Visual and Semiquantitative Analysis of Cortical FDG-PET Scans in Childhood Epileptic Encephalopathies

Colin D. Ferrie, Paul K. Marsden, Michael N. Maisey and Richard O. Robinson

Department of Paediatric Neurology, Leeds General Infirmary, Leeds; Department of Radiological Sciences, Clinical PET Centre, UMDS, London; and Department of Paediatric Neurology, Guy's Hospital, London, United Kingdom

The optimal method for analyzing PET scans in children being considered for epilepsy surgery is unresolved: Fully quantified methods are invasive, and the required controls are generally unavailable. We sought to compare visual inspection with semiquantitative analysis for the detection of cortical metabolic defects. **Methods:** Thirty-two children with cryptogenic epileptic encephalopathies were studied prospectively with ^{18}F-fluorodeoxyglucose (FDG) PET. Visual inspection was performed on separate occasions by independent observers. Four-millimeter circular regions of interest were used to sample radiotracer uptake in selected cortical regions. Asymmetry between homologous regions were calculated to detect focal abnormalities. Bilateral and diffuse abnormalities were assessed by comparing the ratio of cortical-to-cerebellar uptake in patients with historical age-matched controls. The sensitivity and specificity of visual inspection was compared with that of semiquantitative analysis for the detection of focal, bilateral and diffuse cortical metabolic abnormalities. **Results:** Visual inspection revealed full inter-rater agreement for the presence of major focal abnormalities. The sensitivity and specificity for visual inspection compared to semiquantitative analysis were 77% and 92%, respectively, with semiquantitative analysis often revealing abnormalities to be more extensive than had been suspected visually. Compared with semiquantitative analysis, visual inspection had a low sensitivity but high specificity for the detection of bilateral and diffuse hypometabolism. **Conclusion:** Semiquantitative analysis gives clinically useful information additional to that obtained from visual inspection.

Key Words: PET; epilepsy; semiquantitative analysis

J Nucl Med 1997; 38:1891–1894

PET with ^{18}F-fluorodeoxyglucose (FDG) is increasingly used to detect focal cortical abnormalities in children with drug-resistant seizures who are considered potential candidates for epilepsy surgery (*1–5*). The optimal method for their analysis is still undetermined (*6*). Visual inspection, the standard method for interpreting structural imaging scans, is also frequently used for clinical PET scans. Quantification of radiotracer uptake in different cortical regions is suggested as being more objective and likely to detect subtle and bilateral abnormalities missed on visual inspection. However, full quantification with determination of the metabolic rate for glucose, involves repeated blood sampling, usually from an arterial line, and in addition, requires each center to have age-matched control data. Semiquantitative analysis, in which ratios of radiotracer uptake are compared, does not involve additional invasive procedures and may not require center-specific control data, but is more time-consuming then visual inspection alone (*7*).

Semiquantitative techniques involve comparing FDG uptake in computer-generated regions of interest (ROIs). The ROIs are usually circular and are placed by matching the PET scans with an anatomical brain atlas. A template of ROIs can be used to sample different brain structures with, for larger structures, multiple ROIs averaged for improved accuracy. Although automated techniques are useful for studying groups of patients, the regions analyzed rarely correspond to anatomical or functional structures, which make them less suitable for individual clinical studies. Focal cortical abnormalities can be detected by comparing radiotracer uptake in ROIs placed in homologous brain regions. This can be quantified by calculating asymmetry indices (*6*). Alternatively, uptake can be expressed as a ratio of that against a reference such as the cerebellum or ipsilateral hemisphere, allowing detection of focal, bilateral and diffuse cortical defects. Both these techniques require knowledge of uptake patterns in the normal population. However, the use of ratios of uptake may remove the otherwise absolute, but for children ethically unacceptable requirement, for each center to have its own control data. Adult studies have suggested that an asymmetry of homologous cortical regions of 15% or more is definitely abnormal (*8*). Chugani et al. have reported details on the development of cortical FDG uptake from infancy to early adult life. The study subjects were children who were subsequently shown not to have significant neurological disease (*9*). Chugani et al.'s study provides potential historical control data for PET studies in which FDG uptake in different brain regions is assessed against a common reference.

