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Evolution of lobar abnormalities of cerebral glucose metabolism in 41 children with drug-resistant epilepsy

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SUMMARY

Objective—We analyzed long-term changes of lobar glucose metabolic abnormalities in relation to clinical seizure variables and development in a large group of children with medically refractory epilepsy.

Methods—Forty-one children (25 males) with drug-resistant epilepsy had a baseline PET scan at a median age of 4.7 years; the scans were repeated after a median of 4.3 years. Children with progressive neurological disorders, space occupying lesion-related epilepsy, and those who had undergone epilepsy surgery were excluded. The number of affected lobes on FDG-PET at baseline and follow-up were correlated with epilepsy variables and developmental outcome.

Results—On the initial PET scan, 24 children had unilateral and 13 had bilateral glucose hypometabolism, whereas 4 children had normal scans. On the follow-up scan, 63% of the children showed an interval expansion of the hypometabolic region, and this progression was associated with persistent seizures. In contrast, 27% showed less extensive glucose hypometabolism at follow-up; most of these subjects manifested a major interval decrease in seizure frequency. Delayed development was observed in 21 children (51%) at baseline and 28 (68%) at follow-up. The extent of glucose hypometabolism at baseline correlated with

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developmental levels at the time of both baseline ($r=0.31$, $P=0.05$) and follow-up scans ($r=0.27$, $P=0.09$).

Significance—In this PET study of unoperated children with focal epilepsy, the lobar pattern of glucose hypometabolism changed over time in 90% of the cases. The results support the notion of an expansion of metabolic dysfunction in children with persistent frequent seizures and its association with developmental delay, and support that optimized medical treatment to control seizures may contribute to better neuro-cognitive outcome if no surgery can be offered.

Keywords

pediatric epilepsy; positron emission tomography; seizure frequency; development; follow-up

INTRODUCTION

Ictal electroencephalography (EEG) recordings are the main determinants of whether a patient with refractory epilepsy qualifies for surgical intervention¹. However, seizures are sometimes difficult to capture, and interictal abnormalities of EEG activity, MRI, patterns of cerebral glucose metabolism and cerebral blood flow, as well as neuropsychological profile can also contribute to the localization of epileptic foci². When a structural abnormality is not present on MRI, one of the commonly used modalities for pre-surgical mapping of the abnormally functioning cerebral cortex is positron emission tomography (PET) using 2-deoxy-2(¹⁸F)-fluoro-D-glucose (FDG)³. This imaging modality has now been used for more than 30 years to identify epileptic foci, with hypometabolism in the area of the epileptic focus being the most frequent interictal finding⁴. The exact cause of interictal hypometabolism is still not completely understood, although it is assumed to be related to multiple mechanisms, including neuronal loss and altered synaptic activity^{5–8}.

Previous studies have demonstrated that the *extent* of interictal hypometabolism in the epileptic brain can evolve over time. For example, children with recent onset epilepsy often show normal FDG-PET initially but, subsequently, a subset of them will develop cortical hypometabolism⁹. Longitudinal studies in children with medically refractory epilepsy who have not undergone epilepsy surgery have been scarce. A small FDG-PET study of 15 children with medically refractory epilepsy by our group demonstrated both interval decreases and increases in the extent of cortical glucose metabolism as measured by an analysis of asymmetry; metabolic changes in the epileptic hemisphere were associated with interval seizure frequency in that study¹⁰. Reversal of some hypometabolic abnormalities outside the primary seizure focus has also been reported after effective seizure control with medication or resective surgery^{10–13}. These findings point towards a dynamic nature of cortical hypometabolism in epileptic subjects. However, there have been no long-term longitudinal studies evaluating the evolution of cortical glucose metabolism in childhood epilepsy for the whole brain. In the present study, we have attempted to bridge this knowledge gap through a retrospective evaluation of children with drug-resistant epilepsy, who had at least two interictal FDG-PET scans more than one year apart. We evaluated the patterns of longitudinal changes in cortical glucose metabolic abnormalities at the lobar level. In addition, we assessed if the baseline extent and/or interval changes in metabolism

seen on FDG-PET were associated with clinical variables, such as seizure frequency and developmental delay.

METHODS

Study population

This was a retrospective study performed at the Children's Hospital of Michigan, Wayne State University, Detroit, a level 4 epilepsy center. From our pediatric FDG-PET database, we selected and reviewed clinical data and FDG-PET reports of children with medically refractory epilepsy, who had undergone more than one interictal FDG-PET scan over the course of their clinical follow-up at our center, as a part of pre-surgical evaluation between March, 2003 and January, 2016.

