Pediatric Neurology 100 (2019) 12–25

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Positron Emission Tomography in Pediatric Neurodegenerative Disorders

Harry T. Chugani, MD *

Department of Neurology, NYU School of Medicine, New York, New York

ARTICLE INFO

Article history:
Received 1 May 2019
Accepted 9 July 2019
Available online 17 July 2019

Keywords:
PET scanning
Pediatric neurodegenerative disorders
Neuroimaging
Reimbursement
Imaging biomarkers

ABSTRACT

Application of molecular neuroimaging using positron emission tomographic techniques to assess pediatric neurodegenerative disorders has been limited, unlike in adults where positron emission tomography has contributed to clinical diagnosis, monitoring of neurodegenerative disease progression, and assessment of novel therapeutic approaches. Yet, there is a huge unexplored potential of molecular imaging to improve our understanding of the pathophysiology of neurodegenerative disorders in children and provide radiological biomarkers that can be applied clinically. The obstacles in performing PET scans on children include sedation, radiation exposure, and access but, as will be illustrated, these barriers can be easily overcome. This review summarizes findings from PET studies that have been performed over the past three decades on children with various neurodegenerative disorders, including the neuronal ceroid lipofuscinoses, juvenile Huntington disease, Wilson disease, Niemann-Pick disease type C, Dravet syndrome, dystonia, mitochondrial disorders, inborn errors of metabolism, lysosomal storage diseases, dysmyelinating disorders, Rett syndrome, neurotransmitter disorders, glucose transporter Glut 1 deficiency, and Lesch-Nyhan disease. Because positron emission tomographic scans have often been clinically useful and have contributed to the management of these disorders, we suggest that the time has come for glucose metabolism positron emission tomographic scans to be reimbursed by insurance carriers for children with neurodegenerative disorders, and not restricted only to epilepsy surgery evaluation.

Considerable progress has been made in identifying clinically useful molecular neuroimaging biomarkers through studies using positron emission tomography (PET) in adult neurodegenerative disorders. These biomarkers include abnormal patterns of cerebral glucose metabolism, which allow for the differentiation of dementia phenotypes due to Alzheimer disease, Lewy bodies, and frontotemporal lobe degeneration.[1] More specific PET radiotracers have also been developed allowing for imaging of cerebral amyloid, tau protein, and microglia (inflammation) in various types of dementia leading to identification of further biomarkers used for diagnosis and in clinical trials.[2] Very recently, PET tracers have become available for imaging synaptic vesicle protein 2 thus providing images of synaptic density in the adult brain, and these are being applied in the study of dementia.[3]

In contrast, the field has lagged far behind when applying PET technology to the study of *pediatric* neurodegenerative disorders. One of the main reasons for this lag is that children often have to be sedated for a PET scan. However, this is less of an obstacle nowadays because current high-resolution PET scanners with improved sensitivity require no more than 20 minutes (often less) for acquisition of glucose metabolism images during which the child may require sedation. Image acquisition is initiated *after* the "uptake" period of 30 to 40 minutes when the child actually needs to be awake in a separate quiet room. In addition, software tools for motion correction have improved significantly so that some movement by the child during image acquisition can be tolerated and corrected. A second concern in scanning children is the radiation exposure, which is minimal and has been accepted by radiation safety agencies in the past three decades for clinical studies in the child with refractory epilepsy. A third issue in the past was *access* to PET scanners, which, again, should no longer be an obstacle because many hospitals now have PET scanners for oncology imaging and the 18F-fluorodeoxyglucose (^{18}FDG) radiotracer for studies of glucose metabolism is purchased and delivered

Conflict of interest: The author reports no conflicts of interest.

* Communications should be addressed to: Chugani; NYU Langone Comprehensive Epilepsy Center; 223 East 34th Street; New York, NY 10016.
E-mail address: Harry.Chugani@nyulangone.org.

https://doi.org/10.1016/j.pediatrneurol.2019.07.003
0887-8994/

on the same day as the scheduled scan. The cost of ^{18}FDG has decreased significantly to only about US $120 per dose. In fact, PET imaging for neurodegenerative disorders in children is both less cumbersome and less expensive than for intractable epilepsy because concurrent electroencephalographic (EEG) monitoring during the tracer "uptake" period is not necessary for most children with neurodegenerative disorders, whereas ictal activity is typically monitored with EEG in epileptic children because it can affect image interpretation. Admittedly, access to various radiotracers other than ^{18}FDG is still a barrier and, in addition, further barriers include the relative rarity of these conditions, limited access to healthy age-matched control subjects or normative databases to facilitate statistical analyses, and adequate fasting before some PET studies.

At present, PET scans in children are reimbursed by insurance carriers only if there is a suspected epileptic focus where epilepsy surgery is being considered, and not for most of the conditions discussed in this review. Yet, most of the pediatric conditions described in this review are relatively rare, and, therefore, large-scale validation studies are not possible, unlike in adults with dementia. Nevertheless, there are a few "potential" PET biomarkers that have been suggested in various small series or case reports of children with neurodegenerative disorders.

With the ongoing development of new treatments for rare disorders in children and advances in precision medicine, molecular neuroimaging with PET has great potential to yield biomarkers that will aid in diagnosis, as well as monitoring of disease progression and treatment response.

In this review, we summarize the state of the field and encourage validation of "potential" molecular imaging biomarkers that have been observed in children with progressive neurological disorders. We make the argument that PET scans (specifically of glucose metabolism) can be invaluable in the overall management of pediatric neurodegenerative disorders and should be moved into reimbursement status. We now review the various pediatric neurodegenerative disorders that have been studied with PET imaging.

Neuronal ceroid lipofuscinosis

Previously classified according to age of onset, this heterogeneous group of inherited neurodegenerative disorders is now classified based on disease-causing mutations in at least 20 genes described thus far. Management strategies have largely been limited to palliative care and attention to quality of life.[4] A better understanding of the molecular mechanisms underlying neuronal ceroid lipofuscinosis (NCL) (also called Batten disease) is paving the way for specific therapies targeting the various subtypes, one of which has already been approved clinically.[5] This US Food and Drug Administration-approved drug is the cerebrospinal fluid-administered enzyme replacement therapy (Brineura) with the active ingredient being cerliponase alfa. It is a recombinant form of human TPP_1, the enzyme deficient in patients with the CLN2 type of NCL. Although the diagnosis can be made based on DNA testing, a sensitive imaging biomarker would be useful for monitoring disease progression and treatment response. For the NCLs, and indeed many of the pediatric neurodegenerative disorders, magnetic resonance imaging (MRI) is not sensitive to changes as it typically shows nonspecific brain atrophy that gradually worsens with disease progression.

As early as 1990, De Volder et al.[6] reported glucose metabolism PET findings in four siblings with NCL showing hypometabolism in gray matter structures, but most pronounced in thalamus and posterior association cortex. The severity of the hypometabolism correlated with the degree of clinical impairment. Subsequently, Philippart et al.[7] described a similar PET pattern of glucose hypometabolism in seven unrelated subjects with Spielmeyer-Vogt disease (associated with mutations in the CLN3 gene). Five of the seven patients showed a distinctive age-related progression with hypometabolism starting in the calcarine cortex and progressing rostrally to involve the entire cerebral cortex. In the older more affected patients, glucose metabolism remained only in the basal ganglia and brainstem (Fig 1). Similar findings have been reported by others,[8,9] but there have been no larger studies to further develop this rather unique pattern of glucose metabolism as a clinical tool or biomarker.

Imaging of dopamine receptors in NCL using various PET radiotracers has not yielded useful biomarkers but has shown a mild decrease of D1 receptor binding with no change in D2 binding compared with controls.[10] In the NCLs, therefore, PET imaging of *glucose metabolism* is potentially useful in following disease progression and should be incorporated into clinical trials as they become available.

Juvenile Huntington disease

In adult Huntington disease (HD), initial PET studies focused on glucose metabolism and consistently demonstrated hypometabolism in caudate nucleus even before MRI-defined atrophy.[11] In the past several decades, however, PET radiotracers have been applied in adults with HD to study brain dopamine, adenosine, γ-aminobutyric acid (GABA), opioid, and cannabinoid mechanisms to provide a better understanding of the pathophysiology as well as to uncover potential biomarkers to monitor disease progression and efficacy of new therapies.[12] For example, PET imaging of phosphodiesterase 10A (PDE10A, a regulator of intracellular signaling) in 12 asymptomatic HD gene carriers showed lower PDE10A expression in the insular cortex and occipital fusiform gyrus of the gene carriers compared with control subjects, suggesting that dysregulated extra-striatal PDE10A signaling may occur early in the course of HD.[13] An in-depth discussion of PET studies in adults is beyond the scope of this review on children.

Compared with the studies in adults with HD, juvenile HD has been studied with PET at only a rudimentary level. De Volder et al.[14] reported, in two children with juvenile HD, markedly decreased glucose metabolism in caudate nuclei with sparing of the cerebral cortex. The authors conclude that although the phenotype of juvenile HD differs from that of adult-onset HD, the pattern of glucose metabolism is similar. This has also been our experience (Fig 2). There had been no further published studies on this topic until recently, when Diggle et al.[15] reported germline PDE10A mutations in eight individuals from two families who manifested early-onset hyperkinetic movement disorder. One of the affected individuals had a PET scan to image PDE10A activity and this showed a significant decrease of PDE10A signal in the striatum, which appeared anatomically normal on MRI. Although these subjects were not diagnosed with HD and the hyperkinetic movements began in infancy, the abnormal PDE10A signal on PET, which is also abnormal in adult HD subjects, is particularly relevant and a logical next step might be to study juvenile patients with HD using PDE10A PET imaging.

