

Technetium-99m-HMPAO Brain SPECT in Neonates with Hypoglycemic Encephalopathy

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Regional brain injury in three neonates with hypoglycemic encephalopathy are presented using serial ^{99m}Tc -hexamethyl propyleneamine oxime (HMPAO) SPECT and, for comparison, MRI. During the acute stage, both ^{99m}Tc -HMPAO SPECT and MRI reveal abnormalities in the posterior cerebrum. Technetium-99m-HMPAO SPECT reveals further areas of insult, for example the frontal lobes. The degree of hypoperfusion correlates with the clinical severity of hypoglycemia during the neonatal period and subsequent neurological sequelae. Follow-up with HMPAO SPECT several months after insult demonstrates persistent hypoperfusion in some areas, mainly in the occipital and posterior parietal regions. MRI can depict morphological changes with superior resolution. Because morphological change generally follows slowly after functional change, MRI is less sensitive than HMPAO SPECT in detecting and predicting the extent of hypoglycemic cerebral injury during the acute phase. HMPAO SPECT during the acute stage is a valuable tool for evaluating the extent and severity of brain injury in neonates with hypoglycemic encephalopathy.

Key Words: hypoglycemia; neonate; seizure; HMPAO SPECT

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Neonatal hypoglycemia is a common disorder (1,2) and can cause permanent neurological sequelae (3). The prognosis of neonatal hypoglycemia is poor if neurological symptoms, especially seizures, occur (2,3). Because the topography and severity of cerebral injuries determine subsequent neurological sequelae (4), imaging studies may provide useful information. However, to our knowledge there is only one case report presenting CT and MR images of a neonate with hypoglycemic encephalopathy (5), and no brain SPECT imaging has been reported. We report on serial ^{99m}Tc -hexamethyl propyleneamine oxime (HMPAO) brain SPECT imaging of three neonates with hypoglycemic encephalopathy and different degrees of neurological sequelae.

CASE REPORTS

All three neonates were full term and appropriate for gestation age for their birth weights. The pregnancies were normal, delivery course was smooth and Apgar scores were normal. Their metabolic studies, including serum and urine, for fatty acid and carbohydrate metabolisms were within normal limits. None of them had recurrent attacks of hypoglycemia after the neonatal period. All patients underwent ^{99m}Tc -HMPAO SPECT and MRI during the acute stage and follow-up. HMPAO SPECT during the acute stage was quantitatively analyzed using circular regions of interest manually placed on frontal, parietal, occipital and cerebellar areas on the midsagittal slice, and frontal-to-cerebellum, parietal-to-cerebellum and occipital-to-cerebellum ratios were calculated (Table 1).

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TABLE 1
HMPAO SPECT Ratios and Outcomes in Three Neonates with Hypoglycemic Encephalopathy

Patient no.	HMPAO SPECT			Outcome	
	F/C	P/C	O/C	Delay	Epilepsy
1	0.53	0.58	0.51	Severe	+
2	0.60	0.75	0.96	Mild	+
3	0.47	0.56	0.59	Severe	+

F/C = frontal/cerebellum; P/C = parietal/cerebellum; O/C = occipital/cerebellum.

Patient 1

A 15-day-old male neonate, birth weight 3,700 g, had several episodes of tachypnea and cyanosis one night before admission. After admission, mechanical ventilation was used because of frequent generalized tonic clonic seizures, hypotonia, poor response and pulmonary hemorrhage. Blood glucose level was 20 mg/dl and normalized after intravenous high-dose glucose infusion. At age 18 days, MRI revealed edematous change and mass effect over the bilateral parieto-occipital area (Fig. 1A). Technetium-99m-HMPAO (111 MBq) SPECT performed 1 wk later demonstrated hypoperfusion of the bilateral cerebral hemispheres, especially in the posterior cerebral areas. The frontal areas also were involved (Fig. 1B). At age 5 mo, MRI revealed encephalomalacia that was more prominent over the bilateral parieto-occipital lobes and diffuse cerebral atrophy (Fig. 1C). Technetium-99m-HMPAO SPECT demonstrated persistent hypoperfusion in bilateral occipital and posterior parietal areas and cerebral atrophy (Fig. 1D). The patient had frequent myoclonic seizures, marked developmental delay and microcephaly (below the third percentile) at age 1 yr 3 mo.

