Brain damage and IQ in unilateral Sturge–Weber syndrome: Support for a “fresh start” hypothesis

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1. Introduction

Sturge–Weber syndrome (SWS) is a neurocutaneous disorder characterized by congenital facial cutaneous angioma (port-wine stain), leptomeningeal angioma, intracranial calcifications, and glaucoma [1–3]. The intracranial pathology in SWS is most commonly unilateral (85%), and impaired cognitive development is apparent in about one-half of the patients [1,4,5]. However, neurocognitive outcome is difficult to predict on clinical grounds or conventional imaging. Early studies of brain glucose metabolism using 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography (FDG-PET) in SWS demonstrated reduced glucose metabolism of the cortex underlying the leptomeningeal lesion, often extending beyond the area of structural abnormality depicted by CT or MRI [6]. A subsequent small study of 13 children with unilateral SWS suggested an apparently paradoxical relationship between cortical glucose hypometabolism on PET and cognitive function: several patients with extensive severe hypometabolism showed relatively preserved IQ [7]. This could be attributed to functional reorganization, but it remained unclear how this relationship was affected by age or epilepsy [8], and also what extent of cortical damage is required to facilitate effective reorganization.

Sturge–Weber syndrome with unilateral hemispheric involvement represents an etiologically homogeneous disease group and is an excellent clinical model to study the relationship between unilateral, early-onset brain lesions and cognitive development, because: (1) the structural abnormality is strictly unilateral, (2) lesions start early in life, and (3) there is a highly variable rate of progression. As a result, there is great potential for interhemispheric reorganization of critical brain functions in unilateral SWS because the contralateral hemisphere is basically normal early in the course of the disease [9].

In the present study we tested the hypothesis that moderate-sized unilateral metabolic abnormalities will be associated with poor cognitive outcomes, whereas small or extensive areas of unilateral glucose hypometabolism will be associated with relatively preserved cognitive function in children with SWS. We also tested if this presumed relationship between hemispheric hypometabolism and cognitive functions is affected by age, seizure variables, lesion side, and location or severity of hypometabolism. Further, we aimed to determine if there is a threshold to the extent of hemispheric hypometabolism above which cognitive functions started to increase above severe impairment. Finally, we tested if seizure-related variables explained the IQ variations seen in patients with only mild (or no) metabolic abnormalities.
2. Methods

Thirty-five children (mean age: 73 ± 38 months, age range: 30–153 months; 17 males) with unilateral SWS (16 left-sided) underwent neurocognitive assessment, neurological examination, MRI, and interictal FDG-PET scans. Twenty-two children were right-handed, 12 left-handed, and one mixed-handed. Participants were recruited from the Neurology Clinics in Children’s Hospital of Michigan and the Sturge–Weber Foundation and/or were self-referred. They were all enrolled in a prospective clinical and neuroimaging study and data were collected between 2002 and 2010. All patients during this period who fulfilled the following inclusion criteria were included: facial angiomatosis, evidence of unilateral leptomeningeval angiomatosis on gadolinium-enhanced MRI, involvement of the posterior quadrant of the affected hemisphere, and age 30 months to 13 years. Exclusion criteria included leptomeningeval angiomatosis over both hemispheres as detected by MRI and clinical or electrographic seizures during PET. Written informed consent was obtained from the parents. All studies were performed in accordance with the policies of the Wayne State University institutional review board.

2.1. Neuropsychological assessment and classification

Children 30–87 months of age were administered the Wechsler Pre-primary and Pre-school Scale of Intelligence, Third Edition [10], and children (n = 12) older than 87 months, the Wechsler Intelligence Scales for Children, Third Edition [11]. Both measures provide indices of global (FSIQ), verbal (VIQ), and nonverbal (PIQ) cognitive functioning. As all participants had unilateral hemispheric involvement, presumably increasing the likelihood of VIQ–PIQ discrepancies, VIQ and PIQ were used as cognitive outcomes rather than FSIQ, which is more difficult to interpret when there are large VIQ–PIQ discrepancies [12].

