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Long-term outcome in patients with intractable epilepsy showing bilateral diffuse cortical glucose hypometabolism pattern on PET

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Abstract

The objective of this study is to determine the long-term outcome of children with intractable epilepsy who have diffuse cortical hypometabolism on 2-deoxy-2-(18F)fluoro-D-glucose positron emission tomography (FDG-PET) scans. Seventeen children with intractable epilepsy showing bilateral, diffuse cortical hypometabolism on FDG-PET were followed up through telephone interview from 1 year 4 months to 11 years 4 months (mean: 5 years 7 months + 2 years 1 month) after their PET scans. One child succumbed to Sanfilippo disease at age 20 years. Only 2 children were seizure free. Fifty percent had walking difficulties, 56.25% were not toilet trained, all had speech difficulties, 43.75% had behavioral problems, 37.5% had poor eye contact, 75% had socialization difficulties, and 87.5% attended special schools. Three children were found to have genetic causes, including a 4-MB deletion of the mitochondrial genome, MECP2 duplication, and Lafora disease. In conclusion, the long-term outcome in this patient population is poor, and they tend to suffer from genetic/neurodegenerative diseases.

Introduction

Children with epilepsy may respond well to pharmacological therapy; however, around 10–30% continue to have refractory seizures despite multiple anticonvulsant medications^{1–3}. These children benefit from surgery if the seizures originate from a focal area⁴. Presurgical

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Author Contributions

Varun Shandal participated in the formulation of the hypothesis, collected and went through the initial clinical data and PET scans, drafted the questionnaire for telephone interview, and wrote the first draft of the manuscript. Amy L. Veenstra participated in conducting the telephone interviews, which consisted of a questionnaire and the Vineland Adaptive Behavior Scales testing, and organized the follow-up data. Michael Behen structured the telephone interview and substantially revised the manuscript. Senthil Sundaram participated in the design of the study, supervised the follow-up data collection, and substantially revised the manuscript. Harry Chugani participated in the design of the study, formulated the hypothesis, went through initial clinical data and PET scans, supervised the follow-up data collection, and substantially revised the manuscript.

Ethical Approval

The Human Investigations Committee at Wayne State University granted permission for the retrieval and analysis of de-identified PET and outcome data that had been obtained clinically for these children.

Declaration of Conflicting Interests

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evaluation to localize the seizure onset zone includes interictal and ictal electroencephalogram (EEG), magnetic resonance imaging (MRI), neuropsychological evaluation, and functional neuroimaging using 2-deoxy-2- ^{18}F fluoro-D-glucose positron emission tomography (FDG-PET) or single photon emission computed tomography (SPECT)^{5,6}. MRI is the imaging modality of choice for evaluating patients with epilepsy (ILAE Commission on Neuroimaging)⁷. However, when MRI fails to show a focal abnormality, FDG-PET or SPECT may provide the necessary localizing data⁶. When a hypometabolic focus is found on PET and there is strong correlation with the EEG, epilepsy surgery may be offered⁸. If multiple hypometabolic foci are shown on FDG-PET, the EEG often also indicates multifocal abnormalities and surgery is usually not an option, with some exceptions such as tuberous sclerosis⁹.

It is not uncommon for the PET scan to reveal a diffuse or global pattern of glucose hypometabolism in children with intractable epilepsy. In such cases, an underlying structural lesion is unlikely and an underlying genetic or metabolic process is suspected. These patients are almost never candidates for resective epilepsy surgery. The etiology and outcome in children showing a diffuse hypometabolism pattern is not known but, given the global involvement, it is likely to be poor but of heterogeneous etiologies. In the present study, we sought to determine the etiologies and long-term outcome of children with intractable epilepsy and a diffuse pattern of hypometabolism on PET imaging.

