Schizencephaly and intractable epilepsy: an FDG-PET study

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Background: To assess the role of 2-deoxy-2(18F)-fluoro-D-glucose positron emission tomography (FDG-PET) scans in the comprehensive evaluation and surgical decision-making in patients with schizencephaly. **Methods:** We evaluated 11 patients (8M) with schizencephaly (mean follow-up: 4.5 years), including detailed clinical, MRI, FDG-PET, EEG, surgical and neuropathology data. **Results:** Eight patients had unilateral and three had bilateral clefts on MRI. Mean age at seizure onset was 20 months, with seizure being frequent in 10 and rare in one. Multiple seizure types were noted, with complex partial seizures being the most common (n=8) followed by infantile spasms (n=6). FDG-PET showed larger area of involvement than MRI in all the patients which corresponded better with the electrophysiological changes. Five patients (with unilateral disease on MRI) underwent epilepsy surgery (4 hemispherectomy and 1 multilobar resection). Two patients with focal defect on MRI underwent hemispherectomy due to larger area of abnormality revealed by FDG-PET. One patient was excluded from the surgery due to bilateral abnormalities on FDG PET. Six patients (4 with surgery) were seizure-free at last follow-up (average seizure-free duration: 70 months). One patient who underwent hemispherectomy due to apparently unilateral disease on both video-EEG and MRI but having bilateral abnormality on PET continued to have seizures. ACTH treatment had only a brief (1 month to 1 year) or no response in the six infantile spasms patients. **Conclusions:** FDG-PET typically shows a much larger area of involvement than MRI thus supplementing MRI in defining the full extent of malformation and assessing the functional integrity of the contralateral hemisphere. FDG-PET may prove to be a useful tool to aid in surgical decision-making and predicting surgical outcome, as patients with contralateral abnormality on FDG-PET may have poor surgical outcomes. When the malformation is unilateral with an intact contralateral hemisphere, surgery (usually hemispherectomy) may be curative of the epilepsy.

Background

Schizencephaly can be defined as congenital brain clefts, lined by grey matter, extending from the pial surface to the lateral ventricle. It is considered to be a true brain malformation, which develops as a result of developmental failure of a part of the cerebral cortex and not the destruction of preformed cortex [1,2,3]. Neuroblast migration occurs between 16-20 weeks, and when the insult on the developing brain happens before this time, the cleft is lined by grey matter and results in schizencephaly [4]. Schizencephaly may be unilateral or bilateral. It is also classified into open-lip and closed lip, which is more descriptive rather than indicative of a different etiology [5]. It is a rare brain malformation, with a prevalence of around 1.5/100,000 [6, 7], and probably of multifactorial etiology [8, 9].

Magnetic resonance imaging (MRI) is the standard modality for the diagnosis of schizencephaly as it visualizes the cleft, gives details of the cortical anatomy, shows good grey-white distinction, and can demonstrate associated heterotopic grey matter as well as grey matter lining the cleft [10]. However, MRI cannot provide any information about the functional status of the abnormal as well as apparently normal looking cortex. Many of these patients have more widespread and profound

neuro-cognitive impairments, than would be suspected based on MRI, and have multifocal intractable seizures not explained by a single focal brain abnormality shown on the MRI. Therefore, defining the full extent of the malformation is essential not only to understand the true nature of this condition, but also to appreciate and predict the prognosis, neuro-cognitive outcome, and applicability or usefulness of any therapeutic intervention, such as surgery for intractable epilepsy. Functional imaging using positron emission tomography with 2-deoxy-2(18F) fluoro-D-glucose (FDG-PET) may provide an additional dimension towards understanding this malformation more comprehensively [11]. Hence, the purpose of this study was: (i) to evaluate the role of FDG-PET scans in patients with schizencephaly in delineating the extent of functional abnormality and its correlation with structural abnormality, EEG changes and neurocognitive impairment, (ii) to evaluate the functional integrity of normal appearing cortex, and (iii) to determine whether FDG-PET can assist in surgical decision-making.