Patient 2

A female neonate, birth weight 3,200 g, had focal clonic seizures, poor activity and lethargy at age 4 days. Blood glucose level was 24 mg/dl. Seizures and hypoglycemia were corrected soon after intravenous glucose infusion. However, at age 50 days, focal myoclonic seizures developed. The patient was transferred to our hospital and MRI showed an abnormality in the white matter of the bilateral posterior parietal lobes (Fig. 2A). Technetium-99m-HMPAO (111 MBq) SPECT was performed 15 min after an episode of seizures (Fig. 2B), which occurred 4 days after the MRI study. Relatively lower cerebral perfusion was observed in the frontal parietal areas. In addition, a hyperperfused area that was considered to be an epileptogenic focus was noted at the right occipital lobe. Seizures were controlled by phenobarbital therapy. Follow-up MRI at age 5 mo revealed a decrease in the extent of bilateral parietal lesions (Fig. 2C). Technetium-99m-HMPAO SPECT at this time demonstrated mild white matter hypoperfusion that extended outside the parietal area (Fig. 2D). At age 15 mo, the patient had relative microcephaly (3rd to tenth percentile) and mild developmental delay.

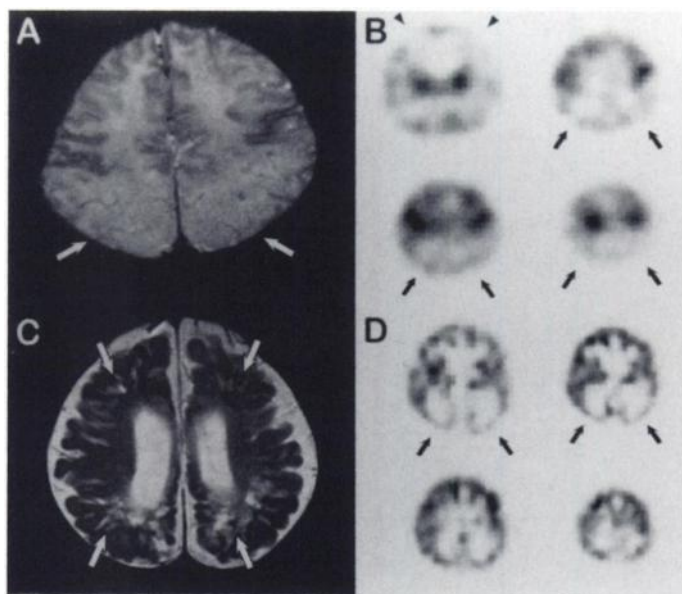


FIGURE 1. Patient 1. (A) Initial T2-weighted axial MR image reveals hyperintense region over bilateral parieto-occipital lobes (arrows). (B) Transverse ^{99m}Tc -HMPAO SPECT image demonstrates relative hypoperfusion in bilateral frontal areas (arrowheads) and pronounced hypoperfusion in bilateral occipital and posterior parietal areas (arrows). (C) Follow-up T2-weighted MR image shows encephalomalacia (arrows) with cerebral atrophy. (D) Technetium-99m-HMPAO SPECT image demonstrates persistent hypoperfusion in bilateral occipital and posterior parietal areas and cerebral atrophy (arrows).

Patient 3

A 2960-g male neonate was healthy until 70 hr of age when cyanosis and seizures developed. The patient was hypotonic, with poor response and low blood glucose level (10 mg/dl) on admission. The patient was treated with a high-dose glucose infusion followed by hydrocortisone for persistent hypoglycemia and intractable clonic seizures. Technetium-99m-HMPAO (111 MBq) SPECT at age 2 wk revealed very low perfusion over frontal,

