Detection of Bilateral and Symmetrical Anomalies in Technetium-99m-HMPAO Brain SPECT Studies

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The detection of bilateral and symmetrical regional cerebral blood flow (rCBF) abnormalities requires knowledge of the antero-posterior rCBF distribution in normal subjects of all age groups. These data are very difficult to obtain in children for ethical reasons and in older subjects because of the necessity of recruiting a large number of healthy volunteers from each age group. Therefore, to obtain normal values of antero-posterior rCBF distribution, we have retrospectively selected a group of patients with a low probability of having cerebral lesions, whose ^{99m}Tc-HMPAO brain SPECT studies were analyzed semiquantitatively. Cerebellum/mean cerebral cortex index when compared to young adults was higher in the neonatal period, slightly lower between 2 mo and 15 yr, and more or less identical after 15 yr. Cortico/occipital indexes exhibit considerable changes during the first year of life due to important differences in maturation timing of cerebral cortical areas. After 1 yr, all cerebral cortical areas approximately displayed a parallel evolution. A slight increase in fronto/occipital and temporo/occipital indexes was, however, still observed during childhood, while in elderly subjects there was a trend towards a decrease in all cortico/occipital indexes (particularly in prefrontal and motor areas). Changes that occurred after 1 yr were, however, usually smaller than inter-individual variation. Despite the large range of "normal" values, the antero-posterior analysis could be useful in various neurologic disorders, because it allows detection of symmetrical rCBF anomalies undiagnosed by the right-left analysis.

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Functional cerebral studies are now routinely performed using SPECT and regional cerebral blood flow (rCBF) tracers such as [^{123}I]iodoamphetamine (IMP) or ^{99m}Tc-hexamethyl propylene amine oxime (HMPAO) (*1–5*). While the tests provide only semi-quantitative measurements, there is usually no difficulty in diagnosing lateralized anomalies because CBF is expected to be symmetrically distributed in the different cerebral areas. Problems arise, however, in detecting bilateral and symmetrical regional abnormalities. For the detection of such anomalies, it is necessary to know the antero-posterior rCBF distribution in normal subjects. Unfortunately, these data are not available now and cannot be obtained easily. In children, for obvious ethical reasons, perfectly healthy subjects cannot be investigated. In adults, because of changes in antero-posterior rCBF distribution with advancing age, it would be necessary to study a large number of subjects in each age group. We therefore used in this study SPECT data from patients with a low probability of having rCBF anomalies to approximate a range of normal values. Then, based on the results obtained, we investigated a series of neurological disorders to determine those conditions where bilateral and symmetrical rCBF anomalies could be detected.

METHODS

Subjects

From more than 1000 ^{99m}Tc-HMPAO brain SPECT studies available in our data bank, 361 were selected. The sole criteria of selection was the absence of regional anomaly on the right-left analysis. The selected patients, ranging in age from a few days to 92 yr, were divided into two groups, according to clinical criteria and to the results of conventional cerebral investigations.

Group 1. This group comprised 205 patients who met the following criteria:

1. Normal neuropsychological examination at the time of the SPECT study and at follow-up, which was at least 12 mo for neonates and 6 mo for older children and adults.
2. Absence of drug abuse.
3. Absence of anomaly on electroencephalogram and on cranial ultrasound or brain CT scan.

These patients were sent to our department for the following reasons: neonates with perinatal trauma or severe prematurity (n=46); loss of consciousness (n=41); headache (n=38); transient focal neurological deficit (n=28); CO intoxication (n=23); and others (n=29).

Group 2. This group was comprised of 156 patients who did not meet the above criteria: 15 neonates with anomalies at neurological examination, electroencephalogram, and/or cranial ultrasonography; 9 infants aged 2 to 12 mo with psychomotor retardation; 11 children older than 1 yr suffering from spastic cerebral palsy; 14 children with learning disabilities; 4 patients

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with CO intoxication and electroencephalographic anomalies or neuropsychological sequelae; 12 epileptic patients; 14 adults with acute cerebrovascular disorders and permanent neurological sequelae; 41 chronic alcoholics; 8 elderly subjects with memory impairment and 10 others with global chronic deterioration of cognitive functions (dementia); and 18 patients with various other neurological problems.

