Prediction of Cerebral Palsy in High-Risk Neonates: A Technetium-99m-HMPAO SPECT Study

R. Denays, T. VanPachterbeke, V. Toppet, M. Tondeur, M. Spehl, A. Piepsz, P. Noël, D. Haumont and H.R. Ham

Departments of Neurology, Pediatrics, Pediatric Radiology and Radioisotopes, St-Pierre Hospital, Free Universities of Brussels, Brussels, Belgium

In infants who have experienced prenatal or perinatal injury, it is often difficult, on the basis of clinical examination and conventional investigations (electroencephalogram, cranial ultrasound scan), to diagnose those with brain damage and to predict the type and the severity of subsequent neurological handicaps. We investigated the predictive value of ^{99m}Tc-HMPAO brain SPECT performed in the first weeks of life in high-risk neonates. Right-left asymmetries in tracer uptake had no predictive value, regardless of their localization or severity. On the other hand, a change in antero-posterior rCBF distribution was found in 7/10 of neonates with adverse outcome (death, major neurological sequelae) and in none of the 78 neonates with no major motor neurological sequelae. Compared to conventional investigations, ^{99m}Tc-HMPAO brain SPECT did not provide additional predictive information when neurological examination, electroencephalogram and cranial ultrasonography were all normal or all abnormal. Conversely, in the 30 patients with anomalies on one or two of the above investigations, SPECT showed an abnormal antero-posterior pattern in 4/6 neonates with major neurological sequelae and no change in the antero-posterior rCBF distribution in the 24 infants who developed normally. In conclusion, our results suggest that ^{99m}Tc-HMPAO brain SPECT, when performed in the first weeks of life, can be useful in high-risk neonates to predict occurrence of major neurological handicaps. Because of the relative invasive character of HMPAO scan in neonates and the overall accuracy of the noninvasive tests, radionuclide examination should not be performed in every high-risk neonate. According to our results, ^{99m}Tc-HMPAO brain SPECT might be indicated in those children where noncongruent results were obtained with conventional studies.

J Nucl Med 1993; 34:1223–1227

In infants who have experienced prenatal or perinatal injury, it is often difficult, on the basis of clinical examination and conventional investigations (electroencephalogram (EEG), cranial ultrasonography (US)), to diagnose those with brain damage and to predict the type and the severity of subsequent neurological handicaps (*1*). Early information about possible neurological sequelae would be of great help in stimulation programs, in which infants are placed under the guidance of learning specialists and receive additional help from physical, occupational and speech therapists (*2,3*).

Technetium-99m-HMPAO SPECT is now widely used as a tool to evaluate regional cerebral blood flow (rCBF) in adult and pediatric patients. In neonates, the results of some preliminary studies have shown that SPECT could visualize areas of hypoactivity not associated with abnormal US or computed tomography (CT) findings (*4,5*).

The aim of this study was to evaluate the predictive value of ^{99m}Tc-HMPAO brain SPECT performed in the first weeks of life in high-risk neonates while taking into account the predictive information already provided by conventional investigations.

PATIENTS AND METHODS

This study was performed according to a protocol accepted by the local committee for medical ethics. Eighty-eight neonates (43 pre-term and 45 full-term) were investigated. All had one or more of the following risk factors during the neonatal period: birthweight less than 1501 g (n = 17), asphyxia at birth as indicated by Apgar scores lower than 6 at 5 min and/or cord-blood pH lower than 7.25 (n = 28), respiratory difficulties needing continuous positive airway pressure for more than 48 hr (n = 19), sepsis (n = 6), glycemia lower than 40% mg (n = 9), hyperbilirubinemia requiring exchange transfusion (n = 4), neurological symptoms such as convulsions, marked hypotonia, rigidity or prolonged feeding difficulties (n = 25).

