Hypometabolic Cortical Lesions in Tuberous Sclerosis with Epilepsy: Demonstration by Positron Emission Tomography

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Abstract: Four patients with a well-established diagnosis of tuberous sclerosis and grand mal type epileptic seizures as their principal clinical symptom were examined by conventional surface electroencephalography (EEG), X-ray computed tomography, and positron emission tomography (PET) using the [¹⁸F]-2-fluoro-2-deoxyglucose method. The interictal EEG showed various abnormalities of poor localizing value, but no focal epileptic discharges. X-ray computed tomography demonstrated subependymal calcifications in all cases, although cortical lesions were found only twice. However, in the PET images of each patient one or two localized cortical foci with a metabolic rate for glucose more than 40% lower than in the respective contralateral region were clearly delineated. It may be assumed that those hypometabolic areas represent the epileptogenic cortical tubers, which are characteristic of the disease but usually cannot be detected *in vivo* by other methods. Index Terms: Epilepsy—Tuberous sclerosis—Cerebral metabolism—Emission computed tomography.

Diagnosis of tuberous sclerosis (TS, Bourneville-Pringle disease) is easily established if the typical triad—adenoma sebaceum, mental deficiency, and epileptic seizures (1)—is present. However, in formes frustes typical skin lesions are often missing (2-6) and further diagnostic procedures must be performed to demonstrate characteristic focal alterations of the brain tissue presenting as cortical tubers and calcified subependymal nodules (7). In X-ray computed tomography (XCT) the latter calcifications—if visible at all—are most conspicuous. Frequently, they cannot be detected despite typical clinical symptoms including seizures (8), although they may be found in some relatives of TS patients not showing any of the typical manifestations of the disease (5.9). The cortical tubers, however, which gave the disease its name, usually are of normal density in XCT and can be seen only in the few cases in which they are calcified (10). These tubers probably represent the epileptogenic foci characteristic of TS and, therefore, their detection may not only be of diagnostic value but also guide therapy, e.g., towards surgical removal of the lesion.

According to Kuhl et al. (11) and Engel et al. (12,13), epileptogenic foci can be detected by positron emission tomography (PET) because those pathological brain regions usually exhibit a decreased uptake of [¹⁸F]-2-fluoro-2-deoxyglucose (FDG) in the interictal state. The present study was performed to investigate the incidence of such hypometabolic cortical lesions in patients with TS presenting with epileptic seizures as their principal clinical symptom.

MATERIALS AND METHODS

Four patients with firmly established TS were examined by PET. In each case diagnosis was based on a typical history, clinical examination, XCT (Siemens Somatom 2000, GE CT/T 8800), and conventional mono- and bipolar surface electroencephalographic (EEG) recordings with electrodes placed according to the international 10/20 system. The routine described by Reivich et al. (14) and Phelps (15) was used to measure local cerebral metabolic

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rate of glucose (LCMRGI): approximately 5 mCi of FDG was injected intravenously, and arterialized blood was sampled from the vein of a heated hand at successively increasing intervals, from the time of injection to the end of the recording period. Plasma FDG and glucose concentrations were determined and entered into the memory of the computer (VAX 11/780, DEC) connected with the tomographic device. Cross-sectional positron images of the brain were obtained with a four-ring/seven slice system (Positron Camera PC 384-7B, Scanditronix) designed by Eriksson et al. (16) starting 30 min after FDG injection. This device has a spatial resolution of 8 mm FWHM in 13 mm slices. The FDG activity in the brain was first recorded for 10 min with the lowest ring positioned in the canthomeatal (CM) plane, yielding further tomograms at 13.5, 27, 40.5, 54, 67.5, and 81 mm above the CM line. Subsequently, for another 10 min run, the patient's head was moved 7 to 20 mm out of the gantry to obtain the activity distribution in sections centered between the first set of parallel planes. That way the entire brain was scanned.

From the local cerebral concentration of ¹⁸F and the plasma concentration curve of FDG, the LCMRGI was calculated according to the equation derived by Sokoloff et al. (17), using the average values of rate constants and the lumped constant given by Phelps (15). The implemented software permitted display of metabolic maps in units of µmol glucose/100 g/min, or the extraction of average LCMRGI values from selected cortical regions of interest (ranging in size between 1.9 and 18.0 cm² in the plane of section). To minimize interindividual variability the metabolic rates of visually suspect regions were compared with those of corresponding contralateral areas and a metabolic index (MI) = LCMRGI suspect/LCMRGI contralateral was computed for each pair.

