Methods

Subjects

The experimental group was a cohort of 64 full-term infants (39 males) with HIE that were referred to the Clinic of Perinatal and Developmental Neurology and Ultrasonography of the Plovdiv Higher Medical School Hospital in the period 1993-1997.

All infants had neonatal neurological examinations and 48 of them had US investigations at the same time. The worst results were assumed for further analysis.

All infants were followed up through their first year with clinical and US examinations at intervals depending on the severity of their clinical symptoms. The number of all postneonatal clinical investigations in the experimental group was 106, and of the US examinations - 103. They were grouped into 4 age periods according to the expected clinical and morphological dynamics: I - 30,60 days after birth; II - 2,3 mo. age, III - 4,6 mo., IV - 7,11 mo. The number of clinical and US examinations and the mean age at the time of examination for each age period were the following: I - 22 clinical and 23 US examinations; II - 32 clinical and 29 US examinations, 2.5 mo. mean age, III - 28, 29, 4.6 mo., respectively, IV - 24, 22, 8.0 mo., respectively. One hundred pairs of simultaneous postneonatal clinical and US examinations were formed.

All infants included in this study had at least one clinical examination between 12 and 24 mo. age (mean age 17 mo.). Some of them (n=28) were the first from the group that were checked at 5 years age.

The study design and the inclusion of subjects was approved by the Ethical Committee of the Plovdiv Higher Medical School.

All subjects were ensured with complete anonymity whenever possible.

Clinical examination

HIE was diagnosed on the basis of well established criteria [2, 12].

The neonatal neurological examination was fulfilled according to P. Ellison, 1992. Neonatal neurological symptoms were graded as follows: mild: normal consciousness or hyperalert, mild abnormalities in muscle tone or primitive reflexes; moderate: lethargy, moderate muscle hypo- or hypertonia, all primitive reflexes depressed; severe: sopor or coma, flaccid, all primitive reflexes absent.

The clinical examinations in the first and second year included: neurological status [3], psychomotor development [10] and Vojta kinesiological examination [13]. The end results were graded as normal, mild impairment (variations from the normal not included in the more severe grade), and severe impairment (at least one of the following: developmental quotient less than 70%, cerebral palsy, epilepsy, auditory or visual impairment, microcephaly [3, 9].

The examination at 5 years was based on a scored neurodevelopmental screening test [11].

Ultrasound examination

Examination was done through the anterior fontanel with a Sigma 1 apparatus (Kontron) and 5 and 7.5 MHz transducers.

In the neonatal period brain hyperechogenicity (BHE) was diagnosed when the intensity was equal to or higher than that of the choroid plexus simultaneously in both coronal and parasagittal scans. BHE was graded as absent, focal and diffuse [4]. A BHE score was estimated [5, 6]. Peri/intraventricular haemorrhage (P/IVH) was diagnosed and graded according to Papille [8] and classified as unilateral and bilateral.

Postneonatal US examination was focused on atrophic lesions. Criteria for ventricular dilatation (VD) were presence of at least one of the following: rounding of the contours of the ventricles; width of the third ventricle >0.5cm at coronal scan; ventricular index >0.31. Dilated interhemispheric fissure (DIF) was diagnosed when the mean of its width at I and II coronal scans was >0.55cm. Multicystic encephalomalacia (MCE) was defined as multiple small pseudocysts scattered throughout brain tissue. All US criteria were verified in a control group of 98 neonates and infants [7]. The postneonatal US results were graded as absent, VD and/or DIF, MCE.

Statistical analysis

The following methods of statistical analysis were used: descriptive statistics; percentage distribution; Fisher exact test, Pearson chi square and correlation tests, Mann-Whitney and Kruskal-Wallis tests. All tests were applied assuming 5% confidence level for the null hypothesis ($P=0.05$). All calculations were performed using the software GraphPAD InStat [GraphPAD Software, Version 1.13,1990], Microsoft Excel 5.0 [Microsoft Corp.], SPSS 5.0.2. [SPSS Inc. 1993].