In the intensive care unit, neonates were regularly examined by an experienced neuropediatrician. At least one EEG and two cranial US scans (one early and one late, before discharge) were available in all neonates. Cranial US was performed with a 5-MHz realtime sectorial probe for brain examination and with a 7.5-MHz linear probe for the study of subdural space. Neonatal neurolog-

Received Oct. 15, 1992; revision accepted Apr. 1, 1993.
For correspondence or reprints contact: Roger Denays, MD, Department of Neurology, Saint-Pierre Hospital, 322, rue Haute, Brussels, Belgium.

TABLE 1
Criteria for Normal or Abnormal Conventional Investigations

Classification	Conventional investigations		
	Neurological examination	EEG	Cranial US
Normal	Normal	Normal	Strictly normal Small echodensities at upper border of lateral ventricles Small lateral ventricle enlargement Subependymal hemorrhage
Abnormal	Doubtful	Doubtful Positive rolandic sharp waves Moderate interhemispheric asynchrony Moderately asymmetric background	
	Clearly abnormal: severe anomalies of sucking, of limb, neck or trunk tone	Clearly abnormal Isoelectric record Paroxysmal activity Gross interhemispheric asynchrony Markedly asymmetric background Diffuse slow background	Intraventricular hemorrhage Parenchymal hemorrhage Cysts Hydrocephaly

ical status, EEG data and US findings were classified as "normals" or "abnormals" according to criteria described in Table 1.

At ages ranging from 12 to 33 mo (mean: 21 mo), infants were assessed for neurological anomalies either directly (n = 54), by the local pediatric staff or by contact with their primary pediatricians (n = 34). Doubtful cases and infants with evident neurological handicaps were all reexamined by a neuropediatrician. Children with cerebral palsy were categorized (in spastic diplegia, spastic quadriplegia, dystonic cerebral palsy) according to the classification system of Hagberg et al. (*6*). Severity of handicap was graded as follows: mild: no interference with function; severe: nonambulant or unable to perform daily tasks without considerable aid; or moderate: those between mild and severe.

The infants were classified in two groups. Group 1 included 78 patients with no major motor neurological sequelae and Group 2 included 10 patients: 8 neonates who developed spastic diplegia or quadriplegia with degrees of handicaps ranging from mild (n = 2) to moderate (n = 5) and severe (n = 1), 1 infant who had severe dystonic cerebral palsy as a result of severe perinatal hyperbilirubinemia (kernicterus) and 1 neonate with severe hypoxic-ischemic encephalopathy (Apgar score of 2 at 5 min, severe hypotonia followed after a few days by axial and limb hypertonia, long periods of isoelectric record on EEG, cerebral edema on US) who died in the intensive care unit.

Technetium-99m-HMPAO SPECT studies were performed at the conceptional age (gestational age at birth + duration of extrauterine life), varying from 33 to 44 wk (mean: 38.4 wk). Duration of extrauterine life ranged from a few days to 9 wk (mean: 3.1 wk). For SPECT studies, the infants were placed in a quiet environment and an intravenous line was inserted into their hands. Three minutes later, 111 MBq of ^{99m}Tc-HMPAO was injected. All babies were awake at the time of the injection and no premedication was used. Neonates were brought to the imaging room 10–60 min after the injection of the tracer. To avoid movement artifacts, the baby was gently wrapped in a specially designed polystyrene vacuum cushion. SPECT imaging was performed using a rotating gamma camera and a low-energy, high-resolution collimator (Elscint Apex 415). Sixty frames of 30 sec were acquired. Transaxial, coronal and sagittal slices 2 pixels thick were reconstructed. No scatter or attenuation correction was applied.

For the analysis of SPECT studies, right-left and antero-posterior hemispheric distribution of the tracer were both considered. Asymmetries of tracer fixation were measured in cortical periventricular areas, thalamic region and sensorimotor cortex. In the absence of available normal values in neonates, right-left asymmetries of more than 12% were defined as abnormals by analogy to adults' values (*7*). For assessment of the antero-posterior hemispheric distribution of the tracer, circular regions of interest (ROIs) (diameter, 4 pixels) were positioned manually in frontal (F), sensorimotor (S), occipital (O), thalamic (T) and cerebellar (C) areas and visualized on the mediosagittal slice. Then, cortico-to-cerebellar (F-to-C, S-to-C, O-to-C), cortico-to-thalamic (F-to-T, S-to-T, O-to-T) and thalamo-to-cerebellar (T-to-C) ratios were calculated.