CASE REPORTS

Case 1

A 9-year-old girl developed episodes of motor agitation during sleep at the age of 7: She cried and struggled with her arms and legs. Then, breathing heavily, she usually became stiff all over. During these seizures no tongue bite or wetting ever occurred. Over the next year, frequency and duration of episodes increased and often series of seizures were observed during a single night and occasionally also during the day. Therefore, anticonvulsant medication was initiated and the epileptic manifestations ceased. When the child was referred to the neurological hospital for clinical evaluation, she complained about impairment of concentration and memory, loss of performance at school, and behavioral disturbances. No heritable diseases were reported in the family.

Clinical findings included adenoma sebaceum, shagreen patches on the trunk, depigmented nevi on the legs. There were no focal neurological signs or mental retardation. The EEG revealed bilateral temporal theta-delta slowing. The XCT demonstrated ventricular dilatation and multiple calcifications in the ventricular walls (Fig. 1a). The PET showed focal hypometabolism in the left frontal cortex (Fig. 1b).

Case 2

A 28-year-old woman was known to have suffered from sudden loss of consciousness and muscle tone at an average attack rate of one every month from early childhood to the age of 16. These episodes, lasting from seconds to minutes, were taken as manifestations of a circulatory insufficiency, and the patient was not seen by a neurologist until she was 28 years old. At that time she was referred to the neurological hospital because of a single grand mal type epileptic seizure. Four years earlier a benign renal hamartoma had been diagnosed, which over the following 3 years had turned into a lipoangioleiomyosarcoma necessitating nephrectomy. Highly vascularized tumors of the other kidney also were described. One year after her first neurological hospitalization, pulmonary cystic myomatosis caused pneumothorax on two occasions. There was no family history of heritable diseases.

Clinical findings included adenoma sebaceum, shagreen patches in the dorsolumbar region, depigmented nevi on both thighs, mild focal neurologic disturbances on the right side, but no mental retardation. The EEG revealed intermittent left precentrotemporal theta slowing, and, following provocation by sleep withdrawal, marked left precentrotemporal dysrhythmia. The XCT demonstrated some frontal cortical and cerebellar atrophy, subependymal calcifications localized in the walls of the body of the lateral ventricles near the foramen of Monro, and blurred areas of slightly reduced density in the right temporal white matter. The PET showed focal hypometabolism in the left parietal cortex.

Case 3

A 22-year-old man, who had been delivered by forceps, suffered his first grand mal seizure at the age of 16, at which time drug treatment was started. Two years later, during a change of anticonvulsant medication, a series of epileptic seizures occurred. At that time an interictal EEG showed a right temporoparietal theta-delta focus with sharp and slow waves. A right carotid angiogram was normal, although a pneumoencephalogram demonstrated dilatation of the lateral ventricles, more marked on the left side. The XCT revealed a hypodense area in the right frontotemporal region. After 2 more years and another series of epileptic seizures, the diagnosis of TS was established. The patient's father had died of kidney failure due to a fibroleiomyosarcoma at the age of 38.

Clinical findings included adenoma sebaceum, but no neurologic or mental deficits. The EEG revealed a right temporoparietal theta-delta focus without epileptic potentials. The XCT demonstrated multiple subependymal periventricular calcified nodule, calcifications in the right frontal subcortical white matter and in the interhemispheric fissure an irregular, patchy area of mixed density in the left frontoparietal cortex and adjacent white matter (Fig. 2a). The PET showed hypometabolic foci in the right frontal and left frontoparietal cortex (Fig. 2b).

