Anatomical and functional brain imaging evidence of lenticulo-insular anomalies in Smith Magenis syndrome

N. Boddaert, a,b,* H. De Leersnyder, c M. Bourgeois, d A. Munnich, c F. Brunelle, a,b and M. Zilbovicius a

a ERM 0205 INSERM-CEA, Service Hospitalier Frédéric Joliot, 91406, Orsay, France
b Service de Radiologie Pédiatrique, Necker Enfants-Malades, 75015, Paris, France
c Service de Génétique, Necker Enfants-Malades, 75015, Paris, France
d Service de Neurochirurgie, Necker Enfants-Malades, 75015, Paris, France

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Smith Magenis syndrome (SMS) is a clinically recognizable contiguous gene syndrome ascribed to an interstitial deletion of chromosome 17p11.2. The neurobehavioral phenotype of SMS includes mental retardation, speech delay, hyperactivity, attention deficit, decreased sensitivity to pain, self-injury, aggressive behavior and sleep disturbance. Therefore, we performed anatomical and functional brain imaging studies in five SMS boys. Anatomical magnetic resonance imaging (MRI) was analyzed using optimized voxel-based morphometry (VBM). This method can detect structural anomalies not apparent on visual inspection of the scans. Two comparison groups with similar mean age were studied: Group A with 12 healthy control children and Group B with 5 children with idiopathic mental retardation. In addition, positron emission tomography (PET) and water-labeled method were used to investigate a putative localized brain dysfunction in SMS. The control group was composed of mentally retarded children (Group B). A significant bilateral decrease of grey matter concentration was detected in the insula and lenticular nucleus in SMS children. In addition, a significant hypoperfusion was found in the same regions in SMS. These anatomical-functional evidences of bilateral insulo-lenticular anomalies in SMS are consistent with neurobehavioral symptoms of the disease. The identification of localized brain anomalies in SMS may help in understanding how this well-defined genetic entity can lead to a relatively specific severe neurobehavioral syndrome.

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Introduction

First described by Ann Smith in 1982, Smith Magenis syndrome (SMS) is a severe neurodevelopmental disorder ascribed to interstitial deletion of chromosome 17p11.2 (Smith et al., 1986). Its prevalence is estimated to 1/25,000 live births. All cases occur de novo. The majority of patients have a common deletion interval spanning 4–5 megabases (range: 2–9 megabases). Numerous genes have been mapped to the critical region within 17p11.2. Thirty-eight to 70 genes could be included in the deletion, suggesting that SMS is a possible contiguous gene syndrome (Elsea et al., 1997). Clinical features include hypotonia, characteristic craniofacial anomalies with mild dysmorphism, ocular anomalies, short stature and brachydactyly (Greenberg et al., 1996; Juyal et al., 1996). Neurobehavioral features include consistent hyperactivity with attention deficit, speech delay, decreased sensitivity to pain, abnormal thermosensory processing, tantrums, self-injury, aggressive behavior, severe sleep disturbance and mental retardation (De Leersnyder et al., 2001; Dykens et al., 1997; Finucane et al., 2001; Smith et al., 1998). Mild dystony and apraxia have also been noted.

Brain imaging, including positron emission tomography (PET) and magnetic resonance imaging (MRI), has been used to explore brain dysfunction underlying developmental disorders (Boddaert and Zilbovicius, 2002; Frank and Pavlakis, 2001). Greenberg et al. (1996) conducted cranial CT of 25 patients with SMS and documented nonspecific ventriculomegaly in 9/25 and an enlarged posterior fossa in 9/25 patients. However, recent brain imaging methodologies have not hitherto been performed for this condition.

We carried out an anatomical 3D-MRI study using optimized voxel-based morphometry (VBM) to detect possible anatomical grey or white anomalies that would have been overlooked by visual inspection of the scans (Good et al., 2001). This study shows anatomical and functional evidence of bilateral insulo-lenticular anomalies consistent with neurobehavioral features characteristic of the disease in five SMS children.

Subjects and methods

Subjects

Five SMS patients (five boys, mean age: 13.3 ± 2.5 years; age range: 11.5–16.5) were studied. Inclusion criteria were (i)
typical neuro-behavioral and dysmorphic phenotype of SMS confirmed by a neuropaediatrician, a geneticist and a psychologist and (ii) evidence of chromosome 17p11.2 deletion detected by FISH analysis using the ONCOR probe (D17S258). All children had mental retardation (mean IQ: 53 ± 11) but no clinical seizures. The IQ was determined using the Wechsler Intelligence Scale for Children (WISC-R). The 24-h electroencephalography recording obtained in four children showed all stages of sleep (although poorly organized).