Results were classified as a function of conceptional age at the time of the SPECT study in four age groups: 33–36 wk, 37–38 wk, 39–40 wk, 41–44 wk. The antero-posterior hemispheric distribution of the tracer was defined as abnormal when at least 2 of the 7 indexes (F-to-C, S-to-C, O-to-C, F-to-T, S-to-T, O-to-T, T-to-C) were out of the "normal" neonatal limits (mean ± 2 s.d.) established for each age group in our previous work (Fig. 1) (*8*). A cortical hypoactivity was diagnosed by low cortico-to-thalamic and cortico-to-cerebellar indexes, a thalamic hypoactivity by high cortico-to-thalamic indices and low T-to-C ratio, a cerebellar hypoactivity by high cortico-to-cerebellar indices and high T-to-C ratio.

The Fisher's exact test was used to evaluate the predictive value of SPECT and conventional investigations in high-risk neonates. A p value of < 0.05 was considered significant.

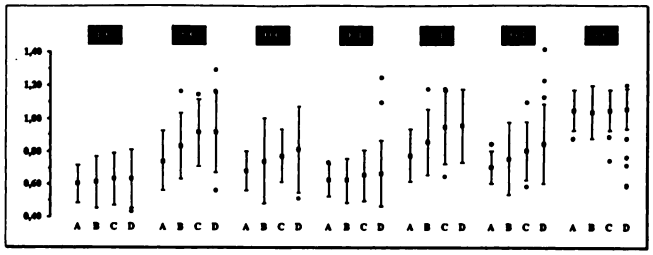

FIGURE 1. Cortico-to-cerebellar, cortico-thalamic and thalamo-to-cerebellar indexes in Group 1 and Group 2 and the age-related normal values. Horizontal bars indicate the normal limits (mean ± 2 s.d.). Circles indicate values out of the normal limits in Group 1 (blank circles) and Group 2 (full circles). Age groups: A = less than 37 wk; B = 37–38 wk; C = 39–40 wk; D = 41–44 wk. F = frontal; S = sensorimotor; O = occipital; T = thalamus; C = cerebellum.

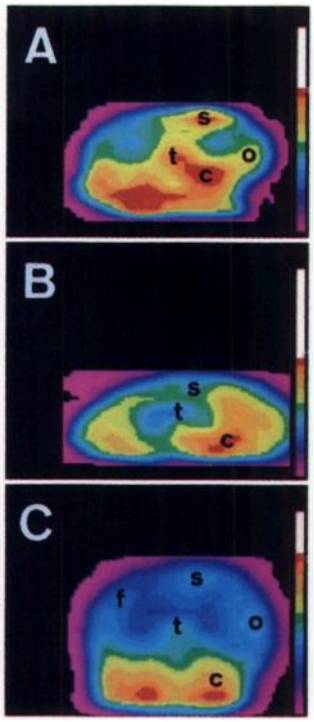

FIGURE 2. (A) Mediosagittal SPECT slice in a 41-wk-old neonate with normal neurological follow-up. Tracer uptake is prominent in cerebellar (C) and thalamic (T) areas, whereas cerebral cortical areas are poorly visualized, with the exception of sensorimotor (S) and occipital (O) regions. (B) Mediosagittal ^{99m}Tc-HMPAO brain SPECT slice in a 42-wk-old neonate who later suffered from moderate spastic quadriplegia. When compared to cerebellar (C) tracer uptake, there is marked thalamic (T) and sensorimotor (S) hypoactivity. (C) Mediosagittal ^{99m}Tc-HMPAO brain SPECT slice in a 44-wk-old neonate who later suffered from severe spastic quadriplegia. When compared to cerebellar (C) tracer uptake, there is a marked decrease of activity in the thalamic (T) and overall cerebral cortical areas (F = frontal; S = sensorimotor; O = occipital).

