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Evolution of cortical metabolic abnormalities and their clinical correlates in Sturge-Weber syndrome

C. Juhasz[a,b,*,1], C.E.A. Batista[a,b,1], D.C. Chugani[a,c], O. Muzik[a,c], H.T. Chugani[a,b,c]

[a]Carman and Ann Adams Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI, USA
[b]Departments of Neurology, Children's Hospital of Michigan, Wayne State University, Detroit, MI, USA
[c]Departments of Radiology, Children's Hospital of Michigan, Wayne State University, Detroit, MI, USA

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ABSTRACT

Background: The natural course of Sturge-Weber syndrome (SWS) is poorly understood, although neurological symptoms are often progressive.
Aims: To track longitudinal changes in brain glucose metabolism measured with positron emission tomography (PET) and their relation to clinical changes during the early course of SWS.
Methods: Fourteen children (age 3 months to 3.9 years at enrollment) with SWS and unilateral leptomeningeal angioma underwent two consecutive glucose metabolism PET scans with a mean follow-up time of 1.2 years. Longitudinal changes of the extent of cortical glucose hypometabolism on the angioma side were measured and correlated with age, clinical seizure frequency and hemiparesis.
Results: An increase in the size of the hypometabolic cortex was seen in 6 children, coinciding with an age-related increase in cortical glucose metabolism measured in unaffected contralateral cortex. These 6 patients were younger both at the initial (mean age 0.75 vs. 2.8 years; $p<0.001$) and the second scan (mean age 1.8 vs. 4.2 years; $p=0.001$) than those with no change in the extent of hypometabolic cortex ($n=6$). The area of cortical hypometabolism decreased in the two remaining children, and this was associated with resolution of an initial hemiparesis in one of them. Seizure frequency between the two scans was higher in children who showed progressive enlargement of cortical hypometabolism, as compared to those with no progression ($p=0.008$).
Conclusions: In SWS, detrimental metabolic changes occur before 3 years of age coinciding with a sharp increase of developmentally regulated cerebral metabolic demand. Progressive hypometabolism is associated with high seizure frequency in these children. However, metabolic abnormalities may remain limited or even partially recover later in some children with well-controlled seizures. Metabolic recovery accompanied by neurological improvement suggests a window for therapeutic intervention in children with unilateral SWS.

*Corresponding author. Division of Pediatric Neurology/PET Center, Children's Hospital of Michigan, 3901 Beaubien Blvd., Detroit, MI 48201, USA.
E-mail address: juhasz@pet.wayne.edu (C. Juhasz).
[1] Dr Juhasz and Dr Batista have equally contributed to this article.
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1. Introduction

Sturge-Weber syndrome (SWS) is a phakomatosis characterized by a port wine stain (PWS) over the trigeminal area, leptomeningeal angiomatosis and ocular abnormalities. The cerebral vascular malformation consists of abnormally developed venous vessels on the brain surface, resulting in an impairment of cerebral blood flow, hypoxia and chronic ischemia in the underlying brain tissue. Neurological outcome in children with SWS is highly variable, ranging from minimal or no neurological signs to a devastating impairment with uncontrolled seizures, hemiparesis, visual field defect and progressive mental retardation.[1]

Neuroimaging studies help establish the diagnosis, assess severity and follow the progression of brain involvement in SWS. MRI detects the leptomeningeal angioma and also can determine the extent of structural brain abnormalities,[2–5] which are correlated, to a certain extent, with the severity of neurological symptoms.[6,7] However, MRI abnormalities are not reliable predictors of neurological deficit in the early stage of the disease. Positron emission tomography (PET) scanning with 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) often shows hypometabolic cortex extending beyond the apparent structural abnormalities.[8,9] Progression of abnormalities in metabolism and perfusion often occur during the course of the disease[8,10] and can be associated with neurologic deterioration.[11]

Although it is generally believed that SWS has an irremissive progression, the natural course of the disease is poorly characterized, largely because of the lack of longitudinal studies that could quantify changes of structural or functional brain abnormalities. Therefore, we have performed a longitudinal neurological and neuroimaging study of children with SWS to test the hypothesis that the majority of progression in the extent of glucose hypometabolism occurs during the critical period when metabolic demand in the brain increases sharply due to normal maturational processes.[12] We also assessed whether the observed hypometabolism is irreversible and how metabolic changes are related to seizures and hemiparesis.

