CURRENT TOPIC

# Positron emission tomography and the central nervous system

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Sixty five years ago artificial radioactivity was discovered.[1] Radioactive tracers such as $^{11}C$, $^{15}O$, and $^{18}F$, which decay by positron emission, were used to derive an image of the distribution in organs during the the mid 1970s. This became clinically important by the 1980s. The physics of position emission tomography (PET) and the logistics of its application are complex. Imaging is based on coincidence detection of annihalation radiation. The unstable radionuclides are neutron deficient and decay by emission of a postively charged electron (positron). The positron travels a few millimetres in the tissue before combining with an electron. Mass is lost and energy is emitted in the form of two gamma rays of energy 511 KeV, which travel in almost opposite directions from the site of annihalation. Multiple detectors on the scanner surrounding the patient identify each event, determine the site of origin, and reconstruct a map of distribution of the radionuclide. Because the path that the positron travels is unpredictable, this sets an irreducible limit to the resolution of the method, which with the currently available systems is in the order of 4–5 mm.

An approximation of the distribution of glucose metabolic rates can be derived by using $^{18}F$ labelled flurodeoxyglucose (FDG)—a glucose analogue. After cell membrane transport, FDG is phosphorylated to FDG-6 phosphate (FDG-6P), which is not metabolised thereafter. Because the cell is impermeable to FDG-6P, and enzymes that reverse this reaction are low in concentration, FDG is trapped within cells sufficiently long enough for rates of glucose uptake to be estimated. FDG uptake takes place over a 45 minute period and reflects the metabolic activity of the brain during that time. Some degree of standardisation of normal brain activity can be imposed by ensuring that during the period of FDG the subject lies with eyes closed in a quiet room. Although brief limited movement can be tolerated, young children may require sedation or a light general anaesthetic. The scan itself takes about 30–45 minutes and is not uncomfortable, threatening, or noisy. Where PET scanning is undertaken in the investigation of epilepsy, electroencephalogram (EEG) monitoring during the period of FDG uptake is recommended because ictal activity increases FDG uptake.

The radioactive isotopes are created in a cyclotron and it is the expense of this that limits the availability of these facilities. The isotopes have to be used within approximately one half life of the decay of the radioactive element. For $^{11}C$ compounds, this is about 20 minutes, but for $^{18}F$ it is about two hours, so FDG studies—for example, do not necessarily have to be on the same site as the cyclotron.

Cerebral blood volume can be derived using $^{11}C$ carboxyhaemoglobin derived from $^{11}C$ carbon monoxide; rates of cerebral blood flow can be derived using $^{15}O$ labelled water.

Consideration of radiation exposure is important but comparable with other procedures. For an FDG examination of the brain, the radiation dose is 6 mSv (effective dose equivalents). For a $^{11}C$ methionine (MET) scan, a further 3.5 mSv will be delivered. This compares with about 8 mSv for a barium enema, 5 mSv for a computed tomography (CT) scan, 4 mSv for an intravenous urogram, 3.8 mSv for a barium meal, and 2.1 mSv for a lumbar spine film. Background irradiation is about 2.2 mSv/year.

For clinical purposes, visual inspection of the images is often sufficient (qualitative PET). Absolute values for tissue metabolic rates, blood flow, and blood volume can be calculated if the activity of arterial samples is determined during the period of uptake (quantitative PET). In general, this has not been thought necessary in children. Alternative methods that measure simultaneous cardiac activity have been proposed. A compromise is to compare the activity of the structure under consideration (the region of interest) either with the whole brain activity, the analogous contralateral structure or a "neutral" structure, such as the cerebellum ("semi quantitative" PET). Each method has merits and disadvantages, particularly for the study of epilepsy (see below), but whichever region of comparison is used, semiqualitative analysis may be more sensitive than visual analysis by experienced personnel when—for example, there are rather diffuse changes in metabolic rate.