2.2. Assessment of seizure frequency

Seizure frequency was estimated using a scheme modified from Engel et al. [13]: (1) ≤1 seizure per year, (2) 2–11 seizures per year, (3) 1–3 seizures per month, (4) 1–6 seizures per week, (5) ≥1 seizure per day. Duration of epilepsy was defined as number of months between onset of the first seizure and the PET scan.

2.3. FDG-PET scanning protocol

Positron emission tomography studies were performed using the CTI/Siemens EXACT/HR positron tomography scanner at Children’s Hospital of Michigan, as described previously [9]. EEG was monitored using surface electrodes during the FDG uptake period. Forty minutes after FDG injection (0.143 mCi/kg), a static 20-minute emission scan of the brain was acquired. Children were sedated as necessary during the scanning (but not during the uptake) period; therefore, sedation had no effect on FDG uptake. All subjects were continuously monitored by pediatric nurses. Calculated attenuation correction was applied to the brain images using automated threshold fits to the sinogram data [14].

2.4. Objective measurement of extent of hypometabolism in affected hemisphere

Cortical areas with glucose hypometabolism on the side of the angioma were objectively defined as described previously [7,15,16], using two different asymmetry thresholds of severity: (1) >10% asymmetry, defining all areas with cortical hypometabolism; (2) >20% asymmetry, defining areas with severe cortical hypometabolism, which have been shown to correspond to cortex with structural damage (including atrophy, calcification) [7]. In brief, the cortical mantle was divided into 60 sectors for each hemisphere in each axial PET plane including cerebral cortex, except the top and bottom planes, that were affected by partial volume effects. Sectors exceeding the asymmetry cutoff threshold (10 or 20%) were marked, provided that at least two adjacent sectors in at least two adjacent image planes exceeded the threshold. Thus, the smallest possible marked cortical region encompassed 2 × 2 sectors in two consecutive axial image planes corresponding to approximately 0.3% of the entire cortex in one hemisphere. A new “marked” image file was created that included all 47 planes of the original frame. After definition of abnormal cortical areas with both asymmetry thresholds, extent of cortical hypometabolism and severe cortical hypometabolism were calculated as percentages of total hemispheric surface as described previously [17]; these values were independent of the actual size of the hemisphere. This procedure was performed using the 3D-Tool software package (Max Planck Institute, Cologne, Germany). In brief, the marked PET image volumes were three-dimensionally surface-rendered using isocontours; the marked PET abnormalities and the hemispheric contours were then delineated on these surface images. The size of the PET abnormality (based on the number of pixels) was calculated as the percentage of the surface size of the ipsilateral hemisphere. The advantages and limitations of this method have been discussed elsewhere [17]. As this method does not rely on absolute or normalized metabolic rates, the values obtained are independent of cerebral metabolic changes related to age [18] or drug effects [19]. On the other hand, this approach cannot detect bilateral symmetric metabolic abnormalities and does not evaluate deep structures such as thalamus and insula. However, none of the patients showed obvious metabolic abnormalities on visual assessment in the hemisphere contralateral to the angioma. The effect ofthalamic hypometabolism on cognitive functions has been reported in a separate study [20].

2.5. Statistical analysis

The sample was divided into two subgroups: patients with severe hypometabolism and patients with no severe hypometabolism on PET. Our primary hypothesis was that extent of severe (>20% decrease) cortical hypometabolism would have a nonlinear-U-shaped relationship to IQ. This hypothesis was tested via stepwise multiple regression analyses with empirically chosen covariates, within the group with severe hypometabolism. Preliminary analyses examined relationships (Pearson correlations unless noted) of age at PET scan, age at seizure onset, epilepsy duration, seizure variables, side of lesion (t test), and presence of frontal lobe involvement (t test) with outcome measures (VIQ and PIQ); those variables that were significantly correlated with outcome(s) were included in the regressions for that outcome measure. Each regression involved entry of covariates in step 1, followed by extent of severe hypometabolism in step 2, and the quadratic expression (severe hypometabolism 2) in step 3. To aid in the interpretation of the linear and quadratic effects of severe hypometabolism, severe hypometabolism was mean centered before the quadratic term was created. Four separate regression analyses were run to test the hypotheses for the two outcome variables for extent of severe hypometabolism (using only participants with at least one cortical area with severe hypometabolism) and then repeated with overall extent of hypometabolism (i.e., using the full sample) as the predictor, to test if the relationships found in the primary analysis remained significant if all (mild and severe) hypometabolic areas were considered.