Data about demographic and clinical variables including the age, seizure type(s), seizure frequency, developmental level, EEG and MRI findings at the time of both scans were obtained through a review of the medical records (Table 1). Children who had surgical resection of the epileptic focus after the first scan were not included in the study. In the study patients, surgery was not performed after the initial scan due to inadequate localizing data, improvement in clinical condition, or caregiver decision. The second PET scan in these children was a part of repeat pre-surgical evaluation at least one year after the first scan. Children with extensive severe MRI abnormalities (e.g., multilobar developmental malformations, tuberous sclerosis) and those with space occupying lesion-related epilepsy, or a history of meningitis or encephalitis, were excluded.

As a result of the above selection process, we identified 41 children (25 males, 16 females) who fulfilled the selection criteria. The median age of these children was 4.7 years (range: 0.4–17.4 years) at the time of the first PET scan, which was repeated after a median of 4.3 years (range: 1.3–11 years). Details of demographic, clinical and imaging characteristics are given in Table 1. Eight of the 41 children showed MRI abnormalities (including five at baseline). MRIs with baseline abnormalities remained stable over time (2 heterotopias, 1 remote intra-ventricular hemorrhage, 1 subtle mesial temporal sclerosis, and 1 cortical dysplasia). Three additional patients had MRI signs of cortical dysplasia that became apparent on the second MRI scan. Six children had genetic abnormalities known at last follow-up: 3 had SCN1A mutation, 1 had SCN2A mutation, 1 had KCNQ5 mutation, and 1 had 2q11.2 and 5q21.2 duplications.

Assessment of seizure frequency

In order to estimate severity of epilepsy, we assigned a seizure frequency score to each patient (modified from previous literature)^{10,14}, both at baseline and follow-up. This score allowed us to assess major changes in seizure frequency over time. Seizure frequency was categorized using a 6-point scale (score 0: no seizures; score 1: occasional seizures, i.e., <1 seizure per month; score 2: monthly seizures, i.e., >1 seizure/month but <1/week; score 3: weekly seizures, >1 seizure/week but <1/day; score 4: 1–9 seizures/day; score 5: 10 seizures/day).

Assessment of developmental status

Medical records of each child were reviewed in order to determine developmental status at the time of baseline and follow-up PET. Children were categorized by a clinical neuropsychologist with extensive experience in psychodiagnostic assessment of children, blind to imaging data, into the following categories: (1) development within normal limits, (2) atypical development, mild/moderate delay, (3) atypical development, severe delay. Children were considered as having development within normal limits if development was within typical limits for the child's chronological age across developmental domains. Children were placed into the atypical, mild/moderate group where at least one area of development was identified to fall outside of typical (and had warranted further evaluation/intervention) for the child's chronological age, but in no domain was there severely involved impairment identified; children were placed into atypical development, severe group, where severe/profound deviations from age-expected development were identified. The supplementary table presents specific developmental characteristics/criteria for each of the 28 patients upon which mild/moderate vs. severe delay determinations were made. Patients with development within normal limits at both time points are not included in the table.

FDG-PET acquisition

All FDG-PET scans were obtained in the interictal state, using either the EXACT/HR PET scanner (CTI/Siemens, Hoffman Estates, IL, USA), or the GE Discovery STE PET/CT scanner (GE Medical Systems, Milwaukee, WI), both located at the PET Center, Children's Hospital of Michigan. The difference between the two scanners was an isotropic image resolution of $5.5 \pm 0.35\text{mm}$ at full-width at half-maximum (FWHM) on the Siemens scanner and $6.0 \pm 0.5\text{mm}$ at FWHM on the GE Discovery scanner. For both scanners, 47 axial image planes were obtained, with a slice thickness of 3.125mm. Four hours of fasting was required prior to the procedure. Intravenous slow bolus of 0.143mCi/kg of FDG was injected, followed by a 30-minute uptake period. Continuous scalp EEG monitoring was performed during tracer uptake. External stimuli were minimized during this time by asking the patients to lie quietly in a semi-dark room with their eyes closed. The children were positioned in the scanner 40 minutes after FDG injection, and a static 20-minute emission scan of the brain was acquired. Automated threshold fits to sinogram data were used to calculate the attenuation correction which was then applied to the brain images. After the tracer uptake period (but not during the uptake period), sedation was used when necessary.

