Brain Single Photon Emission Computed Tomography in Neonates

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This study was designed to rate the clinical value of [^{123}I]iodoamphetamine (IMP) or [^{99m}Tc] hexamethyl propylene amine oxyme (HM-PAO) brain single photon emission computed tomography (SPECT) in neonates, especially in those likely to develop cerebral palsy. The results showed that SPECT abnormalities were congruent in most cases with structural lesions demonstrated by ultrasonography. However, mild bilateral ventricular dilatation and bilateral subependymal porencephalic cysts diagnosed by ultrasound were not associated with an abnormal SPECT finding. In contrast, some cortical periventricular and sylvian lesions and all the parasagittal lesions well visualized in SPECT studies were not diagnosed by ultrasound scans. In neonates with subependymal and/or intraventricular hemorrhage the existence of a parenchymal abnormality was only diagnosed by SPECT. These results indicate that [^{123}I]IMP or [^{99m}Tc]HM-PAO brain SPECT shows a potential clinical value as the neurodevelopmental outcome is clearly related to the site, the extent, and the number of cerebral lesions. Long-term clinical follow-up is, however, mandatory in order to define which SPECT abnormality is associated with neurologic deficit.

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Neurologic handicaps, such as mental retardation, seizures, and cerebral palsy, are frequent in children who have suffered from severe perinatal asphyxia (*1–4*). On an individual basis, however, the neurologic evolution is often unpredictable. Some cerebral abnormalities detected by neurologic examination, electroencephalography, or ultrasonography are usually associated with a poor outcome (*1,5–8*), but unfortunately, in many children with neurologic sequelae all the investigations are normal during the neonatal period (*1,8*). Cerebral blood flow tracers such as iodine-123 iodoamphetamine ([^{123}I]IMP) or technetium-99m hexamethyl propylene amine oxyme ([^{99m}Tc]HM-PAO) are now available in most nuclear medicine departments. Combined with the single photon emission computerized tomography (SPECT) facilities, these tracers allow easy-to-perform functional cerebral studies. The clinical value of this new method, clearly established in adults and children (*9–12*), is still to be evaluated in newborns, more particularly in those at risk to develop cerebral palsy where the need for an early diagnostic tool is real.

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PATIENTS AND METHODS

According to a protocol accepted by the local committee for medical ethics, 36 neonates, 36 to 44 wk old, were investigated during a 12-mo period. All these babies had one or more of the following risk factors during the perinatal period: birth weight <1501 g, asphyxia at birth as indicated by low Apgar scores and/or low cord blood pH, respiratory difficulties needing continuous positive airway pressure, hypoglycemia, hyperbiluribinemia, sepsis, neurologic symptoms such as convulsions, marked hypotonia, rigidity, or prolonged feeding difficulties. Clinical data about these 36 babies are presented in Tables 1 and 2.

For SPECT studies, an i.v. line was inserted into the hands of the babies previously placed in a quiet environment. Three minutes later, 0.5 mCi of high purity [^{123}I]IMP or 3 mCi of [^{99m}Tc]HM-PAO were injected. Iodine-123 IMP was used in 1987 (in 24 neonates) and [^{99m}Tc]HM-PAO in 1988 (in 12 neonates). All babies were awake at time of injection and no premedication was used. The patients were brought to the camera room 30 min after the injection of [^{123}I]IMP and 10 to 60 min after the injection of [^{99m}Tc]HM-PAO. The head and the trunk were gently wrapped in a specially designed polystyrene vacuum-cushion to avoid movement artifacts. SPECT imaging was performed using a rotating gamma-camera and a low-energy, high resolution collimator interfaced to an Elscint Apex 415. Sixty frames of 30 sec were acquired.