As patients with no severe hypometabolism also showed considerable variations in cognitive functions, we also tested if extent of mild hypometabolism and/or seizure-related variables could explain this variability. To evaluate predictors of cognitive outcomes in this subgroup, Pearson correlations between age, age at seizure onset, epilepsy duration, seizure frequency, side of lesion, and extent of...
overall hypometabolism with VIQ and PIQ were performed. \(P<0.05\) was considered significant.

3. Results

Age at seizure onset had three positive outliers, which were winsorized. Median age at seizure onset was 6 months (interquartile range: 5–18 months); mean age at time of PET scan was 72.8 months (SD = 38.2); mean duration of epilepsy was 59.6 months (SD = 40.1); and mean seizure frequency was 2.1 (SD = 1.1). Forty percent (\(n = 14\)) of the patients had hypometabolism that extended into the frontal lobe. Extent of hypometabolic cortex ranged from 0 to 98% (mean = 42%, SD = 33%). For severely hypometabolic cortex the range was 0–95% (mean = 30%, SD = 31%). To determine whether the groups of patients with left (or right)-sided involvement had different distributions of extent of either overall and/or severe hypometabolic cortex, we also examined the number of cases within each group (left vs right) that had intermediate values (between the 20 and 60% “thresholds”—discussed below) and extreme values (below 20% or above 60%). For extent of severe hypometabolism, there were no differences between the left and right sides in the incidence of intermediate-sized involvement (4/13 for left, 5/13 for right, \(\chi^2 = 0.17, P = 0.68\)). Nor did the groups differ on incidence of large or small extent: 2 children with right-sided involvement had large (>60) extent, and 4 with left-sided involvement had large extent, whereas 5 children with left-sided involvement had small (<20) extent and 6 with right-sided involvement had small extent. As for extent of overall hypometabolism, there were no differences between those with left-sided and those with right-sided involvement in the incidence of intermediate involvement (5/13 for left, 6/13 for right, \(\chi^2 = 0.16, P = 0.69\)). Nor did the two groups differ on incidence of large (>60) or small (<20) extent. Seventy-four percent (\(n = 26\)) of the sample met criteria for presence of severe cortical hypometabolism, whereas 26% (\(n = 9\)) of the patients had no severe hypometabolism.

3.1. Neurocognitive profile

The neurocognitive profiles for the overall sample (\(N = 35\)) and for children with (\(n = 26\)) and without (\(n = 9\)) severe hypometabolism are summarized in Table 1. The overall group was measured in the low average and borderline ranges for VIQ (mean = 82) and PIQ (mean = 76), respectively. Comparisons between the two subgroups revealed that the group with no severe hypometabolism had higher VIQ and PIQ, and decreased incidence of impairment in both subdomains; there were increased numbers of children measured within 1 SD of the normative mean (IQ ≥ 85) in both subdomains. The group differences in PIQ (\(t(33) = 2.22, P = 0.033\)), percentage in impaired range for PIQ (\(P = 0.048\), Fisher’s exact test), and incidence of children measured within 1 SD of normative mean in PIQ (\(P = 0.050\), Fisher’s exact test) were statistically significant.

3.2. Clinical predictors of IQ

Preliminary analyses revealed that age at PET scan (\(r = -0.33, P = 0.039\)), duration of epilepsy (\(r = -0.46, P = 0.006\)), and seizure frequency (\(r = -0.34, P = 0.048\)) were negatively correlated with VIQ. Age at seizure onset (\(r = 0.41, P = 0.014\)) was positively correlated with VIQ. Duration of epilepsy (\(r = -0.45, P = 0.006\)) was negatively and age at seizure onset (\(r = 0.42, P = 0.012\)) was positively correlated with PIQ. Neither side of the lesion nor presence of frontal lobe involvement was associated with the cognitive variables.