FDG-PET evaluation

The FDG-PET scans were originally assessed by one of the co-authors (HTC), who has a 30-year experience of reading pediatric PET scans. Each of the PET scans were digitally retrieved and re-evaluated for the purpose of this study by two other co-authors independently (AK, CJ), who were blinded to the clinical and EEG data of the patients, and who recorded lobes showing hypometabolism in each hemisphere. Discrepancies in these readings were resolved by re-reviewing the images and reaching a consensus between the two raters.

Study design and statistical analysis

Spearman's rank correlations were performed to evaluate the association between the clinical and imaging characteristics at the baseline and follow-up PET. Age, seizure frequency score, time of the last clinical seizure before the PET scan, developmental levels at both scans and time interval between baseline and follow-up scans were correlated with the extent of PET abnormalities (number of lobes involved, range: 0–8) as well as the interval change in PET involvement. We also analyzed the association between the interval change in seizure frequency scores and the change in FDG-PET involvement in a subgroup of 30 patients with seizure frequency scores between 2–4 at baseline (<9/day to monthly seizures), i.e., in patients where baseline seizure frequency was more homogeneous (by excluding very severe and mild cases). A Wilcoxon signed rank test was performed to compare the extent of PET abnormality at initial and follow-up PET. Kruskal-Wallis tests followed by post-hoc Mann-Whitney U-tests were performed to compare the number of lobes involved on FDG-PET, based on the developmental delay distribution (normal, mild/moderate, severe). Likewise, the number of lobes involved on FDG-PET were compared between those with vs. without epileptiform activity on PET-EEG and those with focal vs. generalized epilepsy, using Mann-Whitney U-tests. A p-value of <0.05 was considered significant. IBM SPSS version 22.0 (IBM Corp, Armonk, NY) was used for statistical analyses.

RESULTS

Baseline abnormalities and interval changes of lobar PET abnormalities

Of the 41 children, 24 had unilateral and 13 had bilateral hypometabolism, whereas 4 children had normal baseline PET scans. At follow-up, 4 (10%) children showed no change in metabolism, 11 (27%) showed a decrease and 26 (63%) showed an increase in the number of lobes involved, i.e., a substantial expansion of metabolic abnormalities (see example on Figure 1). Among these 26 children, 3 showed progression in the originally affected hemisphere, 12 progressed from uni- to bilateral abnormalities, and 7 already had bilateral involvement at baseline; 4 children had no apparent metabolic abnormality at baseline but showed unilateral (n=1) or bilateral abnormality (n=3) on the follow-up scan. The extent of abnormality on follow-up was significantly different from the initial PET and, in general, showed an increase in extent over time (median number of abnormal lobes 2 [IQR: 1–3] at baseline and 3 [IQR: 2–4] at follow-up; $P=0.04$ on Wilcoxon signed rank test). This change was even more significant in the subgroup of 30 patients with baseline seizure frequency scores between 2–4 ($P=0.02$). In addition, smaller extent of baseline PET abnormalities were associated with greater changes (progression) of metabolic abnormalities during follow-up (Spearman's rho [r] = -0.42 , $P=0.006$). Longer time between the two PET scans showed a non-significant trend with more interval change in extent of PET abnormalities ($r=0.27$, $P=0.08$, Table 2). Patients with baseline MRI abnormalities ($N=5$) showed no or minimal changes on follow-up PET scans (3 unchanged, 1 improvement by one lobe and one progression by 1 lobe); the 3 patients whose second MRI showed a newly detected cortical dysplasia, PET scan showed expansion of hypometabolism by 3–4 lobes. The number of AEDs at baseline or follow-up did not correlate with the number of lobes involved on baseline or follow-up PET, or with the change in PET scores over time ($P>0.1$).

Association between seizure frequency and PET changes

The extent of the baseline PET abnormalities significantly correlated with changes in seizure frequency over time ($r=-0.37$, $P=0.02$), showing that smaller extent of PET abnormality on the baseline scan was associated with a smaller increase in seizure frequency over time. The extent of interval metabolic changes on PET was associated with the change in seizure frequency scores, in children with baseline seizure frequency scores between 2–4 ($n=30$, $r=0.50$, $P=0.005$), indicating that patients with a larger increase in seizure frequency showed a more robust expansion of PET abnormalities during follow-up (Figure 2). The scatter plot demonstrates that children with sustained seizures (even if no change or mild decrease in seizure frequency) tended to have an expanded metabolic abnormality on follow-up PET scan; and only patients with a substantial decrease in seizure frequency (by ≥ 2 scores) showed some resolution of metabolic abnormalities. The change in PET continued to show a significant correlation with the change in seizure frequency ($r=0.43$, $P=0.02$) in children above 1 year of age within this subgroup ($n=27$).