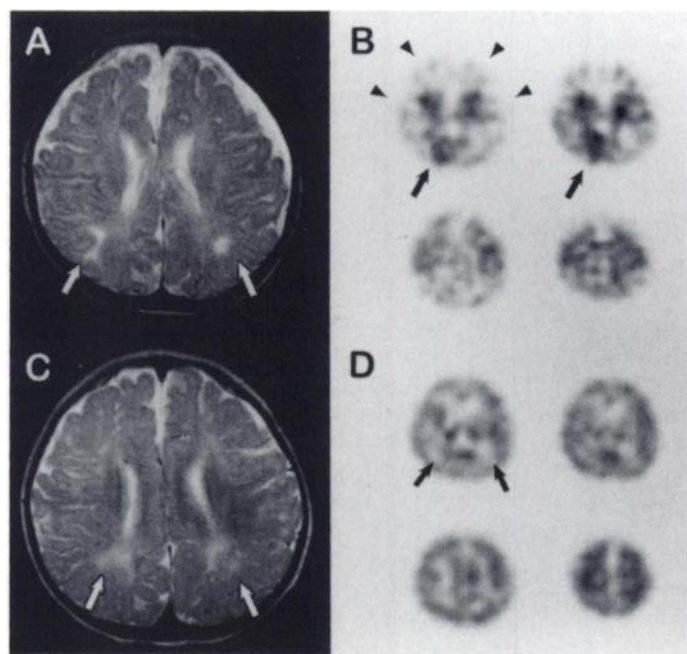


FIGURE 2. Patient 2. (A) Initial T2-weighted axial MR image shows abnormal high signal intensity (arrows) in white matter of bilateral parietal lobes. (B) Technetium-99m-HMPAO SPECT image reveals relative hypoperfusion in frontal and parietal areas (arrowheads). Hyperperfused area in the right occipital area (arrows) is seen also. (C) Follow-up T2-weighted MR image shows partial resolution of parietal lesions (arrows). (D) Technetium-99m-HMPAO SPECT image reveals mild white matter hypoperfusion (arrows).

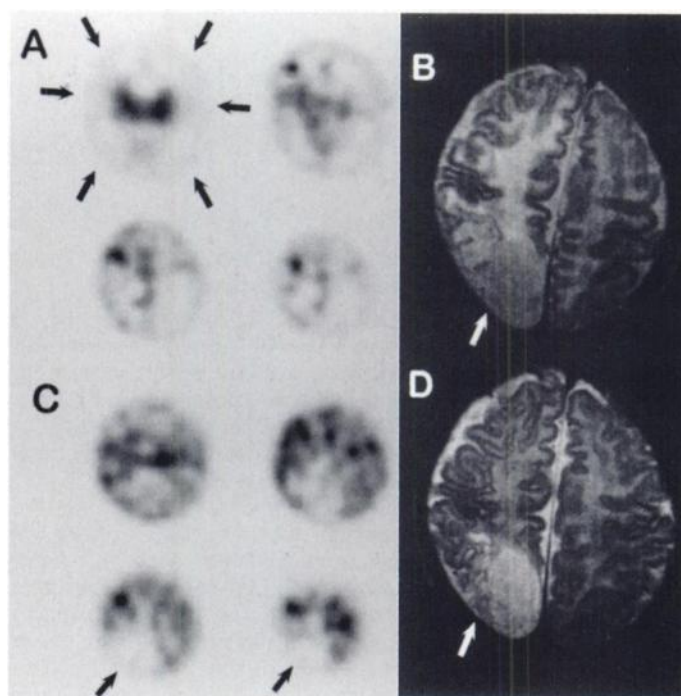


FIGURE 3. Patient 3. (A) Initial ^{99m}Tc -HMPAO SPECT image reveals marked hypoperfusion in bilateral frontal, parietal and occipital areas (arrows). (B) T2-weighted axial MR image shows localized high-signal-intensity lesion in right parieto-occipital lobe with loss of normal gray matter (arrow). (C) Follow-up ^{99m}Tc -HMPAO SPECT image demonstrates decreased perfusion in bilateral parieto-occipital regions, especially on right side (arrows). (D) T2-weighted axial MR image reveals persistence of right parieto-occipital lesion (arrow) accompanied by return of normal gray matter in immediately adjacent areas.

parietal and occipital areas (Fig. 3A). MRI (Fig. 3B) performed at age 1 mo demonstrated an abnormality in the right parieto-occipital area. Follow-up ^{99m}Tc -HMPAO SPECT at age 2 mo showed persistent cerebral hypoperfusion in bilateral parieto-occipital regions, especially on the right side (Fig. 3C). MRI demonstrated persistence of the right parieto-occipital lesion (Fig. 3D). The patient had microcephaly (below the third percentile), recurrent seizures and marked developmental delay at age 8 mo.