The production of new radiotracers offers synthetic chemists exciting but not insurmountable challenges. Thus, mapping the distribution of dopamine, opioid, benzodiazepine, and cholinergic receptors has all been achieved, with more to follow. The increasing

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realisation of the clinical applications of PET technology is being followed by the establishment of more clinical PET centres. The first facility in the world to be installed in a medical institute was at the MRC cyclotron unit at the Royal Post Graduate Medical Centre, London. Subsequent units in the UK have been established at Guy's and St Thomas's, London; Aberdeen Hospital; the National Hospital for Nervous Diseases, London; and Addenbrooke's Hospital, Cambridge

## The epilepsies

Most reports of PET in the investigation of patients with epilepsies have used FDG to study the pattern of cerebral glucose metabolism.[2] This technique depends upon the different metabolic needs (and therefore uptake of FDG) of the cerebral cortex, giving rise to seizures, from that of the surrounding cortex. During seizures, there are large increases in the blood flow to and demand for metabolic substrates in the involved cortical area. This causes increased accumulation of FDG in epileptic foci during seizures ("hypermetabolism").[3] However, the temporal resolution of FDG is ill suited for ictal studies; uptake of FDG takes 30–45 minutes and because most seizures last only a few minutes, "ictal" scans are usually a combination of interictal, ictal, and postictal data,[4] making interpretation difficult.[5] Clinical studies are nearly always planned to take place in the interictal state, with the expectation of detecting reduced FDG uptake ("hypometabolism"). The pathophysiology of interictal hypometabolism is unclear. It might simply reflect an obvious structural abnormality, such as a vascular malformation or hamartoma with decreased numbers of neurones and other metabolically active cells. However, in mesial temporal sclerosis, the degree of hypometabolism correlates poorly with neuronal loss. Reduced synaptic activity in non-functioning inhibitory neurones is an alternative explanation for interictal hypometabolism.[4 6 7]

### ANALYSIS OF PET SCANS IN CHILDREN WITH EPILEPSY

The most commonly used method of analysis of PET scans in patients with seizure disorders is visual inspection. This is analogous to the reporting of CT and magnetic resonance imaging (MRI) scans and depends on the differential uptake of radiotracer in different cerebral structures. Perceived limitations of visual inspection are the poor resolution of PET, the difficulty in identifying cerebral structures, and doubts as to whether the human eye is capable of detecting subtle abnormalities in radiotracer distribution.[8 9]

The uptake of radiotracer in different cerebral structures can be quantified using tracer kinetic models and compared with data from controls. The objectivity of quantified methods makes them intuitively attractive but they are unpopular in clinical practice because large differences in radiotracer uptake between homologous cortical regions are detectable visually. Quantification is important, however, because pronounced asymmetries between homologous cortical regions may exist, despite absolute metabolic rates for each lying within the "normal range". Unfortunately, quantified techniques are invasive, usually requiring repeated blood sampling from arterial lines. In paediatric practice there is also a lack of appropriate controls; maturational changes during infancy and childhood[10–12] make adult control data unsuitable. Obtaining control data from normal children is ethically unacceptable.

Semiquantitative analysis, in which ratios of radiotracer uptake either from homologous brain regions or against a common comparator such as the cerebellum are calculated, is a third technique that avoids many of the problems of fully quantified techniques. Combined visual inspection and semiquantified analysis may maximise the detection of cortical metabolic defects in children with epilepsy.[13]

Techniques for the co-registration of PET and MRI images have been developed.[14–26] However, in patients with epilepsy, the metabolic abnormality revealed by FDG PET is usually large, making it unlikely that co-registration will improve the localisation of the epileptic focus.