Wilson disease

In four adult patients with Wilson disease, PET imaging of brain glucose utilization showed relatively more pronounced hypometabolism in the lentiform nuclei and cerebral cortex with less hypometabolism in caudate nuclei compared to patients with HD.[16] In general, these findings are consistent with those from other investigators. One study reported only mild hypometabolism in the striatum of subjects with Wilson disease who

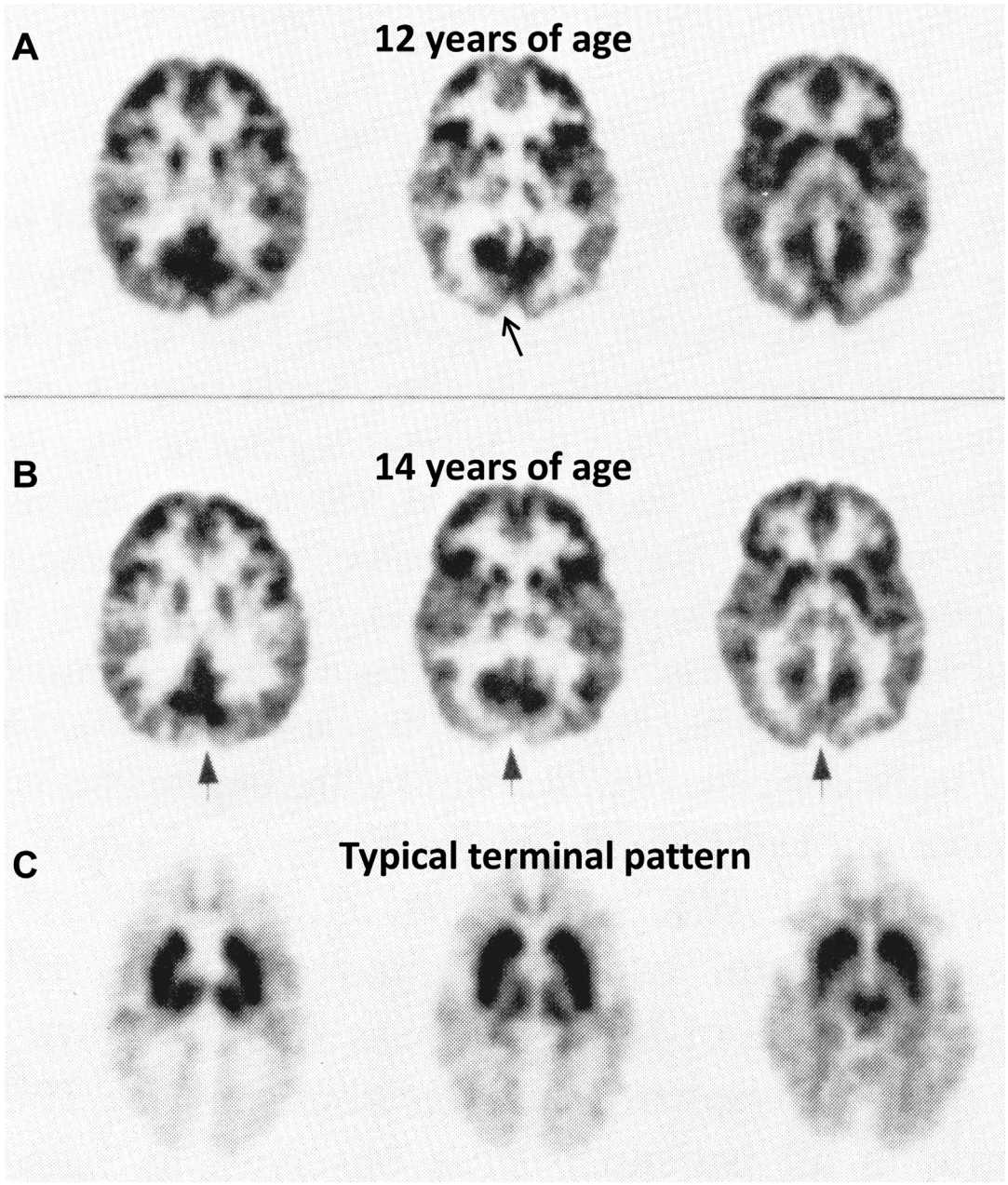

FIGURE 1. (A) Positron emission tomographic images of glucose metabolism in a 12-year-old child with neuronal ceroid lipofuscinosis, showing only very mild calcarine cortex hypometabolism (arrow); (B) two years later, there has been progression of posterior cortex hypometabolism (arrowheads) with sparing of the frontal lobes; (C) hypometabolism is widespread in the advanced stages of the disease in a different child with activity remaining only in the striatum, the brainstem, and to some extent the thalamus.

were receiving "decoppering" (chelation) therapy.[17] Glucose metabolism in the caudate correlated with extrapyramidal symptoms, whereas glucose metabolism in the cerebellum, thalamus, and cerebral cortex correlated with pyramidal symptom severity. PET investigations to assess dopamine reuptake, synthesis, and D2 receptors in patients with Wilson disease suggested that the pathophysiology of striatal degeneration is complex and involves both afferent and efferent projections.[18] Using ^{52}Fe-citrate (which converts to ^{52}Fe-transferrin in blood plasma), Bruehlmeier et al.[19] used PET to evaluate brain iron transport in six subjects with Wilson disease and in 16 healthy control subjects. They found significantly increased brain ^{52}Fe-transferrin uptake in the patients with Wilson disease compared with controls.

Unfortunately, there have been no PET investigations reported on children or adolescents with Wilson disease, but there is certainly opportunity for interesting investigations to address a number of important issues, including ^{18}FDG-PET correlations with phenotype, symptom severity, and treatment response.

Niemann-Pick type C disease

There are only a few published reports of PET investigation in this progressive disorder of childhood. In the first study, PET scans of glucose metabolism in identical twin girls aged four years revealed mild diffuse cortical hypometabolism, particularly in the medial frontal cortex (Fig 3A).[20] When studied again at age six years, there had been dramatic progression in both twins to severe

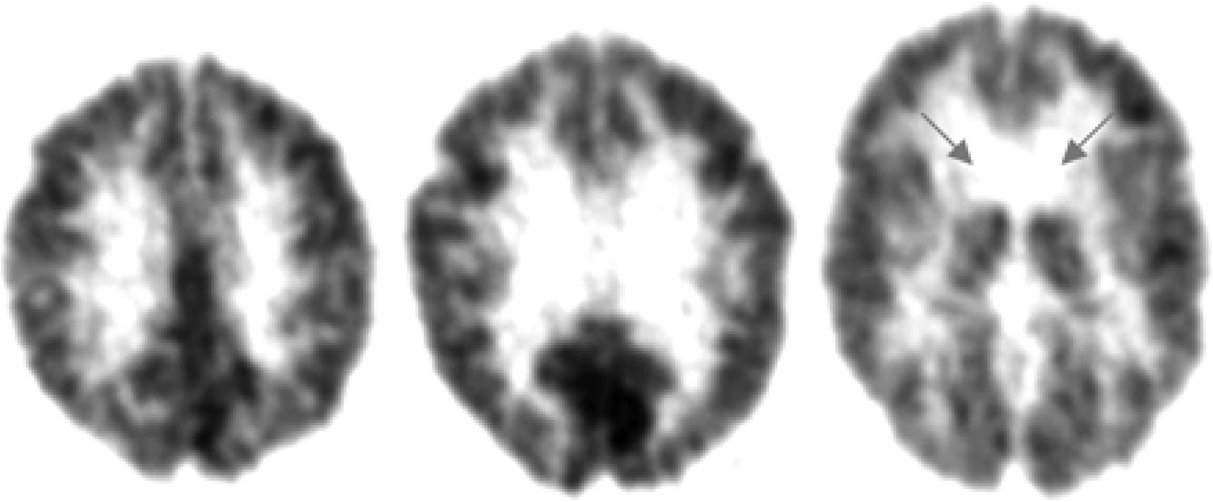

FIGURE 2. Glucose metabolism positron emission tomographic imaging in a child with juvenile Huntington disease showing marked hypometabolism in the caudate nuclei (arrows).

hypometabolism in medial and inferior frontal cortex, thalamus, as well as parietal (medial and lateral portions) and temporal cortex (Fig 3B). The MRI scan appeared normal (Fig 3C). This pattern of hypometabolism appeared unique, i.e., it has not been reported in other childhood disorders, and, therefore, it was suggested that this could constitute a "biomarker" to assess disease progression and response to new interventions.

Unlike the previous report, where the twins were relatively similar phenotypically, Benussi et al.[21] reported monozygotic twins with Niemann-Pick type C, one of whom was severely affected,

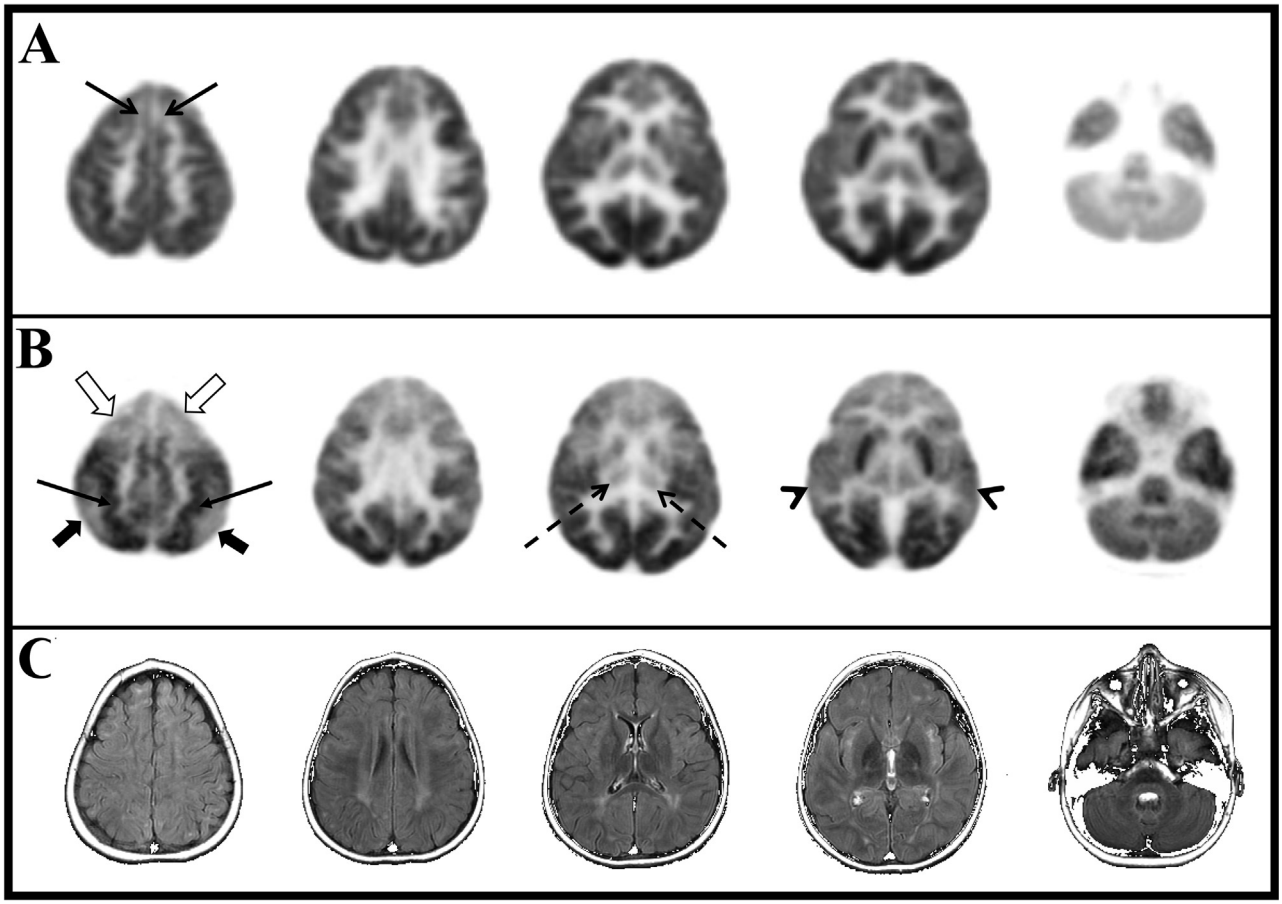

FIGURE 3. (A) Positron emission tomographic images showing glucose hypometabolism in medial frontal cortex (arrows) at age four years in one of the twins with Niemann-Pick C disease. (B) At age six years, with clinical progression, there is now also metabolic progression to include most of the frontal cortex (hollow arrows), thalamus (dotted arrows), and temporal (arrowheads) and parietal cortex (thick short arrows). The deeper layers of the parietal cortex show relatively higher metabolism (long thin arrows). The pattern of hypometabolism in parietal cortex is unique and has not been reported in other disorders of childhood. (C) Normal comparison magnetic resonance images.

whereas the other had only very mild impairment. PET scans in both twins showed frontal and temporal cortex hypometabolism, but the abnormality was more pronounced in the more affected twin. Huang et al.[22] reported MRI, magnetic resonance spectroscopy (MRS), and glucose metabolism PET findings in a 22-year-old male with Niemann-Pick C, showing progressive (age 19 and 22 years) cerebral atrophy particularly in the frontal regions and white matter changes posteriorly. No major findings were seen on MRS, but the PET at 22 years showed hypometabolism in the bilateral prefrontal cortex and dorsomedial thalamus.