The childhood epileptic encephalopathies are a group of severe, drug-resistant childhood epilepsies characterized by multiple seizure types, diffusely slow EEG with generalized or multifocal paroxysmal abnormalities and frequent psychomotor retardation (*10–13*). The best known is the Lennox-Gastaut syndrome arising either de novo or from West's syndrome. Others include severe myoclonic epilepsy in infancy and epilepsy with myoclonic astatic seizures. They are usually considered as generalized epilepsies arising from a cortex which is diffusely abnormal. However, there is increasing evidence that some are associated with focal cortical abnormalities of neuronal architecture and that this may be associated with interictal hypometabolism on FDG-PET scans (*14–18*). It has been suggested that FDG-PET may also have a role in assessing the integrity of the remaining cortex remote from focal abnormalities (*15*).

We have previously reported the FDG-PET findings in a group of 32 children with cryptogenic epileptic encephalopathies in whom other investigations, including advanced magnetic resonance imaging (MRI), was uninformative (*19*). Focal abnormalities were reported on the basis of combined visual inspection and semiquantitative analysis using calculated asymmetry indices for homologous cortical regions. Bilateral and diffuse abnormalities were only reported if evident on visual

Received Nov. 4, 1996; revision accepted Mar. 16, 1997.

For correspondence or reprints contact: Colin D. Ferrie, Department of Paediatric Neurology, Clarendon Wing, Leeds General Infirmary, Leeds, LS2 9NS, UK.

analysis. Unilateral areas of abnormal cortical glucose metabolism were found in 12 patients, bilateral or diffuse hypometabolism in 5 patients and 15 patients had scans that appeared normal.

In this study, we compare the sensitivity of visual inspection with semiquantitative analysis in the detection of focal, bilateral and diffuse cortical metabolic defects in these children.

MATERIALS AND METHODS

Thirty-two children, aged 1–12 yr, with cryptogenic epileptic encephalopathies were studied prospectively. In all patients, extensive investigations including detailed EEG/video-EEG studies and advanced MRI scans had failed to show focal cortical abnormalities. Patients were classified syndromically according to the proposals of the International League Against Epilepsy (*10*). However, patients were not separated by syndrome in this study. FDG-PET with EEG monitoring during radiotracer (3.6 MBq/kg FDG) uptake was performed following a 4-hr fast. During FDG uptake, the lights were dimmed and interactions with the child discouraged. Intravenous diazepam was given to patients with frequent paroxysmal EEG discharges and to agitated patients during the first 10 min of FDG uptake. PET scans were performed 30 min postadministration using a headholder to minimize movements. Six 5-min consecutive frames were acquired with the data summed. Frames with excessive movement were discarded. The images were corrected for attenuation using a calculated method (*20*). The images then were smoothed and reconstructed to give thirty-one 3.4-mm thick planes with an in-plane spatial resolution of 8-mm FWHM and a total axial field of view of 10.4 cm. Images were reconstructed in the axial and coronal planes and in the plane parallel to the long axis of the temporal lobes. The EEG obtained during radiotracer uptake was used to classify scans as exclusively or predominantly ictal or interictal (*19*).

Scans were assessed visually on two separate occasions by independent, experienced nuclear medicine physicians who were blind to the clinical data. The inter-rater agreement was calculated. Semiquantitative analysis was performed, blind to the results of visual analysis, using a template of multiple 4-mm circular ROIs placed in selected brain regions chosen by matching PET planes to an anatomic brain atlas (Fig. 1). Frontal (seven ROIs on each side), parietal (three ROIs on each side) and occipital (four ROIs on each side) cortices were sampled along with the opercular region (three ROIs on each side), medial temporal structures (three ROIs on each side), temporal neocortex (four ROIs on each side) and temporal poles (1 ROI on each side). For each structure, except the temporal poles, multiple ROIs were averaged.

Asymmetry indices were calculated for homologous regions [(difference in uptake/average uptake) × 100%]. An asymmetry of 15% or more was considered as definitely abnormal; an asymmetry of 10%–15% was considered equivocal. The findings on visual analysis were categorized as definite unilateral focal abnormality, equivocal focal abnormality, bilateral abnormality, diffuse abnormality or no abnormality. When there was disagreement between the reports on visual inspection, scans were taken to show the more extensive of the abnormalities reported. The sensitivity and specificity of visual inspection compared to semiquantitative analysis were calculated.

For each region under study, FDG uptake was expressed relative to cerebellar uptake. These were compared to the mean and standard deviations, estimated by the delta method (*21*), of cortical relative to cerebellar uptake in age-matched historical controls (*9*) (Table 1). A ratio greater than 2 s.d. from the mean of control data was considered abnormal. The sensitivity and specificity of visual inspection in the detection of bilateral and diffuse abnormalities was compared to that of semiquantitative analysis.