Results and Discussion

The neonatal neurological and US findings and their association with the outcome in the second year are presented in Table 1. Both graded HIE and BHE displayed strong associations with the out-

Table 1. The clinical status in the second year according to the neonatal neurological and ultrasonographic symptoms

Neonatal variables	Outcome in the second year				P value and χ^2	
	Normal (n=33)	Mild impair. (n=18)	Severe impair. (n=13)	Total (n=64)		
Apgar score	< 3	3	4	5	12	$P < 0.05$
	4 + 6	3	1	1	5	$\chi^2 = 9.58$
	> 6	20	5	2	27	
	unknown	7	8	5	20	
HIE grade	mild	27	8	2	37	$P < 0.001$
	moderate	6	10	2	18	$\chi^2 = 49.92$
	severe	—	—	9	9	
Depressed consciousness	present	4	—	7	11	$P < 0.001$
	absent	29	18	6	53	$\chi^2 = 16.60$
Gen. muscle hypotonia	present	21	16	11	48	$P > 0.05$
	absent	12	2	2	16	$\chi^2 = 4.76$
Muscle hypertonia	present	6	4	6	16	$P > 0.05$
	absent	27	14	7	48	$\chi^2 = 3.99$
Depressed primitive reflex	present	24	14	12	50	$P > 0.05$
	absent	9	4	1	14	$\chi^2 = 2.09$
Convulsions	present	4	7	8	19	$P > 0.05$
	absent	29	11	5	45	$\chi^2 = 11.92$
Apnoea	present	5	3	6	14	$P > 0.05$
	absent	28	15	7	50	$\chi^2 = 5.64$
Bradycardia	present	1	3	4	8	$P > 0.05$
	absent	32	15	9	56	$\chi^2 = 6.95$
Cran. nerves & gaze pathol.	present	2	7	3	12	$P > 0.05$
	absent	31	11	10	52	$\chi^2 = 8.43$
Brain hyper-echogenicity	absent	4	1	0	5	$P < 0.001$
	focal	21	13	3	37	$\chi^2 = 23.02$
	diffuse	1	0	5	6	
	not invest.	7	4	5	16	
Peri-/intraventricular haemorrhage	abs./unilat.	25	13	5	43	$P > 0.05$
	bilateral	1	1	3	5	$\chi^2 = 7.65$
	not invest.	7	4	5	16	

Table 2. Prognostic significance of the neonatal variables arranged by their predictive accuracy. Only those that associate significantly with the outcome in the second year are included.

No	Prediction of normal status in the second year			Prediction of severe impairment in the second year				
	Variable	Accuracy	PPV	NPV	Variable	Accuracy	PPV	NPV
1	Mild HIE	75.0	81.8	67.7	Severe HIE	93.7	69.2	100
3	Apgar score > 6 at 5 th min.	70.4	76.9	61.1	Bilateral P/IVH	93.1	37.5	95.0
4	Absence of convulsions	68.7	87.8	48.4	Diffuse BHE	91.7	62.5	97.5
5	Absence of bilateral P/IVH	64.6	100	30.6	Depressed consciousness	84.3	53.8	92.2
6	Absence cranial nerves & gaze pathology	64.0	93.9	32.2	Bradycardia	79.7	30.8	92.2
7	Absence of diffuse BHE	62.5	96.1	27.7	Apgar score < 3 at 5 th min.	77.3	62.5	80.5
8	Absence of bradycardia	60.9	96.9	22.6	Apnoea	76.6	46.1	84.3
9	Absence of apnoea	57.8	84.8	29.0	Convulsions	75.0	61.5	78.4
10	Absence of depressed consciousness	56.2	87.9	22.6	Cranial nerves & gaze pathology	70.3	23.1	82.3
11	Absence of BHE	47.9	15.4	95.4	BHE	27.1	100	12.5

Abbreviations: PPV - positive predictive value, NPV - negative predictive value, HIE - hypoxic-ischaemic encephalopathy, BHE - brain hyper-echogenicity, P/IVH - peri/intraventricular haemorrhage.

come ($R=0.78$ and $R=0.66$, respectively). The positive and negative predictive values and the predictive accuracy of those signs and symptoms that correlated significantly with the outcome are listed in Table 2. HIE grade proved to be the most powerful predictor. Diffuse BHE and bilateral P/IVH were accurate in predicting severe impairment (all bilateral P/IVH were grades I or II; there was only one P/IVH with a higher grade). Absence of any BHE was the most specific symptom for normal outcome.