Methods

We evaluated 11 patients with schizencephaly, confirmed on MRI scans, between October 1995 and June 2015 at the Children's Hospital of Michigan (Detroit), a tertiary care referral center. Clinical data, neuroimaging (MRI, FDG-PET scans), electrophysiological data (EEG, video-EEG), surgical outcomes and neuropathology data were analyzed. We examined in detail the age at seizure onset, seizure types, medications, seizure control and surgical treatment, if any, with its outcome. The data were subsequently updated, if necessary, by telephone interviews with the family.

Results

Clinical details

Clinical and demographic profile is provided in Table 1. Eight patients were males and three were females, with age at presentation ranging from 1 week to 12 years. Eight of them had unilateral clefts while three had bilateral involvement. Eight of these 14 hemispheres had closed-lip schizencephalies, while 6 had open-lip clefts. All 11 of them had intractable epilepsy. The median age at onset of seizures was 4 months (range: 0.3-144 months). Ten of them had high seizure frequency, ranging from 1-2/day to 20/day. Only 1 patient (#6) had infrequent seizure episodes, up to 1 in 3-4 months. Multiple seizure types were seen in conjunction in these patients, including complex partial seizures in 8 patients, infantile spasms in 6, some episodes of generalized tonic-clonic seizures in 3, and absence and myoclonic seizures in at least 2 patients. The median follow-up duration was 4 years (range: 0-17 years).

No	Schizencephaly	Age at seizure onset (months)	Seizure Frequency	Seizure semiology	Functional status at last follow up	Treatment	Sz status at last follow up	Seizure-free duration (years)
1	Unilateral	52	1-2/day	Absence, CPS	Mild delay-fine motor, language	Depakote	Seizure-free	10
2	Bilateral	5	4-5/day	IS, myoclonic, CPS	Developmental age 9 months at chronological age 4 years	Vigabatrin, ACTH, Topiramate, Oxcarbazepine, Diazepam	Seizure	0
3	Unilateral	144	5-7/day	CPS	Moderate delay	Hemispherectomy	Seizure-free	15.5
4	Unilateral	2.5	1-2/week	CPS	Mild delay	Oxcarbazepine, Phenobarbital, Topiramate	Seizure	0

No	Schizencephaly	Age at seizure onset (months)	Seizure Frequency	Seizure semiology	Functional status at last follow up	Treatment	Sz status at last follow up	Seizure-free duration (years)
5	Unilateral	1	5-6/day	IS, CPS	Developmental as well as gross and fine motor delay	Hemispherectomy	Seizure-free	<1
6	Unilateral	17	1/3-4 mon	CPS, GTCS	Gross motor, personal-social delay	Diazepam	Seizure	0
7	Bilateral	4	5-6/day	IS, GTCS, Myoclonic	Mild delay (high-functioning)	Phenobarbital, Lamotrigine, Phenytoin, Lorazepam, Zonisamide, ACTH	Seizure-free	<1
8	Unilateral	4	2-3/day	IS	Severe global developmental delay	Hemispherectomy	Seizure	0
9	Unilateral	0.3	20/day	IS, CPS	Mild delay	Focal resection	Seizure-free	<1
10	Unilateral	5.5	1/day	IS, CPS	Global developmental delay	Hemispherectomy	Seizure-free	9
11	Bilateral	5	20/day	CPS, GTCS	Severe global developmental delay	Clonazepam, Levetiracetam, Diazepam	Seizure	0
Abbreviations: CPS=complex partial seizures; IS=infantile spasms; GTCS=generalized tonic clonic seizures.								

Table 1. *Clinical and demographic details*

All of the patients were developmentally delayed, and most of them had associated findings, most common being contralateral hemiparesis, seen in 4 patients. Other common associated conditions included congenital hydrocephalus of unknown etiology in 2 patients (#1 and 6), skull abnormalities (including dolichocephaly, plagiocephaly and microcephaly) in 3 (#6, 8 and 11), scoliosis in 1 (#3), spastic cerebral palsy in 4 (#3, 6, 8 and 11), septo-optic dysplasia in 2 (#2 and 11), and other ocular abnormalities (esotropia) in 4 patients (#1, 6, 10 and 11).

