Assessment of cerebral perfusion may elucidate pathogenesis of Landau-Kleffner syndrome (LKS). We obtained \(^{99m}\text{Tc}\)-HMPAO SPECT studies in five children with LKS and in three children with syndromes of verbal-auditory agnosia. In LKS, perfusion showed temporoparietal asymmetry (9.56% ± 3.44%) (n = 4) or bilateral parietal abnormality (n = 1). SPECT in non-LKS patients was normal (n = 1), showed (n = 1) to the hemispheric hypoperfusion accompanying structural abnormality or (n = 1) a pattern resembling but distinct from LKS. Seizures in LKS patients had never occurred (n = 1), were controlled satisfactorily (n = 2), or poorly (n = 2). Maximum EEG abnormality was left centrotemporal-occipital (n = 1), left frontocentral (n = 1), bitemporal/left central (n = 1), and left central/parasagittal (n = 1). Asymmetric temporoparietal perfusion appears characteristic of LKS, differing from findings in other childhood linguistic disturbances. This abnormality occurs across a spectrum of seizure expression, diverging from the distribution of EEG abnormalities. The SPECT abnormalities parallel PET-defined LKS metabolic abnormalities, and may indicate central pathogenetic features of the disorder.


Since the description by Landau and Kleffner in 1957 (1), more than 130 cases of the “syndrome of acquired aphasia with convulsive disorder” have been reported (2). Salient clinical features comprise acquired language disabilities (3), which are primarily comprehensive (4).

EEG abnormalities are invariable, consisting typically of focal and generalized spike-wave discharges, worsening during sleep (5). Although it is uncertain whether these abnormalities should be classified primarily as partial or generalized, pharmacologic response patterns may favor the latter (6). Clinical expression of seizures is not invariable, and their relationship to the evolution and outcome of the disease is not clear, as discussed both in the original and subsequent reports (1,5). EEG spectral and topographic mapping studies (7) found high spectral powers of delta, theta and alpha waves over the fronto-centro-parietal area. These features have been used to suggest electrophysiological dysfunction of the frontocentroparietal areas as a major pathogenetic feature of Landau-Kleffner syndrome (LKS). However, independent corroboration of this hypothesis has not been provided.

There is a well established relationship between physiologic function, energy metabolism and localized blood supply (8). We report the use of \(^{99m}\text{Tc}\)-hexamethylpropyleneamineoxime (HMPAO) single-photon emission computed tomography (SPECT) to assess cerebral perfusion and thereby provide an indirect estimate of brain function in five patients with typical features of LKS, and in three patients with linguistic disorders lacking LKS features.

This study was designed to answer the following questions:

1. What changes in regional cerebral perfusion may be ascertained in a group of patients with clinical and electrographic features of LKS?

\[\text{FIGURE 1. Representative transaxial reconstructed SPECT image from Patient 2. Color bar to left displays the gray scale, with zones of decreasing tracer uptake from top to bottom of the image. There is a relative decrease in cerebral perfusion involving the right temporal and adjacent frontal cortex. Asymmetric perfusion of similar distribution was noted in four other LKS patients.}\]
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Major diagnoses</th>
<th>Seizure type, control</th>
<th>Neuro exam</th>
<th>EEG finding</th>
<th>CT/MRI</th>
<th>Evolution of language disorder</th>
<th>Mean linguistic utterance rating¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.25</td>
<td>M</td>
<td>VAA with episodic discharges</td>
<td>Complex partial, controlled</td>
<td>Nonfocal</td>
<td>Left centro temporal and occipital discharges, increased in sleep.</td>
<td>Normal CT</td>
<td>Autistic features but functioning well in learning disabled public school classroom.</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>8.17</td>
<td>M</td>
<td>VAA with episodic discharges</td>
<td>Complex partial, controlled</td>
<td>Nonfocal</td>
<td>1. Left fronto-central spikes, increased in sleep. 2. Occasional bifrontal bursts of high amplitude delta slowing.</td>
<td>Normal CT, MRI</td>
<td>Normal until 3.5 yr, then lost all language production over 6 mo. Has persistent prosodic and pragmatic defects.</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>8.25</td>
<td>M</td>
<td>VAA with episodic discharges</td>
<td>Complex partial with secondary generalization Poor control</td>
<td>Nonfocal</td>
<td>1. Bilateral temporal discharges, right greater than left. 2. Central high voltage slowing with right mid-temporal slowing in sleep.</td>
<td>Normal CT</td>
<td>Normal until 9 mo. Lost all language production over 3 mo, then showed some recovery but with substantial retardation and autistic features</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>3.17</td>
<td>M</td>
<td>VAA with episodic discharges</td>
<td>Generalized, first episode accompanied by fever Poorly controlled</td>
<td>Nonfocal</td>
<td>1. Normal awake and aslee. 2. Single burst of irregular 2 Hz slow wave with intermitent spikes.</td>
<td>Normal CT, MRI</td>
<td>Loss of all language at approximately 4 mo, following seizures. Poor recovery</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>4.08</td>
<td>M</td>
<td>Higher processing disorder</td>
<td>No history of seizures</td>
<td>Nonfocal</td>
<td>Left central and parasagittal spike discharges in drowsiness and in sleep.</td>
<td>CT Normal</td>
<td>Total loss of language at approximately 2 yr. No recovery with profound comprehension and production deficits</td>
<td>1</td>
</tr>
</tbody>
</table>