RESULTS

Predictive Value of ^{99m}Tc-HMPAO Brain SPECT

Regional CBF SPECT asymmetries ranged from 0% to 29% (mean 8.1%) in Group 1 and from 0% to 32% (mean 8.3%) in Group 2. SPECT asymmetries of more than 12% had no predictive value, regardless of the localization of anomalies, in cortical periventricular areas, thalamic region or sensorimotor cortex (Table 2). Because the normal limit of 12% derived from adults' studies (*7*) might be unapplicable to neonatal SPECT studies, the predictive value of other cut-off levels (from 5% to 25% asymmetries) was also tested. The results indicated that asymmetries were not of predictive value regardless of level. Severe asymmetries of more than 25% were indeed found in Group 1 while, on the other hand, some patients of Group 2 had perfectly symmetrical SPECT study.

Anomaly of antero-posterior rCBF distribution was significantly more often observed in Group 2 than in Group 1 (Table 2, Fig. 1). Change in antero-posterior rCBF distribution had a sensitivity of 70%, a specificity of 100% and an accuracy of 96.5%. In patients with the most severe motor handicaps, rCBF anomalies were usually localized in sensorimotor and thalamic areas. Such anomalies which are suggestive of a status marmoratus were also found in the patient who died. Patients with mild or moderate spastic diplegia had no anomaly or had rCBF anomalies that did not involve the motor cerebral cortical areas. In the patient with kernicterus, SPECT demonstrated a thalamic asymmetry but no change in antero-posterior pattern. An example of normal antero-posterior rCBF distribution in the neonatal period is given in Figure 2A and two cases of an abnormal antero-posterior pattern are illustrated in Figures 2B, C.

Predictive Value of ^{99m}Tc-HMPAO Brain SPECT in Comparison to Other Studies

Neurological examination, EEG and cranial US had a significant predictive value (Table 3). With a specificity of 91% and a sensitivity of 40% and 50%, respectively, EEG and cranial US were the most accurate conventional methods to predict neurological outcome (accuracy 85% and 86%, respectively). Neurological examination had a sensitivity of 80%, a specificity of 78% and an accuracy of 78%.

In 55 neonates, neurological examination, EEG and cranial US were normal. One neonate developed cerebral palsy, a mild spastic diplegia (negative predictive value

TABLE 2
Predictive Value of ^{99m}Tc-HMPAO Brain SPECT

SPECT	Group 1 (n = 78)	Group 2 (n = 10)	p
Cortical anterior periventricular asymmetries	21	3	ns
Cortical posterior periventricular asymmetries	7	3	ns
Sensorimotor asymmetries	9	3	ns
Thalamic asymmetries	4	1	ns
Change in antero-posterior pattern	0	7	<0.001

ns = nonsignificant.

TABLE 3
Predictive Value of Conventional Neurological Investigations

Conventional investigations	Group 1 (n = 78)	Group 2 (n = 10)	p
Abnormal neurological examination	17	8	<0.001
Abnormal electroencephalogram	7	4	<0.05
Abnormal cranial ultrasound scan	7	5	<0.005
Anomalies of 1 or 2 conventional investigations	24	6	ns
Anomalies of the 3 conventional investigations	0	3	<0.005

ns = nonsignificant.

98%). Technetium-99m-HMPAO antero-posterior distribution was normal in the 54 neonates without cerebral palsy as well as in the child who developed neurological sequelae.

In three other neonates, conventional investigations were all abnormal. At follow-up, these infants had developed neurological sequelae. Technetium-99m-HMPAO brain SPECT also showed abnormal antero-posterior rCBF distribution in these patients.

In the last 30 neonates, one or two conventional investigations were abnormal. Six of 30 infants (20%) developed neurological sequelae. Technetium-99m-HMPAO brain SPECT showed abnormal antero-posterior rCBF distribution in four of six infants with cerebral palsy and a normal antero-posterior pattern in the other neonates.