One exciting development in PET radiochemistry is the ability to image activated microglia (neuroinflammation) in the brain by applying radiotracers that bind to the translocator protein (TSPO) in the mitochondria of microglia. TSPO binding is upregulated when microglia are activated, such as during inflammation. Preliminary studies in a patient with Niemann-Pick C using PET with ^{11}C-PK11195 (a TSPO-binding agent) have demonstrated increased uptake in and around the deep gray matter structures (Fig 4).[23] TSPO PET could be a very useful clinical biomarker to monitor disease progression and treatment response in neurological disorders associated with neuroinflammation. For example, miglustat (Zavesca, Actelion Pharmaceuticals, Allschwil, Switzerland), a small iminosugar molecule that reversibly inhibits glycosphingolipid synthesis, is now being used for the treatment of Niemann-Pick C, and both glucose metabolism PET and PET with ^{11}C-PK11195 or newer-generation TSPO radiotracers should prove to be useful in monitoring objectively the efficacy of this treatment.

Dravet syndrome

The MRI scan seldom provides useful information in epileptic channelopathies as it typically shows normal findings and, eventually, nonspecific brain atrophy. Functional brain imaging techniques are, therefore, more likely to show abnormalities early in the course. In a PET study of brain glucose metabolism in 12 children with various epileptic encephalopathies, Ferrie et al.[24] reported abnormalities (unilateral, bilateral, diffuse hypometabolism) in four of eight children diagnosed with severe myoclonic epilepsy of infancy (Dravet syndrome). The locations of hypometabolism were concordant with the brain regions suspected to be abnormal based on seizure semiology.

Kumar et al.[25] recently reported three children with epilepsy and pathogenic mutations in the SCN1A gene who had PET scans when they were aged around 1 year or less. The initial scans showed a normal pattern of brain glucose metabolism. However, when studied again at age four years or later, all three children had developed bilateral glucose hypometabolism, most pronounced in the frontal, parietal, and temporal cortex and thalamus without significant focal features (Fig 5). These findings strongly suggest a progressive course in children with Dravet syndrome. Considering recent new pharmacological treatment of this disorder (e.g., fenfluramine, cannabis), the pattern of glucose metabolism may serve as a biomarker to monitor disease progression and response to various interventions. In a larger study of eight children with genetically confirmed Dravet syndrome, each studied once, Haginoya et al.[26] also found that widespread cortical hypometabolism was seen only beyond the late infantile period, again consistent with the notion that this is a progressive disorder.

Dystonia

Many studies have been performed using PET tracers in adults with primary dystonia.[27] In children with dystonia, there have also been a number of studies using PET techniques. Szyszko et al.[28]

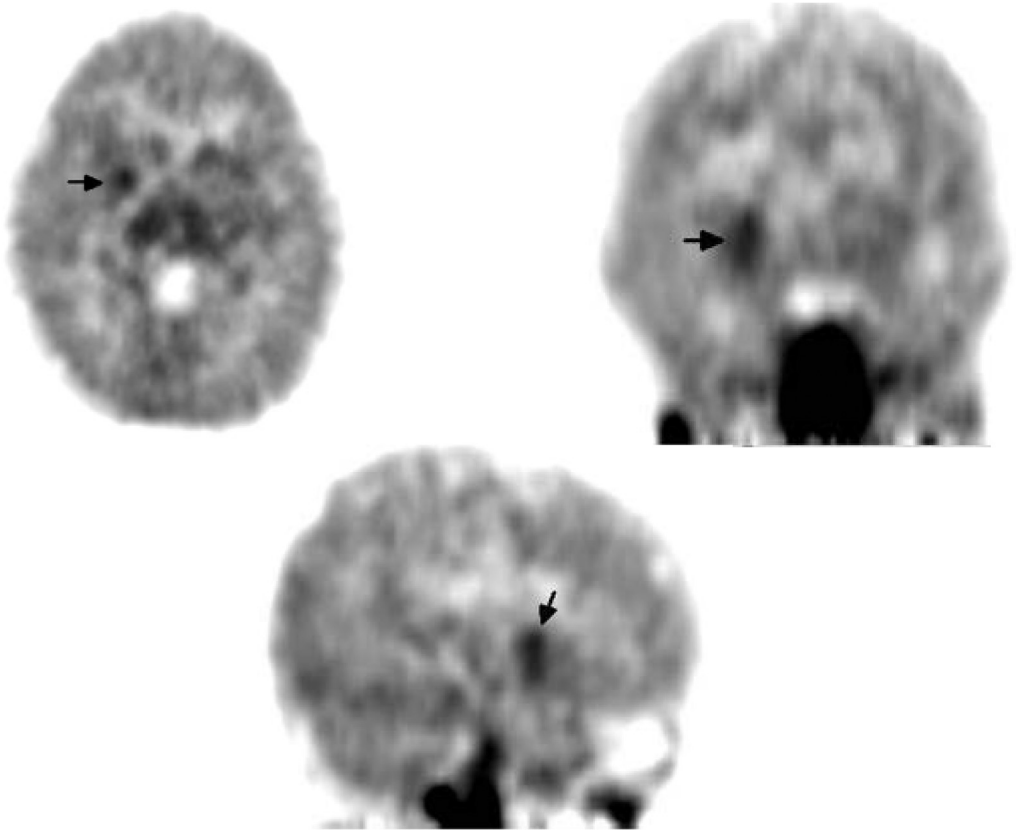

FIGURE 4. Positron emission tomographic scan using ^{11}C-PK11195 in a child with Niemann-Pick C showing inflammation in and around the deep gray matter structures (arrows).

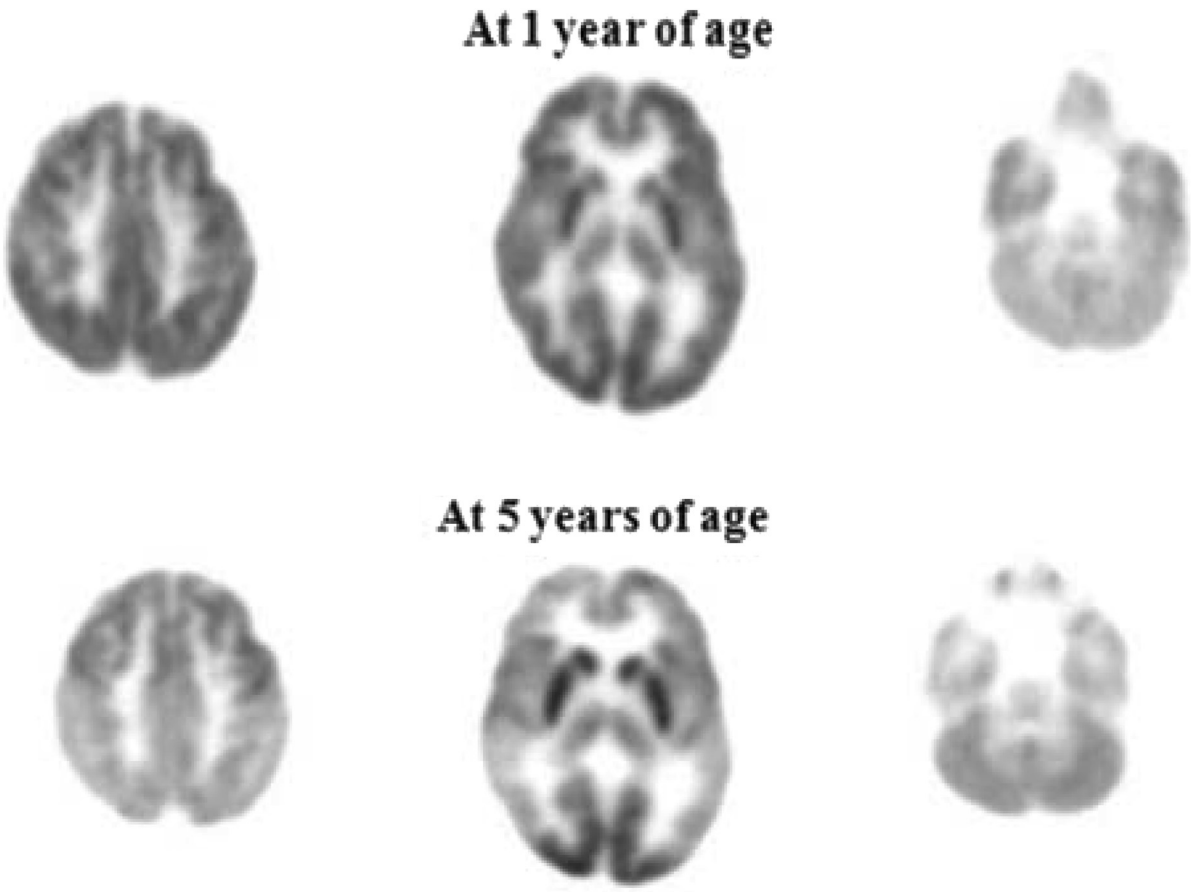

FIGURE 5. Glucose metabolism images acquired by positron emission tomography at two time points in a child with Dravet syndrome (SCN1A pathogenic variant). At age one year, glucose metabolism appears normal, whereas at age five years there is severe hypometabolism in the frontal, parietal, and temporal cortex and thalamus with relative sparing of the occipital cortex and basal ganglia.

performed PET scans of glucose metabolism in 15 children with primary dystonia and 12 children who had neurodegeneration with brain iron accumulation (NBIA). Although visual inspection of the images did not show any appreciable abnormalities, quantitative analysis showed higher uptake in posterior cingulate and posterior putamina, but lower uptake in occipital cortex and cerebellum in the subjects with NBIA compared with those with primary dystonia. However, the two groups of children did not show the same degree of dystonia, which was more severe in the NBIA group. The authors suggested that the more severe dystonia in the NBIA group may be related to higher activity in the putamen and lower activity in the cerebellum and that this pattern (or ratio) could be a useful biomarker for disease severity.