Materials and Methods

Patients

The subjects of the present study were selected from 2166 patients with intractable epilepsy contained in the clinical FDG-PET database of the PET Center, Children's Hospital of Michigan, Detroit. These patients had been scanned at our center between 1993 and 2010. All of these patients had PET scans for localization of the seizure focus and were being considered for possible epilepsy surgery either at our center or other centers which lacked good access to PET. The patients showing a diffuse pattern of glucose hypometabolism are typically marked in our database as potential genetic disease, degenerative disease or inborn errors of metabolism. There were 169 patients who were classified into these categories. Upon further detailed visual evaluation of these 169 patients, 31 patients had an unambiguous pattern of *severe* bilateral diffuse cortical hypometabolism observed on FDG-PET scanning and none were candidates for epilepsy surgery. These patients were then contacted through telephone interview to determine their natural outcome. Fourteen of these 31 patients were lost to follow-up and 1 patient had died. The mean age of the remaining 16 patients at the time of PET scanning was 9 ± 5.85 years with 9 males and 7 females. The mean age of these patients at follow-up was 15 ± 4.88 years. The range of follow-up was from 1 year 4 months to 11 years 4 months (mean, 5 years 7 months $\pm$ 2 years 1 month). The details are provided in Table 1.

PET Procedure

The tracer ^{18}F -FDG was produced in-house using a Siemens RDS-11 cyclotron. ^{18}F -FDG PET studies were performed using a CTI/Siemens EXACT/HR whole-body PET scanner (Knoxville, TN) or a GE Discovery STE PET-CT scanner (Milwaukee, WI). A 20-min static emission scan was acquired after a 30-min ^{18}F -FDG uptake period. Computed attenuation correction was used to correct the brain images for attenuation of 511-keV photons. All patients fasted for 4 h before the ^{18}F -FDG injection (5.291 MBq/kg [0.143 mCi/kg]). During the ^{18}F -FDG uptake period, the children underwent continuous scalp EEG monitoring. During the scanning phase (but not during the uptake period), sedation was used, as necessary. All sedated subjects were continually monitored by pediatric nurses with special

training in the sedation of children for radiologic procedures. Heart rate, blood pressure, and pulse oximetry were also measured during the PET procedure.

Data Analysis

None of these 16 patients were found suitable for resective surgery on the basis of clinical, MRI, PET and EEG data. PET scans were analyzed qualitatively through visual inspection and the scans showing bilateral symmetric hypometabolism in 2 lobes of brain were designated as bilateral diffuse cortical hypometabolism. Review of the clinical charts was performed to identify any known etiologies. In addition, the EEG and MRI scans of all patients were again reviewed to ensure that there were indeed no focal abnormalities. The outcome data was obtained through telephone interview. All studies were performed in compliance with the regulations of Wayne State University Human Investigations Committee.

Telephone Interview

Parents or guardians of the 17 patients were called and informed of the purpose of this study. Since one patient had died, the interview was conducted only for 16 patients. After consenting to participate, they completed a 30 to 80 minute telephone interview, which consisted of a questionnaire and a structured interview. The questionnaire consisted of items pertaining to the patient's current symptoms, medical care, diagnoses, academic functioning, school accommodations, developmental milestones, and behavioral problems. In addition, the Vineland Adaptive Behavioral Scales, Second Edition, a measure that assesses adaptive skills in communication, socialization, daily living skills and motor skills was completed. This measure provides age normalized standard scores for the four domains of functioning as well as an overall score of adaptive function. Higher scores indicate higher levels of functioning. This measure is widely used in research and has good reliability and validity ^{10,11}. Only 15 patients completed the Vineland Adaptive Behavior testing.

Results

The MRI scans were normal in 12 children. Mild ventricular enlargement was seen in 3 children and in 1 child there was mild arrest of myelination in the peritrigonal white matter. The different patterns of diffuse hypometabolism found on PET are given in Table 1 and illustrated in Figure 1. An underlying etiology for the intractable epilepsy was found in 4 children; one had Mecp2 gene duplication, second had Lafora disease and the third patient had a 4 MB deletion of his mitochondrial genome (Table 1) and fourth one had Sanfillipo's disease who had died.

Developmental and seizure outcome

Of the 31 children with diffuse hypometabolism, 14 had their telephone number (available in our database) disconnected and were lost to follow-up. Of the remaining 17, one female died at the age of 20 years. She was diagnosed with Sanfillipo's disease with recurrent thrombocytopenia. She was poorly responsive to external stimuli and had increased tone in all her extremities resulting in her wheelchair bound status.