We found a variety of possible etiologies in our patient cohort. One patient (#8) had a genetic abnormality: 16p11.2 duplication, which was suggested as a cause for the schizencephaly. This patient's mother had threatened preterm labor at 30 weeks, at which time the prenatal ultrasound also showed a single umbilical artery. Two patients had histories of infarcts in-utero; on MR angiography one (#10) showed decreased caliber of the left middle cerebral artery, with a hypoplastic left posterior communicating artery, and the other one (#1) showed developmental absence of a segment of the right anterior cerebral artery. These babies had the schizencephalic clefts in the corresponding areas of distribution of these respective arteries. Another patient (#8), without overt history of infarct in-utero, showed asymmetry and splaying of vessels in the middle cerebral distribution on MRA, in the area of and on the same side as the malformation. One patient (#6) was found to have hydrocephalus at 20 weeks of gestation.

FDG PET findings

In all the patients, FDG-PET scans showed a larger area of abnormality than MRI (Figure 1), and

corresponding better with the electrophysiological changes compared to MRI (Table 2). Also, the area of involvement on the FDG-PET scan showed a positive correlation with the extent of developmental delay; though a formal statistical analysis was not performed due to very small sample size.Five patients, with unilateral disease on MRI, underwent epilepsy surgery (4 hemispherectomy and 1 multilobar resection). Out of these, 2 patients (#5 and 8) had only focal defect on MRI, but both the video-EEG and FDG-PET showed a much larger area of involvement. They underwent hemispherectomy after confirmation with subdural electrode placement, and the widespread involvement was subsequently also corroborated by histopathological examination of the resected brain tissue which showed, in one patient, abnormal neocortical layering/ malformation of cortical development of a significant area of 2 lobes adjacent to the cleft and, in the other patient, scattered foci of vacuolation, myelin loss and gliosis in multiple lobes. One patient (#6) with a unilateral video-EEG abnormality and an equivocal MRI (with a unilateral porencephaly, and possible schizencephaly on the opposite side) was shown to have bilateral disease on PET and, therefore, was not operated. On the other hand, the only patient (#8) who was not seizure-free after surgery had unilateral schizencephaly and video-EEG changes, but bilateral abnormalities on FDG PET.

Figure 1. *FDG PET scan showed a larger area of abnormality compared to MRI.* UPPER ROW: FDG-PET (A) showing hypometabolism in the contralateral lateral and medial parietal cortices also (arrows), suggesting underlying functional abnormality, in a 4-year-old male child (pt#8) with apparently unilateral (right-sided) schizencephaly and normal-appearing corresponding parietal cortex on MRI (B).BOTTOM ROW: FDG-PET (C), in another 1-year-old male child with bilateral schizencephaly (worse on the left side; pt#11), showed hypometabolism in the right temporal-occipital cortices also (broken arrows) which appeared some-what normal on MRI (D).