Association between other seizure characteristics, EEG and PET changes

No correlation was found between the time of the last seizure before baseline and follow-up PET scan and the lobar extent of PET abnormality ($P=0.3$).

At baseline, PET-EEGs showed epileptiform abnormalities in 14, no epileptiform changes in 24 (no EEG monitoring was done in 3 children, and none of them showed signs of seizures during the uptake period). At follow-up, 19 showed epileptiform abnormalities, while 22 did not. The extent of PET hypometabolism at baseline or follow-up PET was not different between patients with PET-EEGs showing epileptiform vs. non-epileptiform abnormalities at baseline ($P=0.1$ at baseline, 0.5 at follow-up). Presence of focal vs. generalized epilepsy could be established reliably in 25 patients. No significant difference was found in the extent of PET abnormalities between focal ($n=16$) and generalized epilepsy groups ($n=9$) at baseline ($p=0.9$) or at follow-up ($p=0.7$).

Association between age, developmental levels, and PET abnormalities

The age of the patients at the initial PET was inversely correlated with the extent of the baseline PET abnormality ($r=-0.37$, $P=0.02$) as well as the developmental status at the initial ($r=-0.32$, $P=0.04$) and follow-up ($r=-0.58$, $P<0.001$) PET scan. This indicated that a child who was younger at the time of the initial scan usually showed a larger extent of metabolic abnormality and ended up with worse developmental outcomes at follow-up. The extent of metabolic abnormality on baseline PET scans correlated with the developmental status at the time of the initial scan ($r=0.31$, $P=0.05$) and showed a similar trend at the follow-up scan ($r=0.27$, $P=0.09$; Table 2) in the whole group and also in children above 1 year of age ($n=37$; $r=0.32$, $P=0.05$ at baseline and $r=0.28$, $P=0.08$ at follow-up). Kruskal-Wallis test did not reveal a significant difference in the mean number of lobes involved among the developmental level groups at baseline or follow-up (Table 3). Post-hoc Mann-Whitney U tests showed a trend for group difference between the FDG-PET lobar involvement between children with normal vs. severe developmental delay at baseline (1.7 vs. 2.7, $p=0.07$). The extent of lobar PET abnormalities did not differ between the normal and mild/moderate (mean lobes involved: 1.7 vs. 2.6, respectively, $p=0.1$) and mild/moderate vs. severe delay

groups ($p=0.9$). No significant difference in the mean number of lobes involved on the follow-up PET was found on follow-up developmental level categorization. However, when data of patients with mild and severe developmental delay were combined into a single developmental delay category, the extent of the baseline PET abnormality was significantly lower in patients with normal as compared to those with delayed development at baseline (mean lobes involved: 1.7 vs. 2.6 respectively, $P=0.04$).

DISCUSSION

This study explored interval changes of lobar glucose uptake in a non-surgical group of children with medically intractable epilepsy who underwent PET scanning at two time points separated by >1 year, and evaluated the clinical factors associated with these changes. We report three main findings: 1. The lobar pattern of glucose hypometabolism changed over time in the majority of cases: most commonly showing an interval expansion to additional lobes, seen in about 60% of the patients, suggesting progression of pathophysiology in those with persistent frequent seizures; interval regression of hypometabolism was also observed, but much less frequently (26%), affecting those with a marked improvement in seizure frequency. 2. Extensive baseline hypometabolism on PET predicted more increase in seizure frequency by the follow-up PET scan. 3. Greater extent of hypometabolism at the baseline scan was also associated with greater developmental delay at baseline and follow-up.

Longitudinal studies tracking brain glucose metabolic changes in epilepsy have been scarce and, as far as we know, this is the largest such study in childhood epilepsy. Our previous study in a small group of children ($N=15$) with drug-resistant epilepsy applied an asymmetry-based analysis, thus considering longitudinal changes only in the presumed epileptic hemisphere¹⁰. Consistent with the present findings, both expansion and decrease in the extent of glucose hypometabolism were observed in that study. Our current findings further demonstrate that progression of hypometabolism often affects both hemispheres, observed in about half of the patients. Interestingly, another study in children with partial epilepsy found no evidence of bilateral progression possibly because the majority of those children did not develop uncontrolled seizures⁹. In our group of children with drug-resistant seizures, common bi-hemispheric involvement may have implications not only on long-term neurocognitive and developmental outcomes, but also suitability for surgery, as bilateral hypometabolism is associated with higher risk for post-operative seizures and surgical failure^{15,16}.