### FDG PET AND PARTIAL EPILEPSIES

Patients with partial seizures arising in the temporal lobes have been the subject of a number of studies with FDG PET. Most patients investigated have been adults with mesial temporal sclerosis. FDG PET detects focal areas of hypometabolism interictally in 70–80% of patients.[27–29] The abnormality usually extends well beyond the mesial temporal lobe structures and the nadir of FDG uptake may be in the lateral temporal lobe. Ipsilateral thalamic hypometabolism may also be seen.[4 30] It has been claimed that FDG PET is more sensitive that MRI in detecting abnormalities in patients with temporal lobe epilepsy.[31] However, this is unlikely to apply to the advanced MRI techniques used today.[32] The superior resolution and localising value of MRI over PET, the lack of exposure to radiation, and the additional anatomical information gained makes it the investigation of choice.[33]

FDG PET is considerably less sensitive in detecting abnormalities in patients with partial seizures arising from the temporal neocortex and extratemporal sites. Fewer than 50% of patients show regions of interictal hypometabolism.[33–36] Moreover, abnormalities are often regional or hemispheric and therefore of poor localising value. It is hoped that newer techniques will improve the sensitivity of FDG PET in these epilepsies.[37]

### INFANTILE SPASMS

Infantile spasms occurring as part of West syndrome are an age dependent reaction to a variety of cerebral insults, both generalised and focal. After conventional investigations a cause is found in 89–90% of cases.[38] Identification of patients whose spasms are caused by focal brain pathology is important because resective surgery might offer the best hope of seizure

control and maximise the developmental potential of the child.[39] The occurrence of partial seizures before or concurrent with spasms, asymmetrical spasms, and atypical forms of hypsarrhythmia (especially if asymmetrical or with a fixed focus) increase the likelihood of focal cerebral pathology.[38 40–43] Full evaluation requires detailed EEG (including video EEG) and high resolution MRI studies.

A number of groups have studied children with infantile spasms using FDG PET.[44–49] Chugani and colleagues have reported about 30 children with either active spasms or a past history of spasms in whom FDG PET revealed focal cortical metabolic abnormalities and who subsequently underwent focal resections.[44–46] Some of these children might reasonably have been operated upon based on clinical, EEG, and structural neuroimaging criteria, but PET made the likelihood of focal cortical pathology more certain in others, enabling surgery to proceed without the need for invasive EEG studies. Histological examination of resected cortex demonstrated circumscribed areas of cortical dysgenesis, often subtle and probably undetectable even with high quality MRI.[50 51] It may even be worthwhile studying those children with spasms who lack electroclinical evidence of focal cortical pathology.[47] However, some caution is required, because some metabolic abnormalities in children with spasms can be transient, possibly dependent on the timing of the PET scans in relation to the duration of the seizure diathesis.[49]

### LENNOX-GASTAUT SYNDROME

A number of different patterns of cerebral glucose metabolism have been reported using FDG PET in the Lennox-Gastaut syndrome. This might reflect differences in how this syndrome is defined. If the definition is extended to include children with drug resistant seizures of multiple type (both generalised, partial, and of undetermined type) and learning difficulties, many children with partial epilepsies will be included and FDG PET may reveal focal, multifocal, or hemispheric metabolic defects.[52–55] These abnormalities are usually congruent with clinical, surface EEG, and structural neuroimaging findings. However, except for case studies,[52] there are no reports on children who have subsequently undergone surgical treatment based on FDG PET findings. If the term Lennox-Gastaut syndrome is confined to patients with multiple generalised seizures (tonic, atonic, and atypical absences, but not frequent myoclonic seizures), with generalised slow spike and wave EEG discharges (and generalised fast spikes in sleep), focal cortical metabolic abnormalities are not shown by FDG PET.[56 57] The most common pattern seen in such patients is one of diffuse interictal hypometabolism.