Rinne et al.[29] evaluated the dopaminergic system (dopamine transporter, D1 and D2 receptors) using PET and specific radiotracers in seven patients with dopa-responsive dystonia who each underwent all three PET studies. They found increased D2 receptor binding in the putamen and caudate nucleus in the patients compared with control, with no changes in D1 receptor or dopamine transporter binding. Based on these very preliminary findings, it was suggested that monitoring of D2 receptor binding with PET may be useful in assessing disease progression but, clearly, the field needs to be developed further.

Mitochondrial disorders

There have been many studies using PET to evaluate the mechanisms of brain injury in patients with mitochondrial disorders, but most of these were performed in adult subjects because of previous difficulties in studying children. Nevertheless, in mitochondrial disorders, findings and concepts derived from adult studies could be extrapolated, in general, to the pediatric population. In one of the earliest applications of PET, which evaluated brain stoichiometry in mitochondrial disorders, Frackowiak et al.[30] studied cerebral oxygen and glucose metabolism in eight patients with mitochondrial disorders and seven normal controls using various PET radiotracers. An uncoupling of cerebral glucose and oxygen metabolism was observed in patients who had central nervous system (CNS) involvement compared with patients without CNS involvement and with normal healthy controls. In patients with CNS disease, the mean ratio between oxygen and glucose utilization was 3.8 moles of oxygen per mole of glucose, whereas this value was 5.6 for controls and 6.4 for patients with myopathy alone. The authors suggested that these differences were the result of aerobic glycolysis to lactate or other intermediate metabolites in patients with CNS involvement. Stoichiometry measurements using PET could be a powerful quantitative approach to assess the severity of mitochondrial impairment in a variety of disorders.

In a study of ^{11}C-pyruvate clearance from the brain measured with PET, Toyoda et al.[31] reported that two patients with mitochondrial encephalomyopathy and one with Leigh disease showed increased uptake of the radiotracer in the cerebral cortex, basal ganglia, and thalamus, as well as slower brain clearance of the ^{11}C-pyruvate compared with patients with epilepsy who served as a control group. The authors suggested that ^{11}C-pyruvate PET may be

useful for the evaluation of brain mitochondrial energy metabolism in a variety of mitochondrial disorders. Other investigators have reported similar findings,[32,33] and there have also been a number of supportive case reports in children.

One interesting study combined proton MRS (^{1}H MRS) and glucose metabolism PET to evaluate the brain energetics in two children with congenital lactic acidosis.[34] The investigators found a massive increase of glycolysis to accomodate energy requirements in brain tissue, with associated lactate accumulation and suggested that combined PET and MRI techniques might shed further light into disorders of brain energetics and provide useful clinical biomarkers.

Haginoya et al.[35] performed PET scans of glucose metabolism in five children with Leigh syndrome, four of whom had reported gene mutations in their mitochondrial DNA. The basal ganglia and cerebellum of the patients showed hypometabolism compared with controls, possibly related to the dystonia and ataxia seen in these patients.

In summary, PET with various radiotracers is a potentially powerful tool to further our understanding of mitochondrial disorders in children and monitor progression of the disease. Although MRI methodology is also being used to investigate the mechanisms and bioenergetics of mitochondrial dysfunction (for a review see Mascalchi et al.[36]), combined PET-MRI data acquisitions using new hybrid PET-magnetic resonance scanners will prove to be invaluable in the clinical arena because both PET and magnetic resonance datasets can be acquired in the same session and the child is sedated (if necessary) only once.

Inborn errors of metabolism

Countries such as Saudi Arabia, which have a high incidence of consanguinity and have ready access to PET imaging, provide unique opportunities for molecular imaging in a number of rare disorders. Various inborn errors of metabolism have been assessed for unique patterns and potential biomarkers using PET scans of brain glucose metabolism. Although the numbers of children studied is small, and sometimes described in case reports, the potential of PET scanning to further our understanding of pathophysiology, and to monitor disease progression and response to new treatments, is emphasized repeatedly in these publications.

Al-Essa et al.[37] studied eight patients diagnosed with *glutaric aciduria type 1*. Both MRI and PET showed involvement of the putamina in all eight subjects studied. The PET scans demonstrated hypometabolism in the head of the caudate nuclei in all the patients. Brain atrophy and the "open" sylvian fissures were better demonstrated by MRI. On the other hand, the cerebral cortex and thalamic structures were found to be normal by MRI in all patients, whereas PET scan showed decreased uptake in the cerebral cortex in seven patients, and in the thalami in three patients. The authors concluded that PET and MRI can be regarded as complementary assessment tools in this disorder.

The same group of investigators[38] studied brain glucose metabolism using PET in four patients with *3-methylglutaconic aciduria*. They found three patterns of abnormality, which allowed them to classify the progression of the disorder into three stages (Fig 6). In stage I, uptake was absent in the heads of the caudate, accompanied by mildly decreased thalamic and cerebellar metabolism. In stage II, uptake was absent in the anterior half and posterior quarter of the putamina, in addition to mild to moderate hypometabolism in the cerebral cortex especially in the parietotemporal region and with continued progression of thalamic and cerebellar hypometabolism. The characteristic feature of stage III was a total absence of metabolic activity in the putamina and severe hypometabolism of the cerebral cortex and cerebellum consistent with brain atrophy seen on MRI. This study demonstrates that PET could identify useful molecular imaging biomarkers to allow staging of the disease, and these patterns can be used to monitor disease progression.

Al-Essa et al.[39] also performed serial MRI and PET scans of brain glucose metabolism in five children with *proprionic acidemia*. They found early PET and MRI scans to be normal. As the disease progressed, MRI showed atrophy and abnormal signal in caudate and putamen with normal thalami, whereas PET showed *increased* uptake in basal ganglia and thalami with further progression to *decreased* uptake in basal ganglia. Thus, there appeared to be a period of *transient hypermetabolism* in the basal ganglia in accordance with the dynamic nature of neurodegeneration during the course of this disorder.

There have also been a number of case reports of PET scanning in several inborn errors of metabolism. A two-year-old boy with *ethylmalonic aciduria* showed a normal MRI scan but bilateral intense *hypermetabolism* in the caudate and putamen on PET (Fig 7). One year later, PET showed bilateral hypometabolism in the putamen, caudate head, and frontal cortex, whereas MRI showed atrophy and infarcts in the basal ganglia.[40] These findings are consistent with the selective vulnerability of the basal ganglia in this disorder.

A case report describing a child with *4-hydroxybutyric aciduria* who underwent a glucose metabolism PET scan described a marked decrease in cerebellar metabolism, presumably related to the cerebellar vermis atrophy seen on MRI.[41]

In summary, these inborn errors of metabolism have somewhat different patterns of glucose metabolism from each other and provide important clues toward our understanding of the pathophysiologic processes associated with selective vulnerability to brain injury. However, identifying precise biomarkers in these disorders will require larger numbers of patients to be studied, perhaps in multicenter collaborations due to the rarity of these disorders. Also, there have been no published studies evaluating how the PET patterns described above for various inborn errors of metabolism might change with treatment interventions.

Lysosomal storage diseases

Increased understanding of the genetics and molecular biological mechanisms contributing to the pathophysiology of the lysosomal storage diseases have led to active investigations in search for new treatment approaches, such as enzyme replacement therapy and gene therapy.[42] Molecular neuroimaging with PET may provide the much needed biomarkers to monitor the effects of emerging treatments for these disorders.

There have been only a few published studies that have used PET technology to evaluate children with lysosomal storage diseases. Brain glucose metabolism was studied in a two-year-old Saudi boy with *infantile GM1 gangliosidosis* using PET.[43] Mild diffuse brain atrophy and dysmyelination or demyelination was seen on the MRI scan. The PET scan revealed mild hypometabolism in the basal ganglia, moderate to severe hypometabolism in the thalamus and visual cortex, and a presumed epileptic focus of increased glucose metabolism in the left frontal lobe. This condition is known to cause seizures but, unfortunately, the EEG was not monitored during the PET tracer uptake period to document that the left frontal hypermetabolic focus represented an epileptic focus.

Lee et al.[44] evaluated a child with *juvenile GM2 gangliosidosis* using MRI at ages two, four, and six years and found progressive brain atrophy, particularly affecting the thalamus. Glucose metabolism PET at age six years showed diffuse atrophy with diffuse

