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Focal abnormalities detected by ^{18}FDG PET in epileptic encephalopathies

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Abstract

A prospective study of 32 children with epileptic encephalopathies 12 years or younger revealed a high incidence of focal cortical metabolic defects on 18-fluorodeoxyglucose positron emission tomography (PET) not suspected from clinical, EEG, or magnetic resonance imaging findings. PET scans were normal in all five children with typical de novo Lennox-Gastaut syndrome but showed cortical metabolic abnormalities in three out of four with atypical de novo Lennox-Gastaut syndrome, five out of six with Lennox-Gastaut syndrome following infantile spasms, six out of eight with severe myoclonic epilepsy in infancy, one out of two with epilepsy with myoclonic-astatic seizures, and four out of six with an unclassified epileptic encephalopathy. This suggests that some children with epileptic encephalopathies previously thought to have primary generalised seizures or seizures due to multifocal pathology may have unifocal cortical origin for their seizures. Such an origin may be amenable to surgery.

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The term 'epileptic encephalopathy' encompasses various severe childhood epilepsies characterised by multiple seizure types and diffusely slow EEG with generalised or multifocal paroxysmal abnormalities. Psychomotor delay with onset preceding or following the onset of seizures is usual.[1 2] The best known of these conditions are West's and the Lennox-Gastaut syndromes (International League Against Epilepsy code 2.2).[3] Others include epilepsy with myoclonic-astatic seizures (2.2) and severe myoclonic epilepsy in infancy (3.2).[3] Their intractable nature, associated developmental problems, and frequent need for residential schooling makes them important conditions both to paediatric neurologists and to general and community paediatricians. Current medical treatment is usually disappointing and has prompted renewed interest in the role of surgical treatment not only for control of seizures but possibly also to improve neurodevelopmental outcome.[4] Seizures in the epileptic encephalopathies are usually considered to be primary generalised, arising from a cortex with diffuse or multifocal abnormalities. Despite this, cases are described in patients with readily detectable localised brain lesions including tumours, porencephalic cysts, and severe migrational anomalies such as pachygyrias.[5]

Seizures are associated with pronounced changes in the metabolism of substrates such as glucose. In partial epilepsies focal reduction (hypometabolism) and increase in glucose consumption (hypermetabolism) in the epileptogenic zone is characteristic of the interictal and ictal states respectively.[6] This can be detected by positron emission tomography (PET) using 18-fluorodeoxyglucose (FDG), a radionucleotide labelled analogue of glucose. Recently FDG PET studies have contributed to the detection of subtle localised abnormalities of neuronal migration in children with certain epileptic encephalopathies with apparently generalised seizures.[7–15] In patients with infantile spasms this has lead to cortical resections with excellent seizure control and improved development.[12–14]

However, these studies used broad definitions, particularly of the Lennox-Gastaut syndrome, and often included patients with clinical, EEG, or structural neuroimaging evidence strongly indicative of focal brain pathology, making the contribution of PET unclear. In earlier studies computer assisted tomography rather than magnetic resonance imaging (MRI) scans was often used, and even when MRI was employed, it is not clear if the technical specifications were sufficient to allow detection of subtle abnormalities. In this study we aimed to establish whether FDG PET detects focal abnormalities in children with epileptic encephalopathies in whom this is not clear from clinical examination, EEG, or high resolution MRI studies, and whether there are syndrome related differences in the PET findings.

Methods

Children of 1 to 12 years of age with an epileptic encephalopathy of unknown aetiology were

studied prospectively. Treatment with at least three major anticonvulsants had failed in all and they were considered potential candidates for surgery. Epileptic encephalopathy was defined as the occurrence of mixed generalised seizures (tonic, atonic, myoclonic, atypical absence, generalised tonic-clonic) with, in the fully evolved syndrome, a diffusely slow EEG with generalised or multifocal interictal paroxysmal abnormalities and (if recorded) generalised ictal abnormalities. Patients with seizures which were difficult to classify but which did not have localising or lateralising value and those with ictal symptoms of uncertain localising value—such as eye deviation during generalised seizures—were included provided other typical seizures were also present. Patients with 'soft' or equivocal focal neurological signs were eligible.