No	Video-EEG	MRI	FDG PET
1	Background disorganization: right temporal	Unilateral closed lip schizencephaly: right frontal	Hypometabolism: right fronto-temporal; Malformation in right frontal
2	Sharp spike & wave: right posterior quadrant	Bilateral open lip schizencephaly: fronto-temporal junction	Hypermetabolism: right hemisphere, schiz region on left
3	Seizures arising from right fron-to-temporal	Unilateral schizencephaly: right fronto-central	Hypometabolism: right fronto-temporal
4	Attenuation of left hemisphere	Unilateral open lip schizencephaly: left frontal	Hypometabolism: left fronto-temporo-parietal; Hypermetabolism: malformation in left parietal-temporal; Cleft in left fronto-parietal
5	Multifocal spike & wave discharges	Unilateral closed lip schizencephaly: left central	Hypometabolism: left frontal, portions of left parietal and superior temporal
6	Frequent spikes: left temporal, intermittent left occipital slowing	Porencephalic cyst on left, possible closed-lip schizencephaly: right posterior parietal	Hypometabolism: right temporo-occipital; ametabolism: left occipital, left calcarine
7	Sharp waves: left and right centro-temporal	Bilateral closed lip schizencephaly: parietal; multiple areas of cortical dysplasia & microgyria; occipital horns: colpocephalic	Hypometabolism: bilateral temporal, lateral occipital; hypermetabolism: both upper & lower lips
8	High amplitude slowing: right hemisphere	Unilateral open lip schizencephaly: right parietal; cystic lesion, left side volume loss, ventriculomegaly and posterior fossa old arachnoid cyst/infarct	Hypometabolism: right hemisphere except right occipital; left temporo-parietal, left cerebellum
9	Seizure onset diffuse: left central, anterior temporal	Unilateral schizencephaly: left parietal, posterior frontal,	Hypermetabolism: left temporo-parietal, lateral

No	Video-EEG	MRI	FDG PET
		temporal, anterior left occipital, left pre-& post central gyri involved	occipital; mild hypometabolism: posterior left frontal margin
10	Spike activity-left, right parietal; Spasms with leading spike: right posterior quadrant (false lateralization)	Unilateral open lip schizencephaly: left parietal, hypoplasia of left temporal	Ametabolism: large central region of left hemisphere, hypometabolism: left hemisphere motor cortex
11	Frequent spike & wave: right frontal, temporo-central-parietal, occipital, left occipital	Bilateral open lip schizencephaly, volume loss greater on left & includes temporal	Left temporal not visualized, rest of bilateral frontal, occipital, right temporal, thalamus & basal ganglia displaced, cerebellum hypometabolic

Table 2. *Comparison of extent of abnormality seen on video-EEG, MRI and FDG PET*

Treatment and seizure outcome

At last follow-up, six patients were seizure-free, but only 2 had discontinued their anti-epileptic medication. These patients continued to have seizures for an average duration of 26 months (range: 3.5-116 months) before achieving seizure- freedom. Seizures in 2 of these 10 patients responded to anti-epileptic medications, including valproic acid in one, and the combination of adrenocorticotropic hormone (ACTH), zonisamide and lamotrigene in the other (median seizure-free duration 56 months, range: 1-120 months). All 6 patients with infantile spasms were treated with ACTH, and four of them responded to it; however, the response was very brief, ranging from 1 month to 1 year, after which the seizures recurred in three of them and one was lost to follow-up. None of the patients was treated with vigabatrin. Five patients underwent epilepsy surgery, after being tried on at least 4 anti-epileptic drugs. Four of these 5 patients were seizure-free at last follow-up (average seizure-free duration: 37 months, range: 0.3-188 months).

Discussion

Clinical findings

Schizencephaly usually presents with developmental delay, seizures and motor deficits [10]. The prevalence of developmental delay in schizencephaly patients was found to be 83%. All of the children in our study had global developmental delay. The severity of the developmental delay depends on the extent of the malformation [10]. In previous studies, the mean age of seizure onset was found to be 13 months and the most common seizure type was complex partial seizures [12]. It has been reported that the prevalence of epilepsy in schizencephaly is 37-65% [1, 13]. However, the median age at seizure onset in our study population was much lower and all the children had intractable epilepsy, probably attributable to the tertiary care epilepsy surgery referral status of our center. Seizures have been reported to be worse in unilateral disease, as bilateral clefts have been hypothesized to inhibit the propagation of epileptiform discharges [10]; however, we found equally worse seizures in cases of bilateral involvement. Other clinical features (e.g., cognitive function) may be worse in bilateral disease due not only to the malformation, but also the lower capacity for cortical reorganization when both hemispheres are abnormal. General intellectual function and neurodevelopmental outcome was found to be dependent on the extent of cortical involvement as well as the presence of other CNS anomalies [14, 15]. Since PET scanning provides a functional assessment of the brain, it can be useful in delineating the extent and severity of the cortical involvement and eventual functional status of the child. We observed that in our cohort of patients, children with larger area of involvement on PET scan, inclusive of the structural abnormality, were more delayed as compared to those with less extensive involvement.