DISCUSSION

The human brain consumes glucose as its primary energy substrate. Severe hypoglycemia can cause cerebral dysfunction or even neuronal death (6). Although the initial physiological response to hypoglycemia is increased cerebral blood flow to compensate for insufficient glucose (7), delayed hypoperfusion has been observed after moderate and severe hypoglycemia (8). The occurrence of hypoperfusion is important because it is related to brain injury (9,10). Therefore, delineating the degree and extent of hypoperfusion is crucial. Technetium-99m-HMPAO brain SPECT is particularly good at detecting perfusion changes, and it was used in this study to assess the effects of hypoperfusion. Using ^{99m}Tc -HMPAO brain SPECT to observe cerebral blood flow changes in neonates with hypoglycemic encephalopathy, we observed that this technique may provide valuable information in patient examination.

Previous studies have shown that cerebral perfusion progresses from the central part of the brain to the cerebellum, sensorimotor and then visual cortex of the cerebrum during maturation in the neonatal period. Cerebral perfusion in the frontal lobes can be relatively low in neonates and young infants up to 1–2 yr of age (11,12). Thus, it is important to recognize cerebral perfusion patterns in the developing brain and compare them with normal patterns. Measuring the cortical

ratio of HMPAO SPECT during the acute stage by Denays' method (13), abnormal cerebral perfusions were seen in all three patients. The cerebral cortical regions in Patient 3 and parietal and occipital areas in Patient 1 had obvious abnormally low perfusion, although only relatively low perfusion was seen in the frontal area in Patient 1. Patient 2 had relatively low perfusion in the frontal and parietal areas, whereas the high perfusion in the occipital area was thought to be caused by a seizure. Therefore, the manifestations of cerebral perfusion patterns in these three patients reflect the effects and severity of hypoglycemia that are not attributable to normal age-related patterns.

Our three patients showed that the degree of hypoperfusion determined by ^{99m}Tc -HMPAO SPECT at an early stage correlated with the degree of encephalopathy caused by acute hypoglycemia and with the severity of subsequent sequelae. During the acute stage, Patients 1 and 3 had more severe symptoms and signs, including lower blood glucose level, cyanosis and intractable seizures, than Patient 2. Seizures and hypoxemia are associated with poor outcomes (2,3,14,15). We found that Patients 1 and 3 had more pronounced cerebral hypoperfusion than did Patient 2 and, at follow-up, Patients 1 and 3 had more severe neurological sequelae than Patient 2. In addition, the markedly decreased cerebral perfusion shown by ^{99m}Tc -HMPAO SPECT during the acute stage of injury predicted the persistence of hypoperfusion at follow-up.

Considering the topography of brain injury, the vulnerability of the posterior cerebrum to hypoglycemia in neonates has been indicated previously by MRI and pathology (5,16). Although normal infants have higher regional cerebral blood flow in the occipital regions (17), other factors, including efficiency of cerebral glucose usage, metabolic requirements and influx of glucose, also contribute to vulnerability to hypoglycemia (18). Using ^{99m}Tc -HMPAO SPECT, we observed that the areas involved in hypoglycemic brain injury are in the posterior cerebrum and in other cerebral regions, such as the frontal lobes. We believe that the difference between this study and previous observations is due to the high sensitivity of ^{99m}Tc -HMPAO SPECT. In this study, which included MRI observations for comparative purposes, during the early states of hypoglycemia, MRI could demonstrate lesions only in the posterior cerebrum, whereas ^{99m}Tc -HMPAO SPECT indicated additional sites of damage. This ^{99m}Tc -HMPAO SPECT finding is of clinical significance. For example, in Patient 1, during the acute stage, ^{99m}Tc -HMPAO SPECT showed diffuse hypoperfusion of bilateral cerebral hemispheres, whereas MRI revealed only an abnormality in the posterior cerebrum. Several months later, however, diffuse cerebral atrophy was seen with MRI.

This study clearly demonstrated that MRI was not as sensitive as ^{99m}Tc -HMPAO SPECT in detecting the extent and severity of hypoglycemic injury during the neonatal period. During the early stage of hypoglycemia, although HMPAO SPECT showed diffuse bilateral involvement of the cerebral hemispheres, MRI could show only severely damaged areas, namely the occipital and posterior parietal areas. Areas of additional involvement could be depicted by MRI only several months later, after morphological changes had occurred.