3.3. Abnormal FDG-PET and IQ

3.3.1. Effect of extent of severe hypometabolism on IQ (\(n = 26\))

For VIQ, age at seizure onset, duration of epilepsy, and seizure frequency entered in the first step, the overall model was significant [\(F(5, 20) = 9.82, P < 0.001\)], and both extent of severe hypometabolism (linear effect) and severe hypometabolism\(^2\) (quadratic effect) emerged as significant independent predictors of VIQ (\(t = -4.51, P < 0.001\), and \(t = 3.83, P = 0.001\), respectively) in the final model (see Figs. 1 and 2). Seizure frequency (\(t = -2.63, P = 0.016\)) also contributed significant unique variance to VIQ; children with greater

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**Table 1**

Neurocognitive profile for overall group and FDG-PET groups.

<table>
<thead>
<tr>
<th></th>
<th>Overall group ((N = 35))</th>
<th>Severe FDG-PET abnormality ((n = 26))</th>
<th>No severe FDG-PET abnormality ((n = 9))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIQ</td>
<td>82.1 (24.6)</td>
<td>79.3 (23.8)</td>
<td>90.2 (26.7)</td>
<td>0.238(^a)</td>
</tr>
<tr>
<td>% impaired</td>
<td>34</td>
<td>42</td>
<td>11</td>
<td>0.121(^b)</td>
</tr>
<tr>
<td>% SS ≥ 85</td>
<td>43</td>
<td>35</td>
<td>67</td>
<td>0.129(^b)</td>
</tr>
<tr>
<td>PIQ</td>
<td>76.4 (21.2)</td>
<td>72.0 (21.3)</td>
<td>89.2 (15.6)</td>
<td>0.033(^b)</td>
</tr>
<tr>
<td>% impaired</td>
<td>43</td>
<td>54</td>
<td>11</td>
<td>0.048(^c)</td>
</tr>
<tr>
<td>% SS ≥ 85</td>
<td>37</td>
<td>27</td>
<td>67</td>
<td>0.050(^c)</td>
</tr>
</tbody>
</table>

\(^a\) % impaired = IQ standard score <70. Standard score = mean = 100, SD = 15.

\(^b\) \(t\) test.

\(^c\) Fisher’s exact test.

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![Fig. 1](Image) Scatterplots of relationship between extent of severe hypometabolism on FDG-PET and VIQ and PIQ. The plots show the curvilinear (quadratic) relationships between extent of severe hypometabolism and verbal and nonverbal cognitive outcome. Both linear and quadratic effects are significant for both VIQ and PIQ.
seizure frequency had reduced verbal IQs. The quadratic effect accounted for 21% of the variance in VIQ over and above the variance by covariates and extent of linear relationship. For PIQ, with duration of epilepsy and age at seizure onset entered in the first step, the overall model was significant [F(2,21) = 8.40, P<0.001]. In the final model, both extent of severe hypometabolism (i.e., linear relationship) (t = −4.16, P<0.001) and the quadratic relationship (t = 3.38, P = 0.003) emerged as significant independent predictors. Age at seizure onset and duration of epilepsy were not significant in the final model. For PIQ, the quadratic effect accounted for 21% of the variance over and above the variance by covariates and linear relationship.

3.3.2. Extent of total cortical hypometabolism and IQ (n = 35)
When the above analyses were repeated for the extent of all cortical hypometabolism (>10% asymmetry, including both mild and severe hypometabolism, see Fig. 3), the overall model for VIQ was significant [F(4,29) = 4.92, P = 0.002]; however, only the linear effect (t = −2.17, P<0.039) contributed significant variance to outcome in this model. For PIQ, the overall model was significant [F(4,30) = 8.94, P<0.001]. Both the linear effect (t = −4.08, P<0.001) and the quadratic relationship (t = 2.60, P = 0.014) were significant predictors.