TABLE 1
Patients with Abnormal Ultrasonography at Time of SPECT

Patient no.	Sex	Age (wk) GA-SA*	Birthweight (g)	Perinatal problems	Ultrasound scan*		SPECT study*
					Previous	At the time of SPECT	
1	M	33–37	1940	Birth asphyxia	Ventr. Dilat. (r-a/p)	Ventr. Dilat. (r-a/p)	Cort. Periventr. Hypoperf. (r-a/p)
2	M	33–37	1850	Hypertonia (r)	Ventr. Dilat. (r-a) PVH I (l)	Ventr. Dilat. (r-a)	Cort. Periventr. Hypoperf. (r-a) Thalamic Hypoperf. (l)
3	M	33–39	1230		Ventr. Dilat. (r-a/p)	Ventr. Dilat. (r-a/p)	Cort. Periventr. Hypoperf. (r-a/p)
4	F	33–39	1760	Birth asphyxia	Ventr. Dilat. (r-a/p)	Ventr. Dilat. (r-a/p)	Cort. Periventr. Hypoperf. (r-a/p)
5	M	38–39	3020	Birth asphyxia	Normal	Periventr. Hyperecho. (r-p)	Cort. Periventr. Hypoperf. (r-p)
6	M	34–41	1320	Hypertonia (r)	Normal	Periventr. Hyperecho. (l-a)	Cort. Periventr. Hypoperf. (l-a/p)
7	F	34–36	2260	Birth asphyxia	PVH I (r)	PVH II (r)	Parietal Hypoperf. (r)
8	F	34–41	1320		Normal	Sylvian Cyst. (r)	Sylvian Hypoperf. (r)
9	F	27–42	940	Birth asphyxia	PVH I (r/l)	Mild Ventr. Dilat. (r/l)	Cort. Periventr. Hypoperf. (r-a/p)
10	M	40–43	3450	Birth asphyxia Hypotonia (r)	Normal	Thalamic Hyperecho. (r/l)	Thalamic Hypoperf. (r/l) Sylvian Hypoperf. (l)
11	M	38–44	1440		Ventr. Dilat. (r-a/p)	Ventr. Dilat. (r-a/p)	Cort. Periventr. Hypoperf. (r-a/p)
12	M	28–40	1185	Birth asphyxia	Mild Ventr. Dilat. (r/l) PVH I (l)	Mild Ventr. Dilat. (r/l)	Cort. Periventr. Hypoperf. (l-p) Temporal Hypoperf. (l)
13	M	30–36	1130		Normal	Mild Ventr. Dilat. (r/l)	Cort. Periventr. Hypoperf. (r-a)
14	M	30–39	1540	Birth asphyxia	PVH I (r/l)	Mild Ventr. Dilat. (r/l)	Thalamic Hypoperf. (l) Cort. Periventr. Hypoperf. (r-p)
15	M	30–36	1150	Sepsis	Normal	Mild Ventr. Dilat. (r/l)	Normal
16	M	40–42	3460	Birth asphyxia	Normal	Major Ventr. Dilat. (r/l)	Subcort. Hypoperf. (r/l)
17	F	30–38	1220	Birth asphyxia Axial hypotonia	Normal	Ventr. Dilat. (r-p/l-p)	Cort. Periventr. Hypoperf. (r-p/l-p)
18	F	32–38	1420	Feeding problems	Normal	Ventr. Dilat. (l-a/p)	Cort. Periventr. Hypoperf. (l-a/p)
19	M	40–42	2770	Birth asphyxia	Normal	Subep. Cyst. (r/l)	Normal
20	F	39–41	2670	Birth asphyxia	Normal	Thalamic Hyperecho. (l)	Thalamic Hypoperf. (l)

* GA = Gestational Age at birth; SA = Age at the time of SPECT.
r = right; l = left; a = anterior; p = posterior.
Cort. = Cortical; Ventr. = Ventricular; Dilat. = Dilatation.
Subep. = Subependymal; PVH I = Subependymal Hemorrhage; PVH II = Subependymal-Intraventricular Hemorrhage.
Hyperecho. = Hyperechogenicity; Hypoperf. = Hypoperfusion.

Transaxial, coronal, and sagittal slices 2 pixels thick (corresponding to 0.5 to 1 cm, depending on the zoom magnification used) were reconstructed. Scans were read by four nuclear medicine physicians unaware of the clinical data, taking into account the normal brain-blood flow distribution in each age group (*13*). Only regional asymmetries of more than 12% were considered significant.