Table 3. Distribution of the postneonatal clinical examination results according to the outcome in the second year

Outcome in the second year	Postneonatal clinical examination results									Total		
	Absent			Mild impairment			Severe impairment			n	%	Sp
	n	%	Sp	n	%	Sp	n	%	Sp			
Normal	28	71.8	7.3	20	40.8	7.1	2	11.1	7.6	50	47.2	4.9
Mild impairment	9	23.1	6.8	20	40.8	7.1	2	11.1	7.6	31	29.2	4.4
Severe impairment	2	5.1	3.6	9	18.4	5.6	14	77.8	10.1	25	23.6	4.1
Total	39	100	—	49	100	—	18	100	—	106	100	—

Table 3 demonstrates the graded results of the postneonatal clinical examinations and their association with the outcome in the second year ($\chi^2 = 47.8$, $P < 0.001$; $R = 0.63$). In more than 70% of the postneonatal examinations with normal results the infants continued to be normal in second year, and the same was true for the examinations revealing severe impairment. Mild impairment in the first year was followed most often by normal status or only mild abnormality afterwards.

The results from the postneonatal US examinations, represented by their major findings - variants of atrophic lesions, and their association with the status in the second year are presented in Table 4 ($\chi^2 = 32.1$, $P < 0.001$; $R = 0.56$). Absence of atrophic lesions predicted either normal outcome or only mild future impairment. Impairment was the sequel in more than 50% of the postneonatal examinations when VD and/or DIF was visualized. MCE was a rare but invariable predictor of severe impairment.

In the 100 pairs of simultaneous postneonatal clinical and US examinations 41 infants revealed abnormalities on both investigations, 22 had only neurological abnormalities, and other 22 - only US

Table 4. Distribution of the postneonatal atrophic lesions frequency according to the outcome in the second year

Outcome in the second year	Postneonatal atrophic lesions									Total		
	Absent			VD/DIF			MCE			n	%	Sp
	n	%	Sp	n	%	Sp	n	%	Sp			
Normal	28	58.3	7.2	21	42.8	7.1	—	—	—	49	47.6	4.9
Mild impairment	18	37.5	6.9	14	28.6	6.5	—	—	—	32	31.1	4.6
Severe impairment	2	4.2	2.9	14	28.6	6.5	6	100	—	22	21.3	4.0
Total	48	100	—	49	100	—	6	100	—	103	100	—

Abbreviations: VD - ventricular dilatation; DIF - dilated interhemispheric fissure; MCE - multicystic encephalomalacia.

pathology. Thus, the addition of US follow-up to the clinical tests reduced the asymptomatic results from 37 to 15%. The association between graded clinical results and graded atrophic lesions was significant ($\chi^2 = 9.49$, $P < 0.01$) with $R = 0.36$

The graded results from the clinical examination, some of the major neurological symptoms, the neurodevelopmental and kinesio-

Predictor	1mo.	2-3 mo.	4-6 mo.	7-11mo.
Clinical abnormality grade				
Muscle hypotonicity				
Primit. reflexes abnormalities				
Muscle hypertonicity				
Neurodevelopmental delay				
Vojta kinesiological abnormal.				
US atrophic lesions				

Legend	$p > 0.05$	$p \leq 0.05$	$p < 0.05$	$p < 0.01$

Fig. 1. Prognostic significance of the postneonatal clinical and ultrasonographic symptoms for the outcome in the second year

logic examinations results and the US atrophic findings were analyzed separately for each postneonatal age group and the significance of their relationship with the outcome was estimated (Fig. 1). The clinical abnormality grade was found as a significant predictor after the 3rd mo. Muscle hypotonicity and abnormalities in the primitive reflexes displayed significant relationship in most of the age periods. Neurodevelopmental delay showed an increasing significance after 3 mo. age. The relationship of the kinesiologic diagnostics results with the outcome was significant after the 3rd mo.