Of the remaining 16 children, 2 were seizure free and 14 continued to have seizures (generalized tonic-clonic in 11 children) (Table 1). The outcome of these patients in the different developmental subdomains is shown in Figure 2. Nine children started walking at 11–15 months of age, 1 child at 18 months, 2 children at 4 years and the remaining 4 were not yet walking. Of the 12 children who were ambulatory, 4 continued to have walking difficulties. One has poor balance, another cannot walk long distances, the third one needs assistance with a walker or gait belt, and fourth one in fact lost his motor skills at age 9

years. Only 7 children were toilet-trained and were independent for their toileting needs. Eight children were non-verbal, 6 had limited speech with 3–4 word sentences and difficulty in finding words; only 2 had near normal speech with some mispronunciation. Behavioral difficulties were present in 7 children; 4 children flap or shake their hands and put fingers in their mouth and 2 even bite their fingers, another 2 children repetitively clap their hands and one child keeps his hands fisted or up like a rabbit. Eye contact was normal in 10 children and the remaining 6 children had poor eye contact. Eight children were socially isolated and were not playing with other children of their age group, 4 try to play but lack interactive social skills, whereas 4 children were normal in their social skills. Two children were not going to school at all because of their profound cognitive impairment, 2 were in a regular school but their performance was on the lower end of their grade level, and 12 children were attending some special school and were receiving occupational, speech and physical therapy. Only 3 children had a family history of epilepsy. Three children had scoliosis and 1 had pleuropulmonary blastoma. In general, the developmental outcome assessed in these children by the Vineland adaptive behavior scale was very poor and the details are given in Table 1.

Discussion

A number of studies have shown that carefully selected patients with medically-refractory epilepsy receive significant benefit from resection of the epileptic focus. In a randomized, controlled trial of temporal lobectomy versus conventional drug therapy in *adult* patients with intractable temporal lobe epilepsy, 58% of patients assigned to surgery became seizure-free while only 8% of patients assigned to drug therapy were seizure-free¹². The best prognosis is observed in patients where the epileptogenic lesions could be localized. In a multivariate analysis of 193 epilepsy patients who underwent resective surgery, it was found that a focal lesion on MRI, correct localization by FDG-PET, and localized ictal onset on EEG were independent predictors of a good outcome¹³.

The outcome of medically-refractory epilepsy patients who are not candidates for epilepsy surgery is less well studied. In a retrospective review of 34 such patients with an average follow-up period of 4 years, only 21% achieved seizure remission¹⁴. Furthermore, a meta-analysis of studies comparing surgical and non-surgical treatments in patients with intractable epilepsy found that only 12% of non-operated patients were seizure-free compared to 44% of surgical patients¹⁵.

The outcome in children with intractable epilepsy after resective surgery is also promising¹⁶. In most centers performing epilepsy surgery on young children, the interictal and ictal EEG, seizure semiology, and the MRI form the basis as to whether resective epilepsy surgery should be pursued. With increased access to PET, which is now available even in small community hospitals receiving daily delivery of ¹⁸F-DG, FDG-PET has assumed a greater role in the pre-surgical evaluation of adults and children with intractable epilepsy being considered for resective epilepsy surgery. This is particularly true when the MRI fails to show a focal abnormality or when presurgical localization data are discordant. At our center, FDG-PET scans play an important role in determining the epileptogenic zone in children with intractable epilepsy, including those with intractable infantile spasms. In the latter group, we have shown 4 different glucose metabolic patterns (focal, multifocal, bitemporal and diffuse cortical hypometabolism)^{17,18}.

In the present study, we excluded those patients who had infantile spasms at the time of evaluation. However, similar patterns of abnormalities on FDG-PET are seen in patients without infantile spasms, and some of these have been described previously. For example, children with intractable epilepsy who showed bilateral medial prefrontal and temporal

neocortical hypometabolism on FDG-PET often showed aggressive behavior¹⁹. This is in contrast to children with infantile spasms and bitemporal (neocortical and medial temporal lobe structures) cortical hypometabolism on FDG-PET, who showed severe developmental delay, low-functioning autism, usually without aggressive behavior¹⁷.