Etiology

The most commonly accepted theory for the development of schizencephaly is vascular disruption in the developing fetal brain around the time of neuronal migration. In fact, the proposed underlying mechanism for viral and drug-induced etiologies of schizencephaly is also vascular disruption [6]. In the spectrum of polymicrogyria-porencephaly-schizencephaly- hydranencephaly, the exact anatomic lesion that will develop depends on the severity and timing of the insult that occurred during brain development [6]. An antenatal and postnatal color-flow Doppler imaging study found middle cerebral artery flow abnormality at 22-32 weeks of gestation, suggesting that early vascular occlusion can cause schizencephaly [16]. In our study, we found that two children had hypoplasia of an intracranial artery on MRA; one involved the posterior communicating artery, and the other one involved the anterior cerebral artery. The MRI scans of these children showed that their clefts were in the area of distribution of these respective arteries, suggesting that the vascular hypoplasia may be etiologically related to the cleft formation.

Response to medical treatment

An interesting observation from our study is the poor response of children with schizencephaly to ACTH. Although infantile spasms often respond well to ACTH, in our patients with coexisting schizencephaly, the response to ACTH was either temporary or completely absent. This finding suggests that ACTH may not be the best choice in schizencephaly with infantile spasms. ACTH is an expensive drug, with multiple side effects including fluid retention, hypertension, bloating, and if its effect is limited in this population, other approaches may be attempted first, such as vigabatrin or ketogenic diet, which were not used in patients from this old series. This is a limitation of our study. However, larger studies are required to confirm that ACTH may not be the best choice.

Imaging and surgical treatment

Some neuronal migration defects are known to have underlying diffuse brain injury that develop during the same period [14]. Schizencephaly, whether unilateral or bilateral, is very often found to be associated with other defects, including cortical dysplasia, cerebral atrophy, and posterior fossa abnormalities. These abnormalities may be found anywhere, such as adjacent to the cleft, ipsilateral but remote, or contralateral in a symmetric or asymmetric distribution [1, 15, 17, 18]. Seizures usually originate from the grey matter surrounding the cleft, but they can also arise from any of the other abnormal areas in the cortex. We still do not have a complete understanding of the spatial correlation between the area of malformation and the epileptogenic zone [19]. MRI is considered the gold-standard for the diagnosis of schizencephaly. One of the drawbacks of MRI, however, is that it is sometimes unable to detect small, subtle defects [20, 21]. Kim et al. [22](19) suggested that the difference in the ability of the MRI and PET scans becomes marked when the defect is small (MRI was able to detect 13%, whereas PET scan could detect 86% of defects. Another problem is that since the grey matter lining the cleft may not always be the epileptogenic region, the EEG and MRI findings can be discordant in many schizencephaly cases [15]. Similarly, EEG, which is the diagnostic test of choice for identifying the epileptic focus, may provide false lateralization or localization in cases of large defects due to dipole distortion. This renders the EEG less useful in such cases and other imaging modalities have to be relied upon [20]. FDG PET can be particularly useful in these cases, as shown in our study.

In the FDG-PET scan, abnormal areas show up as either characteristic hypometabolism or as areas of hypermetabolism. Hypometabolic areas may represent underlying neuronal dysfunction related to several factors, such as absence of cortical matter in the cleft, microdysgenesis/dysplasia of the surrounding cortex or possible epileptogenic cortex, whereas hypermetabolism can be a more specific finding with several possible explanations. First, clinical or subclinical seizures during the tracer uptake period due to the intrinsic epileptogenicity of the dysplastic cortex can result in a hypermetabolic focus on the scan [23, 24, 25], and therefore the hypermetabolic area may represent the epileptogenic cortex, thus helping in seizure lateralization/localization. Continuous EEG monitoring during the FDG uptake period, as routinely done at our center, can be particularly