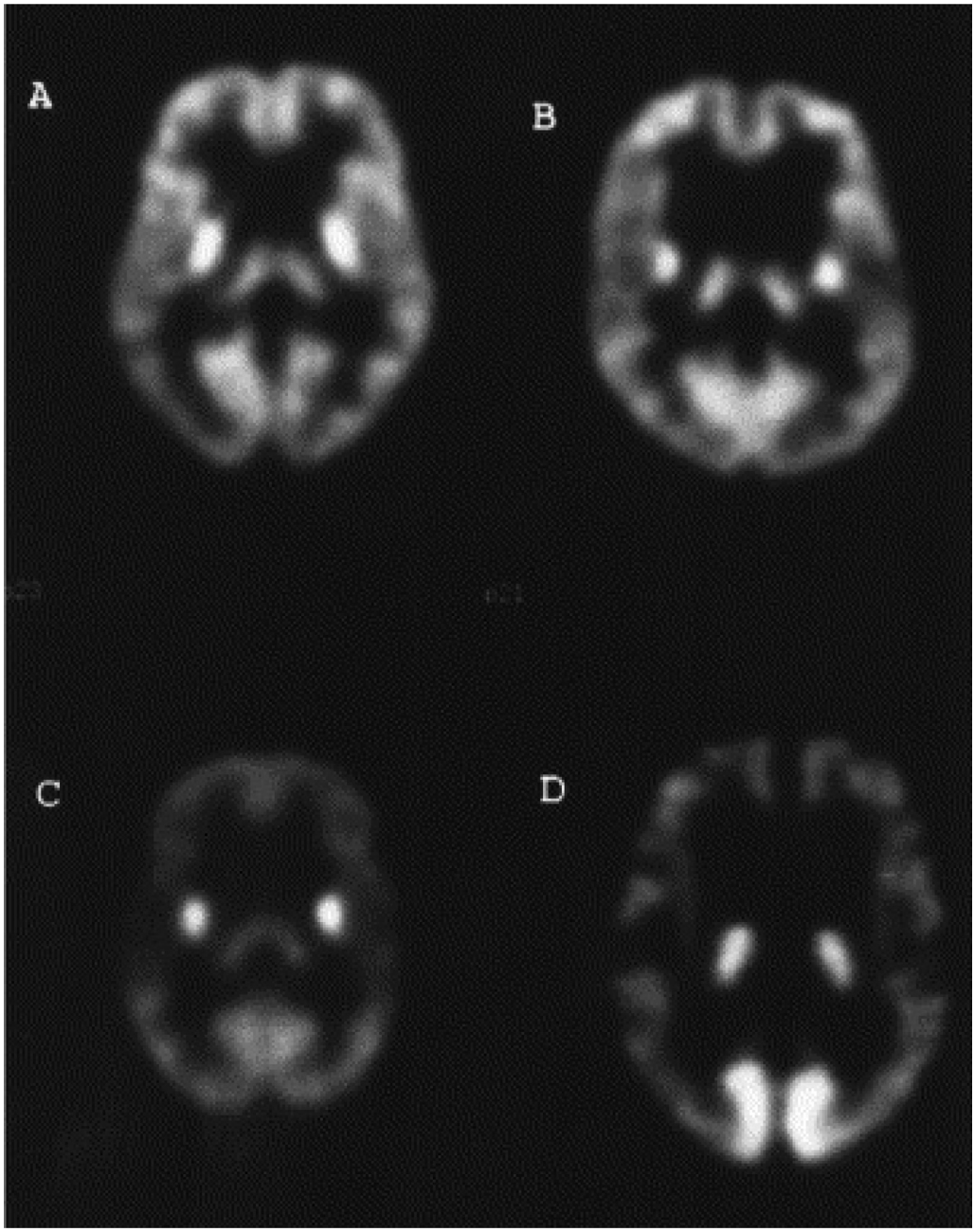

FIGURE 6. Glucose metabolism PET images in a child with 3-methylglutaconic aciduria. (A) Stage I: absent fludeoxyglucose F 18 uptake in the head of the caudate and mild decreased thalamic and cerebellar metabolism. (B and C) Stage II: absent uptake in the anterior half and posterior quarter of the putamina and the heads of the caudate, decreased uptake in the cerebral cortex more prominently in the parietotemporal lobes, and progressively decreased thalamic and cerebellar uptake. (D) Stage III: absent uptake in the putamen and heads of the caudate and severe decreased cortical uptake consistent with brain atrophy. Further decreased cerebellar uptake. The thalamic activity seems to increase when compared with cortical activity.

hypometabolism, also particularly involving the thalamus (Fig 8). Thus, from these very preliminary studies, it appears that the selectively vulnerable areas of brain injury between GM1 and GM2 gangliosidoses are different. If confirmed in larger studies, these metabolic features on PET scanning may be useful as diagnostic aids and biomarkers.

A two-year-old Saudi boy with infantile Krabbe disease, whose MRI revealed mild brain atrophy and white matter disease mainly in the centrum semiovale, was evaluated with PET scanning of glucose metabolism. The PET scan showed marked hypometabolism in the left cerebral cortex and no uptake in the caudate heads, but the thalami, lentiform nuclei, and cerebellum appeared normal.[45] The severe hypometabolism in the heads of the caudate nuclei are presumably related to abnormalities of muscle tone seen in this disorder and could be useful in monitoring disease progression, but further (longitudinal) studies are required.

Dysmyelinating disorders

Demyelinating disorders such as multiple sclerosis have been studied with both glucose metabolism PET and TSPO PET (to detect neuroinflammation), but mostly in adults, and are, therefore, not covered in this review (for reviews see Faria et al.[46]; Singal et al.[47]). However, there have been a number of reports of PET scanning on

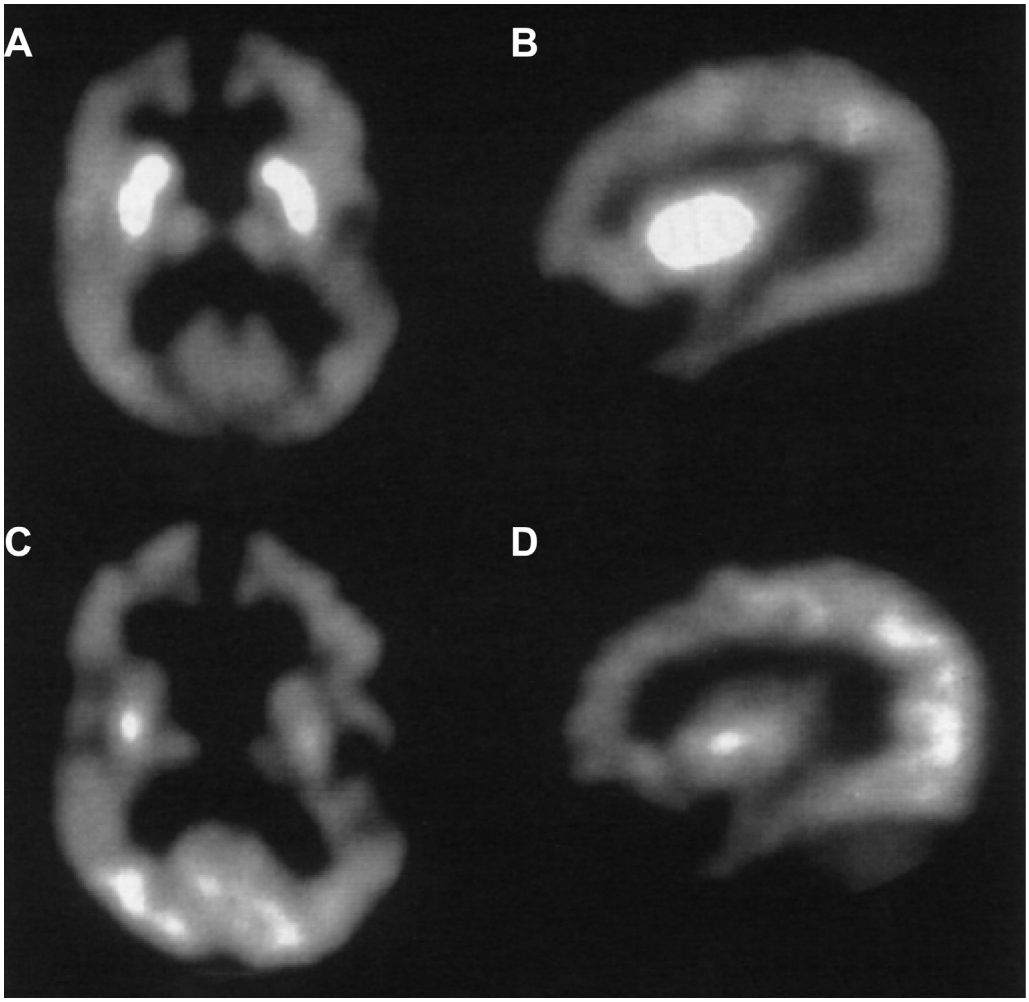

FIGURE 7. (A and B) Glucose metabolism positron emission tomographic images in a six-month-old-infant with ethylmalonic aciduria showing intense bilateral hypermetabolism in the caudate nucleus and putamen and mild frontal cortex hypometabolism. (C and D) Repeat positron emission tomography at age 20 months showed evolution to hypometabolism in caudate and putamen reflecting progressive basal ganglia degeneration. The frontal lobe hypometabolism has also worsened.

various progressive *dysmyelinating* disorders in children and adults. For example, Sawaishi et al.[48] reported on a 13-year-old boy with juvenile Alexander disease whose PET scan showed decreased glucose metabolism in the frontal white matter corresponding to leukodystrophic regions, with preserved glucose metabolism in the overlying gray matter.

Salsano et al.[49] performed glucose metabolism PET on 12 adult subjects with adrenoleukodystrophy and 27 healthy controls. The patients with adrenoleukodystrophy showed a pattern of relatively higher metabolism in frontal lobes and lower metabolism in the cerebellum and temporal lobes. These findings are consistent with those from a number of case reports published earlier. It cannot be determined from visual inspection of the images whether there is an "absolute" hypermetabolism in the frontal lobes or appearance of hypermetabolism due to the hypometabolism in posterior brain regions.

Kumar et al.[50] used ^{11}C-PK11195 PET to study neuroinflammation in a single child with X-linked adrenoleukodystrophy. The investigators found increased tracer binding (i.e., inflammation) in the occipital, parietal, and posterior temporal white matter; corpus callosum genu; bilateral posterior thalami; internal capsule posterior limb; bilateral cerebral peduncles; and brainstem (Fig 9). Interestingly, the cerebellum showed only minimal ^{11}C-PK11195 PET uptake (i.e., minimal inflammation), despite previous observations of cerebellar hypometabolism. We suggest that the glucose hypometabolism in cerebellum may be due to diaschisis from supratentorial involvement and disruption of corticopontocerebellar fibers. We believe that ^{11}C-PK11195 PET may be useful to evaluate the inflammatory burden, disease evolution, and response to novel therapeutic interventions for X-linked adrenoleukodystrophy. Glucose metabolism PET scans may be less useful than MRI in this disorder.

Rett syndrome

Rett syndrome has received significant attention in terms of search for a treatment that can halt the degenerative course, or finding a cure. In a study that employed multimodal imaging in children with Rett syndrome, MRI and MRS revealed that the frontal lobe displayed hypoperfusion, increased choline, and reduced *N*-acetylaspartate concentrations. However, glucose metabolism PET showed *hypermetabolism* of the frontal lobe. The authors suggested that the frontal lobe hypermetabolism may be related to increased glutamate cycling in synapses.[51]

Another study, which evaluated nigrostriatal function using PET in nine patients with Rett syndrome, found reduced fluorodopa uptake in caudate and putamen, but increased dopamine D2