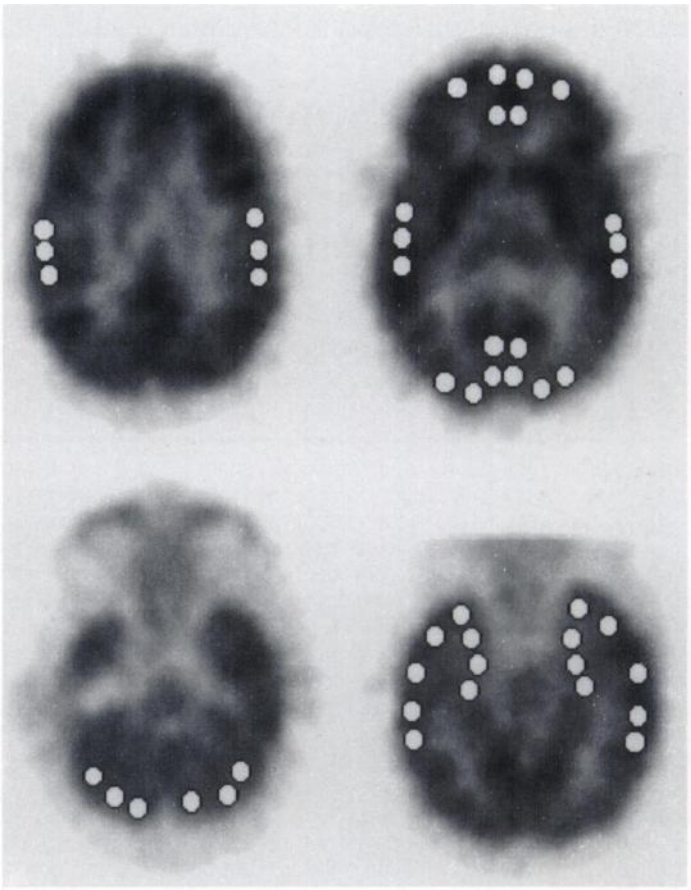

FIGURE 1. Template of ROI used to determine FDG uptake in selected brain regions. Top left: Axial view showing parietal ROI. Top right: Axial view showing frontal, opercular and occipital ROI. Bottom left: Axial view showing cerebellar ROI. Bottom right: View through the long axis of the temporal lobes showing mesial temporal lobe ROI, lateral temporal lobe ROI and temporal pole ROI. In addition to the frontal lobe ROI shown, three more ROIs (bilaterally) on a higher axial plane on each side were used. Each ROI was 4 mm in diameter.

RESULTS

Scans were considered interictal or predominantly interictal in 31 patients. One patient's scan was ictal. This was the only patient whose scan showed cortical hypermetabolism. There was full agreement between visual reporting of PET scans in 25 of the 32 scans (78%). In two patients (6%), an equivocal or minor abnormality was reported by one observer only, and in five patients (16%), one observer reported an abnormality as being substantially more extensive than the other (i.e., involving one or more additional cortical regions). In no patient was a major abnormality reported by one observer only. The inter-rater agreement rate was therefore 78%, rising to 100% for major abnormalities.

Thirteen patients were identified on visual inspection as

TABLE 1
Relative FDG Uptake in Control Subjects

Age (yr)	Frontal	Parietal	Occipital	Temporal
1–2	1.52 ± 0.27	1.47 ± 0.26	1.67 ± 0.28	1.56 ± 0.27
3–8	1.67 ± 0.10	1.67 ± 0.10	1.75 ± 0.11	1.52 ± 0.09
9–15	1.63 ± 0.07	1.57 ± 0.07	1.67 ± 0.05	1.46 ± 0.06

Mean and standard deviations of FDG uptake in selected cortical regions relative to cerebellar uptake in control subjects from data published by Chugani et al. (*9*). The standard deviations were calculated by the delta method (*21*).

showing unilateral focal cortical metabolic defects. Unequivocal asymmetry was found in 10 patients (77%) and equivocal asymmetry in 2 patients (15%) by semiquantitative analysis. In one patient (8%), there was neither definite nor equivocal asymmetry. In 13 patients, visual inspection revealed no abnormalities or only minor focal abnormalities not felt to be significant. For semiquantitative analysis, no asymmetry was seen in five scans (38%), equivocal asymmetry was detected in seven scans (54%) and definite asymmetry in one scan (8%). In three scans in which no significant asymmetry was found by semiquantitative analysis, inspection revealed a focal abnormality. Conversely, one scan reported as being normal on visual inspection had a definite asymmetry on semiquantitative analysis. Therefore, the sensitivity of visual inspection for focal abnormalities was 77%, and the specificity was 92%. Additionally, in three of the ten scans (30%) in which visual analysis had identified focal abnormalities, semiquantitative analysis revealed asymmetries extending into additional cortical regions.