VAA = verbal auditory agnosia.
¹ Does not meet DSMIIIR criteria for infantile autism.
² Mean linguistic utterance rating in phonemic units.
TABLE 2
Patients with Verbal-Auditory Agnosia Without Features of LKS

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Major diagnoses</th>
<th>Seizure type, control</th>
<th>Neurologic examination</th>
<th>EEG findings</th>
<th>CT/MRI</th>
<th>Evolution of language disorder</th>
<th>Mean linguistic utterance rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3.5</td>
<td>F</td>
<td>Cerebral dysgeneses, verbal dyspraxia</td>
<td>None</td>
<td>Short stature. No focal abnormality</td>
<td>Normal awake and asleep</td>
<td>MRI: callosal dysgenesis hypomyelination, megalicisterna magna</td>
<td>Has decreased verbal output but comprehends well and uses signs</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>3.5</td>
<td>M</td>
<td>Major language disorder</td>
<td>None</td>
<td>Nonfocal</td>
<td>Normal awake and asleep</td>
<td>MRI normal</td>
<td>Verbal-auditory dyspraxia with autistic features</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>3.6</td>
<td>M</td>
<td>VAA without epileptiform features</td>
<td>None</td>
<td>Nonfocal</td>
<td>Normal sleep record</td>
<td>Not available</td>
<td>Loss of all language at approximately 19 mos. Poor recovery with autistic features</td>
<td>1</td>
</tr>
</tbody>
</table>

VAA = verbal-auditory agnosia.

* Mean linguistic utterance in phonemic units.

† Does not meet DSMIII-R criteria for infantile autism.
2. Do patterns of regional perfusion covary with clinical or electrophysiologic variables?
3. Are regional perfusion patterns in LKS different from those found in other childhood language disorders?

Our findings support the hypothesis that LKS patients show a characteristic pattern of perfusion abnormality, differing from that seen in other forms of developmental dysphasias, and which may be directly related to the pathogenesis of the disorder.

MATERIALS AND METHODS

Patient Population

Relevant clinical and electrophysiologic findings are presented in Tables 1 and 2.

Technetium-99m-HMPAO SPECT

Patients received HMPAO (10.1–12.6 mCi, 200 μCi/kg) intravenously. Following tracer administration, sedation was administered intramuscularly as 0.07 ml/kg of “Demerol Compound,” containing (per ml) Meperidine 25 mg, Chlorpromazine 6.25 mg, and Promethazine 6.25 mg.