Technetium-99m-HMPAO SPECT Study

Patients laid on a stretcher with eyes open in a quiet room. An intravenous line was inserted and a few minutes later 18.5 MBq/kg body weight of ^{99m}Tc-HMPAO (minimum: 111 MBq, maximum: 555 MBq) were administered. Ten to 60 min after injection, SPECT imaging was performed using a rotating gamma camera and a low-energy collimator. Sixty 30-sec frames were acquired. Transaxial, coronal and sagittal slices, 2 pixels thick, were reconstructed on an Elscint Apex 415 computer system. No attenuation or scatter correction was applied.

In order to obtain a semi-quantitative assessment of the antero-posterior hemispheric distribution of the tracer in patients older than 1 mo, circular regions of interest (ROIs) (diameter: 4 pixels) were positioned manually, using an anatomical atlas, in the cerebellum and in six cerebral cortical areas (prefrontal, superior motor, parietal, occipital, inferior motor and temporal cortex on four representative sagittal slices, located at 25%, 40%, 60%, and 75% of the width of the head (Fig. 1A). For the cerebellum and for each cerebral cortical area, the right and left activities were averaged, yielding a single value. Six indices were then calculated: the cerebellum/mean cerebral cortex index and five cortico/occipital indices (prefrontal/occipital, superior motor/occipital, inferior motor/occipital, parietal/occipital, temporal/occipital).

In neonates, tracer uptake was measured on the mediosagittal slice and in the frontal, parietal, occipital, thalamic and cerebellar areas (Fig. 1B). Cerebellum/mean cerebral cortex, frontal/cerebellum, parietal/cerebellum, occipital/cerebellum, frontal/thalamus, parietal/thalamus, occipital/thalamus, frontal/occipital, parietal/occipital then were calculated.

Results obtained from Group 1 were used to determine the limits of "normal" values, defined for each index as mean ± 2 s.d. in each age group. Group 2 data were used to study in which neurological disorders anomalies of antero-posterior hemispheric distribution could be detected, with the "normal" criteria established in Group 1. In patients older than 1 mo, changes in flow to a cerebral cortical area were diagnosed by an alteration of the corresponding cortico/occipital index. An occipital change was suggested by anomalies of all cortico/occipital indices and a cerebellar anomaly by a cerebellar/mean cerebral index out of the "normal" limits (mean ± 2 s.d.). In neonates, a cortical anomaly was diagnosed by a cortico/thalamic and a cortico/cerebellar index out of the 'normal' range, a thalamic or a cerebellar change by anomalies of all cortico/thalamic indices or of all cortico/cerebellar indices, respectively.

Statistics

Data were presented as mean ± s.d. Statistical analysis consisted of modified t-test for multiple comparisons using the Bonferroni method.

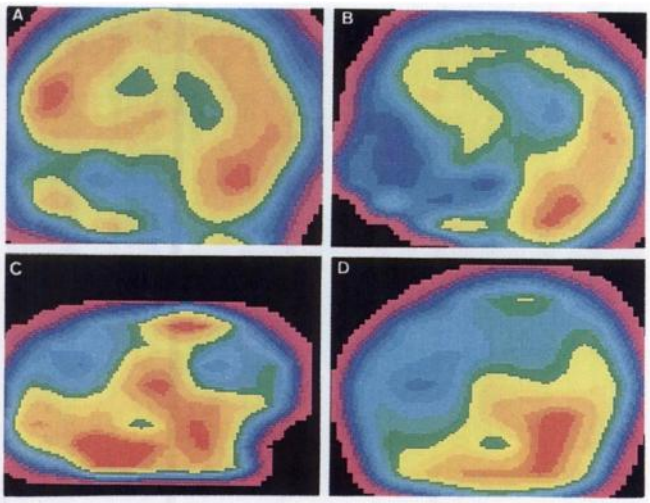

FIGURE 1. (A) In patients older than 1 mo, four sagittal slices, located at 25% (frame A), 40% (frame B), 60% (frame C) and 75% (frame D) of the width of the head, were used for the antero-posterior analysis of ^{99m}Tc-HMPAO SPECT studies. ROIs corresponded respectively to inferior motor (1), temporal (2), prefrontal (3), superior motor (4), parietal (5), occipital (6) and cerebellar (7) areas. (B) In neonates, for the antero-posterior analysis, tracer uptake was measured on the mediosagittal slice in frontal (F), parietal (P), occipital (O), thalamic (T) and cerebellar (C) areas.