### OTHER CATASTROPHIC EPILEPSIES OF EARLY CHILDHOOD

There is little experience of FDG PET in other severe childhood epilepsies. FDG PET findings have been reported in a few children with severe myoclonic epilepsy in infancy and epilepsy with myoclonic astatic seizures.[47] No consistent pattern of abnormalities was revealed, although there was a high incidence of diffuse or multifocal metabolic defects. FDG PET abnormalities have also been described in children with Sturge-Weber syndrome, tuberous sclerosis, and hemimegalencephaly.[58–61] These conditions are all better diagnosed with structural imaging methods, although there are anecdotal claims that FDG PET can give useful additional information regarding disease progression in the Sturge-Weber syndrome[58] and abnormalities of the "non-involved" hemisphere in hemimegalencephaly.[61] Reports of FDG PET findings in Raussmussen's encephalitis suggests that either focal hypermetabolism or widespread hypometabolism may be seen, presumably reflecting the timing of the scan in relation both to seizures and to the chronicity of the process.[62] In the Landau-Kleffner syndrome, FDG PET findings appear to be variable. Maquet *et al* found focal or regional hypermetabolism during both sleep and wakefulness in five of six children scanned during the active phase of the disease.[63] In the other patient, decreased metabolism was apparent during wakefulness, with a variable pattern during sleep. In the recovery phase of the disease, cortical metabolism was either normal or showed various patterns of focal or regional hypometabolism.

### PET AND SPECT

The relative merits of PET and single photon emission computed tomography (SPECT) in the investigation of children being considered for epilepsy surgery have been debated. SPECT tracers for the measurement of cerebral blood flow are commercially available, making the technique widely available for centres with gamma cameras. Interictal SPECT is substantially less sensitive than interictal PET in detecting cortical abnormalities in patients with temporal lobe seizures.[64] However, the temporal characteristics of the main radiotracers used in SPECT while studying cerebral blood flow make ictal scans feasible. This latter facility is particularly attractive for studying patients with seizure disorders. The sensitivities of ictal SPECT and interictal PET are similar, at least for the detection of temporal lobe foci.[65] The resolution of SPECT is substantially inferior to that of PET, and the areas of abnormality detected are larger than those typically seen with PET. Claims that the two techniques (ictal SPECT and interictal PET) might be complimentary need further evaluation, bearing in mind the radiation exposure. The FDG technique has now been adapted for use with SPECT, but there are as yet no reports in which this has been compared with interictal FDG PET.

### OTHER PET LIGANDS AND OTHER INSIGHTS PROVIDED BY PET

Experience with ligands other than FDG is limited. Flumazenil is an antagonist at benzodiazepine receptors and shows reduced interictal binding in the epileptic focus of patients with partial seizures. In such patients, the extent of

abnormality revealed with flumazenil appears to be smaller than that shown by FDG, giving improved localisation.[66] Flumazenil might also be more sensitive than FDG in the detection of extratemporal foci,[67] and might be useful in detecting areas of cortical dysgenesis.[68] The total radiation exposure is considerably less with flumazenil than with FDG.

PET offers unique opportunities to study the pathogenesis of seizure disorders and the action of antiepileptic drugs. The role of various neurotransmitter systems in seizure disorders can be studied using specific ligands.[4] FDG PET has revealed differential effects of antiepileptic drugs on cerebral glucose metabolism, which might help to explain their different profiles of adverse effects.[69–73] In the future, the distribution and binding of specific drugs will be studied by means of drug labelled PET ligands.

FDG PET studies have revealed evidence of subcortical, particularly thalamic, involvement in partial and idiopathic generalised epilepsies and in the epileptic encephalopathies of childhood, including the Lennox-Gastaut syndrome.[57] In West's syndrome, there is evidence of lenticular and brain stem activation by "antiepileptic drugs",[74] leading to new hypotheses concerning the aetiology of these seizure disorders. FDG PET studies have suggested a relation between frontal lobe hypometabolism and the mental dysfunction commonly seen in the childhood epileptic encephalopathies.[75] A further area of interest is the future use of PET activation studies for the non-invasive localisation of eloquent areas of cortex[76]—an ability already possible with functional MRI, with which PET will need to be compared.