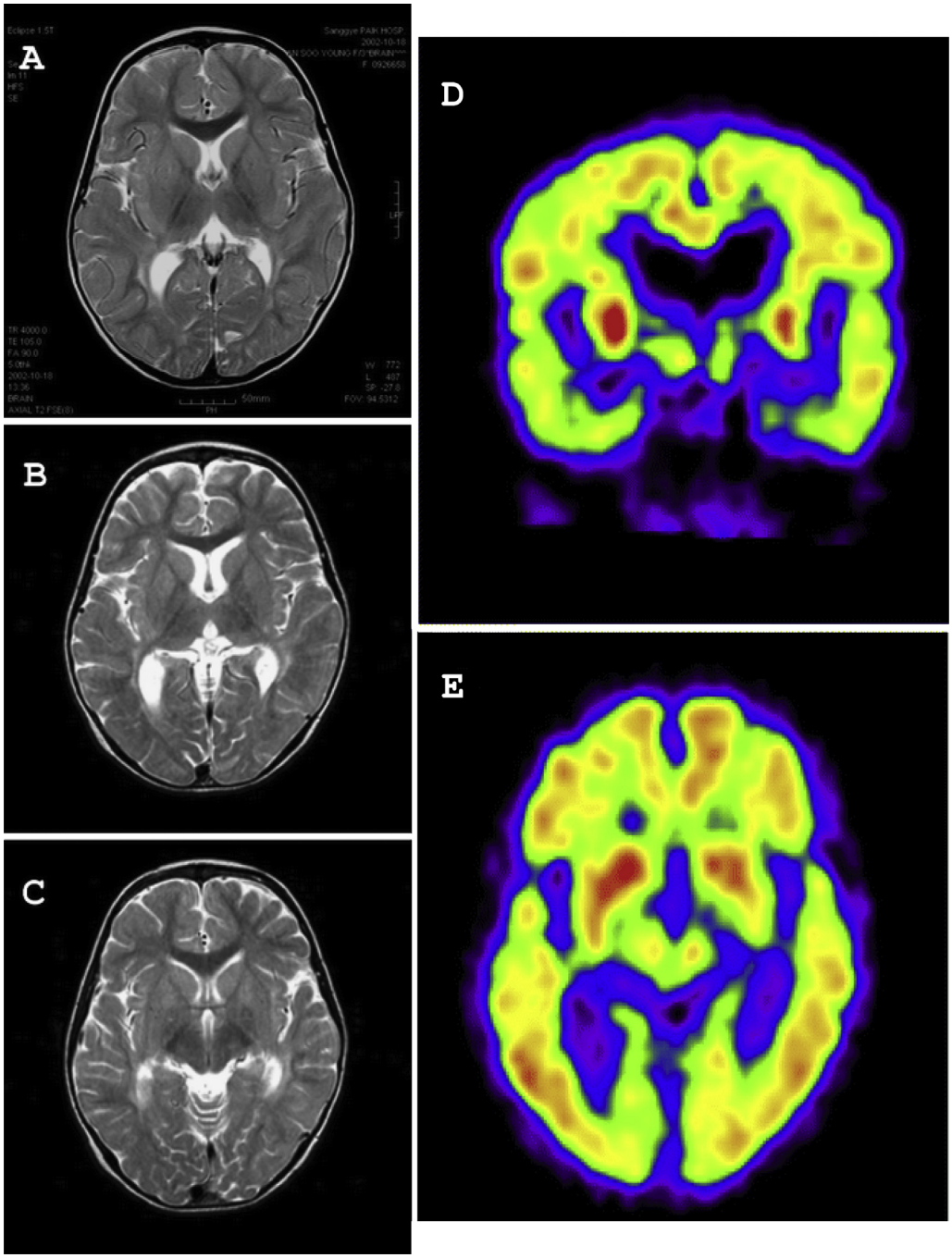

FIGURE 8. Magnetic resonance imaging and positron emission tomographic scans in a child with juvenile GM2 gangliosidosis. The magnetic resonance imaging scans at ages three (A), four (B), and six (C) years showed progressive cerebral atrophy, particularly involving the thalamus. Glucose metabolism positron emission tomographic scan at age six years (D and E) showed diffuse cerebral hypometabolism, also particularly involving thalamus. Note the relative sparing of the basal ganglia.

receptor binding in the same regions.[52] These observations suggested a mild presynaptic deficit of nigrostriatal activity, and that this could be a potential biomarker to monitor disease progression in Rett syndrome. Further studies showed that D2 receptor density was significantly reduced in the striatum of women with Rett syndrome compared with control subjects and, moreover, dopaminergic dysfunction was also present in the Mecp2-deficient mouse model of the disease.[53] Together, these PET findings add to our understanding of the pathophysiology of Rett syndrome and provide avenues of research that could lead to the discovery of useful biomarkers.

Neurotransmitter disorders

Pearl et al.[54] have performed PET scans of $GABA_A$ receptor binding using the radiotracer ^{11}C-flumazenil in seven patients with succinic semialdehyde dehydrogenase (SSADH) deficiency. Reduced binding was observed in the amygdala, hippocampus, cerebellar vermis, and the frontal, parietal, and occipital cortex in patients with SSADH deficiency compared with healthy controls (Fig 10). These findings are presumably due to down-regulation of $GABA_A$ receptors in response to the high endogenous brain GABA levels in this disorder where there is an

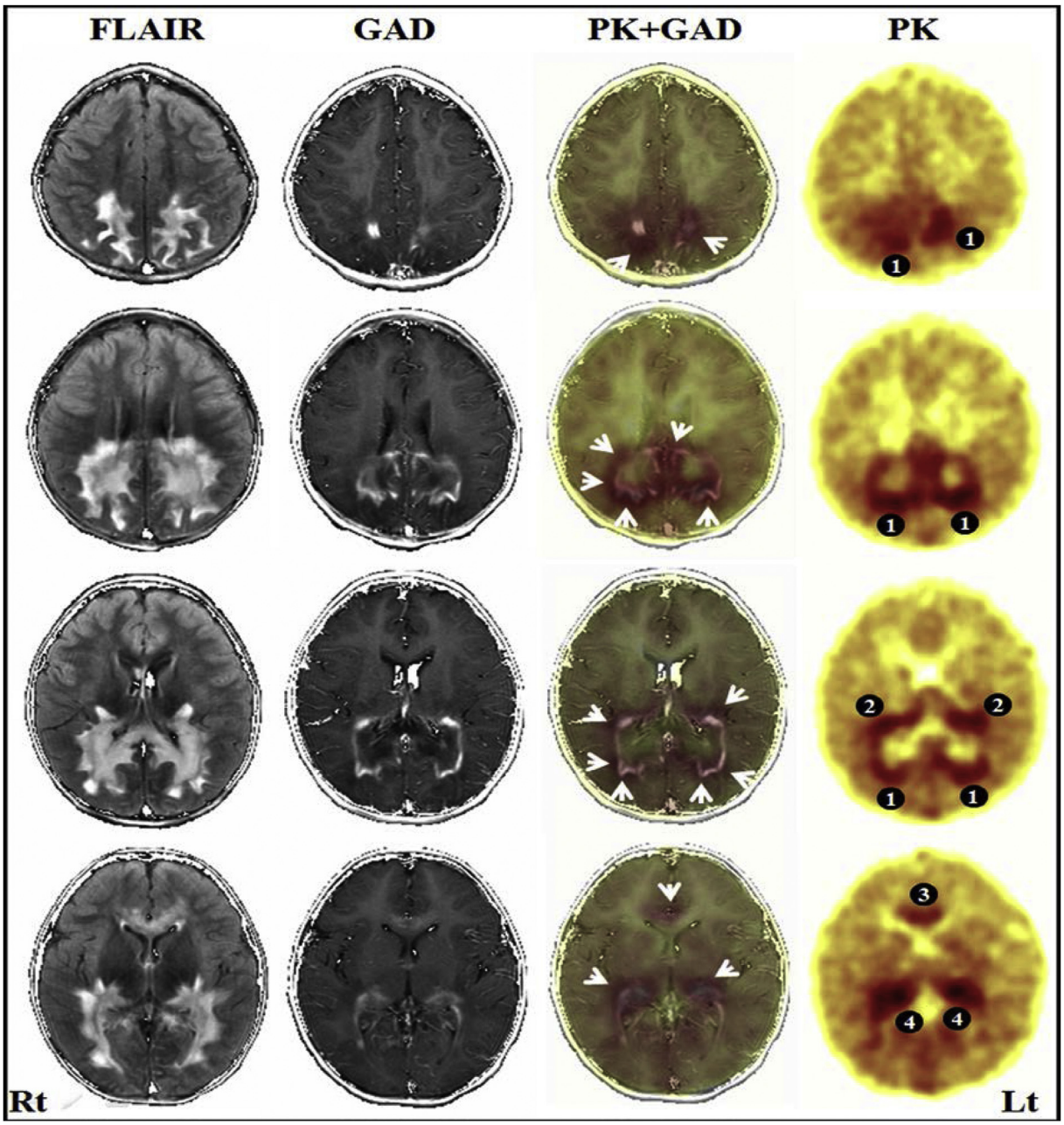

FIGURE 9. Fluid-attenuated inversion recovery magnetic resonance (MR) image, gadolinium-enhanced T1-weighted MR image, and ^{11}C-PK11195 positron emission tomographic images superimposed on gadolinium-enhanced T1-weighted MR images (small white arrows) and ^{11}C-PK11195 PET images in child with X-linked adrenoleukodystrophy. Increased ^{11}C-PK11195 binding is seen in the occipital, parietal, and posterior temporal white matter (1), posterior limb of internal capsule (2), genu of corpus callosum (3), bilateral posterior thalami (4), bilateral cerebral peduncles, and brainstem (not shown here).

impairment of GABA metabolism. Further studies using transcranial magnetic stimulation and murine genetic models of mutations in the ALDH5A1 gene, which cause SSADH deficiency, have led to therapeutic trials wherein ^{11}C-flumazenil PET scanning might provide an important measure of treatment success.[55]

Glucose transporter Glut1 deficiency

Pascual et al.[56] performed glucose metabolism PET scans on 14 patients with microcephaly, developmental delay, seizures, and mutations of the glucose transporter Glut1. Although MRI scans appeared normal except for the microcephaly, the PET scans showed diffuse hypometabolism in the cerebral cortex, particularly medial temporal regions. Hypometabolism was very pronounced in the thalami, but not basal ganglia. The authors suggested that this metabolic pattern on PET scans may be a radiological "signature" of the disease.

Lesch-Nyhan disease

The clinical features of choreoathetosis, dystonia, aggression, and self-injurious behavior in Lesch-Nyhan disease suggest dopaminergic dysfunction. Indeed, postmortem studies in three patients with Lesch-Nyhan disease have revealed a deficit in dopamine, homovanillic acid, and dopa decarboxylase in the basal ganglia.