2. Methods

2.1. Subjects

Fourteen children (9 girls, age 3 months to 3.9 years at the time of the first scan; mean age: 1.9 years) with the clinical and radiological diagnosis of SWS with unilateral hemispheric involvement (based on location of leptomeningeal angioma on post-contrast MRI) and a history of seizures were included in the study (Table 1). All patients underwent FDG PET scanning twice; the interval between the two PET scans was within 3 years (range: 0.6–2.8 years, mean 1.2 ± 0.7 years). These patients were either prospectively recruited to participate in a longitudinal imaging study with yearly follow-ups or had a previous PET scan as part of a presurgical evaluation but were not operated and were re-scanned later. Frequency of clinical seizures was estimated for the period before the first PET scan (since the onset of the first seizure) as well as between the two PET scans by interviewing the parents and also by reviewing clinical charts. An estimated yearly seizure frequency was then calculated; this included all clinical seizures observed by the parents. None of the patients had status epilepticus. Age at the first clinical seizure (in months) was also recorded. Motor strength was clinically evaluated by one of the co-investigators (H.T.C.). Because some of the patients were enrolled retrospectively, and they had no detailed, standardized motor evaluation available, motor strength was categorized on a robust 3-point scale (0: normal motor strength; 1: mild/moderate weakness in the arm, hand and/or leg; 2: severe hemiparesis). Based on these categories, longitudinal change of gross motor functions between the two scans was categorized as: (1) no significant change; (2) progression, when the patient developed hemiparesis between the two scans or the degree of paresis worsened, and (3) improvement, when the paresis observed at the first time was not seen at the second evaluation or when the degree of hemiparesis decreased. 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.

2.2. PET image acquisition

The PET protocol was performed as previously described.[9,13] In brief, all patients underwent their PET scans using the CTI/Siemens EXACT/HR PET scanner. This scanner has a 15 cm field of view and generates 47 image planes with a slice thickness of 3 mm. The reconstructed image in-plane resolution obtained is 5.5 ± 0.35 mm at full-width-at-half-maximum and 6.0 ± 0.49 mm in the axial direction (reconstruction parameters: Shepp-Logan filter with 0.3 cycles/pixel cutoff frequency). FDG was produced using a Siemens RDS-11 cyclotron, applying the synthesis module purchased from Siemens/CTI (Knoxville, TN). Subjects fasted for 4 h prior to the PET procedure. A venous line was established for injection of FDG (0.143 mCi/kg). The lights were dimmed and interactions were discouraged in order to reflect a resting awake state. All PET scans were done at least 24 h after the last clinical seizure and the median time between the last seizure and the PET scan was 9 and 7 weeks for the first and second scans, respectively (first scans: 2 weeks–2 years; second scans: 1 day–4 years). All scans were acquired in the interictal state as demonstrated by scalp EEG recorded throughout the uptake period. Thus, ictal/post-ictal states were not confounding factors for interpretation of the PET results. After 40 min of FDG uptake, patients were positioned in the scanner and a static 20 min emission scan of brain was performed. Children below 2 years of age were sedated with chloral hydrate (50–100 mg/kg by mouth), and children older than 2 years were sedated with nembutal (3 mg/kg), followed by fentanyl (1 μg/kg).

2.3. PET image analysis

Calculated attenuation correction was applied to the brain images using automated threshold fits to the sinogram data. The hemispheric extent of cortical glucose hypometabolism on the side of the angioma was obtained by using a