Previous studies have shown the presence of diffuse hypometabolic pattern in specific disease populations. This has been observed particularly in children with various metabolic and degenerative diseases of the nervous system. Pascual et al performed the FDG-PET on 14 patients with microcephaly, developmental delay and seizures with known mutations of GLUT1 receptors and found diffuse glucose hypometabolism throughout the brain cortices of all patients²⁰. The thalami were more hypometabolic than the cortices and a more pronounced hypometabolism in mesial temporal lobe structures was observed, which did not correlate with performance impairment or coexistence of epilepsy. Philippart et al studied 7 patients with Spielmeier-Vogt disease using FDG-PET and found an age-related progression of glucose hypometabolism starting in calcarine area and then spreading rostrally to whole cortex²¹. Calcarine hypometabolism was mild in the patients when they were young and it increased in concordance with age. Chugani et al. found 4 major subtypes (unilateral focal, unilateral diffuse, bilateral diffuse and normal) of glucose hypometabolism in a group of 15 Lennox-Gastaut syndrome patients²². Bilateral diffuse hypometabolism was the most common (8 out of 15 patients) pattern found in these patients which was also shown earlier by Theodore et al.²³. De Volder et al. investigated the regional brain glucose utilization by FDG-PET in 3 children with adenylosuccinase deficiency and found a marked hypometabolism in all cortical structures with cerebellum, thalamus and basal ganglia being spared²⁴. In 8 children with glutaric aciduria type, Al-Essa et al. found diffuse decreased glucose uptake in whole cerebral cortex in 7 and in thalami in 3 children²⁵. In a study by Molnar et al., 15 patients with mitochondrial diseases (mitochondrial myopathy [n=5]; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS] [n=4]; and chronic external ophthalmoplegia [n=6]) were investigated to determine their cerebral glucose metabolism²⁶. The authors found decreased FDG uptake in majority of the cerebral regions, and greatest glucose hypometabolism was demonstrated in temporal region (temporal pole and mesial temporal gyrus) and occipital poles. A recent case series of 2 children with Niemann-Pick disease type C by Kumar and Chugani²⁷ reported a distinctive pattern of severe hypometabolism on FDG-PET of the bilateral medial and inferior frontal cortex, as well as the bilateral parietal and temporal cortex. The intermediate parietal region was spared as compared to lateral and medial aspects.

We have suspected that the children included in this study may have an underlying neurogenetic, metabolic or degenerative disorder accounting for their diffuse cortical hypometabolism pattern found on FDG-PET and for their seizure intractability. Figure 1 demonstrates that, even within this group, several more distinct patterns are seen, thus supporting the heterogeneity of this patient population. This pattern is likely to be a heterogeneous group with respect to etiology as well. While four different genetic abnormalities could be detected in individual patients, we could not identify the etiology in the vast majority of patients. One of these patients suffered from Lafora disease caused by a mutation in the Laforin gene. The typical age of onset of progressive neurodegeneration in this disease is between 8 and 18 years of age and the myoclonic seizures become intractable with age. Presence of additional modifying factors could be responsible for early age of onset in this patient. Mecp2 duplication syndrome is a recently described severe neurodevelopmental disorder inherited in an X-linked manner²⁸. It is characterized by epilepsy, hypotonia, mental retardation, autistic behaviors and ataxia. The third patient had a large 4 MB deletion of mitochondrial genome and the significance of this finding is unclear. The fourth patient died due to Sanfillipo's disease at age 20 years.

Even though diffuse hypometabolic pattern has been described in such specific populations, much less is known about their long-term outcomes. In general, a poor outcome can be expected in children with diffuse cortical glucose hypometabolism on PET, with some exceptions. This observation can be used to provide prognostic information for parents about their children. Surprisingly, a specific diagnosis had been reached in only 4 of the 17 subjects that could be followed up. This emphasizes the need for better diagnostic tools in evaluating these children. With more access to genetic testing, it is likely that various other disorders will be uncovered in this population.