Thirty patients had bilateral cortical regions in which FDG uptake relative to cerebellar uptake was more than 2 s.d. below that in control subjects. In nine of these, bilateral or diffuse metabolic abnormalities were noted on visual inspection. All patients with suspected bilateral abnormalities on visual inspection had congruent findings on semiquantitative analysis. The sensitivity and specificity of visual inspection compared to semiquantitative analysis for the detection of bilateral abnormalities was therefore 30% and 100%, respectively. In 21 patients, the relative uptake in all cortical regions was more than 2 s.d. below that in control subjects (i.e., global cortical hypometabolism). In four of these patients, PET scans assessed visually showed diffuse hypometabolism, unilateral unifocal abnormalities were observed in seven, bilateral abnormalities were seen in three and seven patients had normal scans. Therefore, in patients with global hypometabolism on semiquantitative analysis, visual inspection had a sensitivity of 67% for the detection of any abnormality but only 19% for the detection of global hypometabolism. In each case, the specificity was 100%. In patients with bilateral, but not global, cortical metabolic defects, cortical uptake was spared in the frontal regions of nine patients, in the parietal regions of eight patients and in the temporal and occipital regions in only three patients each.

DISCUSSION

Intuitively, fully quantified methods for reporting of PET scans seems ideal. In pediatric practice, however, this may not be so. The designation of metabolic rates obtained by such methods as "absolute" is spurious. In reality, they are calculated values based on a number of estimates and assumptions. Partial volume effects mean that all are likely to be lower than the actual value (*22*). This imposes an absolute requirement for each center to obtain its control data, matched for age and obtained under similar conditions to the those used to scan patients. Obtaining such data in children would be unethical as it would involve significant exposure to radiation. Moreover, the identification of abnormality in fully quantified studies involves detecting metabolic rates which deviate, for example, by more than two standard deviations from the mean in controls. However, it is quite possible for the metabolic rate for a particular cortical region to be within the "normal range" but for a clinically significant asymmetry to exist between it and the contralateral cortex. Fully quantified analysis would miss this defect. Visual inspection and semiquantified analysis of PET scans are therefore attractive reporting methods in clinical pediatric practice. However, little is known about their sensitivity and specificity. In this study, we compared visual inspection to the more objective semiquantified analysis.

There was excellent agreement in inter-rater reporting of major abnormalities on FDG-PET scans but disagreement over the presence of minor abnormalities in around one-fifth of scans. However, the only clinical indication for PET scans in children with epilepsy is in the identification of possible surgical foci; it is unlikely that any of these minor disagreements would have been important clinically. The finding of high inter-rater reliability in the visual reporting of PET scans contrasts with a previous report in which observers disagreed over visual findings on SPECT scans in 42% of cases (*23*). There are several possible explanations for this:

1. The greater resolution provided by PET over SPECT means that "anatomical structures" are more evident. This may provide more visual landmarks for the observer, making asymmetries and other abnormalities more apparent.
2. The nature of the abnormalities may be different. Those in the SPECT study were described as "patchy" while ours were more usually focal. Clearer boundaries of the latter may have aided their detection.
3. Details from the observers were not given for the SPECT study but reporting by experienced observers would be expected to improve accuracy.
4. The SPECT study involved patients with migraine. It is unlikely that such patients were scanned routinely. The observers in our study were familiar with the type of PET abnormalities expected in children with seizures which may have increased their discriminatory ability in reporting normal from abnormal.

We found that visual inspection had high specificity for detecting focal defects compared with semiquantitative analysis. This suggests that visual analysis does not lead to significant over-reporting of focal defects. However, calculation of asymmetry indices leads to occasional recognition of significant focal cortical metabolic defects not suspected on visual inspection. In addition, defects noted visually were often shown to be more extensive on semiquantitative analysis. This is in agreement with previous studies which have suggested that visual analysis of functional imaging scans may fail to detect important cortical abnormalities (*23*).