helpful in these cases. Indeed, three of our patients showed focal/ generalized spike and wave activity with hypermetabolism on the PET scan. Second, associated heterotopic malformations, which are often present in the cortex of these patients can themselves be seen as hypermetabolic as a result of the dense accumulation of neurons and neuronal connections [11, 20, 26]. In addition, these heterotopias, can also cause functional reorganization of adjacent areas or even contralaterally [20, 26, 27]. Epilepsy surgery can be offered if the seizures become intractable and the epileptogenic zone can be identified. Although the occurrence and type of seizures are not correlated with the type of schizencephaly, it has been found that bilateral open lip schizencephalies commonly have an earlier age of onset and are refractory to multiple seizure medications [17]. However, children with bilateral clefts are not eligible for surgical treatment. There are two important pre-surgical considerations for a good surgical outcome, the first being the exact identification and demarcation of the epileptogenic zone that will be resected and the second, the evaluation of the remaining brain, to ensure that the post-surgical functional deficit will be acceptable. Here again, FDG-PET can be helpful, as it can identify the epileptogenic cortex, as well as provide information about the functional status of the remaining brain.

In our study, we found that FDG-PET scans always showed a larger area of involvement as compared to MRI, and the PET findings corresponded better with the EEG. This observation is in agreement with other studies indicating that the cortex beyond the cleft may also be functionally deficient [22]. We found that the histopathological examination of the resected brain tissue corroborated with the PET scan findings, showing malformation of cortical development or foci of vacuolation, gliosis and myelin loss, where no abnormality was detected on the MRI scan. This shows that PET scans can identify non-structural abnormalities and guide the decision of the eligibility of a particular candidate for surgery. In one patient, bilateral abnormality on PET scan helped in re-evaluation of an unequivocal unilateral MRI, precluding hemispherectomy in a child who would otherwise have had a poor surgical outcome as the remaining hemisphere would also have been abnormal. One of our patients who did have a hemispherectomy, despite bilateral functional abnormalities on PET scan, continued to have seizures (Figure 1). We note that ambiguous findings on MRI scans should be re-evaluated in the light of positive PET scan findings to detect subtle defects [20, 28].

Although pre-resection subdural grid electrode placement is the final and most accurate way to identify the epileptogenic region, it is an invasive procedure, which should be avoided if the patient has already been determined to be suboptimal for surgery through non-invasive tests [17]. We suggest that FDG-PET scans may be an adjunctive tool in the pre-surgical evaluation of schizencephaly, providing additional information, especially when MRI findings are either normal or discordant with EEG and before resorting to subdural grid placement [29].

Our study does have some limitations. First, patients with very small schizencephalic clefts may be under-represented in our tertiary center series, since they have mild symptoms and may not have been scanned for a cerebral abnormality, or may not have referred to a tertiary center. Second, the small sample size precludes making conclusive inferences, though this may be an unavoidable problem due to the rarity of this condition and associated logistic constraints.

Conclusions

Schizencephaly has diverse presentations, with unilateral being more common than bilateral. Unilateral schizencephaly presents with higher frequency and earlier onset seizures. Children with schizencephaly and intractable epilepsy generally do not respond well to anti-epileptic medications. Even infantile spasms in schizencephaly respond poorly to ACTH. Unilateral clefts with intractable epilepsy, may however, be amenable to surgical treatment if the contralateral hemisphere is found to be normal. FDG-PET may prove to be a useful tool in surgical decision-making and predicting surgical outcome, as patients with contralateral abnormality, revealed on FDG-PET, may have poor surgical outcomes.

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Competing interests

The authors have declared that no competing interest exists.

Author contributions

TG-D participated in the collection and analysis of data, helped in the design of the study and wrote the first draft of the manuscript. AK participated in the design of the study, formulated the hypothesis, helped in data collection, manuscript writing and manuscript revision. PK participated in the data collection, manuscript writing and subsequent revision. HC participated in the design of the study, formulated the hypothesis, and substantially revised the manuscript.

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