A cranial ultrasound scan was performed within a period of 1 to 3 days of SPECT study with a 5-MHz realtime sectorial probe for brain examination and with a 7.5-MHz linear probe for the study of subdural space.

RESULTS

Patients with Abnormal Ultrasonography at Time of SPECT (n=20)

The majority of the patients with structural lesions shown by ultrasonography had congruent SPECT abnormalities (Table 1): cortical periventricular hypoperfusion was found in all patients (n=10) with lateral ventricular dilatation or periventricular hyperechogenicity; sylvian hypoperfusion in case 8 with a sylvian

TABLE 2
Patients with Normal Ultrasonography at Time of SPECT

Patient no.	Sex	Age (wk) GA-SA*	Birthweight (g)	Perinatal Problems	Ultrasound scan*		SPECT study*
					Previous	At the time of SPECT	
21	M	40–42	3520	Birth asphyxia Seizures	Normal	Normal	Normal
22	F	40–41	2800	Birth asphyxia	Normal	Normal	Normal
23	F	35–38	1300	Birth asphyxia	Normal	Normal	Normal
24	M	35–39	2840	Birth asphyxia	PVH I (r/l)	Normal	Normal
25	M	30–36	1370	Birth asphyxia	PVH I (r/l)	Normal	Normal
26	M	33–37	2040	Birth asphyxia	Normal	Normal	Normal
27	M	36–39	2590	Birth asphyxia	PVH I (r)	Normal	Normal
28	M	38–40	2560	Seizures	Normal	Normal	Cort. Periventr. Hypoperf. (l-a/p)
29	M	36–39	1760	Birth asphyxia	Normal	Normal	Normal
30	M	34–36	1870	Hypotonia (l)	Normal	Normal	Cort. Periventr. Hypoperf. (r-a/p)
31	M	40–44	3280	Birth asphyxia	Cerebral edema	Normal	Parasagittal Hypoperf. (r)
32	M	40–41	2900	Birth asphyxia	Normal	Normal	Parasagittal Hypoperf. (l)
33	M	33–36	2000	Birth asphyxia	Normal	Normal	Cort. Periventr. Hypoperf. (l-a, r-p)
34	M	40–43	3450	Hypotonia Birth asphyxia	Normal	Normal	Parasagittal Hypoperf. (l)
35	F	33–37	2080	Birth asphyxia	Normal	Normal	Cort. Periventr. Hypoperf. (l-a/p, r-a)
36	F	40–41	3330	Seizures	Normal	Normal	Parasagittal Hypoperf. (l)

* GA = Gestational Age at birth; SA = Age at the time of SPECT.
r = right; l = left; a = anterior; p = posterior.
Cort. = Cortical; Ventr. = Ventricular.
PVH I = Subependymal Hemorrhage.
Hypoperf. = Hypoperfusion.

porencephalic cyst; thalamic hypoperfusion in cases 10 and 20 with thalamic hyperechogenicity; bilateral subcortical hypoperfusion in case 16 with important bilateral ventricular dilatation.

However mild bilateral ventricular dilatation (cases 9, 12, 13, 14, 15) and bilateral subependymal porencephalic cysts (case 19) diagnosed by ultrasound were not associated with an abnormal SPECT finding.

In contrast, in eight patients (cases 2, 6, 7, 9, 10, 12, 13, 14) SPECT showed more abnormalities than ultrasonography, that is, cortical periventricular (cases 6, 9, 12, 13, 14), sylvian (case 10), thalamic (cases 2, 14), temporal (case 12), or parietal (case 7) hypoperfusion. In four babies (cases 2, 7, 12, 14) these additional parenchymal hypoperfusions were localized in the same side than the subependymal and/or intraventricular hemorrhages revealed by simultaneous or previous ultrasound scans. In three patients (cases 2, 6, 10), the supplementary SPECT hypoperfusions were consistent with the abnormal neurologic findings.