Smaller extent of baseline hypometabolism on FDG-PET was associated with larger expansion on follow-up PET in the present study. Presumably, a smaller abnormality has a greater potential for expansion, while those with a large abnormality at baseline may have already undergone progression in the past, before the baseline scan. Therefore, a small area of glucose metabolic abnormality on FDG-PET may not always indicate a good prognosis regarding future extent of hypometabolism, as the metabolic abnormalities are likely to progress over time if seizures persist. In addition, we found no dependence of the extent of change in PET abnormality on the length of follow-up. Whether these changes reflect a

change in underlying epileptic networks remains to be determined, but we hypothesize that this may be the case.

We found that the baseline extent of hypometabolism was moderately correlated with the change in seizure frequency over time ($r=0.37$). Similar results were obtained in the previous study by our group¹⁰, and in the univariate analysis in a cross-sectional retrospective study by Zhu et al¹⁷; however, their multivariate analysis showed that the only significant determinant of extent of hypometabolism was time since last seizure. This latter variable was not associated with the number of hypometabolic lobes in our present cohort. We also found a strong correlation between change in seizure frequency and change in extent of hypometabolism when analyzed in a subgroup with moderate baseline seizure frequencies. This is consistent with our previous findings¹⁰. Our present data suggest that a noticeable (lobar) improvement in the hypometabolism occurs only when seizures become controlled or at least show a major reduction. Sustained or even mildly improving seizure frequency may still be associated with expansion of metabolic abnormalities.

The mechanism of cortical hypometabolism and its progression during the clinical course of epilepsy is still unclear. The incidence of focal hypometabolism in children at the beginning of epilepsy is relatively low, observed in only about 20% of the cases in one study¹⁸. This initial hypometabolism may be a consequence of the underlying epileptogenic etiology^{9,19}. Eventually, with seizure progression, the hypometabolic area may expand. Spatial extension of metabolic abnormalities may partly be the result of recurrent seizures, possibly due to related synaptic loss to the functionally connected cortical area. Recent studies suggest that hypometabolism extends well beyond the epileptic network, probably due to remote inhibition as a result of cellular neurophysiological changes²⁰. Recurrent seizures can lead to neuronal loss, resulting in decreased cell density, which in turn, is correlated with hypometabolism seen on FDG-PET^{21–23}. More recent studies indicate that cortical hypometabolism may also be related to altered GABA_A receptor function or mitochondrial dysfunction and resultant failure of cellular energy production in the epileptic zone neurons^{24, 25}. Seizure propagation to connected ipsi- and/or contralateral areas of the brain leads to reverberating electrical activity in the involved network²². Hypometabolism in such connected areas may be a result of either deafferentation or tonic hyperpolarization of inhibitory neurons^{26, 27}. As seen in post-operative PET studies, once this neural network is disrupted through surgical resection, hypometabolism in the functionally connected areas can reverse^{26, 28, 29}. Overall, these previous data together with our present findings support the notion that epilepsy is a chronic evolving process, which generally leads to expansion of the hypometabolic regions over time, unless seizures are brought under control either by anti-epileptic drugs or by surgical resection of the seizure onset area²².

Children who were scanned at a younger age had a larger extent of hypometabolism and more severe developmental delay at baseline as well as follow-up. Such children likely had an early onset and more aggressive disease course, compared to those who developed seizures (and were scanned) later. Early onset (and subsequently intractable) epilepsy would have a strong impact on future development of the child. There have been only a few studies on this topic, and several confounding factors make the interpretation challenging, including variable etiology, the use of AEDs, seizure type, and reorganization of language and other

networks, that may all affect the developmental outcome^{30–32}. Association of extensive, often bilateral hypometabolism with developmental delay, as found in the present study, is not surprising. Our study also shows that while the extent of glucose hypometabolism is a predictor of the developmental level at that point, it is not as predictive of the future developmental progression of the child. This is understandable as future developmental abnormalities are likely affected not only by the cumulative effect of seizures, but also by medical interventions, and other, yet unknown environmental factors. Nevertheless, these data support that optimizing seizure control may not only reverse some of the metabolic abnormalities but also improve developmental outcome.

