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Imaging increased glutamate in children with Sturge–Weber syndrome: Association with epilepsy severity

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ABSTRACT

Background: Sturge–Weber syndrome (SWS) is strongly associated with epilepsy. Brain tissue studies have suggested that epileptic activity in SWS is driven by glutamatergic synaptic activity. Here, we used proton magnetic resonance spectroscopic imaging (MRSI) to test if glutamate (GLU) concentrations are increased in the affected hemisphere and if such increases are associated with severity of epilepsy in children with SWS. We also studied the metabolic correlates of MRSI abnormalities, using glucose positron emission tomography (PET) imaging.

Methods: 3T MRI and glucose PET were performed in 10 children (age: 7–78 months) with unilateral SWS and a history of epilepsy. MRSI data were acquired from the affected (ipsilateral) and non-affected (contralateral) hemispheres. GLU, N-acetyl-aspartate (NAA) and creatine (Cr) were quantified in multiple voxels; GLU/Cr and NAA/Cr ratios were calculated and compared to seizure frequency as well as glucose PET findings.

Results: The highest GLU/Cr ratios were found in the affected hemisphere in all children except one with severe atrophy. The maximum ipsilateral/contralateral GLU/Cr ratios ranged between 1.0 and 2.5 (mean: 1.6). Mean ipsilateral/contralateral GLU/Cr ratios were highest in the youngest children and showed a strong positive correlation with clinical seizure frequency scores assessed at the time of the scan ($r = 0.88$, $p = 0.001$) and also at follow-up (up to 1 year, $r = 0.80$, $p = 0.009$). GLU increases in the affected hemisphere coincided with areas showing current or previous increases of glucose metabolism on PET in 5 children. NAA/Cr ratios showed no association with clinical seizure frequency.

Conclusions: Increased glutamate concentrations in the affected hemisphere, measured by MRSI, are common in young children with unilateral SWS and are associated with frequent seizures. The findings lend support to the role of excess glutamate in SWS-associated epilepsy.

1. Introduction

Sturge–Weber syndrome (SWS) is a neurocutaneous disorder characterized by a facial capillary malformation ("port wine stain"), leptomeningeal vascular malformation and, in about half of the cases, glaucoma (Bodensteiner and Roach, 2010). Intracranial involvement is unilateral in about 85% of SWS cases. A somatic mutation in the G-α q gene, identified both in the port wine stain and affected brain, may be the underlying cause of the SWS vascular abnormalities (Nakashima et al., 2014; Shirley et al., 2013). Neurologic complications, most commonly seizures, motor impairment, and peripheral visual field deficit develop due to the lack of proper cortical venous drainage, leading to venous stasis, hypoxia and tissue damage in affected brain regions.

SWS is strongly associated with epilepsy: up to 80% of SWS patients develop seizures, which most commonly start during the first 1–2 years of life (Comi, 2010; Lo et al., 2012; Sujansky and Conradi, 1995). Early seizure onset and medically refractory epilepsy are associated with poor cognitive outcome (Jagtap et al., 2013; Pascual-Castroviejo et al., 2008). In such patients, surgical resection (hemispherectomy or focal resection) can be highly effective in controlling the seizures and, possibly, prevent or reverse cognitive decline (Bourgeois et al., 2007; Kossoff et al., 2002). However, seizure outcome and associated neuro-cognitive decline

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cannot be predicted based on clinical or conventional imaging criteria at the early disease stages.

SWS intracranial involvement is most commonly evaluated by contrast-enhanced MRI, which can detect the leptomeningeal venous malformation, deep venous abnormalities, atrophy, calcification and other associated brain abnormalities (Juhasz, 2010; Lo et al., 2012). Functional imaging studies, such as glucose positron emission tomography (PET), can be useful clinically in selected SWS patients as part of the evaluation for epilepsy surgery. Decreased glucose metabolism detected in the affected hemisphere(s) can extend beyond structural brain abnormalities depicted by CT and MRI (Alkonyi et al., 2012; Chugani et al., 1989). However, a subset of young children with SWS show paradoxically increased glucose metabolism in the affected hemisphere on interictal PET both before and after the onset of the first clinical seizure(s) (Chugani et al., 1989; Alkonyi et al., 2011). Such hypermetabolic cortical regions were most commonly observed shortly (within months) before and/or after the onset of the first clinical seizure(s) (Alkonyi et al., 2011), i.e., during the presumed period of epileptogenesis (Dudek and Staley, 2011).

The pathophysiology of SWS-associated epilepsy and the role of these transient metabolic changes in SWS epileptogenesis remain poorly understood. One plausible mechanism involves the role of excess glutamate (GLU) released due to chronic hypoxia; indeed, excessive stimulation of glutamate receptors in the affected brain could facilitate seizures and also lead to excitotoxic brain injury (Johnston, 2005; Kostandy, 2012). Tissue studies have shown that epileptiform activity in affected SWS cortex is driven by glutamatergic synapses (Tyzio et al., 2009).