RESULTS

Group 1

Cerebellar Tracer Uptake as a Function of Age. In the neonatal period, tracer uptake was prominent in the cerebellum, while cerebral cortical areas, with the exception of sensorimotor cortex, were poorly visualized. The cerebellum/mean cerebral cortex index was significantly higher than that in young adults ($p < 0.01$) (Fig. 2). Between 2 mo and 15 yr, due to the development of cerebral cortical areas, this index was slightly lower than that in young adults, differences being significant till 5 yr ($p < 0.01$). After 15 yr, this index remained more or less constant. Compared to young adults, no significant difference could be demonstrated, even at an advanced age.

Cerebral Cortical Tracer Uptake as a Function of Age. ***Neonatal Period.*** Forty-six neonates, whose gestational age at the time of SPECT ranged from 33 to 44 wk, were investigated. During this period, tracer uptake was the highest in sensorimotor area and the lowest in frontal cortex (Table 1). Compared to values observed in neonates with a gestational age of 33 to 36 wk, a significant increase was found for parietal cortex/cerebellum index ($p< 0.01$), parietal cortex/thalamus index ($p< 0.01$), occipital cortex/cerebellum index ($p< 0.05$) and occipital cortex/thalamus index ($p< 0.05$) at the gestational age of 39–40 wk. In the 41–44 wk gestational age group, occipital activity still increased compared to the 39–40 wk gestational age group, but not significantly. Tracer uptake in the frontal cortex remained low during the entire neonatal period; no significant increase was observed from 33 to 44 wk of gestational age.

To study the influence of duration of extrauterine life upon rCBF distribution, the neonates studied at a gestational age of 37–38 wk and those investigated at a gesta-

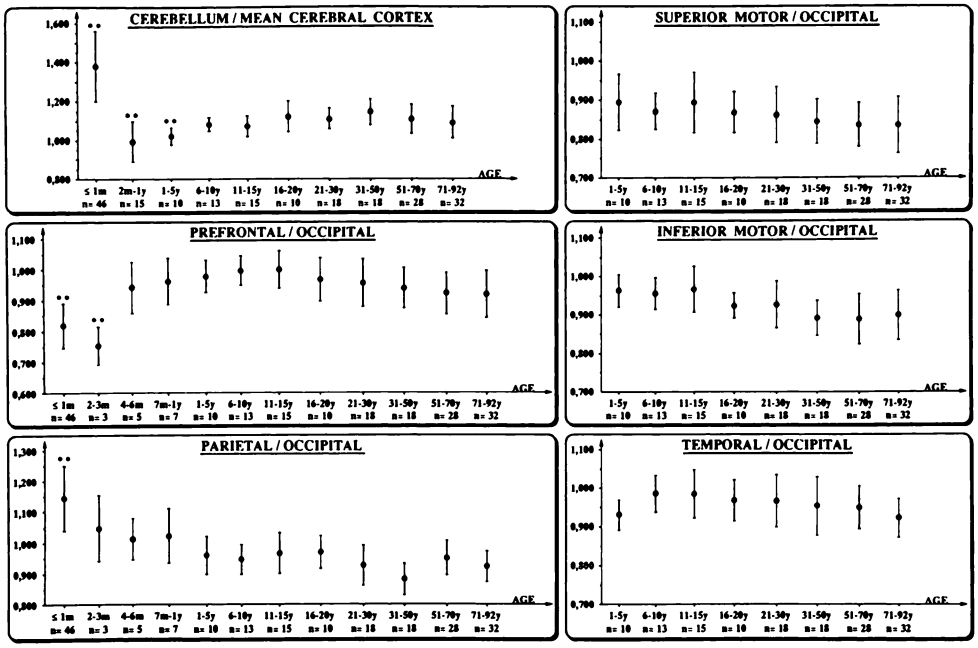

FIGURE 2. Cerebellum/mean cerebral cortex and cortico/occipital indexes (mean ± s.d.) as a function of age (n = number of subjects, m = month, y = year). In each age group, indexes have been compared to values of 21- to 30-yr-old adults with a modified t-test for multiple comparisons, using the Bonferroni method (** = $p < 0.01$).