Our study has several limitations. Due to the retrospective nature of the study, our cohort represents a heterogeneous group in terms of age, type of epilepsy and location of epileptic foci. A selection bias (referral of patients to a level 4 epilepsy center) is also likely. We also recognize that seizure types, the length of individual seizures, fluctuations in seizure frequency, subclinical seizures, or the potential effects of the wide variety and changes in AED types and doses cannot be accounted for, and unrecognized seizures just prior to the PET scan may also affect glucose metabolism. Our study relied on the subjective, visual assessment of the PET scans. However, objective, operator-independent assessment of bilateral PET metabolic abnormalities in young children is not trivial due the lack of healthy control groups and the lack of validated objective approaches. The lobar approach used in this study can only appreciate major interval changes, while milder, intra-lobar metabolic fluctuations are not accounted for. Our patients did not have formal neuropsychological evaluations. Therefore, we assessed developmental delay in broad categories, that could be executed reliably even in a retrospective study. A few patients in our study had some known genetic mutations; however, the small number of such patients and inconsistent genetic testing precluded their evaluation as a separate group. On review, they showed heterogeneous PET abnormalities and variable interval changes.

Despite these limitations, we believe that our study has important clinically relevant implications. First, since the metabolic abnormalities seen on the initial PET are not static in most cases, it may be advisable to repeat FDG-PET prior to epilepsy surgery if the scan was done more than 1 year before the planned surgery. Further, the correlation between metabolic *changes* and seizure frequency *changes* suggests that, if no surgical resection can be offered for any reason, optimized non-surgical seizure treatment may slow down metabolic progression or, in some cases, possibly even reverse extensive hypometabolism; this, in turn, may be associated with better developmental outcome. This latter conclusion can be further addressed in future, prospective, longitudinal studies involving objective image analysis and formal neuro-cognitive assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Wheless J, Willmore L, Breier J, et al. A comparison of magnetoencephalography, MRI, and V-EEG in patients evaluated for epilepsy surgery. *Epilepsia*. 1999; 40:931–941. [PubMed: 10403217]
2. Rosenow F, Lüders H. Presurgical evaluation of epilepsy. *Brain*. 2001; 124:1683–1700. [PubMed: 11522572]
3. Salamon N, Kung J, Shaw S, et al. FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. *Neurology*. 2008; 71:1594–1601. [PubMed: 19001249]
4. Willmann O, Wennberg R, May T, et al. The contribution of ¹⁸F-FDG PET in preoperative epilepsy surgery evaluation for patients with temporal lobe epilepsy: a meta-analysis. *Seizure*. 2007; 16:509–520. [PubMed: 17532231]
5. Bouillieret V, Ridoux V, Depaulis A, et al. Recurrent seizures and hippocampal sclerosis following intrahippocampal kainate injection in adult mice: electroencephalography, histopathology and synaptic reorganization similar to mesial temporal lobe epilepsy. *Neuroscience*. 1999; 89:717–729. [PubMed: 10199607]
6. Dubé C, Boyet S, Marescaux C, et al. Relationship between neuronal loss and interictal glucose metabolism during the chronic phase of the lithium-pilocarpine model of epilepsy in the immature and adult rat. *Exp Neurol*. 2001; 167:227–241. [PubMed: 11161611]
7. Chassoux F, Semah F, Bouillieret V, et al. Metabolic changes and electro-clinical patterns in mesio-temporal lobe epilepsy: a correlative study. *Brain*. 2004; 127:164–174. [PubMed: 14534161]
8. Casse R, Rowe CC, Newton M, et al. Positron emission tomography and epilepsy. *Molecular Imaging & Biology*. 2002; 4:338–351. [PubMed: 14537108]
9. Gaillard WD, Weinstein S, Conry J, et al. Prognosis of children with partial epilepsy: MRI and serial ¹⁸FDG-PET. *Neurology*. 2007; 68:655–659. [PubMed: 17325271]
10. Benedek K, Juhász C, Chugani DC, et al. Longitudinal changes in cortical glucose hypometabolism in children with intractable epilepsy. *J Child Neurol*. 2006; 21:26–31. [PubMed: 16551449]
11. Benedek K, Juhász C, Muzik O, et al. Metabolic changes of subcortical structures in intractable focal epilepsy. *Epilepsia*. 2004; 45:1100–1105. [PubMed: 15329075]
12. Maeda N, Watanabe K, Negoro T, et al. Evolutional changes of cortical hypometabolism in West's syndrome. *Lancet*. 1994; 343:1620–1623. [PubMed: 7911927]
13. Matheja P, Weckesser M, Debus O, et al. Drug-induced changes in cerebral glucose consumption in bifrontal epilepsy. *Epilepsia*. 2000; 41:588–593. [PubMed: 10802765]
14. Behen ME, Juhász C, Wolfe-Christensen C, et al. Brain damage and IQ in unilateral Sturge–Weber syndrome: Support for a “fresh start” hypothesis. *Epilepsy Behav*. 2011; 22:352–357. [PubMed: 21852199]
15. Chugani HT, Da Silva E, Chugani DC. Infantile spasms: III. Prognostic implications of bitemporal hypometabolism on positron emission tomography. *Ann Neurol*. 1996; 39:643–649. [PubMed: 8619550]
16. Blum DE, Ehsan T, Dungan D, et al. Bilateral temporal hypometabolism in epilepsy. *Epilepsia*. 1998; 39:651–659. [PubMed: 9637608]
17. Zhu Y, Feng J, Wu S, et al. Glucose metabolic profile by visual assessment combined with Statistical Parametric Mapping analysis in pediatric patients with epilepsy. *J Nucl Med*. 2017; 58:1293–1299. [PubMed: 28104740]
18. Gaillard W, Kopylev L, Weinstein S, et al. Low incidence of abnormal ¹⁸FDG-PET in children with new-onset partial epilepsy A prospective study. *Neurology*. 2002; 58:717–722. [PubMed: 11889233]
19. Juhász C, Chugani DC, Muzik O, et al. Relationship between EEG and positron emission tomography abnormalities in clinical epilepsy. *J Clin Neurophysiol*. 2000; 17:29–42. [PubMed: 10709809]
20. De Tiège X, Trotta N, Bourguignon M, et al. Neurophysiological activity underlying altered brain metabolism in epileptic encephalopathies with CSWS. *Epilepsy Res*. 2013; 105:316–325. [PubMed: 23561286]