Patients with seizures with localising value were excluded except if they occurred before the onset of infantile spasms or in those classified as severe myoclonic epilepsy in infancy in whom focal ictal symptoms are characteristic.[3] Patients whose EEG showed consistent asymmetries or focal abnormalities were excluded, as were those with clear focal neurological deficits and those in whom previous neuroimaging showed focal abnormalities or other abnormalities likely to preclude surgery. Specific metabolic conditions were excluded by measurement of plasma biotinidase, lactate, pyruvate, ammonia and amino acids, urine organic acids, cerebrospinal fluid (CSF) lactate, pyruvate, and glycine, the CSF:blood glucose ratio (for glucose carrier protein deficiency),[16] and by a trial of oral pyridoxine.

A detailed clinical review, examination findings, and EEG including sleep and video recordings was used to classify patients syndromically according to recommendations of the International League Against Epilepsy supplemented by those of leading authorities.[1-3 17-22] Additionally, patients were divided according to whether they were typical or atypical of the particular syndrome. Features leading to a designation as atypical included onset of seizures outside the age limits considered normal for the syndrome, clinical signs (for example, equivocal plantar responses, non-sustained ankle clonus, or brief postictal Todd's paresis), or ictal symptoms (for example, eye deviations, limb posturing) of 'soft' localising value, or the presence of unclassified seizures without localising features. Classification was blind to both MRI and PET findings.

All patients underwent MRI (Phillips Gyroscan ACS 1.5T) with 6 mm thick axial proton density and T2 weighted spin echo images of the whole head and 3 mm thick fast spin echo images and 4 mm thick T1 weighted coronal images orthogonal to the temporal lobes. In patients without focal MRI findings or abnormalities which would preclude surgery, FDG PET (Siemens ECAT 951R PET scanner) with EEG monitoring during radiotracer uptake was performed. Patients were fasted for four hours before injection of 3.6 MBq/kg FDG. During radiotracer uptake lights were dimmed and interactions with the child discouraged. Intravenous diazepam was given to patients with frequent paroxysmal EEG activity before or during the first 10 minutes of FDG uptake, and also to agitated patients. Patients were scanned after 30 minutes of FDG uptake, using a head holder to minimise movement. Six 5 minute consecutive frames were acquired with the data summed. Frames with excessive movement were discarded. Following correction for attenuation, images were smoothed and reconstructed to give 31, 3.4 mm thick planes with an in plane spatial resolution of 8 mm and a total axial field of view of 10.4 cm. The images were reconstructed in axial and coronal planes and in the plane parallel to the long axis of the temporal lobes.

MRI and PET images were inspected visually blind to the clinical information and to each other. Semiquantitative analysis of PET data was performed using a template of multiple 4 mm diameter circular regions of interest (ROI) placed in selected areas chosen by matching PET planes to an anatomical brain atlas. ROI were placed on anatomical grounds rather than on functional imaging findings; thus areas of apparent increased or decreased FDG uptake were not preferentially selected. Frontal, parietal, occipital, medial, and lateral temporal and cerebellar cortices as well as lentiform and caudate nuclei, thalami, mid-brain, and pons were sampled. Control PET data for normal children is lacking for ethical reasons. FDG PET studies in adults with partial seizures suggest an asymmetry of 15% or more in homologous cortical regions is abnormal.[23] Studies in children show important regional changes during development but did not suggest greater side to side asymmetries.[24] We used an asymmetry of greater than 15% to define unequivocal abnormality. Detection of bilateral and diffuse abnormalities on semiquantitative analysis is difficult. We report it only when obvious on visual inspection. Close observation of the patient and the EEG recorded during radiotracer uptake was used to classify scans as ictal (paroxysmal EEG activity generally acknowledged as ictal with or without clinical events) or as interictal (no ictal-type paroxysmal EEG activity and no clinical events).[25] A degree of uncertainty must exist with such classification, given the inherent difficulty of clearly designating some patterns—such as bursts of spike and wave—as being ictal or interictal.[25] When such abnormalities were unaccompanied by clinical events they were considered as probably interictal.

Results

Thirty five patients were recruited to the study but two were excluded before PET because of multiple cortical abnormalities on MRI. An additional patient did not proceed to MRI as seizures came under control. The median age of onset of seizures in the remaining 32 patients was 11.5 months (range 3 weeks to 7 years); 18 were boys. The median age at PET study was 9 years (range 2 to 12). Unilateral areas of abnormal cortical metabolism were

seen in 12 patients and bilateral or diffuse hypometabolism in five. Scans were considered normal in 15 patients. Table 1 gives the syndromic diagnosis of the patients along with the frequency of PET abnormalities in each. Unilateral focal PET abnormalities involved the temporal lobes only (five cases) (see fig 1), or included the frontal and/or parietal and/or occipital lobes (six cases). After integration of uptake EEG and PET findings, one of these scans was designated as ictal showing focal hypermetabolism. The others were designated as interictal or predominantly interictal and showed hypometabolic focal abnormalities. Bitemporal hypometabolism occurred in two patients (asymmetrical in one). In three patients diffuse, bilateral hypometabolism was seen, in each case being maximal on the right.