tional age of 39–40 wk were divided into two subgroups according to their duration of extrauterine life at the time of the SPECT study (in the two other gestational age groups, the number of patients was too small to allow valuable statistical comparison). No significant difference could be found, for any region, between the neonates with a duration of extrauterine life of 4 wk or more and the neonates born 3 wk or less before the SPECT study (Table 2).

Between 2 Months and 1 Year. In this period of life, only 15 patients could be investigated: 3 aged 2 to 3 mo, 5 aged 4 to 6 mo and 7 aged 7 to 12 mo. At 2–3 mo, while the frontal cortex was still poorly visualized, tracer uptake in the occipital cortex had strikingly increased, compared to the parietal cortex. Prefrontal/occipital and parietal/occipital indexes were therefore lower at 2–3 mo than in the neonatal period (Fig. 2). By the age of 4–6 mo, tracer fixation in frontal region was markedly more important and was still slightly higher in the following age group (7–12 mo). In other cerebral cortical areas (motor and temporal cortices), tracer uptake was between frontal and occipital activity (mean ± s.d. of superior motor/occipital, inferior motor/occipital, temporal/occipital indexes, between 2 mo and 1 yr, were respectively: 0.94 ± 0.111, 0.976 ± 0.082, 0.902 ± 0.04).

Between 1 and 15 Years. Compared to occipital activity, tracer uptake continued to increase till the age of 10–15 yr in prefrontal cortex and till the age of 5–10 yr in temporal cortex (Fig. 2). However, changes were slight: whatever the age group, between 1 and 15 yr, prefrontal/occipital and temporal/occipital indexes were not significantly different from those observed in young adults. The three other cortico/occipital indexes remained more or less constant between 1 and 15 yr.

After 15 Years. Compared to occipital tracer uptake, there was a slight tendency after 15 or 20 yr for a relative decline of activity in all other cerebral areas, particularly in prefrontal and motor areas (Fig. 2). Decline due to aging was, however, usually less than interindividual variations. Cortico/occipital indexes in elderly subjects were not significantly different from values observed in young adults.

Group 2

Using the normal criteria established for each age group with Group 1 data, bilateral and symmetrical rCBF anomalies were found in 5/15 neonates with anomalies at neurological examination, electroencephalogram, and/or cra-

TABLE 1
Cortico/Cerebellar and Cortico/Thalamic Indexes (mean ± s.d.) in Neonates (Related to Gestational Age at the Time of the SPECT Study)

Age group	n	F/C	P/C	O/C	F/T	P/T	O/T
<36 wk	8	0.59 ± 0.06	0.73 ± 0.09	0.67 ± 0.06	0.61 ± 0.05	0.76 ± 0.08	0.69 ± 0.05
37–38 wk	14	0.60 ± 0.08	0.82 ± 0.10	0.73 ± 0.13	0.61 ± 0.07	0.84 ± 0.10	0.74 ± 0.11
39–40 wk	17	0.62 ± 0.08	0.90 ± 0.10	0.76 ± 0.08	0.64 ± 0.08	0.93 ± 0.11	0.79 ± 0.09
41–44 wk	7	0.62 ± 0.09	0.90 ± 0.12	0.80 ± 0.13	0.65 ± 0.10	0.94 ± 0.11	0.83 ± 0.12

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

TABLE 2
Cortico/Cerebellar and Cortico/Thalamic Indexes (mean ± s.d.) in Neonates (Related to Duration of Extrauterine Life)