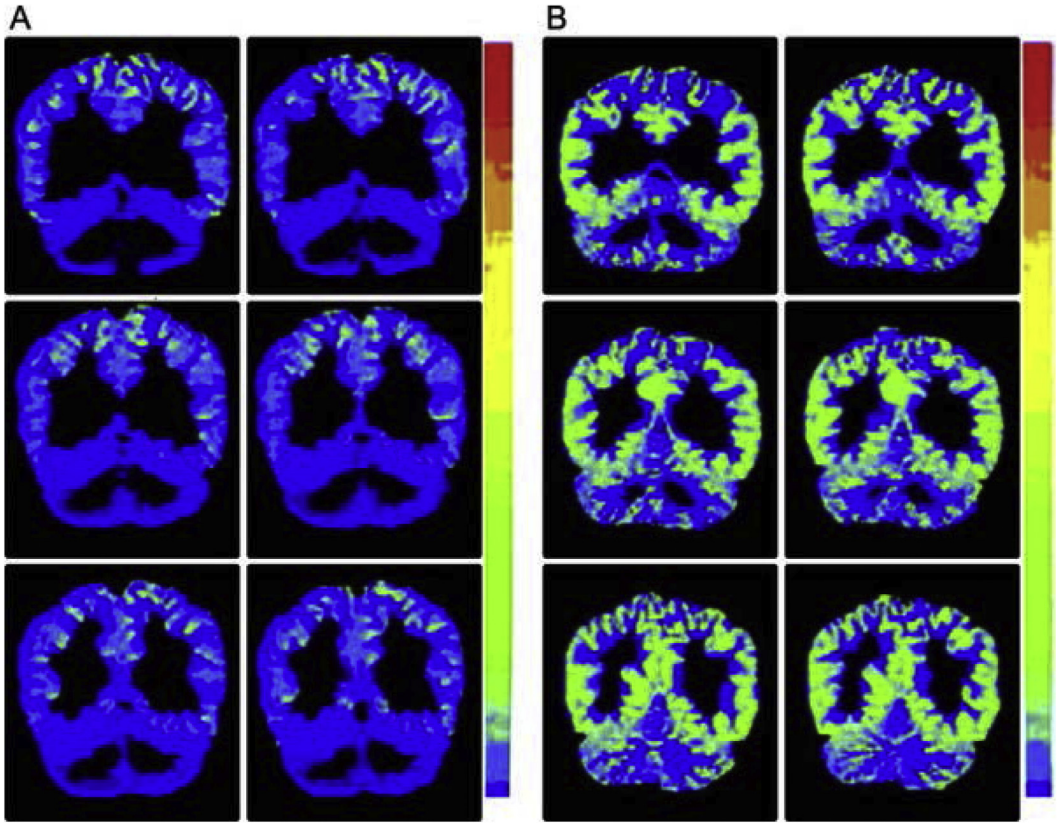

FIGURE 10. ^{11}C-flumazenil positron emission tomographic scans in a patient with succinic semialdehyde dehydrogenase (SSADH) deficiency (A) and in a control subject (B). Note the severe reduction of $GABA_A$ receptor binding involving multiple regions in the patient.

Dopaminergic dysfunction in this disorder is further substantiated by PET studies. Using PET with the presynaptic radiotracer ^{18}F-fluorodopa in 12 patients with Lesch-Nyhan disease, Ernst et al.[57] reported decreased uptake in putamen (31% of control values), caudate nucleus (39%), frontal cortex (44%), and ventral tegmental complex (substantia nigra and ventral tegmentum: 57%) in the patients compared with uptake in 15 healthy control subjects. In another study, which used the PET radiotracer ^{11}C-WIN-35,428 to image dopamine transporters, Wong et al.[58] found 50% to 63% reduced binding in the caudate and 64% to 75% reduced binding in the putamen of patients with Lesch-Nyhan disease compared with a normal control group. Thus, in addition to providing further insights into the pathophysiology of Lesch-Nyhan disease, PET studies have also provided potentially useful biomarkers to monitor the course of the disease and assess the efficacy of therapeutic interventions.

"Biomarkers" in search of a disease

A pattern of diffuse bilateral glucose hypometabolism in PET scans is not infrequently seen in children with developmental delay and epilepsy without a specific genetic diagnosis. In a retrospective study, Shandal et al.[59] found 31 patients with *severe* bilateral diffuse cortical hypometabolism in a PET database. Of these, 14 patients were lost to follow-up and one patient was deceased. The authors analyzed data (follow-up period: 15 ± 4.8 years) from the 16 remaining cases (nine males). The MRI was normal in 12 and showed nonspecific changes in four. At the time of analysis, a specific diagnosis had been reached in only four of the 16 cases, one each with Mecp2 gene duplication, Lafora disease, 4-Mb deletion of mitochondrial genome, and Sanfillippo disease. Of the 16 patients, 14 continued to have seizures, but this is not surprising because of the patient selection bias in an epilepsy center. There were at least six patterns of glucose hypometabolism seen on the PET scans (Fig 11). As advanced genetic testing was not available in most of these patients, most often due to insurance denial, a correlation between genotype and PET phenotype could not be made. However, with increasing access to whole-exome and whole-genome sequencing, we should be able to better understand the complex patterns of diffuse hypometabolism (biomarkers) associated with various pathogenic gene variants.

Conclusion

In this review, we have attempted to summarize findings from PET studies over the past three decades in children with neurodegenerative disorders, with only brief mention of the plethora of PET data from adults. We emphasize that the field has not flourished in pediatric disorders, in contrast to in adult neurodegenerative disorders, and there remains an enormous opportunity to improve our understanding of pediatric neurodegenerative disorders through molecular imaging with PET technology. PET biomarkers will be important as treatments become available for these relatively rare disorders. Finally, there is adequate evidence to indicate that glucose metabolism PET scans are clinically useful in children with neurodegenerative disorders, and the time has come for health care insurers to expand coverage of these scans beyond epilepsy surgery evaluation. More specific PET scans to evaluate neurotransmitter and enzyme function, on the other hand, should be assessed on a case-by-case basis, but will likely remain at a research level at least for now.

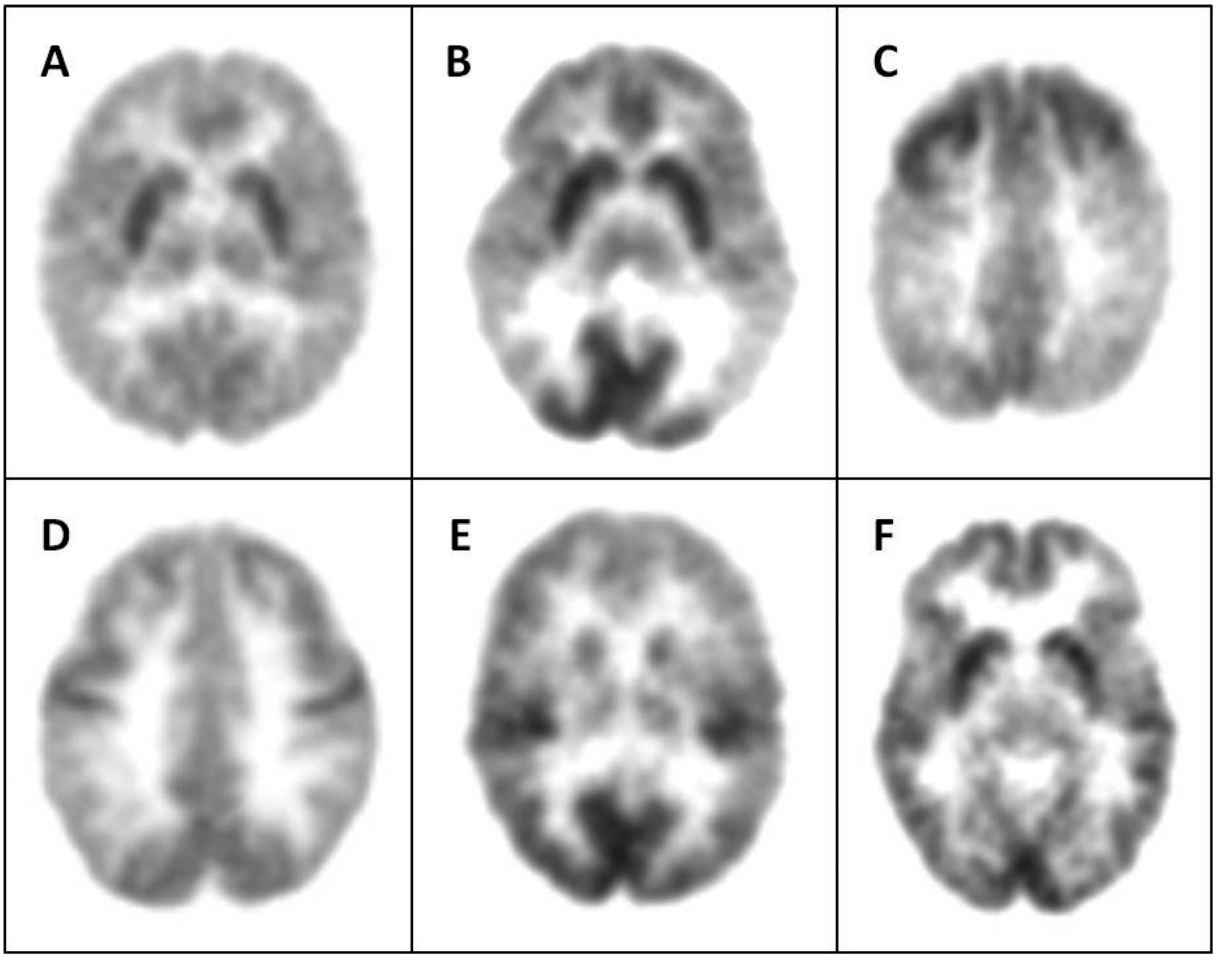

FIGURE 11. Different patterns of bilateral diffuse glucose hypometabolism on PET scans. (A) Diffuse hypometabolism involving all the lobes. (B) Diffuse hypometabolism sparing medial occipital cortex. (C) Diffuse hypometabolism sparing portions of frontal cortex. (D) Diffuse hypometabolism sparing motor cortex. (E) Diffuse hypometabolism sparing auditory and occipital cortex. (F) Diffuse hypometabolism sparing medial frontal and medial occipital cortices.