3.3.3. Predictors of IQ for group with no severe hypometabolism on FDG-PET (n = 9)
Results of correlations between predictors and IQ metrics revealed that duration of epilepsy was negatively correlated with VIQ and PIQ (r = −0.68, P = 0.046, and r = −0.67, P = 0.049 respectively). Though nonsignificant, the correlation between age at PET scan and IQ was moderate (r = −0.57, P = 0.112, and r = −0.62, P = 0.078 respectively). Age at seizure onset (r = 0.13, P = 0.741, and r = 0.01, P = 0.989), seizure frequency (r = −0.37, P = 0.329, and r = −0.20, P = 0.609), and side of lesion (r = −0.18, P = 0.861, and r = −0.51, P = 0.624) were all unrelated to the cognitive variables within this group.

3.4. Exploratory analyses of FDG metabolic extent threshold
To determine the cutoff at which the relationship of VIQ/PIQ to extent of severe (>20%) hypometabolism shifts from a negative (IQ decreases as extent of hypometabolic cortex increases) to a positive (IQ increases with extent) relationship, we set the first derivative of the quadratic equations from the full models for VIQ and PIQ to 0 and solved for the levels of hypometabolism. The threshold was determined to be 56.0% of the hemisphere for VIQ and 57.2% for PIQ, based on the minimum value of the quadratic curve. The scatterplot of the extent of severe hypometabolism on FDG-PET and VIQ and PIQ (Fig. 3) was examined to determine the lower limit or the extent of severe hypometabolism at which IQ is measured below normal. Inspection of the scatterplots for VIQ and PIQ indicates that, for both outcomes, none of the patients with less than 16% extent of severe hypometabolism had measured IQs below 80 (Fig. 1).

4. Discussion
Sparing and/or reorganization of cortical function following brain damage may depend on a number of factors including age, size, and
location of lesion, integrity of surrounding and contralateral brain regions, and disease characteristics (e.g., epilepsy) [9]. The present study demonstrates a close relationship between cognitive functions and extent of unilateral brain damage (reflected by glucose hypometabolism) in children with early-onset unihemispheric injury caused by SWS, even after controlling for age and seizure variables. The results strongly suggest that the relationship of extent of severe hypometabolism (but not total hypometabolism) to cognitive outcome is nonlinear or U-shaped. Specifically, our data suggest that although absent and/or very small extent of severe hypometabolism is often associated with good cognitive functions, very large extent (involving more than half of the hemispheric surface) may also, paradoxically, be associated with relatively preserved (although not normal) IQ measures; this is particularly true for VIQ, as six children with the largest areas with severe hypometabolism (all >60% of the hemisphere) had a better (>65) IQ than several other children with smaller areas of hypometabolism. On the other hand, long duration of epilepsy was associated with worse cognitive functions even in the subgroup with no severe hypometabolism, suggesting that chronic seizures may be a key factor in poor cognitive outcome even in patients without significant structural damage.

A U-shaped relationship between lesion size and sparing and/or recovery of function has been proposed previously [9,21], involving the hypothesis that size of lesion and behavioral deficit vary directly, but only to a threshold. As the threshold is reached, further increase in lesion size results in improved behavioral recovery, presumably related to a “switch” from intra- to interhemispheric reorganization [9]. In support of this hypothesis, a meta-analysis of 283 lesion studies of monkeys using various behavioral tasks found a U-shaped relationship between lesion size and behavioral outcome [22]. In summarizing this work, Bates referred to a “fresh start hypothesis” involving the idea that beyond a threshold (approximately 60% of the brain volume was identified as the threshold), the affected hemisphere is sufficiently damaged to allow the unaffected hemisphere to take over its function [21,23]. Midsize lesions, on the other hand, are large enough to cause impairment, but fail to promote reorganization [22]. However, to date, there has been little empirical support for this hypothesis in humans. For instance, the size of the threshold in humans is not known; neither are the mechanisms that govern intra-versus interhemispheric reorganization. Our results suggest that when the extent of severe hypometabolism is less than approximately 15–20% of the hemisphere, a good outcome is probable. Further, as the area of severe hypometabolism extends beyond approximately 60%, the relationship between cognitive functioning and extent of functional lesion becomes positive; that is, IQ actually increases with extent of severe functional lesion (Fig. 1). Our data, therefore, provide empirical support for Bates’ “fresh start hypothesis” in humans [21,23].