Age group	n	D.E.L.	F/C	P/C	O/C	F/T	P/T	O/T
37–38 wk	6	<4 wk (mean ± s.d.: 2 ± 1)	0.60 ± 0.08	0.83 ± 0.09	0.75 ± 0.13	0.61 ± 0.05	0.84 ± 0.03	0.76 ± 0.09
37–38 wk	8	>3 wk (mean ± s.d.: 5 ± 1)	0.60 ± 0.10	0.82 ± 0.12	0.72 ± 0.14	0.61 ± 0.09	0.84 ± 0.13	0.73 ± 0.14
39–40 wk	10	<4 wk (mean ± s.d.: 1 ± 1)	0.63 ± 0.07	0.89 ± 0.09	0.77 ± 0.06	0.65 ± 0.09	0.94 ± 0.13	0.81 ± 0.10
39–40 wk	7	>3 wk (mean ± s.d.: 6 ± 2)	0.62 ± 0.10	0.92 ± 0.13	0.77 ± 0.10	0.62 ± 0.08	0.92 ± 0.09	0.77 ± 0.06

D.E.L. = duration of extrauterine life. Other definitions as in Table 1.

nial ultrasonography, in 4/9 infants with psychomotor retardation, in 4/11 children suffering from spastic cerebral palsy (3 had severe and 1 had moderate handicap), in 10/41 chronic alcoholics and in 2/10 elderly subjects with severe dementia. In other neurological disorders, bilateral and symmetrical rCBF anomalies were rarely or never observed: CO poisoning (0/4); epilepsy (1/12): learning disabilities (0/14); acute cerebrovascular disorders (2/14); memory impairment (0/8) (Table 3).

Bilateral and symmetrical rCBF anomalies were particularly severe and extensive in chronic alcoholics and in children with severe diplegia or tetraplegia: they usually involved frontal and parietal areas.

Examples of normal ^{99m}Tc-HMPAO SPECT patterns and of symmetrical rCBF anomalies are shown in Figure 3.

DISCUSSION

rCBF SPECT studies are now widely performed because of their convenience and their usefulness in a variety of neurologic disorders of adults and children (*1–5*). rCBF anomalies, when lateralized, can indeed be easily diagnosed by a semi-quantitative right-left analysis of the SPECT study. Bilateral but symmetrical rCBF abnormalities could theoretically be detected by means of antero-posterior analysis using a predefined cerebral area as reference (*6–9*). However, as antero-posterior rCBF distribution could be age-dependent (*10–16*), such analysis requires knowledge of the regional distribution of the tracer in normal subjects of all age groups.

In this work, we retrospectively selected a group of patients with a low probability of having cerebral lesions. Their ^{99m}Tc-HMPAO brain SPECT studies, analyzed semi-quantitatively, were used to approximate normal values of antero-posterior rCBF distribution, as a function of age. No attenuation correction was used, because as the thickness of the cranium changes with age, it would have been necessary to estimate a correcting factor for each age group. In the absence of attenuation correction, thalamic activity in neonates may be significantly underestimated. In other

TABLE 3
Bilateral and Symmetrical rCBF Anamolies in Group 2

		Localisation of rCBF anomalies									
NEUROLOGICAL DISORDERS	*n*	*PF*	*SM*	*IM*	*PA*	*TE*	*OC*	*CE*	*TH*	*Number of patients with anomalies*	
Neonates with anomalies of neurological examination, electroencephalogram or cranial echography	15	1			4		1		2	5	(33 %)
Psychomotor retardation (before 1 year)	9	4	1	1	1	0	0	0		4	(44 %)
Cerebral palsy (after 1 year)	11	2	2	4	4	0	0	0		4	(36 %)
CO intoxication	4	0	0	0	0	0	0	0		0	(0 %)
Epilepsy	12	0	1	0	0	0	0	0		1	(8 %)
Learning disabilities	14	0	0	0	0	0	0	0		0	(0 %)
Acute cerebrovascular disorders	14	1	0	2	1	0	0	0		2	(14 %)
Chronic alcohol abuse	41	6	6	4	5	1	0	1		10	(24 %)
Dementia	10	1	1	1	0	0	0	0		2	(20 %)
Memory impairment	8	0	0	0	0	0	0	0		0	(0 %)
Others	18	1	0	0	0	0	0	0		1	(5 %)
TOTAL	156	16	11	12	15	1	1	1	2	29	(18,5 %)

n = number of patients. PF = prefronial. SM = superior motor. IM = inferior motor. PA = parietal. TE = temporal. OC = occupital. CE = cerebellum. TH = thalamus

