Functional Imaging of Brain Maturation in Humans Using Iodine-123 Iodoamphetamine and SPECT

M. Rubinstein, R. Denays, H.R. Ham, A. Piepsz, T. VanPachterbeke, D. Haumont, and P. Noël

Departments of Radioisotopes, Neurology and Pediatrics, St. Pierre Hospital and Free Universities of Brussels, Brussels, Belgium

The application of regional cerebral blood flow (rCBF) study by means of lipophilic radiotracers and single photon emission computed (SPECT) devices in very young infants is hampered by the considerable changes of rCBF pattern as a result of the cerebral maturation process. In an attempt to determine the normal evolution of [^{123}I]IMP SPECT pattern as a function of age, we retrospectively selected the studies of 30 babies with normal clinical examination, EEG and CT or ultrasound scans at time of SPECT. There was a marked predominance of the thalamic perfusion over cortical areas until the end of the second month. The distribution of regional cortical activity followed a strict sequence. The perfusion of both parietal and occipital areas was well-visualized around the 40th week of gestational age and thereafter rapidly rose, always, however, with a slight predominance of the parietal activity. At the opposite, frontal activity which remained scarcely recognizable up to the second month tremendously rose to present the adult-like pattern at the beginning of the second year. The rCBF changes described above are well in agreement with the behavioral evolution occurring during prime infancy.

J Nucl Med 30:1982–1985, 1989

The clinical value of regional cerebral blood flow (rCBF) study by means of lipophilic radiotracers and single photon tomography devices has been established in adults and children (*1–4*). The application of the method for the study of very young infants is hampered by the considerable changes of rCBF pattern due to cerebral maturation process and hence, implies the knowledge of the normal evolution of the single photon emission computed tomography (SPECT) pattern during the first months of life. Unfortunately, for obvious ethical reasons, experimental study in normal children cannot be performed, and the normal pattern must be deduced from data obtained in infants suspected or at risk of having neurologic disorders.

In this paper, we describe the approach we employed as well as the results obtained in our attempt to determine the normal evolution of iodine-123 iodoamphetamine SPECT pattern in young infants.

Received Feb. 21, 1989; revision accepted Aug. 10, 1989.

For reprints contact: M. Rubinstein, MD, Dept. of Radioisotopes, St-Pierre Hospital, 322, rue Haute, 1000 Bruxelles, Belgium.

PATIENTS AND METHODS

We investigated, in 1987, 47 neonates and infants according to a protocol which has been approved by our local Committee for Medical Ethics. Thirty patients were included in the study: 23 were newborns (gestational age (GA): 36 to 44 wk) at risk to develop cerebral palsy. Inclusion criteria were birth weight <1.501kg, neonatal asphyxia (Apgar score <4 at 5 min), perinatal hypoglycemia (<30 mg%). The last seven patients were infants aged 2 mo to 2 yr and were seen after a first episode of tonic-clonic seizures. In each of the newborns, one EEG and two ultrasound scans (at birth and prior the exit) have been performed. None was studied by CT scan. The seven older patients had each two EEG and one CT scan. All patients had normal clinical examination, EEG and CT or ultrasound scans at time of SPECT.

An i.v. line was inserted into the hand of babies previously placed in a quiet environment. A few minutes later, 0.05 mCi/kg (with a minimum of 0.5 mCi) of high purity [^{123}I]IMP were administered. All babies were awake at time of injection, and no premedication was used. They were taken to the camera room ~30 min after the injection. To avoid movement artifacts, the head and the trunk were gently wrapped in a specially designed polystyrene vacuum-cushion. SPECT imaging was performed using an Elscint rotating gamma-camera interfaced

to an Apex 415. Sixty frames of 30 sec were collected. Transaxial, coronal, and sagittal reconstructions were calculated using the backprojection method after a high-frequency cutoff. Slices were 2 pixels thick (0.5 to 1 cm).

The SPECT results were interpreted by four qualified observers who were unaware of the age and clinical data of the patients, and different patterns of regional brain perfusion were determined. Then, the age of each patient presenting specific SPECT pattern was noted.

RESULTS

Six typical SPECT patterns, with more or less activity in the thalamic and/or cortical areas have been individualized with an excellent agreement between examinators (Fig. 1). As shown in Table 1 these SPECT patterns were closely related with gestational age of the baby at time of SPECT.

Pattern 1

Prominent rCBF in the thalamus. Low activity in the parietal and occipital cortical areas. Very poor frontal visualization. This pattern is found before the 40th week GA.

Pattern 2

Prominent activity in the thalamus. Important activity in the parietal cortex. Low activity in the occipital area. Very poor frontal visualization. This pattern is found around the 40th week GA.