Acquisition and reconstruction of images were performed according to the protocol previously described from our laboratory (9). Briefly, studies were obtained using a rotating gamma camera (Orbiter 7500; Siemens Medical Systems, Inc., Hoffman Estates, IL), equipped with a 30-degree slant hole collimator. The system provided transaxial resolution (full width at half maximum) of 14 mm. Tomographic imaging began at 30-60 min following tracer administration (150,000-300,000 counts per frame) and continued for 45–60 min. Image reconstruction and analysis was performed using an ADAC computer system (ADAC Laboratories, San Jose, CA). Iterative backprojection reconstruction and Chang attenuation correction were employed. The “volume image” extended from the cranio-cervical junction to the upper cerebral convexity. Prior to analysis, all images were resliced parallel to the orbitomeatal plane. Axial, coronal and sagittal projections were displayed.

Analysis of HMPAO SPECT Images

Visual. All studies were read independently by three observers (STT, JMM, LOT) blinded to the history and physical findings in each patient. To avoid bias, the studies were randomly selected from a group that included other HMPAO SPECT studies, and the reader was unaware of whether the study was derived from a patient with LKS, or from a child being imaged for some other indication. Images were magnified to a factor of 1.5x, and contiguous slices were grouped in triplets for analysis. To standardize the reading, the upper discriminator threshold was adjusted so as to render pixel values within the cerebellar cortex within the most intense color range of the continuous tone table display. Slices were analyzed to assess symmetry of tracer distribution between homologous neocortical areas in the frontal, parietal, occipital and temporal lobes. Only asymmetries that were evident in both transaxial and coronal images were considered. Perfusion abnormalities were classified as mild, moderate or severe.

Semiquantitative Analysis. Irregular regions of interest (ROIs) were placed to conform with the area of visually defined asymmetry in the temporal lobes, using the coronally reconstructed slice. We conducted the analysis on the coronal slices which allow the most unequivocal display of a cross-sectional volume of the temporal lobe, and allow one to separate its limits clearly from adjacent frontal and parietal regions. To delineate the cortex from the adjacent subcortical regions, pixels with radioactivity values corresponding to the uppermost two levels of the color table were used. For evaluation of the contralateral cortex, irregular regions were placed with comparable configuration and size. The size of the region (mean 37.2 ± 14.32 pixels; or 42 ± 16.18 mm²) varied according to individual anatomy. The uptake of 99mTc-HMPAO within the ROI was expressed as: \( \text{[(Lr-Rt)/Lr] \times 100} \),

where Lr is HMPAO uptake within the temporal ROI placed within the temporal ROI of higher tracer distribution and Rr is HMPAO uptake within the temporal ROI of lower tracer distribution.

RESULTS

Clinicoelectrophysiologic Features for LKS

All subjects were right-handed (latency index >50 by Oldfield criteria) and represented a spectrum of severity for clinical expression of LKS. No evidence of structural brain disorder was found in any patient by either computed tomographic or magnetic resonance imaging. In reaching the diagnosis of LKS, primary hearing loss and mental retardation were excluded as a basis for the child’s linguistic problems. No patient presented features of tuberous sclerosis or other neurocutaneous disorders, fragile X syndrome, phenylketonuria or degenerative disorders, such as Rett’s syndrome, or progressive myoclonus epilepsy. Two children were described as showing “autistic features,” but lacked current diagnostic criteria (10) for a primary autistic disorder. One child never had been noted to have seizures. Seizure control was good in two and poor in two of the remaining patients. The degree of language recovery also was variable. One child showed good recovery (MLU 6 phonemic units), allowing function within a classroom setting for students with learning disability. In the remaining four patients, recovery was more limited within varying degrees. EEG was normal in one and abnormal in four patients.

Patients with Verbal Apraxia, Without LKS Features

See Table 2 for clinicoelectrographic features. Patient 6 was a child with multiple cerebral dysgeneses associated with trisomy 9p. Severe volume loss of the right cerebral hemisphere was identified on MR scanning. This patient had features of verbal apraxia, but lacked clinical or electrographic expression of seizures required for a diagnosis of LKS. Patients 7 and 8 had features of verbal-auditory agnosia, without any aspects to suggest LKS.