References

1. Kato T, Inui Y, Nakamura A, Ito K. Brain fluorodeoxyglucose (FDG) PET in dementia. Ageing Res Rev. 2016;30:73–84.
2. Valotassiou V, Malamitsi J, Papatriantafyllou J, et al. SPECT and PET imaging in Alzheimer's disease. Ann Nucl Med. 2018;32:583–593.
3. Chen MK, Mecca AP, Naganawa M, et al. Assessing synaptic density in Alzheimer disease with synaptic vesicle glycoprotein 2A positron emission tomography imaging. JAMA Neurol. 2018;75:1215–1224.
4. Williams RE, Adams HR, Blohm M, et al. Management strategies for CLN2 disease. Pediatr Neurol. 2017;69:102–112.
5. Mole SE, Anderson G, Band HA, et al. Clinical challenges and future therapeutic approaches for neuronal ceroid lipofuscinosis. Lancet Neurol. 2019;18:107–116.
6. De Volder AG, Cirelli S, de Barsy T, et al. Neuronal ceroid-lipofuscinosis: preferential metabolic alterations in thalamus and posterior association cortex demonstrated by PET. J Neurol Neurosurg Psychiatry. 1990;53:1063–1067.
7. Philippart M, Messa C, Chugani HT. Spielmeyer-Vogt (Batten, Spielmeyer-Sjogren) disease. Distinctive patterns of cerebral glucose utilization. Brain. 1994;117:1085–1092.
8. Iannetti P, Messa C, Spalice A, Lucignani G, Fazio F. Positron emission tomography in neuronal ceroid lipofuscinosis (Jansky-Bielschowsky disease): a case report. Brain Dev. 1994;16:459–462.
9. Philippart M, da Silva E, Chugani HT. The value of positron emission tomography in the diagnosis and monitoring of late infantile and juvenile lipopigment storage disorders (so-called Batten or neuronal ceroid lipofuscinoses). Neuropediatrics. 1997;28:74–76.
10. Rinne JO, Ruottinen HM, Nagren K, Aberg LE, Santavuori P. Positron emission tomography shows reduced striatal D1 but not D2 receptors in juvenile neuronal ceroid lipofuscinosis. Neuropediatrics. 2002;33:138–141.
11. Hayden MR, Martin WR, Stoessl AJ, et al. Positron emission tomography in the early diagnosis of Huntington's disease. Neurology. 1986;36:888–894.
12. Pagano G, Niccolini F, Politis M. Current status of PET imaging in Huntington's disease. Eur J Nucl Med Mol Imaging. 2016;43:1171–1182.
13. Wilson H, Niccolini F, Haider S, et al. Loss of extra-striatal phosphodiesterase 10A expression in early premanifest Huntington's disease gene carriers. J Neurol Sci. 2016;368:243–248.
14. De Volder A, Bol A, Michel C, et al. Brain glucose utilization in childhood Huntington's disease studied with positron emission tomography (PET). Brain Dev. 1988;10:47–50.
15. Diggle CP, Rizzo SJS, Popiolek M, et al. Biallelic mutations in PDE10A lead to loss of striatal PDE10A and a hyperkinetic movement disorder with onset in infancy. Am J Hum Genet. 2016;98:735–743.
16. Hawkins RA, Mazziotta JC, Phelps ME. Wilson's disease studied with FDG and positron emission tomography. Neurology. 1987;37:1707–1711.
17. Kuwert T, Hefter H, Scholz D, et al. Regional cerebral glucose consumption measured by positron emission tomography in patients with Wilson's disease. Eur J Nucl Med. 1992;19:96–101.
18. Westermark K, Tedroff J, Thuomas KA, et al. Neurological Wilson's disease studied with magnetic resonance imaging and with positron emission tomography using dopaminergic markers. Mov Disord. 1995;10:596–603.
19. Bruehlmeier M, Leenders KL, Vontobel P, Calonder C, Antonini A, Weindl A. Increased cerebral iron uptake in Wilson's disease: a 52Fe-citrate PET study. J Nucl Med. 2000;41:781–787.
20. Kumar A, Chugani HT. Niemann-Pick disease type C: unique 2-deoxy-2[^{18}F] fluoro-D-glucose PET abnormality. Pediatr Neurol. 2011;44:57–60.
21. Benussi A, Alberici A, Premi E, et al. Phenotypic heterogeneity of Niemann-Pick disease type C in monozygotic twins. J Neurol. 2015;262:642–647.
22. Huang JY, Peng SF, Yang CC, Yen KY, Tzen KY, Yen RF. Neuroimaging findings in a brain with Niemann-Pick type C disease. J Formos Med Assoc. 2011;110:537–542.
23. Kumar A, Chugani HT, Muzik O, Chakraborty P. [C-11]PK-11195 as a positron emission tomography biomarker of brain inflammation in children with Niemann-Pick disease type-C. J Nucl Med. 2009;50(suppl 2):96P.

24. Ferrie CD, Maisey M, Cox T, et al. Focal abnormalities detected by 18FDG PET in epileptic encephalopathies. Arch Dis Child. 1996;75:102–107.
25. Kumar A, Juhász C, Luat A, et al. Evolution of brain glucose metabolic abnormalities in children with epilepsy and SCN1A gene variants. J Child Neurol. 2018;33:832–836.
26. Haginoya K, Togashi N, Kantea T, et al. [^{18}F]fluorodeoxyglucose-positron emission tomography study of genetically confirmed patients with Dravet syndrome. Epilepsy Res. 2018;147:9–14.
27. Alongi P, Iaccarino L, Perani D. PET neuroimaging: insights on dystonia and Tourette syndrome and potential applications. Front Neurol. 2014;5:183–196.
28. Szyszko TA, Dunn JT, O'Doherty MJ, Reed L, Lin JP. Role of ^{18}F-FDG PET imaging in paediatric primary dystonia and dystonia arising from neurodegeneration with brain iron accumulation. Nucl Med Commun. 2015;36:469–476.
29. Rinne JO, Iivanainen M, Metsähonkala L, et al. Striatal dopaminergic system in dopa-responsive dystonia: a multi-tracer PET study shows increased D2 receptors. J Neural Transm (Vienna). 2004;111:59–67.
30. Frackowiak RS, Herold S, Petty RK, Morgan-Hughes JA. The cerebral metabolism of glucose and oxygen measured with positron tomography in patients with mitochondrial diseases. Brain. 1988;111:1009–1024.
31. Toyoda M, Sakuragawa N, Arai Y, et al. Positron emission tomography using pyruvate-1-11C in two cases of mitochondrial encephalomyopathy. Ann Nucl Med. 1989;3:103–109.
32. Yokoi F, Hara T, Iio M, Nonaka I, Satoyoshi E. 1-[11C]pyruvate turnover in brain and muscle of patients with mitochondrial encephalomyopathy. A study with positron emission tomography (PET). J Neurol Sci. 1990;99:339–348.
33. Shishido F, Uemura K, Inugami A, et al. Cerebral oxygen and glucose metabolism and blood flow in mitochondrial encephalomyopathy: a PET study. Neuroradiology. 1996;38:102–107.
34. Duncan DB, Herholz K, Kugel H, et al. Positron emission tomography and magnetic resonance spectroscopy of cerebral glycolysis in children with congenital lactic acidosis. Ann Neurol. 1995;37:351–358.
35. Haginoya K, Kaneta T, Togashi N, et al. FDG-PET study of patients with Leigh syndrome. J Neurol Sci. 2016;362:309–313.
36. Mascalchi M, Montomoli M, Guerrini R. Neuroimaging in mitochondrial disorders. Essays Biochem. 2018;62:409–421.
37. Al-Essa M, Bakheet S, Patay Z, et al. Fluoro-2-deoxyglucose (18FDG) PET scan of the brain in glutaric aciduria type 1: clinical and MRI correlations. Brain Dev. 1998;20:295–301.
38. Al-Essa M, Bakheet S, Al-Shamsan L, Patay Z, Powe J, Ozand PT. 18Fluoro-2-deoxyglucose (18FDG) PET scan of the brain in type IV 3-methylglutaconic aciduria: clinical and MRI correlations. Brain Dev. 1999;21:24–29.
39. Al-Essa M, Bakheet S, Patay Z, et al. 18Fluoro-2-deoxyglucose (18FDG) PET scan of the brain in propionic acidemia: clinical and MRI correlations. Brain Dev. 1999;21:312–317.
40. Al-Essa MA, al-Shamsan LA, Ozand PT. Clinical and brain 18fluoro-2-deoxyglucose positron emission tomographic findings in ethylmalonic aciduria, a progressive neurometabolic disease. Eur J Paediatr Neurol. 1999;3:125–127.
41. Al-Essa MA, Bakheet SM, Patay ZJ, Powe JE, Ozand PT. Clinical, fluorine-18 labeled 2-fluoro-2-deoxyglucose positron emission tomography (FDG PET), MRI of the brain and biochemical observations in a patient with 4-hydroxybutyric aciduria; a progressive neurometabolic disease. Brain Dev. 2000;22:127–131.
42. Biffi A. Gene therapy for lysosomal storage disorders: a good start. Hum Mol Genet. 2016;25(R1):R65–R75.
43. Al-Essa MA, Bakheet SM, Patay ZJ, Nounou RM, Ozand PT. Cerebral fluorine-18 labeled 2-fluoro-2-deoxyglucose positron emission tomography (FDG PET), MRI, and clinical observations in a patient with infantile G(M1) gangliosidosis. Brain Dev. 1999;21:559–562.
44. Lee SM, Lee MJ, Lee JS, et al. Newly observed thalamic involvement and mutations of the HEXA gene in a Korean patient with juvenile GM2 gangliosidosis. Metab Brain Dis. 2008;23:235–242.
45. Al-Essa MA, Bakheet SM, Patay ZJ, Powe JE, Ozand PT. Clinical and cerebral FDG PET scan in a patient with Krabbe's disease. Pediatr Neurol. 2000;22:44–47.
46. Faria Dde P, Copray S, Buchpiguel C, Dierckx R, de Vries E. PET imaging in multiple sclerosis. J Neuroimmune Pharmacol. 2014;4:468–482.
47. Singhal T, Weiner HL, Bakshi R. TSPO-PET imaging to assess cerebral microglial activation in multiple sclerosis. Semin Neurol. 2017;37:546–557.
48. Sawaishi Y, Hatazawa J, Ochi N, et al. Positron emission tomography in juvenile Alexander disease. J Neurol Sci. 1999;165:116–120.
49. Salsano E, Marotta G, Manfredi V, et al. Brain fluorodeoxyglucose PET in adrenoleukodystrophy. Neurology. 2014;83:981–989.
50. Kumar A, Chugani HT, Chakraborty P, Huq AH. Evaluation of neuroinflammation in X-linked adrenoleukodystrophy. Pediatr Neurol. 2011;44:143–146.
51. Naidu S, Kaufmann WE, Abrams MT, et al. Neuroimaging studies in Rett syndrome. Brain Dev. 2001;23(Suppl 1):S62–S71.
52. Dunn HG, Stoessl AJ, Ho HH, et al. Rett syndrome: investigation of nine patients, including PET scan. Can J Neurol Sci. 2002;29:345–357.
53. Wong DF, Blue ME, Brašić JR, et al. Are dopamine receptor and transporter changes in Rett syndrome reflected in Mecp2-deficient mice? Exp Neurol. 2018;307:74–81.
54. Pearl PL, Gibson KM, Quezado Z, et al. Decreased GABA-A binding on FMZ-PET in succinic semialdehydedehydrogenase deficiency. Neurology. 2009;73:423–429.
55. Pearl PL, Parviz M, Vogel K, Schreiber J, Theodore WH, Gibson KM. Inherited disorders of gamma-aminobutyric acid metabolism and advances in ALDH5A1 mutation identification. Dev Med Child Neurol. 2015;57:611–617.
56. Pascual JM, Van Heertum RL, Wang D, Engelstad K, De Vivo DC. Imaging the metabolic footprint of Glut1 deficiency on the brain. Ann Neurol. 2002;52:458–464.
57. Ernst M, Zametkin AJ, Matochik JA, et al. Presynaptic dopaminergic deficits in Lesch-Nyhan disease. N Engl J Med. 1996;334:1568–1572.
58. Wong DF, Harris JC, Naidu S, et al. Dopamine transporters are markedly reduced in Lesch-Nyhan disease in vivo. Proc Natl Acad Sci U S A. 1996;93:5539–5543.
59. Shandal V, Veenstra AL, Behen M, Sundaram S, Chugani H. Long-term outcome in children with intractable epilepsy showing bilateral diffuse cortical glucose hypometabolism pattern on positron emission tomography. J Child Neurol. 2012;27:39–45.