GUIDELINES

Investigating children with seizure disorders using functional neuroimaging should only be undertaken as part of a planned programme in patients being considered for possible epilepsy surgery. The choice between PET and SPECT is likely to be determined mainly by local availability. All children with partial epilepsies that are not within the spectrum of the idiopathic (age related) epilepsies of childhood, who are resistant to appropriate antiepileptic medication, should be considered as potential surgical candidates. Clinical evaluation, surface EEG (including video telemetry recordings) and high resolution MRI are the key investigations. If all point clearly to a mesial temporal lobe focus and there are no conflicting data or data suggesting bilateral foci, functional neuroimaging is probably redundant.[77] Where two of the modalities indicate a likely mesial temporal lobe focus, but the third is non-informative, or functional neuroimaging findings are equivocal, resective surgery should proceed without invasive EEG studies. When there is conflict or discrepancy between clinical, electrical, and MRI data, functional neuroimaging may help in the planning of invasive EEG studies.

Localisation of seizures arising in sites other than the mesial temporal lobes is more difficult. Unless a lesion is apparent on MRI, nearly all such patients will require invasive EEG studies. Functional neuroimaging has a potential role in such patients in helping to plan invasive EEG studies. However, the reduced sensitivity of PET and SPECT in detecting abnormalities in extratemporal sites limits their usefulness.

Children with cryptogenic infantile spasms who do not respond rapidly to medical treatment should be investigated carefully by a tertiary epilepsy centre for the possibility of a cortical focus. PET might have a useful role to play in such cases. PET has not been shown to be sufficiently useful in other childhood epilepsies to justify its use outside of research studies.

## Brain tumours

To date, most work with PET has been in adults with malignant gliomas. The resulting findings, extensive and promising as they are, unfortunately cannot be extrapolated directly to childhood brain tumours, because the spectrum of histology differs, and where the tumour type is identical, its clinical behaviour may vary with age.[78] In addition, the pattern of metabolic activity in the infant brain is different from the adult brain; children's brains attain adult characteristics by the age of 4, with only minor changes occurring through the rest of the first 2 decades.[79 80]

PET has the potential to play an important role in the prediction of tumour grade and therefore prognosis, assessing the response to treatment, differentiating between iatrogenic lesions and residual and recurrent tumour, evaluating the neurotoxicity of treatment, and finally studying the action of chemotherapeutic agents.

The rationale behind PET in brain tumours is that the rate of glycolysis of rapidly growing malignant tumours is greater than that of normal tissue.[81] In 1982, Di Chiro *et al* demonstrated, in vivo, not only that FDG uptake is increased in malignant cells, but also that the increase is proportional to the histological grade of cerebral gliomas.[82] Subsequently, this has been shown to hold true for posterior fossa tumours in children.[83 84] The rate of FDG uptake correlates well with patient survival time,[85–88] with some authors claiming superiority of PET over histological grade in predicting long term outcome.[89] Thus, in the future, the need for taking tumour biopsies associated with a high risk of morbidity may be reduced. PET might provide an additional tool to deal with two of the challenging characteristics (among many others) of brain tumours: the potential for heterogenous histology within a tumour and the potential to transform from a benign to a malignant tumour. Remembering that the histological grade of a heterogeneous tumour is determined by the cell(s) with the greatest malignant transformation, PET can be useful in guiding a stereotactic biopsy needle to the area of greatest FDG uptake.[90–93] Malignant change in low grade gliomas may be identified by PET before clinical manifestations of the disease or MRI changes become apparent.[94 95]

Because FDG uptake is an indicator of the overall rate of glycolysis and glucose cell membrane transport, a specific marker for protein synthesis, such as an amino acid, might also be expected to reflect tumour activity. This is indeed true, with the radiotracer MET having several advantages over other amino acids in the study of cerebral protein synthesis.[96] The uptake of methionine by tumours is related to cell membrane transport of the amino acid and the rate of protein synthesis,[97] not to changes in the blood–brain barrier.[98 99] The advantages of MET over FDG is that it has a higher tumour to normal brain uptake ratio, thereby delineating the extent of the tumour more acccurately, particularly for lower grade tumours.[98 100] Although the degree of MET uptake correlates broadly with histologically assessed tumour grade, it is not as sensitive as FDG in this respect.[98 101] There is evidence to suggest that amino acid transport into tumour cells, rather than uptake and protein synthesis, is more closely associated with tumour grade.[102]

FDG and MET uptake occurs not only in tumours but also in inflammatory or infectious foci.[103–105] For this reason, patients with AIDS pose a particular problem. To date, no ligand has been identified to differentiate the above two pathologies.