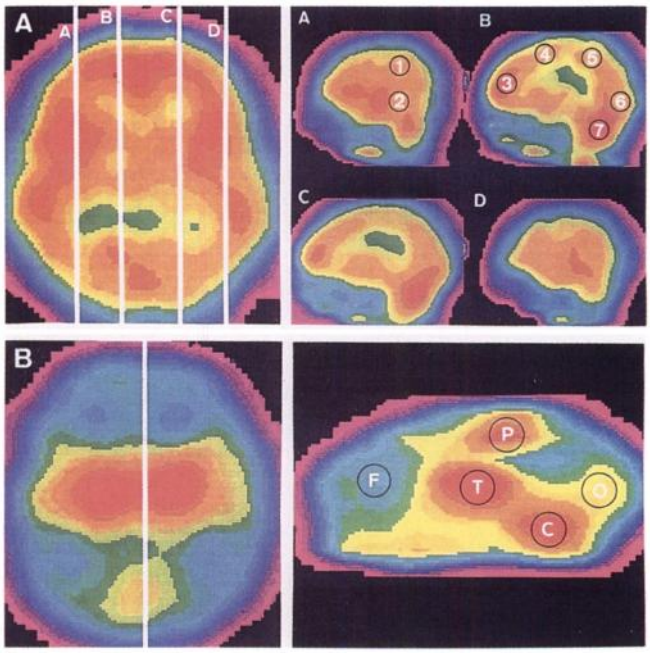

FIGURE 3. Sagittal ^{99m}Tc-HMPAO SPECT images obtained in two adults (A,B) and in two neonates (C,D). (A) A 25-yr-old "normal" adult with important tracer uptake in the cerebellum and in all cerebral cortical areas. (B) A 42-yr-old chronic alcoholic with decreased tracer uptake in the frontal and parietal cortices. (C) A "normal" neonate (gestational age of 40 wk) at the time of the SPECT study has prominent tracer uptake in the thalamic and cerebellar areas, while cerebral cortical regions, with the exception of primary sensorimotor cortex, are poorly visualized. (D) A neonate with diffuse hypotonia studied with SPECT at a gestational age of 42 wk has decreased tracer uptake in the thalamic area and sensorimotor cortex.

age groups, the problem associated with lack of attenuation correction is not so great because the comparisons involved regions of interest in the periphery of the brain.

The cerebellum/mean cerebral cortex index during the neonatal period was significantly higher than that in young adults. This is in agreement with the PET study of Chugani et al., where, when compared to adults, the cerebellum in its central portion (vermis) showed relatively high local cerebral metabolic rates for glucose as early as the fifth day of life, while cerebral cortical areas, with the exception of primary sensorimotor area, had comparatively low regional glucose metabolism (*10*). Between 2 mo and 15 yr, the cerebellum/mean cerebral cortex index was lower than in young adults, suggesting that in childhood the part of the CBF used to cover the metabolic needs of cerebral cortical areas could be proportionally more important. These results, which can probably be explained by the development of cerebral cortical areas during this period of life, also corroborate those of Chugani et al. Using PET, these authors found that, between 1 and 15 yr, cerebral cortical areas as a whole underwent a higher proportional increase in local cerebral metabolic rates for glucose than the cerebellar area (*10*). After 15 yr, the cerebellum/mean cerebral cortex index remained more or less constant, even at an advanced age. These results suggest an almost parallel evolution of cerebellar and cerebral cortical blood flow in adults of all age groups, which differs from results of previous studies, where a more rapid decline of blood flow in cerebral cortical areas than in cerebellum was observed (*13,17*).