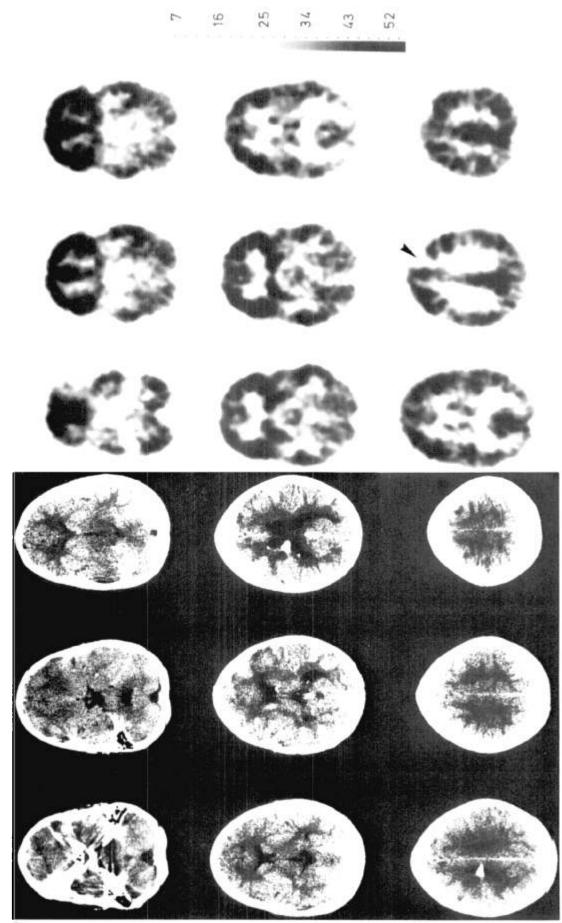


FIG. 1. a: XCTs of Case 1 from 13 to 67 mm above the canthomeatal plane show ventric- pcular dilatation and multiple nodular calcifications, the largest one in the body of the right relateral ventricle. b. Corresponding PET images of Case 1 show a clearly delineated hy-

pometabolic focus in the left frontal cortex (arrowhead, slice No. 8). Metabolic rates (see reference grey scale) are given in μ mol·100 g/min.

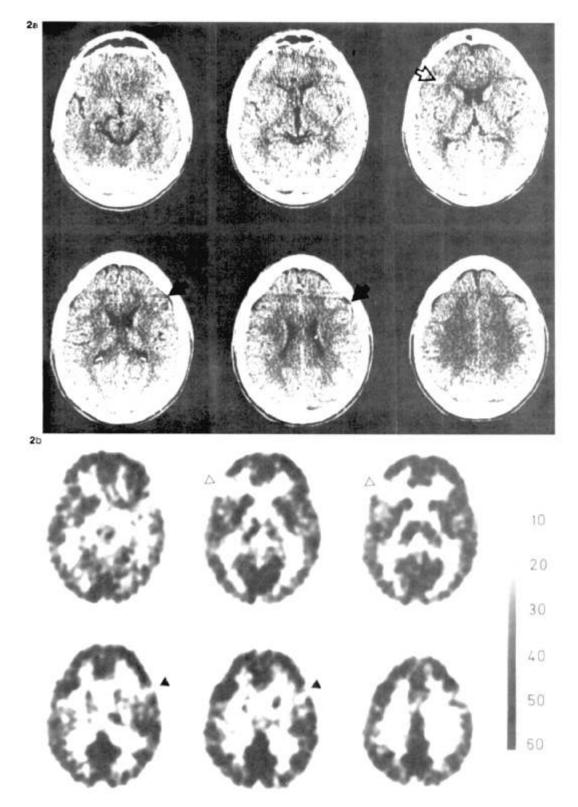


FIG. 2. a: XCTs of Case 3 from 20 to 54 mm above the canthomeatal plane show multiple subependymal calcifications, a calcified nodule in the right frontal subcortical white matter (open arrow), calcifications in the anterior interhemispheric fissure, and an irregular, patchy area of mixed density (partially calcified?), in the left frontal lobe (solid arrows). b: Corresponding PET images of Case 3 show a large hypometabolic area in the right frontal cortex (open arrowhead) and a smaller one in the left frontoparietal cortex (solid arrowhead). Metabolic rates (see reference grey scale) are given in μmol 100 g min.

Case 4

A 38-year-old man had been operated on for an aneurysm of the right anterior cerebral artery after his first generalized epileptic seizure at the age of 4½. Fourteen years later, when repeated seizures occurred, antiepileptic medication was started. A pneumoencephalogram at that time showed a dilatation of the right lateral ventricle due to postsurgical atrophy. At 22 years the patient noticed nodular lesions in his face and in the nail bed of his fingers. Histological examination led to the dermatological diagnosis of Pringle disease. After a series of epileptic seizures at the age of 33, the patient was admitted to the neurological hospital.

Clinical findings included an adenoma sebaceum, Koenen tumors of the nails, depigmented nevi, and café-aulait spots, but no neurological or mental deficits. The EEG revealed severe generalized paroxysmal dysrhythmia and a right temporal theta-delta focus. The XCT showed dilatation of the lateral ventricles, more marked on the right side, as well as two calcified nodules close to the body of the lateral ventricles.