When analyzing the relationships of these clinical variables by age the greatest number of significant results was obtained in 4-6 mo. age period.

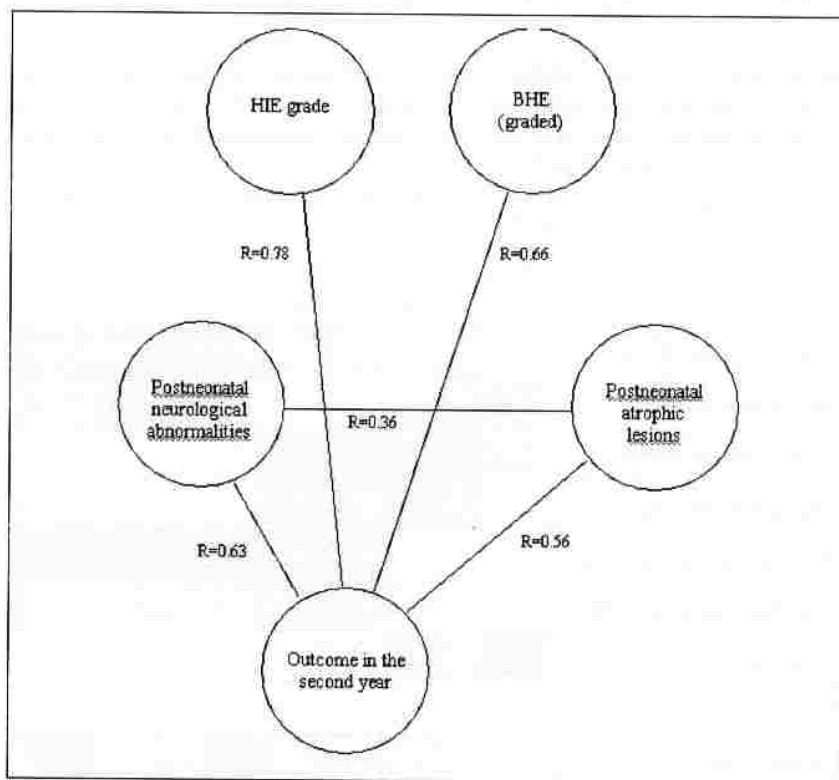


Fig.2 Correlation of the clinical and ultrasonographic abnormalities with the outcome in the second year

Atrophic lesions revealed a significant association with the outcome only when observed in the first three months. The analysis of the results from US examinations after that age found a significant relationship only between vast VD (dilation of all parts of the lateral ventricles) and severe impairment.

The analysis of the correlation coefficients of the clinical and US investigations in the different age periods with the outcome in the second year is shown in Fig. 2. The strongest association was that of the HIE grade, followed by the BHE grade. The association of the postneonatal neurological and US abnormalities with the outcome was also strong while the association between them appeared weaker, although the difference was not statistically significant. We hypothesize that such a discrepancy may be due to differences in the pathogenetic forces that induce the clinical and the morphological findings and to differences in their dynamics, too.

The preliminary data from the 5-year follow-up disclosed a significant association between the outcome in the second year and the neurodevelopmental score at 5 years ($P < 0.01$). The analyses of the relationships of the BHE grade and of the postneonatal atrophic lesions with the status at 5 years age also suggested an association.

Conclusions

Neonatal neurological symptoms are major predictors in HIE. Postneonatal neurological examinations are most predictive in the 4-6 mo. period.

US contributes to prediction in HIE patients. Diffuse BHE is associated with severe impairment and the absence of BHE is a favourable sign. Atrophic lesions, visualized by US, have prognostic significance in the first 3 months after birth -earlier than most of the significant clinical predictors. The vast ventricular dilatation retains its predictive value in the next months. The postneonatal clinical and US findings should be analyzed as partially independent and complementary to one another

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