What Can We Learn From Functional Neuroimaging in Children?

Although the primary imaging modality in the management of neurological disorders in children is magnetic resonance imaging (MRI), functional neuroimaging often provides complementary information and, in a number of situations, provides unique information that cannot be obtained with MRI. The functional neuroimaging methods most commonly used in children include positron emission tomography (PET) and single photon emission computed tomography (SPECT) but, technically, functional MRI (fMRI) and MR spectroscopy (MRS) as well as MR methods being developed to evaluate cerebral blood flow might also be classified under the category of functional imaging.

Positron Emission Tomography (PET)

With PET methodology one can measure regional uptake and affinity of ligands or metabolic substrates in brain and other organs. The most commonly used PET tracer is 2-deoxy-2-[18F] fluoro-D-glucose (FDG), which provides images of absolute or relative rates of brain glucose utilization, and is clinically useful in localizing the epileptogenic zone in epilepsy[1]. Evaluation with FDG PET scanning is particularly useful when the MRI scan fails to show a lesion, yet the EEG and the seizure description (semiology) suggest that the episodes are of partial (*i.e.*, focal) onset. In such cases, the PET scan is the only imaging modality to guide the neurosurgeon and epilepsy team towards successful surgical treatment.

In some conditions, PET imaging has led to new forms of treatment. For example, glucose metabolism PET studies in children with intractable cryptogenic infantile spasms have shown unifocal and, more commonly, multifocal cortical areas of hypometabolism interictally. Less commonly, increased focal glucose utilization may be seen if the study is performed ictally or in the presence of an actively discharging focus on the EEG. The discovery of these focal cortical metabolic abnormalities on PET has allowed some infants with refractory spasms to be treated with cortical resection. Thus, when a single region of abnormal glucose metabolism is present, and there is good correlation between the region localized with PET and the focus identified on the EEG, surgical removal of the epileptogenic region results not only in seizure control but also in complete or partial reversal of the associated developmental delay[2,3]. Unfortunately, about 65% of infants with cryptogenic spasms show more than one area of cortical hypometabolism on the PET scan and are therefore not ideal candidates for cortical resection. Within this group is a subgroup of infants with bilateral temporal hypometabolism and a typical clinical phenotype, comprising about 10% of all infants with cryptogenic spasms. The clinical features include severe developmental delay (particularly in the language domain) and autism.

In an effort to pinpoint the epileptic focus more precisely than FDG PET, a number of ligands have been labeled also with positron emitting isotopes and used to image neurotransmitter synthesis, transport and receptor binding using PET techniques. Of these, the most commonly used in epilepsy is

[11C]flumazenil (FMZ) which binds to GABAA receptors(4,5). In our institution, we have developed the application of alpha-[11C]methyl-L-tryptophan (AMT) which measures tryptophan metabolism for epilepsy surgery evaluation, and this method is capable of differentiating between epileptogenic and non-epilptogenic tubers is patients with tuberous sclerosis(6,7). Other PET tracers with the potential for detecting epileptic brain regions include radiolabeled ligands which bind to opioid receptors, histamine H1 receptors, monoamine oxidase type B enzyme, N-methyl-D-aspartate receptors, peripheral-type benzodiazepine receptors, and serotonin 1A receptors.

SPECT

SPECT is also a noninvasive functional imaging technique but uses simpler and less expensive equipment than does PET. SPECT provides tomographic imaging through the use of either a single rapidly rotating gamma camera or multiple gamma cameras to detect and reconstruct gamma-ray emissions(8). Because of the longer half-life of SPECT isotopes compared with the isotopes used in PET, and the readily available equipment, SPECT is suited for even the smallest hospitals and clinics. The isotopes can be obtained commercially and can be stored on-site. However, the spatial resolution of SPECT images is about half of that achieved with PET, a distinction that is particularly relevant in pediatric studies. Furthermore, SPECT techniques are semiquantitative at best, compared with PET, which is fully quantitative.

In brain studies, SPECT has been used primarily to provide an index of cerebral blood flow. Radioactive probes developed for this purpose have included xenon, iodamines, technetium-99m hexamethyl propylene amine oxime (99mTc-HMPAO), and technetium-99m-ethyl cysteinate dimer (ECD). Scanning of the brain can be initiated at leisure after the brain uptake phase because the trapped agent remains relatively stable for at least 1 hour, and the isotopes used in SPECT have rather long half-lives (*e.g.*, 123I has a half-life of 13 hours). These properties are particularly favorable for studies in children(9).