By definition no patients had definite focal abnormalities on MRI. However, five patients with focal metabolic defects had minor asymmetries, but no signal abnormalities, in the temporal lobes. These were congruent with PET findings in only three patients. Eleven patients had seizures with 'soft'— or in those with severe myoclonic epilepsy in infancy, definite—focal features or had equivocal focal neurological findings. Congruent unifocal or bilateral but asymmetrical PET abnormalities were seen in six of these 11 patients. None had abnormalities on the opposite side ($p < 0.05$). Eight patients had unclassified seizures. Seven of these had abnormal PET scans with unifocal or bilateral metabolic defects ($p < 0.05$). Four out of eight patients with severe myoclonic epilepsy in infancy had lateralised seizures. One had contralateral temporal lobe hypometabolism. Two others had asymmetrical temporal lobe FDG uptake, lower on the contralateral side. In both cases the side to side difference was 13%, just lower than that required for significance. The fourth patient had predominantly but not exclusively left sided clonic seizures. PET showed bilateral temporal lobe hypometabolism with suggestive asymmetry. Sixteen patients had either equivocal focal neurological findings, focal ictal features, or unclassified seizures. Eleven of these had normal scans ($p > 0.05$).

Clear syndrome related differences in PET findings were seen (table 1). No patient (out of five) with typical de novo Lennox-Gastaut syndrome had focal cortical metabolic abnormalities, compared with three of four with atypical de novo Lennox-Gastaut syndrome ($p < 0.05$, Fisher's exact test). PET abnormalities were seen in all the other syndromes investigated, with no significant differences between those classified as typical and atypical. No syndrome related differences in the sites of focal metabolic abnormalities was seen but on visual inspection they generally appeared to be more extensive in those with Lennox-Gastaut syndrome secondary to infantile spasms than in the other syndromes.

Discussion

This study significantly extends that of previous reports of FDG PET in patients with epileptic encephalopathies. It reports relatively frequent focal cortical abnormalities in patients in whom clinical features, EEG, and high quality MRI found either no suggestion of focal pathology or only equivocal findings. Re-examining MRI scans in the knowledge of PET findings did not improve detection. It also used a strict syndromic approach using the International League Against Epilepsy classification and found significant syndrome based variations in the occurrence of cortical metabolic defects.

It is possible that newer techniques employing T1 volume acquisition and 3D rendering would have detected more abnormalities.[26] However, pathological studies suggest that abnormalities involving neuronal misalignments—'cerebral microdysgenesis'—rather than neuronal loss and gliosis are associated with the epileptic encephalopathies.[27–31] This is probably not detectable by any current structural imaging technique.

The patients we studied lacked clinical, EEG, or neuroimaging evidence of focal cerebral pathology. However, 'soft' ictal symptoms or clinical signs were permitted and in those with severe myoclonic epilepsy in infancy clear ictal focal features were allowed, as these had not previously been shown to have localising value. These were not always associated with definite cortical abnormalities but when they were there was significant congruence between the site of the metabolic defect and contralateral clinical manifestations. Seizures which were without localising or lateralising features but which were difficult to classify

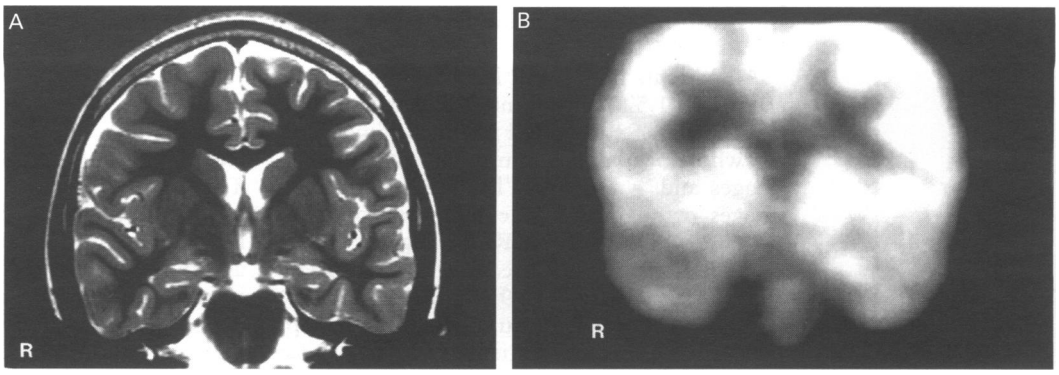

Figure 1 Coronal MRI (T2 weighted) and FDG PET scans from a 10 year old boy with typical severe myoclonic epilepsy in infancy. Seizure types included clonic seizures which were predominantly left sided. Uptake in the right (R) medial temporal lobe was 33% less than in the left.