21. Dlugos DJ, Jagg J, O'Connor WM, et al. Hippocampal cell density and subcortical metabolism in temporal lobe epilepsy. *Epilepsia*. 1999; 40:408–13. [PubMed: 10219265]
22. Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia*. 2002; 43:219–227. [PubMed: 11906505]
23. Decarli C, Hatta J, Fazilat S, et al. Extratemporal atrophy in patients with complex partial seizures of left temporal origin. *Ann Neurol*. 1998; 43:41–45. [PubMed: 9450767]
24. Pumain R, Ahmed MS, Kurcewicz I, et al. Lability of GABA_A receptor function in human partial epilepsy: possible relationship to hypometabolism. *Epilepsia*. 2008; 49:87–90. [PubMed: 19049598]
25. Tenney JR, Rozhkov L, Horn P, et al. Cerebral glucose hypometabolism is associated with mitochondrial dysfunction in patients with intractable epilepsy and cortical dysplasia. *Epilepsia*. 2014; 55:1415–1422. [PubMed: 25053176]
26. Bruehl C, Witte OW. Cellular activity underlying altered brain metabolism during focal epileptic activity. *Ann Neurol*. 1995; 38:414–420. [PubMed: 7668827]
27. Joo EY, Hong SB, Han HJ, et al. Postoperative alteration of cerebral glucose metabolism in mesial temporal lobe epilepsy. *Brain*. 2005; 128:1802–1810. [PubMed: 15872014]
28. Spanaki MV, Kopylev L, DeCarli C, et al. Postoperative changes in cerebral metabolism in temporal lobe epilepsy. *Arch Neurol*. 2000; 57:1447–1452. [PubMed: 11030796]
29. Hajek M, Wieser H, Khan N, et al. Preoperative and postoperative glucose consumption in mesiobasal and lateral temporal lobe epilepsy. *Neurology*. 1994; 44:2125–2132. [PubMed: 7969971]
30. Mizrahi EM, Clancy RR. Neonatal seizures: early-onset seizure syndromes and their consequences for development. *Ment Retard Dev Disabil Res Rev*. 2000; 6:229–241. [PubMed: 11107188]
31. Jozwiak S, Goodman M, Lamm SH. Poor mental development in patients with tuberous sclerosis complex: clinical risk factors. *Arch Neurol*. 1998; 55:379–384. [PubMed: 9520012]
32. Liégeois F, Connelly A, Cross JH, et al. Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. *Brain*. 2004; 127:1229–1236. [PubMed: 15069021]

Key Point Box

- Lobar glucose metabolic pattern changes during long-term follow-up in 90% children with intractable epilepsy
- Patients with a larger increase in seizure frequency showed a more robust expansion of PET abnormalities during follow-up
- Larger baseline hypometabolism was associated with more severe developmental delay at baseline and follow-up
- Effective non-surgical seizure treatment may slow down, or even reverse, metabolic progression

Figure 1.