Pattern 3

Prominent activity in both thalamus and parietal cortex. Important activity in occipital area. Very poor frontal visualization. This pattern is found around the 44th week GA.

Pattern 4

Regional cerebral blood flow becomes slightly predominant in parietal and occipital cortex. Frontal activity is still low. This pattern is found around 2 mo.

Pattern 5

Marked cortical predominance. Increase in frontal activity, which remains lower than parietal and occipital activity. This pattern is found around 6 mo.

Pattern 6

Important activity in all cortical areas. This pattern is found around 1 yr.

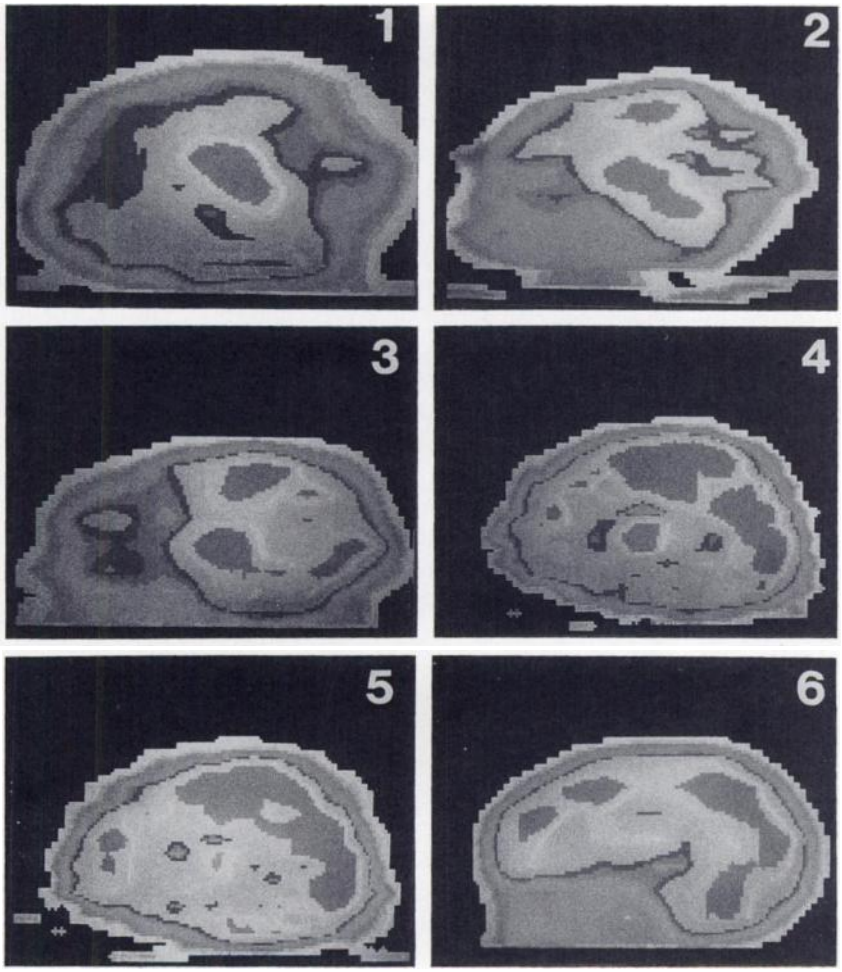

FIGURE 1
Six patterns of regional cerebral blood flow distribution (see text for detailed description) closely related with age of the baby at time of SPECT have been individualized from mediosagittal slices: pattern 1: preterm period, pattern 2: at term, pattern 3: 1 mo, pattern 4: 2 months, pattern 5: 6 mo, pattern 6: 1 yr. In this black and white reproduction of colored figures, gray indicates more activity than white.

TABLE 1
Age of Patients in Relation to SPECT Patterns

PATTERN 1 BA*-SA†	PATTERN 2 BA-SA	PATTERN 3 BA-SA	PATTERN 4 BA-SA	PATTERN 5 BA-SA	PATTERN 6 BA-SA
30–36 w‡	35–39 w	36–43 w	38 w–2 m§	39 w–6 m	38 w–12 m
31–36 w	36–39 w	39–43 w	40 w–3 m	40 w–7 m	40 w–24 m
34–36 w	37–40 w	40–43 w		38 w–10 m	
32–37 w	38–40 w	38–44 w			
34–37 w	39–40 w	40–44 w			
35–37 w	40–41 w				
36–38 w	40–41 w				
37–38 w	29–42 w				
38–38 w	36–42 w				

* Gestational age at birth.
† Age at the time of SPECT.
‡ Weeks.
§ Months.

A few premature babies were seen around the 40th week GA and could be compared with age-matched term infants in order to test the hypothesis whether the extra-uterine life could exert an influence upon the brain maturation process. No significant difference was seen.