Five years later a clinical reexamination because of repeated seizures failed to show any changes. The EEG revealed theta-delta dysrhythmia over the left hemisphere intensified by hyperventilation. The XCT showed ventricular dilatation, more marked on the right side; calcifications in the lateral walls of both lateral ventricles; and localized right frontal atrophy following aneurysm surgery. The PET demonstrated hypometabolic areas in the right frontal and left parieto-occipital cortex.

RESULTS

Pertinent data on the four patients are summarized in Table 1. At the time of the PET study the interictal surface EEG showed various uncharacteristic abnormalities, including slow wave activity of variable degree and dysrhythmic changes in all four patients. However, no typical epi' ic discharges were recorded and the observed are malities were of poor localizing value. Previous attempts to demonstrate an epileptic EEG focus in the drug-free interictal state had equally failed in all but one patient (Case 3).

In each case XCT showed the characteristic lesions of TS (3,6,10,18-21). Multiple calcified nodular lesions adjacent to the ependyma of the body and the frontal horns (Cases 1 and 3) or in the subcortical white matter (Case 3) were found. Only one patient (Case 3) exhibited a partially calcified cortical lesion. Furthermore, XCT revealed dilatation of the ventricles in Cases 1 and 4, and cortical atrophy and an area of lower density in the temporal white matter in Case 2.

In each of the four patients at least one localized cortical area of markedly decreased glucose metabolism could be demonstrated by PET. All regions with metabolic indices of less than 0.6 were located in the frontal (Fig. 1) or parietal cortex. Only three of them showed some correspondence with a lesion

visible in XCT: the left frontoparietal cortical area of mixed density in Case 3 (Fig. 2) appeared smaller than the hypometabolic area in the PET image, and the same patient's right frontolateral hypometabolic focus was exactly superimposed on a subcortical nodular calcification. A frontal hypodense area in the XCT of Case 4 probably corresponded with scar formation following surgery; PET determination of glucose metabolism in this area gave an MI of 0.52.

DISCUSSION

Interictal PET with FDG demonstrated one or two hypometabolic cortical foci in all of our patients with TS in whom epileptic seizures were the principal symptom. These abnormalities were rather conspicuous although XCT revealed normal cortical structures in all hypometabolic areas except one, in which a calcified cortical tuber corresponding to a previously documented epileptic focus in EEG was found, and another, in which a tissue lesion was demonstrated as a sequel of surgery. All hypometabolic foci were clearly delineated and could easily be identified by visual inspection of the tomographic images. This quantitative approach was substantiated by qualitative evaluation: in all pathological areas side-to-side differences of LCMRGI exceeded 40%, whereas for normal cortical regions an average difference of 6.5% and a maximum value of 18.7% were found (Table 2).

All the described hypometabolic areas were located in the frontal or parietal cortex, the most common site of cortical tubers in TS (7). Those tubers exhibit a disorganization of the cortical architecture with a marked decrease in the overall density of cells, which are extremely variable in size and shape, often appearing as glial monster cells with astrocytic features (22). Consequently, the total number of neurons consuming significantly more energy than glial cells is markedly reduced compared with the surrounding normal cortical areas, which may largely explain the observed focal hypometabolism. Furthermore, neuronal activity may also be reduced by abnormal neuroglial junctions suggesting aberrant synapse formations as observed in cortical tubers (23). These peculiarities of defective cortical development in TS form the morphological basis of epileptogenic foci, often characterized by loss of neurons, glial proliferation, and abnormalities in the dendritic and synaptic structures (24).

From the above characteristics of cortical tubers it follows that both altered morphology and depression of functional activity may give rise to those changes in metabolism which manifest themselves as hypometabolic lesions in the interictal PET. It is this combination of possible causes that may explain why morphological changes either are not vis-