PET versus SPECT

Both PET and SPECT have advantages and disadvantages. In patients with severe epilepsy, interictal PET with FDG and other tracers is a powerful tool for determining functional disturbances in the cortex associated with the epilepsy. When PET is not available, ictal SPECT can provide localization of seizure onset. Sensitivity and spatial accuracy of ictal SPECT findings can be enhanced by using subtraction ictal SPECT co-registered to MRI (SISCOM), *i.e.*, the interictal SPECT images are subtracted from the ictal images and the results displayed on co-registered MR images. In patients with a single epileptic focus and seizures that are frequent and last at least a minute or so, ictal SPECT may be sufficient. However, when multiple foci, large epileptogenic regions, or brief and infrequent seizures are present, ictal SPECT is of limited value. In addition, interictal SPECT is not nearly as sensitive as PET in delineating epileptogenic zones. Ictal PET, on the other hand, is not practical with these patients, since PET isotopes have a short half-life (*e.g.*, 108 minutes for 18F and 20 minutes for 11C), and only 18F-labeled agents are commercially available. Importantly, the routine use of functional neuroimaging in presurgical evaluation has reduced the necessity for chronic invasive EEG monitoring in many children undergoing epilepsy surgery(10).

In this Issue

In this issue of Indian Pediatrics, Kabakus

and colleagues(11) have used Tc-99m HMPAO SPECT to study cerebral blood flow in 8 children with acute Sydenham's chorea. All 6 patients with generalized chorea showed hypoperfusion (N = 5) or hyperperfusion (N = 1) in basal ganglia with or without accompanying right frontal cortex hypoperfusion, although these perfusion abnormalities tended to be unilateral despite the generalized chorea. Furthermore, when frontal cortex was also involved, the response to treatment with haloperidol and valproic acid was poor. Interestingly, the two children with hemichorea had normal SPECT scans. This study suggests that functional imaging may be used to predict treatment response and provide prognostic information for this pediatric movement disorder.

Most of the functional neuroimaging studies performed in patients with movement disorders have been on adults with disorders such as parkinsonism, Huntington's disease, and dystonia. For these and other dyskinesias in adults, PET studies using 18F-labeled 6-fluorodopa to measure presynaptic dopaminergic function have been particularly useful. But use of PET with FDG or other PET ligands-for example, [11C]raclopride, which labels the dopamine D2 receptors, and [11C]-l-deprenyl, which labels monoamine oxidase B-has also provided useful information. Only a few studies have been performed in children, and most of these have been case reports.

Other applications

Abnormal basal ganglia metabolism is seen in children with juvenile Huntington's disease, in whom the caudate and lenticular nuclei show markedly decreased glucose utilization(12). This finding is interesting because it is similar to what is found in adult Huntington's disease, yet the clinical presentations are quite different between the two forms. The juvenile form is characterized by intellectual decline, rigidity, seizures, and behavioral difficulties, whereas the adult form has as major manifestations chorea and dementia.

In the few children with Tourette syndrome who have been studied with FDG-PET, no consistent abnormalities have been found. However, a perfusion SPECT study reported subcortical asymmetries in TS patients due to reduced right basal ganglia perfusion(13). Several studies evaluated various aspects of dopaminergic transmission, since it is believed that disturbances in the dopaminergic system contribute to the pathophysiology of Tourette syndrome. Such studies reported elevated striatal dopamine transporter levels and also abnormal presynaptic DOPA decarboxylase activity.

In the full-term infant who has suffered from perinatal asphyxia, a static encephalopathy associated with chorea, athetosis, or dystonia may be seen. The neuropathological correlate of this disorder is usually gliosis and dysmyelination of the thalamus and basal ganglia, particularly the striatum. FDG-PET studies in a number of such children have shown either absent or markedly depressed glucose metabolism in the thalamus and lenticular nuclei, with relative sparing of the caudate nucleus(14). The cerebral cortex is also relatively spared, a finding that is consistent with the clinical observation that most of these children have relative preservation of cognitive function compared with their severe motor impairment. We currently use FDG PET with this group of children to evaluate their cognitive potential as a guide to early intervention.

Thus, we can indeed learn more about pediatric neurological disorders from functional imaging. The past two decades has

seen impressive advances in neuroimaging techniques and rapid progress continues to be made. However, application of these techniques to disorders in children is coming at a much slower pace. The study by Kabakus and colleagues(11) in this issue is a welcome addition, but much more needs to be done.

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