Semiquantitative analysis using historical age-matched control subjects suggested frequent diffuse hypometabolism in children with epileptic encephalopathies. Visual inspection usually failed to detect such abnormalities. Conversely, diffuse hypometabolism detected by visual inspection was always confirmed by semiquantitative analysis. Comparing results obtained on one PET scanner with those obtained on another scanner is problematic (*24–28*) because of partial volume effects, which cause underestimation of radiotracer uptake that is more marked in scanners with lower spatial resolution. However, as we have discussed in detail elsewhere (*29*), the relative resolution of the PET scanners used to study our patients and the control subjects would be expected to increase the ratio of cortical-to-cerebellar FDG uptake in our patients relative to that in control subjects (i.e., the opposite to that observed), making this an unlikely explanation for the high incidence of diffuse metabolic defects in our patients. In patients being considered for epilepsy surgery, FDG-PET has been proposed as useful in assessing the integrity of the cortex remote from presumptive surgical foci (*15*). This study suggests that visual inspection alone is ill-suited for this.

CONCLUSION

Semiquantitative analysis of FDG-PET scans in childhood epileptic encephalopathies adds clinically useful information to that obtained from visual inspection. Detection of focal abnormalities is improved when visual findings are combined with calculation of asymmetry indices, while semiquantitative analysis using ratios of uptake relative to a common reference may reveal bilateral and global metabolic defects not apparent on visual inspection.

ACKNOWLEDGMENTS

This work was supported by grants from the Special Trustees of Guy's Hospital and from Marion Merrell Dow & Co.

REFERENCES

1. SPECT and PET in epilepsy [Editorial]. *Lancet* 1989;1:135–136.
2. Ell PJ. PET reflections. *Eur J Nucl Med* 1990;17:1–2.
3. Chugani HT, Shewmon DA, Shields WD, et al. Surgery for intractable infantile spasms: neuroimaging perspectives. *Epilepsia* 1993;34:764–771.
4. Chugani HT, Shewmon DA, Peacock WJ, Shields WD, Mazziotta JC, Phelps ME. Surgical treatment of intractable neonatal-onset seizures: the role of positron emission tomography. *Neurology* 1988;38:1178–1188.
5. Chugani HT. PET in preoperative evaluation of intractable epilepsy. *Pediatr Neurol* 1993;9:411–413.
6. Theodore WH. Epilepsy. In: Mazziotta JC, Gilman S, eds. *Clinical brain imaging: principles and applications*. Philadelphia: FA Davis; 1992:136–165.
7. Sadzot B, Debets R, Maquet P, Comar C, Franck G. PET studies of patients with partial epilepsy: visual interpretation versus semiquantification. *Acta Neurol Scand* 1994;152(Suppl):175–178.
8. Theodore WH, Fishbein D, Dubinsky R. Patterns of cerebral glucose metabolism in patients with partial seizures. *Neurology* 1988;38:1201–1206.
9. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Ann Neurol* 1987;22:487–497.
10. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389–399.
11. Aicardi J. Epileptic encephalopathies of early childhood. *Curr Opin Neurol Neurosurg* 1992;5:344–348.
12. Aicardi J. *Epilepsy in children*. New York: Raven Press; 1994.
13. Donat JF. The age-dependent epileptic encephalopathies. *J Child Neurol* 1992;7:7–21.
14. Gur RC, Sussman NM, Alavi A, et al. Positron emission tomography in two cases of childhood epileptic encephalopathy (Lennox-Gastaut syndrome). *Neurology* 1982;32:1191–1194.
15. Chugani HT, Mazziotta JC, Engel J, Phelps ME. The Lennox-Gastaut syndrome: metabolic subtypes determined by 2-deoxy-2-fluro-D-glucose positron emission tomography. *Ann Neurol* 1987;21:4–13.
16. Chugani HT, Shields WD, Shewmon DA, Olson DM, Phelps ME, Peacock WJ. Infantile spasms. I. PET identifies focal cortical dysgenesis in cryptogenic cases for surgical treatment. *Ann Neurol* 1990;27:406–413.
17. Yani K, Linuma K, Matsuzawa T, et al. Cerebral glucose utilization in pediatric neurological disorders determined by positron emission tomography. *Eur J Nucl Med* 1987;13:292–296.
18. Miyauchi T, Nomura Y, Ohno S, Kishimoto H, Matsushita M. Positron emission tomography in three cases of Lennox-Gastaut syndrome. *Jpn J Psychiatry Neurol* 1988;42:795–804.
19. Ferrie CD, Maisey M, Cox T, et al. Focal abnormalities detected by ^{18}FDG PET in epileptic encephalopathies. *Arch Dis Child* 1996;75:102–107.
20. Bergstrom M, Litton J, Erihsson L, Bohm L, Blomquist G. Determination of object contour from projections for attenuation correction in cranial positron emission tomography. *J Comput Assist Tomogr* 1982;6:365–372.
21. Armitage P. *Statistical methods in medical practice*. Oxford: Blackwell; 1971.
22. Phelps ME. Positron emission tomography (PET). In: Mazziotta JC, Gilman S, eds. *Clinical brain imaging: principles and applications*. Philadelphia: F.A. Davis; 1992:71–107.
23. Friberg L, Lonborg-Jensen H. Visual inspection versus quantified analysis of functional brain images. *Acta Neurol Scand* 1994;152(suppl):169–174.
24. Grady CL, Berg C, Carson RE, Daube-Witherspoon ME, Friderich RP, Rapoport SI. Quantitative comparison of cerebral glucose metabolic rates from two positron emission tomographs. *J Nucl Med* 1989;30:1386–1392.
25. Grady CL. Quantitative comparison of measurements of cerebral glucose metabolic rate made with two positron cameras. *J Cereb Blood Flow Metab* 1991;11(suppl 1):57–63.
26. Camargo EE, Szabo Z, Links JM, Sostre S, Dannals RF, Wagner HN. The influence of biological and technical factors on the variability of global and regional brain metabolism of 2-[^{18}F]Fluoro-2-deoxy-D-glucose. *J Cereb Blood Flow Metab* 1992;12:281–290.
27. Strother SC, Allard C, Moeller JR, et al. Methodological factors affecting patterns of regional cerebral glucose metabolism as determined by ^{18}F-fluorodeoxyglucose/positron emission tomography. *J Cereb Blood Flow Metab* 1987;7(suppl 1):443.
28. Kumar A, Braun A, Schapiro M, Grady C, Carson R, Herscovitch P. Cerebral glucose metabolic rates after 30 and 45 minute acquisitions: a comparative study. *J Nucl Med* 1992;33:2103–2105.
29. Ferrie CD, Marsden PK, Maisey MN, Robinson RO. Cortical and subcortical glucose metabolism in childhood epileptic encephalopathies. *J Neurol Neurosurg Psychiatr* 1997;63:181-187.