Table 1 Summary of the major PET abnormalities seen, according to epilepsy syndromes

Classification	No of patients	Age at seizure onset [median (range)]	Age at PET scan [median, (range)]	Sex (M:F)	Major PET findings
Lennox-Gastaut syndrome following typical infantile spasms	3	6 m (3-6)	10 y (5-10)	1:2	*Normal - 1, Unilateral focal hypometabolism - 2 (TPO, TP)
Lennox-Gastaut syndrome following atypical infantile spasms	4	21/2 m (3 w - 8 m)	10 y (7-12)	0:4	Normal - 1, Unilateral focal hypometabolism - 2 (TF, T), Extensive unilateral hypermetabolism - 1
Typical de novo Lennox-Gastaut syndrome	5	3 y (2-5)	9 y (8-11)	4:1	Normal - 5
Atypical de novo Lennox-Gastaut syndrome	4	3 y (1-3)	7 y (5-10)	4:0	Normal - 1, Unilateral hypometabolism - 2 (TP, T), Bilateral, asymmetrical posterior hypometabolism - 1
Typical severe myoclonic epilepsy in infancy	6	5 m (2-7)	10.5 y (3-12)	3:3	Normal - 3, Unilateral hypometabolism - 1 (T), Bitemporal hypometabolism - 1, Marked, diffuse hypometabolism - 1
Atypical severe myoclonic epilepsy in infancy	2	12 and 15 m	4 and 10 y	2:0	Normal - 1, Bilateral, asymmetrical posterior hypometabolism - 1
Atypical myoclonic-astatic epilepsy	2	11 m and 2 y	11 and 12 y	1:1	Normal - 1, Unilateral focal hypometabolism - 1 (TP)
Unclassified	6	20 m (5 m - 7 y)	5.5 y (2-12)	3:3	Normal - 2, Unilateral focal hypometabolism - 3 (T, T, TP), Bitemporal hypometabolism - 1

T = temporal lobe; P = parietal lobe; F = frontal lobe; o=occipital lobe; m = months; w = weeks; y = years.
* Visual and semiquantative analysis failed to reveal asymmetries of > 15% between homologous cortical regions, and bilateral/global abnormalities were not seen on visual inspection.

were significantly associated with cortical metabolic defects, suggesting that some may have been unusual complex partial seizures. Totally normal neurological examination and typical seizure semiology is not predictive of a normal PET scan.

LENNOX-GASTAUT SYNDROME

The nosology of the childhood epileptic encephalopathies is controversial.[1 2] Patients in this study all had refractory generalised seizures, diffuse EEG abnormalities, and developmental delay. According to some definitions, including those used in some previous PET studies, most could have been classified as Lennox-Gastaut syndrome. A stricter approach appears justified by this study. The likely presence of focal cortical metabolic defects in patients with atypical Lennox-Gastaut syndrome and Lennox-Gastaut syndrome following infantile spasms may be predicted by strict classification. No focal PET abnormalities were found in the one previous study of patients with Lennox-Gastaut syndrome which used strict inclusion criteria similar to this study.[9] In studies in which focal abnormalities were seen,[7 8 10 11] application of the criteria used here would have lead in all patients with such abnormalities to classification as atypical Lennox-Gastaut syndrome or as syndromes other than Lennox-Gastaut syndrome. Conversely patients which we would have designated as typical de novo Lennox-Gastaut syndrome all had normal PET scans or on quantitative analysis globally reduced glucose metabolism. The latter may reflect factors unrelated to seizure aetiology such as anticonvulsant medication, the effect of uncontrolled seizures, or associated cognitive deficits. These findings appear to justify the previously suggested separation of a 'genuine' or 'true' Lennox-Gastaut syndrome from a clinically similar (but not identical) condition with partial seizures which rapidly generalise.[1 17 18] The former condition may be caused by non-structural abnormalities such as neurotransmitter, receptor, or membrane defects.