Advances in ^{1}H-magnetic resonance spectroscopic imaging (^{1}H-MRSI) allow non-invasive measurement of cerebral GLU concentrations in multiple voxels simultaneously (Hu et al., 2007; Yang et al., 2008). In a recent study using GLU chemical exchange saturation transfer imaging in patients with temporal lobe epilepsy, increased glutamate was invariably found in the epileptic temporal lobe (Davis et al., 2015). In the present study, we utilized GLU ^{1}H-MRSI to test if children with unilateral SWS show increased GLU levels in the affected (epileptic) hemisphere as compared to the unaffected side. We also evaluated if GLU abnormalities, measured by ^{1}H-MRSI, are related to severity of clinical epilepsy. Finally, we evaluated glucose metabolic correlates of ^{1}H-MRSI GLU asymmetries using PET imaging.

2. Material and methods

Ten children with SWS (8 girls, 2 boys, age: 7–78 months; mean: 35 months) were prospectively enrolled in a clinical neuroimaging research study (Table 1). All 10 children had a history of seizures and unilateral SWS brain involvement in the form of a leptomeningeal venous malformation detected by contrast-enhanced MRI. All 10 children underwent a 3T MRI with MRSI and 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG)-PET performed with scalp EEG monitoring during the uptake period; typically, MRI and PET studies were performed on consecutive days. All children were on at least one antiepileptic medication (Table 1). Clinical seizure frequency was evaluated by parent interviews and medical charts, and a seizure frequency score was assigned to each patient based on clinical seizures occurring during the one year period prior to the imaging study (or since seizure onset, if seizures started less than one year before the study). The scoring system was slightly modified from a previous study on children with SWS (Behen et al., 2011), and the scores were determined as follows: 0 = no seizure in the last 1 year; 1: 1–11 seizures per year; 2: 1–4 seizures per month; 3: >4 seizures per month. Similar scores were also determined at follow-up, i.e., 1 year after baseline or at the time of epilepsy surgery, if surgery was done within one year after the baseline studies (Table 1). Epilepsy surgery was performed in two children (#2 and #5, 6 and 3 months after the imaging studies, respectively). The study was approved by the Human Investigation Committee at Wayne State University, and written informed consent of the parent or legal guardian was obtained.

2.1. MRI studies

All MRI studies have been performed on a Siemens MAGNETOM Verio 3T scanner (Siemens Medical Solutions, Erlangen) located at the Harper University Hospital, Detroit Medical Center. The MRI protocol included an axial T1 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) with 1 mm slice thickness, axial T2 turbo spin-echo, axial T2/fluid-attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI) and diffusion tensor imaging. During bolus-injection of Gadolinium-diethylene triamine pentaacetic acid (DTPA; dose: 0.1 mmol/kg of body weight), dynamic contrast enhanced MR perfusion-weighted imaging was acquired, followed by a post-contrast axial 3D MPRAGE image.

Table 1
Clinical data of the 10 children with unilateral Sturge–Weber syndrome.

Pt. No.	Gender	Age (mo)	PWS	LMA	Glaucoma	Age at epilepsy onset (mo)	Seizure type(s)	AED	Seizure frequency score		FDG-PET	EEG (at PET)
									Baseline	Follow-up		
1	F	7	R V1	R FTPO	No	1	IS, focal	OXC, LEV	3	2	R FTP incr	Few spikes
2	F	13	R V1-3	R FTPO	No	5	Focal (SE)	OXC, LEV	2	3[b]	R TPO decr, F incr	No epi
3	F	18	L V1-3	L FTPO	No	4	Focal	OXC	0	1	L FTPO incr	No epi
4	F	20	R V1-3, L V3	R TPO	Yes	5	Focal	OXC, LEV	2	1	R TPO > F decr	No epi
5	F	30	L V1-2	L OT	No	4	Focal	LEV	2	2[b]	L O > TP decr	No epi
6	F	38	R V1-2	R FTPO	Yes	29	Focal	OXC, GAB	1	1	R TO > FP decr (incr)[a]	No epi
7	M	40	R V3	R P	No	10	Focal	OXC, LEV	2	2	R PO decr	No epi
8	M	44	None	R TP	No	7	Focal	LEV, ZON	1	n/a	R TPO > F decr (P incr)[a]	No epi
9	F	65	R V1-3, L V3	R FTPO	Yes	3	Focal	OXC, LEV	0	0	R FTPO decr	No epi
10	F	78	L V1	L TPO	No	6	Focal	PHB	0	0	L TPO > F decr	No epi

Abbreviations: F = female; M = male; mo = month(s); PWS = port-wine stain; R = right; L = left; V1-3 = branches 1–3 of the trigeminal nerve innervation area; LMA = leptomeningeal angiomatosis; IS = infantile spasms; SE = history of status epilepticus; AED = antiepileptic drug; OXC = oxcarbazepine; LEV = levetiracetam; GAB = gabapentin; ZON = zonisamide; PHB = phenobarbital; n/a = not available; epi = epileptiform EEG activity.

[a] Had increased FDG uptake on previous PET 1 year earlier but decreased FDG uptake at the time of MRSI.

[b] Had epilepsy surgery (therefore, follow-up was <1 year: 6 months for patient #2 and 3 months for patient #5).