CONCLUSION

Although further studies are needed, the findings from studying these three patients suggest that cerebral hypoperfusion may be related closely to hypoglycemic encephalopathy in neonates and that ^{99m}Tc -HMPAO brain SPECT is a valuable tool in the detection of these cerebral insults during the acute phase. Technetium-99m-HMPAO brain SPECT proved to be more sensitive than MRI in delineating affected areas during the neonatal period. The extent and severity of cerebral hypoperfusion demonstrated by ^{99m}Tc -HMPAO brain SPECT correlated well with subsequent neurological outcome. Finally, this limited study agrees with previous studies indicating that the occipital and posterior parietal regions seem more vulnerable to hypoglycemic injury than other brain structures in neonates. However, this study indicates that hypoglycemic injury may occur at additional sites, for example, the frontal lobes. It was observed that hypoperfusion may persist many months after onset and is undetectable with MRI. Therefore, we suggest that ^{99m}Tc -HMPAO brain SPECT be considered during the evaluation of hypoglycemic neonates, especially during the acute phase.

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REFERENCES

1. Solomon T, Felix JM, Samuel M, et al. Hypoglycemia in pediatric admissions in Mozambique. *Lancet* 1994;343:149-150.
2. Koivisto M, Blanco SM, Krause U. Neonatal symptomatic and asymptomatic hypoglycaemia: a follow-up study of 151 children. *Dev Med Child Neurol* 1972;14:603-614.
3. Haworth JC, McRae KN. The neurological and developmental effects of neonatal hypoglycemia: a follow-up of 22 cases. *Can Med Assoc J* 1965;92:861-865.
4. Chugani HT, Muller RA, Chugani DC. Functional brain reorganization in children. *Brain Dev* 1996;18:347-356.
5. Spar JA, Levine JD, Orrison WW Jr. Neonatal hypoglycemia: CT and MR findings. *AJNR* 1994;15:1477-1478.
6. Auer RN. Hypoglycemic brain damage. *Stroke* 1986;17:488-496.
7. Pryds O, Greisen G, Friis-Hansen B. Compensatory increase of CBF in preterm infants during hypoglycaemia. *Acta Paediatr Scand* 1988;77:632-637.
8. Abdul-Rahman A, Agardh CD, Siesjo BK. Local cerebral blood flow in the rat during severe hypoglycemia, and in the recovery period following glucose injection. *Acta Physiol Scand* 1980;109:307-314.
9. Agardh CD, Kalimo H, Olsson Y, Siesjo BK. Hypoglycemic brain injury. I. Metabolic and light microscopic findings in rat cerebral cortex during profound insulin-induced hypoglycemia and in the recovery period following glucose administration. *Acta Neuropathol* 1980;50:31-41.
10. Kalimo H, Agardh CD, Olsson Y, Siesjo BK. Hypoglycemic brain injury. II. Electron-microscopic findings in rat cerebral cortical neurons during profound insulin-induced hypoglycemia and in the recovery period following glucose administration. *Acta Neuropathol* 1980;50:43-52.
11. Haddad J, Constantinesco A, Brunot B, Messer J. Cerebral perfusion studies during maturation using single photon emission computed tomography in the neonatal period. *Biol Neonate* 1994;65:281-286.
12. Chiron C, Raynaud C, Maziere B, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med* 1992;33:696-703.
13. Denays R, Ham H, Tondeur M, Piepsz A, Noel P. Detection of bilateral and symmetrical anomalies in technetium-99m-HMPAO brain SPECT studies. *J Nucl Med* 1992;33:485-490.
14. Volpe JJ. Hypoglycemia and brain injury. In: Volpe JJ, ed. *Neurology of the newborn*, 3rd ed. Philadelphia: WB Saunders; 1995:467-489.
15. Himwich HE, Bernstein AO, Herlich H, et al. Mechanisms for the maintenance of life in the newborn during anoxia. *Am J Physiol* 1942;135:387.
16. Anderson JM, Milner RDG, Strich S. Effects of neonatal hypoglycemia on the nervous system: a pathologic study. *J Neurol Neurosurg Psychiatry* 1967;30:295-310.
17. YOUNKIN D, Delivoria-Papadopoulos M, Reivich M, Jaggi J, Obrist W. Regional variations in human newborn cerebral blood flow. *J Pediatr* 1988;112:104-108.
18. LaManna JC, Harik SI. Regional comparisons of brain glucose influx. *Brain Res* 1985;326:299-305.