SPECT Findings for LKS

Four patients (nos. 1 through 4) showed a basically similar pattern of perfusion abnormality (Table 3). A relative decrease in HMPAO uptake was noted involving the temporoparietal lobes: the zone of relatively decreased perfusion was located within the left hemisphere in Pa-
Patients 1, 3 and 4, and within the right hemisphere in Patient 2. In all cases, the temporal cortex was primarily involved, although the abnormality extended into the adjacent part of the parietal lobe. Within the temporal lobes the abnormality was most evident in the superior and lateral aspects and predominated in the region of the Sylvian fissure. Figure 1 shows a representative image. Patient 5 showed two separate areas of abnormal perfusion asymmetry involving the inferior and posterosuperior aspects of the left and right parietal cortex, respectively.

Semiquantitative Analysis

Semiquantitative analysis supported the visual assessment of radiotracer distribution. In the four cases with visually evident temporal lobe asymmetry, the mean left-right asymmetry of perfusion for regions encompassing the visual abnormality as estimated on the selected coronal slices was 9.56% ± 3.44%, but only amounted to 2.8% in Patient 5, in whom no visual abnormality was apparent in the area of interest.

SPECT Findings in Patients with Verbal Apraxia Without LKS Features

Patient 6 showed a global relative decrease of perfusion throughout the entire right cerebral hemisphere, most marked in the region of the parietal cortex (Table 3). This finding corresponded closely to the abnormality shown in the MR scan. No regional abnormality of hemispheric radiotracer concentration was noted. Patient 7 showed no abnormality of regional cortical perfusion. Patient 8 showed a pattern of relative hypoperfusion involving the left temporoparietal lobe. This abnormality resembled that noted in Patients 1–4, with the exception that there was less selective involvement of the perisylvian cortex.

By using semiquantitative analysis, mean left-right asymmetry of perfusion for regions encompassing the temporal lobes as estimated on coronal slices was 2.89% for Patient 7 and 8.5% for Patient 8. An analysis was not attempted for Patient 6 because of the areas showing marked volume loss.

SPECT Findings Versus Clinical and Electrophysiological Variables for LKS

In Patients 1–4, a relatively consistent pattern of perfusion abnormality occurred across a very heterogeneous spectrum of clinical expression. This heterogeneity extended to all of the salient neurologic features (seizure frequency, presence and distribution of EEG abnormality, and extent of ultimate recovery of language).

DISCUSSION

Our patients present a typical spectrum of expression and severity of LKS (2,11,12).

The validity of the HMPAO SPECT method is well established for estimation of physiologic changes in regional cerebral perfusion (13–15) as well as for assessment of clinical disease characterized by abnormal blood flow (16–19). In this study, we placed major reliance on a subjective visual blinded analysis of the images, rendered according to the clinical experience of experienced nuclear medicine physicians. This technique has been validated in studies of regional perfusion in epilepsy (20).

Our SPECT perfusion findings received limited semiquantitative assessment, since this approach has been suggested as a means of increasing objectivity of the assessment (21). Lassen et al. (22) undertook absolute quantification of brain SPECT HMPAO imaging using kinetic modeling. We did not attempt such an assay in our patients since the requirement for arterial blood sampling seemed prohibitive in children. Consequently, we chose a semiquantitative approach, using each patient’s brain as its own control and using the count rate in selected regions to obtain an estimate of the percentage of asymmetry of perfusion between the cortical areas that had been judged visually abnormal. While the use of square (23) or rectan-
regular (24) regions has the advantage of producing geometrically regular, and symmetrical regions, their use was felt inappropriate to our study images, where the boundaries of the abnormal zone were not linear and showed considerable intersubject variability. The use of the irregular regions allowed us to apply quantitative assessment most accurately to the sections of the image showing visual abnormality.

The semiquantitative analysis of brain perfusion shows a trend that is parallel to the qualitative impression. In ROI sampling sites of visible abnormality, the mean left-right asymmetry of tracer uptake in all the patients showing temporoparietal perfusion differences exceeded by more than three-fold the asymmetry noted for Patient 5. In view of the limitations of quantitative assessment of blood flow with SPECT, which reflect inadequacies of current methods for attenuation and scatter correction (25), our estimate of the magnitude of the left-right asymmetry for temporal lobe perfusion should be regarded as a first approximation. However, we found a mean difference of the order of 8%, and this value is comparable to that reported in SPECT studies of another behavioral disorder of childhood, attention deficit disorder (26).