Hyperventilation Technetium-99m-HMPAO Brain SPECT in Moyamoya Disease to Assess Risk of Natural Childbirth

Norihiko Kume, Kohei Hayashida, Yoriko Shimotsu and Naofumi Matsunaga

Department of Radiology, National Cardiovascular Center, Osaka; and Department of Radiology, Yamaguchi University School of Medicine, Yamaguchi, Japan

We report a pregnant 19-yr-old patient with moyamoya disease who had undergone bilateral superficial temporal artery to middle cerebral artery anastomosis and encephalomyosynangiosis at 8 yr with an uneventful postoperative course and who desired natural delivery after becoming pregnant at 18 yr. We determined her cerebral vascular reserve since natural delivery can result in decreased cerebral blood flow during labor. Technetium-99m-HMPAO brain SPECT, with hyperventilation challenge, was performed to assess cerebral vascular reserve since the stress of hyperventilation was thought likely to rehearse that of labor. The brain SPECT images, obtained using 333 MBq ^{99m}Tc-HMPAO, revealed maintenance of cerebral vascular reserve. In addition, whole-body images including the 27-wk-old fetus were obtained. These images demonstrated accumulation in the fetal liver. Natural delivery was, thus, considered indicated for this patient, who subsequently delivered a healthy baby girl. Technetium-99m-HMPAO brain SPECT with hyperventilation challenge was useful for estimating cerebral vascular reserve and for determining whether natural delivery was indicated for this patient with moyamoya disease.

Key Words: hyperventilation challenge; cerebral vascular reserve; labor stress; technetium-99m-HMPAO; moyamoya disease

J Nucl Med 1997; 38:1894–1897

Moyamoya disease is a chronically progressive cerebrovascular occlusive disease affecting the brain. The age distribution of patients includes two characteristic peaks, one in childhood and the other in adulthood (*1*). In the pediatric group, the initial

Received Jan. 27, 1997; accepted Mar. 6, 1997.

For correspondence or reprints contact: Kohei Hayashida, MD, National Cardiovascular Center, Department of Radiology, 5-7-1 Fujishirodai, Suita, Osaka, 565 Japan.