TABLE 1. Summary of patient data

| | | PET | | |
|----------------------|---|--|--------------------|--|
| Case age (years) sex | Manifestations of tuberous sclerosis | Localization of hypometabolic cortical focus | Metabolic index | Average metabolic rate in contralateral cortical region (µmol 100 g min |
| 19 F | Grand mal epilepsy, skin lesions | Left frontal | 0.32 | 37.6 |
| 2 20 F | Grand mal epilepsy, mild focal neurological signs on the right, skin lesions, kidney tumors, pulmonary cystic myomatosis | Left parietal | 0,59 | 25.5 |
| 3 22 M | Grand mal epilepsy, skin lesions | Right fronto- lateral | 0.44 | 43.8 |
| | | Left fronto- parietal | 0.30 | 36.6 |
| 4 38 M | Grand mal epilepsy, skin lesions | Right frontal Left parieto- occipital | 0.52 0.56 | 32.1 27.2 |
| | | XCT | | , |
| Case age (years) sex | Abnormality corresponding to cortical PET focus | Other abnormalities | | Interictal EEG abnormalities |
| 19 F | _ | Ventricular dilatation, multiple nodular subependymal cal- cifications and areas of lower density | | Bilateral temporal theta-delta slowing |
| 2 20 F | | Frontal basal cerebral cortical and cerebellar atrophy, two nodular subependymal calcifications, right temporal white matter area of lower density | | Marked left precentral temporal dysrhythmia following provocation by sleep withdrawal |
| 3 22 M | Nodular calcification in frontal white matter adjacent to PET focus | Multiple nodular calcifications around the ventricles and in the interhemispheric fissure | e | Right temporoparietal theta-delta focus |
| | Area of lower density and small irregular ring of calcification in cortex and adjacent white matter | | | _ |
| 4 38 M | Postsurgery defect and localized cortical atrophy | Internal hydrocephalus and bilateral nodular subependymal cal- cification at the level of the body of the lateral ventricles | | Left hemispheric theta- delta dysrhythmia in- tensified by hyperventilation |

ible in XCT or are much smaller in size than in PET. The latter observation is in good agreement with findings of Engel et al., who noticed in 19 of 22 cases of temporal lobe epilepsy with focal histopathologic lesions that the zone of hypometabolism usually was much larger than the actual lesion area

even if artifactual influences, e.g., partial volume effects, were considered (13).

Determination of absolute values of LCMRGI was restricted to obviously normal cortical regions, since it depends on a variety of assumptions as to the value of rate constants and the lumped constant

| Case no. | Metabolic rate for glucose in normal cortical regions of right cerebral hemisphere (mean ± SD) | Metabolic rate for glucose in normal cortical regions of left cerebral hemisphere (mean ± SD) | Side-to-side differences of the metabolic rate in corresponding regions of normal cerebral cortex (% of larger value, mean ± SD) |
|----------|--|---|--|
| 1 | 37.1 ± 6.36 | 38.0 ± 6.25 | 5.3 ± 3.33 |
| 2 | 25.9 ± 2.72 | 25.0 ± 2.49 | 6.8 ± 3.60 |
| 3 | 36.6 ± 3.44 | 36.7 ± 3.91 | 5.6 ± 3.43 |
| 4 | 28.7 ± 3.90 | 30.6 ± 3.90 | 8.2 ± 5.87 |
| Total | 32.7 ± 6.09 | 33.2 ± 6.14 | 6.5 ± 4.41 |

TABLE 2. Comparison of cortical glucose utilization in the two hemispheres

(14,15,25). According to Hawkins et al., the rate constants are different in pathological tissue (26), and the same may be true for the lumped constant (27). However, if regional rate constants were determined by dynamic PET in pathological and normal areas (28), no significantly different results were encountered.

As demonstrated by Kuhl et al. (11) and Engel et al. (12.13), epileptogenic lesions that may be suited for surgical removal can be identified as hypometabolic areas by PET using the FDG method. Results from the present study indicate that this technique is useful also in the detection of cortical tubers, which are a likely cause of seizures in patients with TS. Moreover, those tubers may slowly increase in size. Their metabolic activity corresponds to that determined in low-grade astrocytomas (22 $\pm \mu$ mol/100 g/min) (29). Their early detection would, therefore, serve two purposes: the long-term follow-up of potentially malignant tumorous cortical lesions and the detection of epileptogenic foci that can successfully be treated by surgery. In a study reported by Perot et al. (30) excision of cortical tubers cured epilepsy in three of six TS patients, and substantially reduced the seizure rate in the other cases. Removal of a calcified subependymal nodule, on the other hand, did not result in any improvement.

In conclusion it would appear that PET examinations of TS not only are of great value for the understanding of the pathogenesis of symptomatic epilepsy, but also can provide a better rationale for medical or surgical therapy, prognosis, and genetic counseling, particularly in the formes frustes of the disease.

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