The finding that total area of hypometabolism (including mild hypometabolism is not associated with the shift to a positive correlation with VIQ outcome at any extent (see Fig. 3) suggests that severity of the functional lesion may also be a critical factor in promoting reorganization from affected to nonaffected area(s). Penfield noted that abnormal and particularly “nociferous” cortex can interfere with normal function [24]. Results of the present study support the notion that areas of milder hypometabolism may reflect living tissue that is functioning enough to interfere with verbal cognitive skill, but not damaged sufficiently to promote reorganization of that skill to other brain regions. This is consistent with the notion that severely involved cortex is more likely to be associated with reorganization, and with Penfield’s [24] observation that absence of such a region may be better for function than the presence of a nociferous cortex.

Our data revealed that cognitive functions for large and severe functional lesions were measured in the borderline to mildly impaired range, better than outcome for intermediate-sized, but not fully comparable to small-sized lesions. This suggests that reorganization is not complete and that functions subserved are at least minimally affected in the process of reorganization. However, the sample included a relatively small number of subjects at the extreme end of functional lesion extent, and the restriction of range at this end may underestimate the “true” curve.

The association between epilepsy variables and cognitive outcomes in SWS has been reported by others [25–27]. Seizure frequency contributed significant variance to outcome over and above age and extent of cortical damage; and duration of epilepsy was the only variable that predicted IQ in children who did not show severe hypometabolism. As noted above, seizures may be associated with mildly hypometabolic cortex seen on FDG-PET [7]; uncontrolled seizures may prevent or interfere with reorganization and, thus, adversely influence cognitive outcome.

Although all participants in the present study had unilateral SWS, the sample was heterogeneous in terms of side and location of lesion (although involvement of the posterior hemispheric quadrant was present in all cases). However, somewhat surprisingly, neither side of lesion nor presence of frontal lobe involvement was associated with IQ. Despite the strong relationships between lesion location and outcomes in adult samples, empirical studies of pediatric samples (particularly for language outcomes) have not supported robust associations between lesion side (or location) and outcomes [21]. However, because nondominant lesions have not been shown to promote reorganization of visuospatial functions (with attendant verbal crowding) in the same way that dominant lesions promote verbal reorganization [28,29], we anticipated different curvilinear relationships for verbal functions than for visuospatial functions. Although our data hinted at different laterality–function curves (the curve for nonverbal IQ may be less robust), they nevertheless did not support this expectation. This finding is consistent with a previous study of children with unilateral lesions and language functions that also failed to support direct laterality and function relationships [21]. Nevertheless, the current results strongly suggest that children with early unihemispheric lesions caused by SWS can expect best cognitive outcomes if their lesion remains small; moderate cognitive decline may occur as a function of epilepsy. In contrast, patients with more extensive unihemispheric damage involving about half of their hemisphere will likely be severely impaired, regardless of seizures; in these cases, early progression of severe hypometabolism involving the majority of the affected hemisphere may facilitate improved cognitive outcome. Further research is needed to determine whether those with an intermediate extent of unilateral damage may benefit from early, extensive resective brain surgery (such as multilobar resection or hemispherectomy) not only in alleviating seizures, but also in forcing more effective reorganizational processes to take place.

Conflict of interest statement

None are reported.

Contributors

The first author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Behen, Juhasz, Wolfe-Christensen, Chugani. Acquisition of data: Behen, Wolfe-Christensen, Guy, Halverson. Analysis and interpretation of data: Behen, Juhasz, Janisse, Chugani. Drafting of the article: Behen, Juhasz, Wolfe-Christensen. Critical revision of the article for important intellectual content: Rothermel, Chugani. Statistical analysis: Janisse, Behen, Juhasz, Obtained funding: Juhasz, Chugani. Administrative, technical, and material support: Behen, Juhasz, Wolfe-Christensen. Study supervision: Chugani, Juhasz.
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