Patients with Normal Ultrasonography at Time of SPECT (n=16)

The SPECT study was normal in eight patients, showed cortical periventricular hypoperfusion in four babies (cases 28, 30, 33, 35) and parasagittal hypoactivity in the four others (cases 31, 32, 34, 36) (Table 2). Out of the eight babies with abnormal SPECT, two had an abnormal neurologic examination (cases 30, 34).

Examples of SPECT images obtained in neonates are presented in Figure 1 (cases 1, 10, 29).

DISCUSSION

Despite constant progress in the neonatal intensive care, hypoxic events remain an important perinatal cause of neurologic morbidity (*1–4*). The topography of the cerebral injuries differ as a function of the gestational age (*1*). In preterm infants, lesions are usually located in the white matter adjacent to the external angles of the lateral ventricles (periventricular leukomalacia) and/or in the germinal matrix (subependymal hemorrhage eventually complicated by intraventricular or parenchymal bleedings). Except for hemorrhage limited to the subependymal region, these lesions are usually associated with a poor neurologic outcome (*6–8*). Cranial ultrasonography is currently the most performed method to detect and follow the evolution of these cerebral injuries (*6–8,14–16*). However, periven-

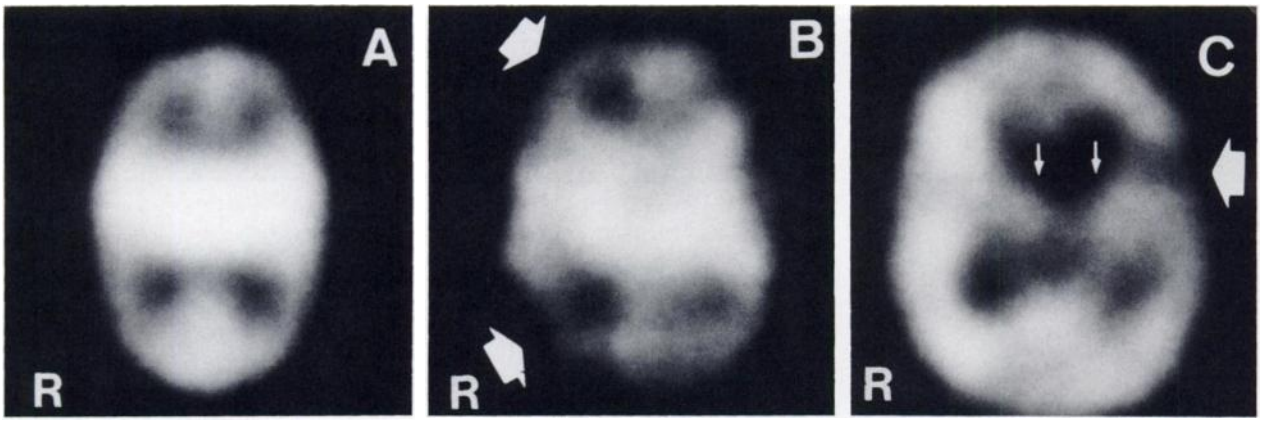

FIGURE 1
Transaxial SPECT images in three neonates. Slice level is ~2 cm above the orbitomeatal line. No background substraction is used. A: Normal tomography (Patient 29, [^{99m}Tc]HM-PAO). B: Right (R) anterior and posterior cortical periventricular hypoperfusion (arrows) (Patient 1, [^{123}I]IMP). C: Bilateral thalamic (small arrows) and left sylvian hypoperfusion (large arrow) (Patient 10, [^{99m}Tc]HM-PAO). The tracer is mainly distributed in the cortical areas which is quite unusual in a 43-wk-old baby. This is the result of bilateral lesions of the thalamic areas as confirmed by ultrasound scan.

tricular leucomalacia can be missed when it is microscopic or out of the range of the detector, far posteriorly or far anteriorly (*14*). This could explain why all the ultrasound scans are normal in a non-negligible proportion of prematures who will later develop neurologic sequelae (*1,8*). In full-term neonates, the lesions are usually located in the watersheds of the major cerebral arteries, that is in the parasagittal and parieto-occipital areas. This has been shown by neuropathologic studies and, in the living human infant, by conventional radionuclide brain scanning and by positron emission tomography (*17–20*). These cerebral insults are in most cases not revealed by CT or ultrasound scans.