Newer developments include the study of DNA synthesis with $^{11}$C thymidine or iodine labelled pyrimidine analogues, such as iododeoxyuridine, which could provide a more specific measure of tumour cell division.[106 107] This information has not yet been applied clinically on any scale. Benzodiazepine receptors have been shown to be increased 20-fold in brain tumours compared with normal brain.[108] As a result, $^{11}$C flumazenil, a benzodiazepine antagonist, can now be used to delineate the outer margins of brain tumours.[109 110]

PET has the potential to monitor treatment. A large reduction in the rate of glucose utilisation within a tumour reflects effective treatment.[111–113] Chemotherapy and radiotherapy can cause an initial rise in FDG uptake, which falls over the subsequent seven to 30 days. The amount of rise and fall are inversely and directly proportional, respectively, to patient survival.[114–116] In a small study, FDG was useful in assessing the response to treatment of medulloblastoma in children.[84] In our experience, this has been useful, especially after radiotherapy, when the FDG uptake of a tumour may be reduced relative to the uptake of the surrounding brain. In a more recent study, MET was found to be superior to FDG in monitoring the effects of treatment in low grade gliomas.[117] Combining information obtained from iododeoxyuridine and FDG uptake was a sensitive indicator of response in glial tumours.[118] The dose of radiation involved in PET limits the frequency of serial studies.

Routine MRI (with the exception of diffusion weighted MRI)[119 120] and CT cannot reliably distinguish residual or recurrent tumours from postoperative inflammatory changes or radionecrosis.[117 118 121–123] The distinction is crucial in planning future management. PET can be invaluable in this regard because postoperative change in itself does not cause increased FDG uptake at the site of surgery.[124 125] Radiation necrosis causes decreased FDG uptake[126–128] allowing ready discrimination from tumour. Low grade tumours may cause a problem because FDG uptake in these tumours may be less than is found in normal cortex. In this situation, combining FDG with MET PET is particularly helpful.[129] In our experience, this has been useful, especially during the post-radiotherapy reduction in FDG uptake. Additional sensitivity may be gained by prior phenylalanine loading. Phenylalanine competitively inhibits MET uptake in brain tumours but not in non-neoplastic lesions.[98 99]

Resolution of PET (at best ~ 4 mm) remains poor when compared with morphological imaging. As a result, anatomical localisation using PET alone may be difficult. However, co-registration of PET with CT or MRI is now possible, enabling accurate matching of cellular activity with anatomy.

PET can be used to monitor the unwanted effects of treatment. Long term survivors of acute lymphoblastic leukaemia, who received cranial irradiation and intrathecal chemotherapy, had a reduction in FDG uptake proportional to the reduction in their overall IQ.[130]

PET can be used to study the delivery and the pharmacokinetics of chemotherapeutic agents, the most readily studied being 1,3-bis(2-chloroethyl)nitrosurea (BCNU).[131 132] PET has also been used to monitor the kinetics of radiolabelled monoclonal antibodies—a technique with potential for identifying, as well as treating, tumours.[132–135] Both of these applications of PET remain research based.

## Conclusion

The amount of information to be gained from applying the increasing number of radionuclides in a variety of pathological situations is potentially very great. However, expense and scarcity of resources, as well as the radiation, discomfort, and anxiety to the individual child has, as with all diagnostic procedures, to be weighed against the potential benefit to be derived from the information gained from the investigation. Although the radiation involved is trivial in relation to radiotherapy doses, and is similar to many *x* ray and SPECT procedures, we feel that PET examination is only justifiable when the information is likely to affect management decisions, such as whether to offer surgery to a child with intractable epilepsy or re-operate in a child with recurrent tumour.

The technique is still in its infancy. Most of the references in this review were written within the past five years. There can be no doubt that the development of further ligands will find applications in a wide variety of conditions in paediatrics.

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