DISCUSSION

In high-risk neonates, the ideal predictive method should be easy to perform, free of adverse effects and able to predict as soon as possible the occurrence of subsequent neurological handicaps, their type and their severity.

Neurological examination, EEG and cranial US can all be performed without any discomfort to the neonates. Cranial US is currently the most accurate method to predict development of spastic cerebral palsy in pre-term infants (*1,9–11*). The predictive value of cranial US in premature infants who develop dystonic cerebral palsy and in high-risk full-term neonates has not been specifically investigated. It is probably rather low, due to the difficulties of echography to visualize nonhemorrhagic lesions in thalamic and parasagittal cerebral areas (*1,12*).

Functional information on the different regions of the brain in neonates is now attainable using SPECT and rCBF tracers such as ^{123}I-iodoamphetamine or ^{99m}Tc-HMPAO (*4,5,8,13*). The principal disadvantages of SPECT studies are radiation exposure, cost and the need to transport patients from the intensive care unit.

Right-left asymmetries had no predictive value, regardless of localization or severity. This could be explained by the fact that most Group 2 patients suffered from bilateral and symmetrical motor handicaps. Furthermore, some SPECT asymmetries could correspond to structural lesions leading to neurological disabilities, such as dysphasia or attention disorder (*14,15*), undetectable in early childhood.

Technical factors specific to neonatal SPECT studies may also play a role. Cortical periventricular asymmetries could be the result of a partial volume effect. Furthermore, because there are major regional differences in cerebral tracer uptake in neonates, a slight realignment error could produce important artifactual asymmetries.

Changes in antero-posterior rCBF distribution had a predictive value in 7/10 neonates who later developed neurological sequelae and in none of the 78 neonates with no major motor neurological sequelae. Furthermore, severity of SPECT anomalies, on antero-posterior analysis, in our limited series, seemed well related to severity of outcome. The low sensitivity (70%) and the high specificity (100%) of antero-posterior SPECT anomalies could be explained by the importance of normal interindividual variation. Only important changes in antero-posterior rCBF distribution resulting from severe bilateral cerebral injury were considered as abnormal.

Predictive values have also been observed in the few available CBF PET or SPECT studies in newborns. In a PET study of 17 asphyxiated full-term newborns, Volpe et al. (*16*) reported lower values for CBF to parasagittal regions in the nine infants who died or later exhibited spastic quadriplegia than in the eight infants with normal outcome. In the nine infants with adverse follow-up, the CBF level was, however, not clearly related to the severity of the outcome. In a PET study of six pre-term neonates with intraventricular hemorrhage and hemorrhagic intracerebral involvement, Volpe et al. (*17*) found a qualitatively similar reduction of CBF throughout the affected hemisphere in the four infants who died and in the two who developed spastic hemiparesia. The less severe decrease of CBF was found in one of the two survivors. Uvebrant et al. (*5*) used ^{99m}Tc-HMPAO SPECT and found hypoperfusion in the parasagittal regions, basal ganglia and upper brainstem in an infant who subsequently died after severe birth asphyxia. At autopsy, there was a status marmoratus in the same region. Fockele et al. (*13*) found no ^{99m}Tc-HMPAO SPECT anomaly in an infant who had severe birth asphyxia and perinatal seizures but a normal 3-mo follow-up.

A new test is useful when it provides information not given by already available procedures or when it gives equivalent information at a lower cost. This is surely not the case for SPECT as far as money, time expenditure and

patient discomfort are concerned. In our series, a good or poor outcome was correctly predicted in most patients with conventional investigations (neurological examination, EEG, cranial US) when these methods gave all normal or abnormal results. In these cases, SPECT did not provide additional predictive information. On the other hand, 80% (24/30) of neonates did develop normally despite anomalies in one or two of the three "soft" investigations. In these instances, an abnormal antero-posterior pattern in the SPECT study was associated with a poor outcome in all patients (n = 4), whereas normal antero-posterior distribution correctly predicted good outcome in 92.3% (24/26) of patients. One-third (2/6) of the patients with cerebral palsy were not, however, identified by SPECT.