The distribution of perfusion asymmetry was relatively constant in four of our five LKS patients. The most constant site of asymmetry was in the perisylvian cortex. This area of maximum abnormality was spatially localized, but showed varying degrees of extension into the adjacent temporal, parietal or frontal lobes. The remaining patient (with the most severe linguistic abnormality) failed to show the typical pattern.

The reproducible temporoparietal perfusion abnormality was not entirely specific for the children showing the classical features of the LKS syndrome. Two patients with verbal and verbal-auditory apraxia, but lacking the clinical signature of LKS, failed to show the distinctive regional asymmetry of tracer uptake. However, one child with verbal-auditory agnosia who lacked the clinicoelectrographic criteria for LKS (Patient 8) showed a pattern that was similar to Patients 1–4. The perfusional abnormality in Patient 8 involved the temporoparietal lobe more homogenously and without the predilection for the perisylvian cortex that was noted in LKS. However, this distinction was subtle, especially at our resolution limits, and the findings were otherwise indistinguishable from Patients 1–4. It is not surprising that in Patient 8 the functional image hints at a site of cortical dysfunction similar to that for LKS, where the linguistic abnormalities were so similar. It is possible that the full-blown expression of LKS may later become manifest in this child.

We have found only one previous report of SPECT findings in LKS (27) where it is stated that “SPECT results were normal” in a single patient. The significance of this observation is difficult to assess since the report lacks information as to the radiopharmaceutical used, characteristics of the camera or the criteria for interpretation.

Reports of functional imaging studies in other childhood language disturbances mention perfusion abnormalities differing in varying details from the findings in LKS as defined in this study. In “congenital dysphasia”, Denays et al. (28) described an area of hypoperfusion involving Broca’s area. In a group of children satisfying criteria of “primary progressive aphasia” (29), SPECT with $^{133}$Xe and HMPAO showed unilateral frontotemporal hypoperfusion extending to become bifrontal (30). Lou et al. found symmetric, bilateral perfusion defects, most often involving the central frontal lobes, in children with attention deficit-hyperactivity disorder (31). Further observations from the same group (31,32) described a pattern of striatal and posterior periventricular hypoperfusion with occipital hyperperfusion.

The perfusion changes demonstrated by SPECT cannot be explained merely as a manifestation of the PET (33) and SPECT (34) abnormalities known to be associated with epileptogenic lesions. There was a total lack of correlation between the relatively reproducible perfusion changes and the marked variation in the severity of the clinical and EEG expression of the disorder, as well as in the site of maximum EEG abnormality. In this respect, our findings are consistent with the proposal of Holmes et al. (35) that in LKS abnormalities in the temporal lobe independently cause both seizures and language disorders. The homogeneity of the perfusion abnormality parallels the stereotyped language disturbance which was fluent in all patients. This parallel behavior also suggests that the perfusion abnormalities reflect a central dysfunction.

A $^{18}$fluorodeoxyglucose PET study in three LKS patients showed metabolic abnormalities predominating over the temporal lobes (36). The findings were either of a left-right asymmetry of glucose utilization between, or a bilateral abnormality within the temporal lobes. In two patients, the asymmetry involved the posterior temporal, or anterior temporal-perisylvian areas, respectively. The third child showed bilateral temporal lobe hypometabolism. The anatomic distribution of these findings is highly reminiscent of the perfusion abnormalities in our cases, and provides further evidence that they are "coupled" to metabolic abnormalities, and indicative of central dysfunction.

**Limitations of the Method**

We cannot exclude the possibility that Patients 1–5 may have shown bilateral changes in cerebral perfusion that may not have been detected by our method. However, a detailed hypothesis to relate our findings to linguistic abnormalities of LKS has been developed from the results described above.

The use of sedation is unlikely to have influenced our results, since patients received HMPAO before the administration of medication. Furthermore, changes in brain metabolism that have been attributed to sedation tend to be symmetric, or bilaterally regional, rather than lateralized. Foster et al. (37) observed no change in regional
patterns of glucose utilization after diazepam sedation. Franck et al. (38) found bilaterally symmetric regional changes in metabolism using \(^{18}F\)2-fluoro-2-deoxy-D-glucose PET during Stage III and Stage IV sleep. Heiss et al. (39) noted generalized depression of metabolism during slow-wave sleep.