DISCUSSION

A flow tracer suitable for SPECT imaging is a lipophilic molecule which should diffuse freely from the vascular bed into nervous cells, and which should not redistribute before the imaging procedure is completed. Iodine-123 IMP is a weak base whose "trapping" mechanism is supposed to be at least partially based upon the pH difference between blood (7.4) and neurons (7.1): the circulating form is apolar and perfectly diffusible, whereas the dissociated (polar) form is predominant in neurons and is unable to move back across the cell membrane (*5*). The use of [^{123}I]IMP as a CBF tracer has been validated in adults (*6,7*).

To our knowledge, no data have been published about the behavior of that molecule in human newborns where global intracellular pH, measured using phosphorus-3-magnetic resonance spectroscopy, has been found higher than in adults (*8*). Therefore, ratios of activities between two regions at different maturation stages may not be considered to reflect perfusion ratios. However, the approximation is acceptable, as indicated by the concordance of fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) PET studies with our findings (*9*).

For obvious ethical reasons, all our children were selected among diseased groups: newborns were at risk to develop cerebral palsy and older babies have presented a convulsive episode. However, as shown in Table 1, the different scintigram patterns correspond to well defined age-groups. In other words, the major determinant of individual rCBF variations was found to be as a matter of fact the gestational age. For this reason, even though the infants in this study may not be considered as normals, the patterns observed indicate the scintigraphic brain maturation. It has to be mentioned additionally that all selected patients had normal neurological examination, EEG, ultrasound or CT studies at time of SPECT.

There was a marked predominance of the thalamic perfusion over cortical areas until the end of the second month. The distribution of regional cortical activity followed a strict sequence. The perfusion of both parietal and occipital areas was well visualized around the 40th week of the gestational age and thereafter rapidly rose, always, however, with a slight predominance of the parietal activity. At the opposite, frontal activity which remained scarcely recognizable up to the second month tremendously rose to present the adult-like pattern at the beginning of the second year.

It must be emphasized that the method just provides semiquantitative, i.e., relative indication of rCBF distribution. Indeed, an increase of absolute cerebral glucose consumption has been shown as late as the 8th year, using [^{18}F]FDG and PET (*9*). Nevertheless, the relative rCBF changes described above are well in agreement with the behavioral evolution occurring during prime infancy. Behavior of the first two months of life is dominated by reflexes and automatisms which are mediated by brainstem and diencephalic structures; however two cortical regions, sensori-motor and occipital areas, are already functional, as indicated by the ability to discriminate tactile from painful stimuli, which is present as early as the 28th week GA and to imitate facial gestures at 1 mo of age. The first obvious frontal manifestation is probably the socially responsive smile which occurs by the end of the second month of life.

ACKNOWLEDGMENT

This study was supported by Grant No. 1543888 from the FRSM.

REFERENCES

1. Hill TC, Magistretti PL, Holman BL, et al. Assessment of regional cerebral blood flow (rCBF) in stroke using SPECT and N-isopropyl-(I-123)-p-iodoamphetamine (IMP). *Stroke* 1984; 15:40–45.
2. Magistretti PL, Uren RF, Parker JA, et al. Monitoring of regional cerebral blood flow by single photon emission tomography of I123-n-isopropyl iodoamphetamine in epileptics. *Ann Radiol* 1983; 26:68–71.
3. Podreka I, Suers E, Goldenberg G. Initial experience with technetium-99m HM-PAO brain SPECT. *J Nucl Med* 1987; 28:1657–66.
4. Denays R, Rubinstein M, Ham H, et al. Single photon emission computed tomography in seizure disorders. *Arch Dis Child* 1988; 63:1184–1188
5. Kung HF, Blau M. Regional intracellular pH shift: A proposed new mechanism for radio-pharmaceutical uptake in brain and other tissues. *J Nucl Med* 1980; 21:147–152.
6. Kuhl DE, Barrio JR, Huang SC, et al. Quantifying local cerebral blood flow by N-isopropyl-p-^{123}I iodoamphetamine (IMP) tomography. *J Nucl Med* 1982; 23:196–203.
7. Lassen NA, Henriksen L, Holm S, et al. Cerebral blood-flow tomography: xenon-133 compared with isopropyl-amphetamine-iodine-123: concise communication. *J Nucl Med* 1983; 24:17–22.
8. Cady EB, Dawson MJ, Hope PL, et al. non-invasive-investigation of cerebral metabolism in newborn infants by phosphorus nuclear magnetique resonance spectroscopy. *Lancet* 1983; 14:1059–1062.
9. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Ann Neurol* 1987; 22:487–497.