In conclusion, the results of this study suggest that ^{99m}Tc-HMPAO brain SPECT when performed during the first weeks of life, can predict the occurrence of major neurological handicaps in high-risk neonates. Because of the relative invasive character of the HMPAO scan in neonates and the overall accuracy of noninvasive tests, it would not be feasible to perform routine radionuclide examinations in every high-risk neonate. According to our results, ^{99m}Tc-HMPAO brain SPECT might be indicated in those children in whom noncongruent results were obtained with conventional studies. These conclusions should be considered very cautiously because of the small number of patients. Finally, all children in this study should be reevaluated at school age to investigate the value of ^{99m}Tc-HMPAO brain SPECT in predicting the occurrence of nonmotor neurological handicaps.

ACKNOWLEDGMENTS

This study was supported by grant number 1543888 from the FRSM.

REFERENCES

1. Volpe JJ. *Neurology of the newborn*, 2nd edition. Philadelphia: W.B. Saunders Co.; 1987:69–128.
2. Soboloff HR. Early intervention: fact or fiction? *Dev Med Child Neurol* 1981;23:261–266.
3. Diamond M. Rehabilitation strategies for the child with cerebral palsy. *Pediatr Ann* 1986;15:230–236.
4. Denays R, Van Pachterbeke T, Tondeur M, et al. Brain single-photon emission computed tomography in neonates. *J Nucl Med* 1989;30:1337–1341.
5. Uvebrant P, Bjure J, Hedström A, Ekholm S. Brain single photon computed tomography (SPECT) in neuropediatrics. *Neuropediatrics* 1991;22:3–9.
6. Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954–1970. I. Analysis of the general changes. *Acta Paediat Scand* 1975;64:187–192.
7. Podreka I, Suess E, Goldenberg G, et al. Initial experience with technetium-99m HM-PAO brain SPECT. *J Nucl Med* 1987;28:1657–1666.
8. Denays R, Ham H, Tondeur M, Piepsz A, Noël P. Detection of bilateral and symmetrical anomalies in technetium-99m HMPAO brain SPECT studies. *J Nucl Med* 1992;33:485–490 (correction: *J Nucl Med* 1992;33:1282).
9. Monod N, Pajot N, Guidasci S. The neonatal EEG: statistical studies and pronostic value in full-term and pre-term babies. *Electroencephal Clin Neurophys* 1972;32:529–544.
10. Cooke RWI. Early and late cranial ultrasonographic appearances and outcome in very low birthweight infants. *Arch Dis Child* 1987;62:931–937.
11. Graham M, Levene MI, Trounce JQ, Rutter N. Prediction of cerebral palsy in very low birthweight infants: prospective ultrasound study. *Lancet* 1987; 2:593–596.
12. Wilson-Davis SL, Lo W, Filly RA. Limitations of ultrasound in detecting cerebral ischemic lesions in the neonate. *Ann Neurol* 1983;14:249–251.
13. Fockele DS, Baumann RJ, Shih WJ, Ryo UY. Tc-99m HMPAO SPECT of the brain in the neonate. *Clin Nucl Med* 1990;15:175–177.
14. Billard C, Dulac O, Raynaud C, et al. Xenon-133 brain SPECT imaging in developmental childhood dysphasia [Abstract]. *J Nucl Med* 1988;29:792.
15. Denays R, Tondeur M, Foulon M, et al. Regional brain blood flow in congenital dysphasia: studies with technetium-99m-HM-PAO SPECT. *J Nucl Med* 1989;30:1825–1829.
16. Volpe JJ, Herschowitch P, Perlamn JM, et al. Positron emission tomography in the asphyxiated term newborn: parasagittal impairment of cerebral blood flow. *Ann Neurol* 1985;17:287–296.
17. Volpe JJ, Herschowitch P, Perlamn JM, et al. Positron emission tomography in the newborn: extensive impairment of regional cerebral blood flow with intraventricular hemorrhage and hemorrhagic intracerebral involvement. *Pediatrics* 1983;72:589–601.