Baseline FDG-PET in a 9 years 9 months old girl with two axial sections (**A** and **B**) showing hypometabolism in the left frontal, temporal (**A**) and parietal (**B**) lobes (arrows). Follow-up PET (**C** and **D**) 4.3 years later showed metabolic worsening now also extending to the right temporal (**C**) and parietal (**D**) lobes, while the child had persistent uncontrolled seizures. Conversely, baseline FDG-PET (**E**) in a 1 year 11 months old boy showed moderate bitemporal, with mild bilateral frontal hypometabolism. Follow-up PET (**F**) 2 years 11 months later showed persistent hypometabolism in the bilateral temporal cortex with improvement of the frontal cortex metabolism in both hemispheres. He had monthly generalized tonic clonic seizures and infantile spasms at baseline; the seizures became controlled for 2 years 4 months before the follow-up scan.

Figure 2.

Positive correlation between change in seizure frequency scores (time2-time1) and change in PET involvement over time (number of affected lobes, time2-time1), in a subgroup of 30 children with baseline seizure frequency scores 2–4 (i.e., <9/day to 1/month) ($r=0.50$, $P=0.005$). Negative values of change in PET involvement and change in seizure frequency denote improvement, while positive values denote progression.

Table 1

Demographic profile of the cohort of 41 children with epilepsy.

Characteristics	N=41
Gender	
Male [n (%)]	25 (61)
Female [n (%)]	16 (39)
Age at baseline PET scan [median (IQR)]	4.7 (1.4–7.4)
Age at follow-up PET scan [median (IQR)]	9.3 (5.3–13.1)
Time difference between scans (years) [median (IQR)]	4.3 (2.5–6.1)
Seizure frequency score at baseline PET [median (IQR)]	3 (2–4)
Seizure frequency score at follow-up PET [median (IQR)]	3 (1–4)
Seizure semiology at baseline	
-Infantile spasms [n (%)]	7 (17.1)
-Focal seizures [n (%)]	23 (56.1)
-Generalized tonic clonic seizures [n (%)]	10 (24.4)
-Myoclonic/Tonic seizures [n (%)]	1 (2.4)
Developmental level at baseline PET	
-within normal limits [n (%)]	20 (48.8)
-mild/moderate delay [n (%)]	11 (26.8)
-severe delay [n (%)]	10 (24.4)
Developmental level at follow-up PET	
-within normal limits [n (%)]	13 (31.7)
-mild/moderate delay [n (%)]	12 (29.3)
-severe delay [n (%)]	16 (39.0)
No. of lobes involved on baseline PET scan [median (IQR)]	2 (1–3)
No. of lobes involved on follow-up PET scan [median (IQR)]	3 (2–4)
EEG pattern at baseline PET (number [%])	
No epileptiform discharges	22 (53.7)
Epileptiform discharges present	19 (46.3)
EEG pattern at follow-up PET (number [%])	
No epileptiform discharges	22 (53.7)
Epileptiform discharges present	19 (46.3)
MRI (number [%])	
Lesional	8 (19.5)
Non-lesional	33 (80.5)

IQR= interquartile range

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Table 2

Correlation matrix between extent and interval change of PET abnormalities and the clinical characteristics.

Clinical characteristics	PET lobe involvement			
	Baseline PET		Change in PET	
	r	P value	r	P value
Age at baseline	−0.37	0.02	0.15	0.3
Time difference between two scans	−0.01	0.9	0.27	0.08
Seizure frequency at baseline	0.30	0.06	−0.11	0.5
Seizure frequency at follow-up	−0.13	0.4	0.21	0.2
Change in seizure frequency	−0.37	0.02	0.29	0.07
Developmental level at baseline	0.30	0.05	−0.10	0.5
Developmental level at follow-up	0.26	0.09	0.06	0.7

Table 3

Comparison of number of lobes involved on FDG-PET based on developmental level categories at baseline and follow-up.

Developmental delay categories	Number of lobes involved on PET (Mean $\pm$ SD)	P-value (Kruskal-Wallis test)
Baseline development	Baseline PET	0.1
-Normal (n=20)	1.7 $\pm$ 1.0	
-Mild/moderate delay (n=11)	2.6 $\pm$ 1.8	
-Severe delay (n=10)	2.7 $\pm$ 1.5	
Follow-up development	Baseline PET	0.2
-Normal (n=13)	1.8 $\pm$ 0.8	
-Mild/moderate delay (n=12)	2.0 $\pm$ 1.8	
-Severe delay (n=16)	2.6 $\pm$ 1.4	
Follow-up development	Follow-up PET	0.2
-Normal (n=13)	2.2 $\pm$ 1.5	
-Mild/moderate delay (n=12)	3.6 $\pm$ 2.2	
-Severe delay (n=16)	3.2 $\pm$ 2.3	

SD=Standard deviation