Limitations of this study

There are a number of limitations in the present study. First, this is a retrospective study of patients scanned over 17 years, and many of the subjects were not local patients who could be followed up easily, but had been referred for a PET scan from many centers across the country and even from overseas. Therefore, a consistent pattern of evaluation of these children for underlying etiology is not likely to be the case. Secondly, we selected only cases who showed severe hypometabolism, the reason being that some anticonvulsant medications^{29–33} as well as a recent seizure³⁴ may be associated with a mild cortical hypometabolism. Importantly, we excluded patients who were on the ketogenic diet at the time of PET, since we have found the PET results to be uninterpretable in such cases.

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Figure 1. showing the different variants of diffuse hypometabolic pattern. 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.

Figure 2. showing outcome of the patients in different developmental subdomains. Notably, all children had speech difficulties and the majority of them had multiple developmental difficulties.

showing the demographics, etiology and outcome of intractable epilepsy patients with diffuse hypometabolism

Table 1

Patient no.	Age (years) at PET scan	Age (years) at FU	Sex	PET pattern (involved regions)	EEG findings during PET scan	Seizure type	Seizure frequency at FU	Etiology	Current diagnosis	Vineland composite score	Degree of delay at FU
1	5	10	m	PL, TL, OL	Multifocal S/W; BS	GTC	2/week	UK	epilepsy	43	moderate
2	4	10	m	FL, PL, TL, OL	Intermittent posterior dominant 7 Hz activity	GTC	2–3/week	UK	epilepsy	63	mild
3	12	18	m	FL, PL, TL	Diffuse slow delta activity; BS	GTC	2/week	UK	epilepsy	25	severe
4	21	24	m	FL, PL, TL; auditory cortex spared	No epileptiform activity	GTC	2/week	UK	epilepsy; MR; autism	20	severe
5	13	14	f	FL, PL, TL; auditory & SM cortex spared	Diffuse S/W; BS; 2 seizures captured	myoclonic; GTC; absence; partial-complex	5–20/day	UK	epilepsy; LGS; MR	44	moderate
6	17	22	f	FL, PL	Multifocal S/W; BS	absence; atonic; clonic	10–40/day	UK	epilepsy; LGS	23	severe
7	2	13	f	PL, TL	Multifocal as well as diffuse S/W; BS	GTC	intermittent; 4–5/week	UK	epilepsy	40	moderate
8	4	13	m	PL, TL	Multifocal S/W; 2 seizures captured	none	none in past 6–7 years	4 MB deletion of mitochondrial genome	epilepsy; mitochondrial disease; autism; MR	31	severe
9	6	8	m	FL, PL, TL; auditory & SM cortex spared	Multifocal as well as diffuse S/W; BS	GTC	<1/month	Lafora disease	epilepsy; mitochondrial disease	45	moderate
10	3	11	f	FL, PL, TL	Normal	complex partial	<1/month	UK	epilepsy	92	normal
11	16	21	f	FL, PL, TL; auditory cortex spared	Multifocal S/W; BS; 1 seizure captured	GTC; atonic	1–2/week	UK	epilepsy; autism	28	severe
12	2	10	f	PL, TL, OL	Single spike in left posterior quadrant; BS	tonic-clonic	2/day	UK	epilepsy; hydrocephalus; speech apraxia, cognitive delay	66	mild
13	13	20	f	FL, PL, TL	BS	GTC; absence	3–4/week	UK	epilepsy; MR	N/A	N/A
14	8	16	m	FL, PL, TL	Diffuse cerebral dysfunction s/o LGS	none	none	MECP2 duplication	epilepsy; LGS; MECP2 duplication	28	severe
15	11	12	m	FL, PL, TL, OL	Multifocal S/W; BS	GTC	4–5/week	UK	epilepsy; receptive language disorder; ADHD	67	mild
16	11	15	m	PL, TL; hippocampus spared	Multifocal S/W	GTC; absence	1/day	UK	seizure disorder NOS; MR; autism	26	severe

Abbreviations: ADHD – attention deficit hyperactivity disorder; BS – background slowing; FL – frontal lobe; FU – follow-up; GTC – generalized tonic-clonic; LGS – lennox-gastaut syndrome; MR – mental retardation; NOS – not otherwise specified; OL – occipital lobe; PL – parietal lobe; SM – sensory motor; S/W – spike and wave; TL – temporal lobe; UK – unknown; N/A - not available.