In the past few years, several cerebral blood flow tracers became available. Contrasting with the "old" brain scanning agents which accumulate in the brain only when the blood-brain barrier is disrupted, these new lipophilic tracers cross the normal blood-brain barrier and distribute, in a first approximation, proportionally to regional cerebral blood flow. As there is usually an intimate coupling between metabolism and blood flow, this new technique allows noninvasive physiologic brain studies. The clinical value of cerebral blood flow studies with SPECT has already been established in adults and children in a variety of neurologic disorders (*9–12*).

The use of SPECT in newborns, however, raises some specific problems. This technique cannot be performed in the intensive care unit and is therefore inappropriate for the critically ill baby. Increases in regional cerebral blood flow are known to occur in response to a variety of physiologic stimuli, including visual or auditory input and voluntary motion (*21–23*). An i.v. line was therefore placed 3 min before the injection of the tracer. During the acquisition, children have to be perfectly immobile to avoid artifactual asymmetries. The absence of cooperation, however, is not a real problem as movements can usually be prevented by wrapping the neonates in a vacuum-cushion. According to the small size of the newborn's head and to the relatively poor spatial resolution of this technique, some cerebral areas cannot be delineated accurately, for example caudate nucleus from thalamus. Some cerebral regions (particularly the frontal lobes) are physiologically hypoperfused in neonates and are therefore poorly visualized on SPECT studies (*13*). Finally, it should also be noted that, in order to obtain good quality images, the administered activity in neonates is approximately three times greater, on a per kilo basis, than that usually given to adult patients. The absorbed dose is therefore about twice that of an adult patient (*24*).

In the present study, mild bilateral ventricular dilatation and bilateral subependymal porencephalic cysts diagnosed by ultrasound were not associated with an abnormal SPECT finding. This is not surprising as only regional asymmetries are considered in the diagnosis of SPECT abnormalities. In contrast, some cortical periventricular and sylvian lesions and all the parasagittal lesions, well visualized on SPECT studies, were not diagnosed by ultrasound scans. In four children with subependymal and/or intraventricular hemorrhage the existence of a parenchymal abnormality was only diagnosed by SPECT.

The absence, for obvious ethical reasons, of healthy controls is currently the most important limitation. So, without pathologic confirmation, the reality of the additional SPECT abnormalities is questionable. It is, however, supported by the topography of the lesions (in "critical" areas), by the fact that similar degrees of cerebral blood flow impairment were found in patients with structural lesions demonstrated by ultrasound scans and by their concordance in some cases with

neurologic impairment. Moreover, our results are in agreement with positron emission tomography studies (*20,25,26*).

In conclusion, this study indicates that cerebral blood flow studies with SPECT in neonates can detect regions of hypoperfusion not associated with abnormal ultrasound findings. This has potential clinical value as the neurodevelopmental outcome is clearly related to the site, the extent and the number of cerebral lesions (*6–8*). Long-term clinical follow-up is however mandatory to define which SPECT abnormality is associated with neurologic deficit.