For cerebral cortical areas, important changes in their relative activity was observed during the first year of life. During the neonatal period, the most prominent cerebral cortical area was the primary sensorimotor cortex. The remaining cerebral cortical regions, particularly the frontal cortex, had very low tracer uptake. By 2–3 mo, uptake in the occipital region had considerably increased, while frontal areas remained poorly visualized. Frontal activity progressively increased in the following months, and by the age of 1 yr, all cerebral cortical areas had significant tracer uptake. During childhood, tracer uptake continued to increase slightly in frontal and temporal areas. After 15 yr, when compared to occipital activity, there was a trend towards a progressive relative decline of tracer uptake in all other cerebral cortical areas, particularly in prefrontal and motor areas. The changes, however, in rCBF distribution that occurred after 1 yr were minor, as indicated by the absence of significant differences between each cortico/occipital index and the young adults' values.

The sequence of major changes in regional cerebral cortical ^{99m}Tc-HMPAO uptake that we found in the first year of life is similar to what has previously been described in our [^{123}I]IMP SPECT study (*11*) and to the metabolic changes described by Chugani et al. in their PET study (*10*). For the more subtle changes that occurred after 1 yr, there is also a good concordance between our findings and the results of various SPECT and PET studies. In a xenon SPECT study (*12*), it was noted that in children under 5 yr a relatively high level of rCBF was found posteriorly and a relatively low level, anteriorly. In children between 5 and 9 yr, the distribution of rCBF values showed a reversal of the earlier pattern so that relatively greater blood flow was found anteriorly. In the 10–15-yr-old group, this antero-posterior gradient had still increased, to become similar to that of adults. In elderly subjects, several authors have reported a relative preservation of posterior metabolism and blood flow (*13–16*), while Naritomi et al. found a significant reduction of gray matter flow with advancing age in the regional distribution of the middle cerebral artery, when compared with regions in the distribution of other cerebral arteries (*17*).

In our study, the absence of statistical significance in changes of cortico/occipital indexes after the first year, could be explained by the importance of interindividual variation. This great variability, which has also been observed in various SPECT or PET studies (*6–8,13,16,18*), could be due to: differences in the biological state of the patients during tracer administration, external factors (ambient lighting or noise) (*19–21*), or to internal factors (anxiety, intellectual tasks, etc.) (*22,23*) that are known to

influence tracer distribution. It must be noted, moreover, that in a semi-quantitative analysis (as in ^{99m}Tc-HMPAO brain SPECT), the variability is even greater because two variables are taken into account. The fact that the study was carried out on patients rather than on normal subjects undoubtedly also contributed to this variation.

In the present work, abnormal indexes were found in children with motor or mental handicap, in chronic alcoholics, in dementified elderly subjects, in epileptics and in patients with acute cerebrovascular disorders. It must be noted, however, that in children with motor and/or mental handicap, rCBF anomalies were found only in the most severe cases, and that no rCBF change could be demonstrated in elderly subjects with dementia at an early stage. The finding of extensive frontoparietal hypoactivity in chronic alcoholics, even in the absence of dementia, is more surprising. In a ^{99m}Tc-HMPAO SPECT study, Erbas et al. found a similarly high incidence of frontal hypoactivity in chronic alcoholics (*24*). Using PET, in a limited series of six "normal" chronic alcoholics, Sanson et al. also found a selective reduction of glucose metabolism in mediofrontal areas, more pronounced in patients who performed poorly at fine neuropsychological tests (*25*). In patients with epilepsy and in those with acute cerebrovascular disorders, the finding of a symmetrical rCBF anomaly could correspond to bilateral structural lesions or to a structural lesion associated with a functional hypoactivity in the mirror-image area (transhemispheric diaschisis) (*26*).

In summary, we have described normal values of antero-posterior rCBF distribution in ^{99m}Tc-HMPAO SPECT studies. Tracer uptake in the cerebellum and in cerebral cortical areas exhibited considerable evolution during the first years of life. After this period, changes were usually smaller than interindividual variation. Despite the large range of "normal" values, the antero-posterior analysis allowed us to detect rCBF anomalies undiagnosed by the right-left analysis in various neurological disorders.

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