CONCLUSIONS

In four of five patients with LKS, using HMPAO SPECT, we have defined a consistent pattern of perfusion asymmetry involving the temporal lobes and a maximal pattern in the perisylvian cortex. The different scintigraphic findings in these two patients with verbal apraxia without features of LKS, together with the cited literature review, raise the possibility that our findings may have diagnostic specificity for LKS. The plausibility of this association is increased by the remarkable similarity of our SPECT findings to those reported with PET-defined glucose utilization abnormalities. However, examination of a larger number of children with this characteristic aphasia will be necessary to assess to what extent SPECT findings are distinctive.

The scintigraphic abnormalities described in this study presumably involve neural pathways located within, or associated with, activation of the temporal cortex. HMPAO SPECT may allow further definition of these mechanisms and facilitate early diagnosis, which is essential for effective remediation of LKS and related disorders (40,41).

ACKNOWLEDGMENT

A preliminary account of this work was presented at the 38th Annual Meeting of the Society of Nuclear Medicine, Cincinnati, OH, June 14, 1991.

REFERENCES

37. Foster NL, VanDerSpek AF, Aldrich MS, et al. The effect of diazepam

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**SELF-STUDY TEST**

**Gastrointestinal Nuclear Medicine**

Questions are taken from the *Nuclear Medicine Self-Study Program I*, published by The Society of Nuclear Medicine

**DIRECTIONS**

The following items consist of a heading followed by numbered options related to that heading. Select those options you think are true and those that you think are false. Answers may be found on page 1818.

---

Drugs that typically slow gastric emptying include which of the following?

1. nicotine
2. verapamil
3. isoproterenol
4. levodopa
5. metoclopramide
6. domperidone

---

True statements concerning scintigraphy for detection of Meckel’s diverticulum include which of the following?

16. Pretreatment with cimetidine increases the frequency of false-negative studies.
17. Uterine blood-pool activity occasionally causes false-positive studies.
18. Small bowel duplication is usually distinguishable from Meckel’s diverticulum.
19. Technetium-99m pertechnetate is selectively concentrated in parietal cells of ectopic gastric mucosa.

---

True statements concerning Barrett’s esophagus include which of the following?

7. More than half of patients with Barrett’s esophagus will develop squamous cell cancer of the esophagus.
8. The radiologic appearance on upper gastrointestinal radiography is diagnostic in most patients.
9. In patients with gastroesophageal reflux, an increase in symptoms suggests development of Barrett’s esophagus.
10. Sequential [99mTc] pertechnetate imaging in patients with Barrett’s esophagus is helpful in determining which patients will develop malignancy.

---

True statements regarding Meckel’s diverticula in adults include which of the following?

20. Most are symptomatic.
21. Two-thirds of affected elderly patients present with melena.
22. Technetium-99m pertechnetate imaging has a sensitivity of greater than 80%.

---

True statements concerning scintigraphic evaluation of porto-neovenous shunt patency include which of the following?

11. Because of its low specificity, it is not helpful in most cases.
12. When 99mTc MAA is injected intraperitoneally, non-visualization of the efferent limb of the shunt indicates shunt malfunction.
13. The afferent portion of the shunt is the most frequent site of shunt malfunction.
15. Direct puncture of the efferent limb of the shunt occasionally is necessary to precisely locate the site of malfunction.

---

True statements concerning blood cell labeling techniques with 99mTc include which of the following?

23. When the modified in vivo (“in vitro”) method is used, heparin rather than acid citrate dextrose (ACD) is preferred as the anticoagulant.
24. Stanus pyrophosphate and 99mTc should be injected through the same indwelling catheter when either the in vivo or the modified in vivo technique is used.
25. The bladder is the organ receiving the highest radiation exposure when the in vivo method of red blood cell labeling is used.
26. Technetium-99m binds predominantly to the red blood cell membrane.