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REFERENCES

1. Volpe JJ. Neurology of the newborn. Philadelphia: W. B. Saunders, 1981: 141–298.
2. Vorh BR, Garcia Coll CT. Neurodevelopmental and school performance of very low-birth-weight infants: a seven-year longitudinal study. *Pediatrics* 1985; 76:345–350.
3. Eclers BL, Desai NS, Wilson MA, et al. Classroom performance and social factors or children with birth weights of 1,250 grams or less. Follow-up at 5 to 8 years of age. *Pediatrics* 1986; 77:203–208.
4. Atkinson S. Spastic diplegia among children of low and normal birthweight. *Dev Med Child Neurol* 1983; 25:693–708.
5. Monod N, Pajot N, Guidasci S. The neonatal EEG: statistical studies and prognostic value in full-term and pre-term babies. *Electroenceph Clin Neurophys* 1972; 32:529–544.
6. Fawer CL, Diebold P, Calame A. Periventricular leucomalacia and neurodevelopmental outcome in preterm infants. *Arch Dis Child* 1987; 62:30–36.
7. Weinding AM, Rochefort MJ, Calvert SA, et al. Development of cerebral palsy after ultrasonographic detection of periventricular cysts in the newborn. *Dev Med Child Neurol* 1985; 27:800–806.
8. Cooke RWI. Early and late cranial ultrasonographic appearances and outcome in very low birthweight infants. *Arch Dis Child* 1987; 62:931–937.
9. Royal HD, Hill TC, Holman BL. Clinical brain imaging with isopropyl-iodoamphetamine and SPECT. *Semin Nucl Med* 1985; 15:357–376.
10. Podreka I, Suess E, Goldenberg G, et al. Initial experience with technetium-99m HM-PAO brain SPECT. *J Nucl Med* 1987; 28:1657–1666.
11. Denays R, Rubinstein M, Ham HR, et al. Single photon emission computed tomography in seizure disorders. *Arch Dis Child* 1988; 63:1184–1188.
12. Lambert R, Gilday DL, Ash JM, et al. Interictal SPECT HMPAO in children [Abstract]. *J Nucl Med* 1988; 29:792.
13. Rubinstein M, Denays R, Van Pachterbeke T, et al. Brain maturation in human newborns: a cerebral blood flow (CBF) study using 123-I-IMP and SPECT [Abstract]. *J Nucl Med* 1988; 29:893.
14. Rushton DI, Preston PR, Durbin GM. Structure and evolution of echo dense lesions in the neonatal brain. A combined ultrasound and necropsy study. *Arch Dis Child* 1985; 60:798–808.
15. Szymonowicz W, Schafler K, Cussen LJ, et al. Ultrasound and necropsy study of periventricular haemorrhage in preterm infants. *Arch Dis Child* 1984; 59:637–642.
16. Babcock DS, Han BK. The accuracy of high resolution, real-time ultrasonography of the head in infancy. *Radiology* 1981; 139:665–676.
17. Norman RM, Urich H, McMenemey WH. Vascular mechanisms of birth injury. *Brain* 1957; 80:49–58.
18. Volpe JJ, Pasternak JF. Parasagittal cerebral injury in neonatal hypoxic-ischemic encephalopathy: clinical and neuroradiological features. *J Pediatr* 1977; 91:472–476.
19. O'Brien MJ, Ash JM, Gilday DL. Radionuclide brain-scanning in perinatal hypoxia/ischemia. *Dev Med Child Neurol* 1979; 21:161–173.
20. Volpe JJ, Herschowitch P, Perlman JM, et al. Positron emission tomography in the asphyxiated term newborn: parasagittal impairment of cerebral blood flow. *Ann Neurol* 1985; 17:287–296.
21. Phelps ME, Kuhl DE, Mazziotta JC. Metabolic mapping of the brain's response in visual stimulation: studies in humans. *Science* 1981; 211:1445–1448.
22. Mazziotta JC, Phelps ME, Carson RE, et al. Tomographic mapping of human cerebral metabolism. Auditory stimulation. *Neurology* 1982; 32:921–937.
23. Olesen J. Contralateral focal increase of cerebral blood flow during arm work. *Brain* 1971; 94:635–646.
24. Webster EW, Alpert NM, Brownell GL. Radiation doses in pediatric nuclear medicine and diagnostic x-ray procedures. In: James AE, Wagner HN, Cooke RE. Pediatric Nuclear Medicine. Philadelphia: W. B. Saunders Company, 1974: 34–58.
25. Volpe JJ, Herschowitch P, Perlman 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.
26. Doyle LW, Nahmias C, Firnau G, et al. Regional cerebral glucose metabolism of newborn infants measured by positron emission tomography. *Dev Med Child Neurol* 1983; 25:143–151.