INFANTILE SPASMS

Patients with a previous history of cryptogenic infantile spasms, whether typical or atypical, had a high incidence of cortical metabolic defects in the present study. This is in agreement with previous reports.[12 13 15] Maeda *et al* suggested that such defects may be transient in patients responding to treatment who subsequently developed normally.[15] In contrast, in patients with persisting PET abnormalities or those who developed such abnormalities, seizures continued with ensuing developmental delay. When 11 of our patients with unifocal cortical metabolic defects were rescanned at a median of one year from the initial scan, 10 had similar abnormalities on the repeat scan (Parker A, *et al.* Consistency of focal abnormalities detected by ^{18}FDG PET in epileptic encephalopathies. British Paediatric Neurology Association XXII Annual Meeting, 1996. Abstract, p 43.) Taken together, these studies suggest that there is a high incidence of focal cortical defects in refractory cryptogenic infantile spasms. Recent video-EEG studies have shown that spasms are frequently asymmetrical or are preceded by focal seizures.[32 33] Had video-EEG been done in our patients during active spasms more may have been classified as atypical.

SEVERE MYOCLONIC EPILEPSY IN INFANCY

There are no previous reports on PET findings in patients with severe myoclonic epilepsy in infancy. However, some patients classified as Lennox-Gastaut syndrome in previous studies may have been examples of this syndrome. The focal ictal symptoms which characterise it have not previously been shown to have localising

value for cortical pathology. We showed a correlation between focal ictal symptoms and contralateral PET abnormalities in some, suggesting a focal onset of seizures with rapid bilateral synchrony. However, bilateral or diffuse defects were also seen.

EPILEPSY WITH MYOCLONIC-ASTATIC SEIZURES OR UNCLASSIFIED EPILEPTIC ENCEPHALOPATHIES

Two of our cases had frequent myoatonic seizures and EEG features compatible with epilepsy with myoclonic-astatic seizures. However, many of the other features of the syndrome were lacking and an alternative designation as myoclonic variant of Lennox-Gastaut syndrome (that is, among the atypical de novo Lennox-Gastaut syndrome cases) would have been possible. Given these reservations, the findings in these patients should not be generalised to more typical examples of epilepsy with myoclonic-astatic seizures. As in previous studies, a significant minority of our patients did not fit into any of the currently recognised epilepsy syndromes. Given the high frequency of metabolic defects in these patients, they merit careful evaluation for possible surgical foci.

This study adds further evidence that apparently generalised refractory epilepsies are not infrequently caused by focal cerebral abnormalities. These arise by secondary bilateral synchrony from a unilateral cortical discharge.[34 35] This can be apparent on scalp EEG but may require special techniques for its detection. Mesial frontal foci are often considered to be most likely to give rise to secondary bilateral synchrony. However, as in this study, it may be as likely, or more so, to arise in the temporal lobes.[34] The metabolic abnormality in children with epileptic encephalopathies is usually larger than that seen in partial epilepsies, presumably reflecting a wider epileptogenic zone. Widely synchronous regional spike foci are more apt to produce secondary bilateral synchrony than discrete foci.[35] Children presenting with infantile spasms generally appeared to have the largest focal cortical defects. If the focal hypometabolism suggests cerebral microdysgenesis it may be that those with larger abnormalities present earlier with infantile spasms.

Identification of focal areas of abnormality offers the prospect that some patients may be candidates for resective surgical treatment. PET cannot be used yet as the basis on which to select for this.[36] Traditionally, scalp EEG has been the principal investigational technique in identifying focal onset of seizures. However, its value in the epileptic encephalopathies of childhood is limited by the speed of secondary bilateral synchrony and by the abundance of generalised abnormalities masking focal abnormalities. Additionally, the location of apparent focal or lateralising abnormalities frequently varies. MRI may identify structural abnormalities where EEG is non-contributory but even with optimal techniques will not detect subtle abnormalities, such as cerebral microdysgenesis. PET appears sensitive in detecting focal cortical abnormalities in a significant number of these patients and may help select candidates for more invasive investigation. However, it is premature to conclude that all such lesions are causative. In all our cases PET scans were performed some years after the onset of seizures which were both extremely frequent and intractable. It is conceivable that this may lead to secondary focal cortical damage reflected in PET studies. However, this is unlikely as mesial temporal sclerosis with neuronal loss and gliosis rather than microdysgenesis is associated with uncontrolled seizures. Serial scans starting soon after the onset of these epileptic encephalopathies along with pathology study of surgically resected material should resolve this issue.

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