For the MRI study, the control group was composed of 12 healthy children (Group A) with similar mean age (seven boys and five girls, mean age: 10.8 ± 2.7 years; age range: 7–15). None of them had any history of neurological or psychiatric disorders and all had normal schooling. All children had normal MRI on visual analysis. In addition, an additional control group was composed by six boys with idiopathic mental retardation (Group B) matched for IQ (48 ± 14.5) with similar mean age (mean age: 11.2 ± 3.2 years; age range: 7–15). They had idiopathic mental retardation according to the DSM-IV criteria with no associated neurological disorder. The IQ was determined using the Wechsler Intelligence Scale for Children (WISC-R). The following conditions were excluded: known infectious, metabolic or chromosomal diseases, epilepsy or recognizable neurological syndromes. All children have normal MRI on visual analysis. In the mentally retarded children group (Group B), the 3D T1 MRI sequence of one child presented some movement artifacts so we excluded this subject from the VBM study.

For the PET study, the children with Smith Magenis syndrome were compared to six boys with mental retardation (Group B). We did not perform a PET study on normal control children for ethical reasons, precluding the inclusion of healthy children as control group.

Four patients received melatonin treatment and all patients received beta blockers to restore circadian rhythms of melatonin (Table 1). A previous pharmacokinetic study of the same children showed rapid decrease of melatonin levels 6 h after intake; half-life of beta blockers is 7.4 ± 3.1 h, and complete elimination is observed after 40 h (De Leersnyder et al., 2003). All treatments were discontinued 72 h before brain imaging. Any child had current treatments with neuroleptics, psychostimulants, antidepressants or antipsychotics. There were no sedation for any child.

The protocol was approved by the Ethical Committee of French Public Hospitals and written informed consent of the parents was obtained in each case.

**Brain imaging**

MRI was analyzed using both clinical review of scans by two neuroradiologists and VBM analysis to search for localized grey or white matter anomalies. VBM is a novel method for characterizing regional differences in cerebral tissue concentration (Good et al., 2001).

MRI was performed on a 1.5 T Sigma General Electric scanner using a 3D T1-weighted FSPGR sequence (TR/TE/TI/NEX: 10.5/2.2/600/1, 10°, matrix 256 × 192, 124 axial slices and a thickness of 1.2 mm). A T2-weighted spin-echo sequence was acquired in the axial plane and a T2-FLAIR sequence was acquired in the coronal plane (MRI duration: 15 min).

The 3D T1 anatomical MRIs were analyzed using Optimized VBM, which is a fully automated whole-brain technique that delivers a voxel-wise assessment of regional grey and white matter concentration. Optimized VBM analysis includes five steps: (1) customized templates, that is, creation of separate grey and white matter MRI templates of normal children, (2) segmentation and extraction of a brain image, (3) normalization of grey and white matter images using our children’s template, (4) segmentation of normalized whole brain images and (5) smoothing: optimally normalized and segmented images are smoothed with a 12-mm full-width half-maximum kernel (Good et al., 2001).

Functional studies were performed using PET and water-labeled (H215O) method. PET images were obtained on a Siemens ECAT Exact-HR+962 camera. Relative regional cerebral blood flow (rCBF) was determined from the distribution of radioactivity after one bolus intravenous injection of 7 mCi of H215O during rest. Data were collected over a period of 80 s. Attenuation-corrected data were reconstructed into 63 slices with a resulting resolution of 5 mm. The spatial resolution is uniform and isotropic over 10-cm diameter central field of view and it degrades to 5.8 mm at 10 cm from the center of the field of view. The images were taken 10 min after the catheter placement. All children had their eyes closed, they were all relaxed and were not sedated (PET duration: 20 min).

**Statistical analysis**

Anatomical and functional data were analyzed using SPM99 (Friston et al., 1995) (http://www.fil.ion.ucl.ac.uk/spm). For statistical analyses of VBM studies, regionally specific differences in grey and white matter between groups were statistically assessed using a two-tailed contrast, namely, testing for an increased or decreased probability of a voxel being grey or white matter; concentration changes were assessed using segmented images. Normalization for global differences in voxel intensity across scans was performed by including the global mean voxel value as a confounding covariate in an analysis of covariance (ANCOVA). The resulting Z-maps were threshold at \( P < 0.05 \) corrected height threshold.

For statistical analyses of PET studies, data were analyzed with the group comparison block design. Global intensity differences were corrected by using proportional scaling. Comparisons

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**Table 1. Clinical features of Smith Magenis patients**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Subject</th>
<th>Subject</th>
<th>Subject</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>15.5</td>
</tr>
<tr>
<td>IQ</td>
<td>48</td>
<td>48</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Speech  delay</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>ADHDa</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Self-injury</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>DYSMORPHY</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Small stature</td>
<td>++</td>
<td>++</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Insensitivity to pain</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Ocular anomalies</td>
<td>Myopia</td>
<td>–</td>
<td>Strabismus</td>
<td>Myopia</td>
</tr>
<tr>
<td>Treatments</td>
<td>Beta blockers</td>
<td>Melatonin</td>
<td>Beta blockers</td>
<td>Melatonin</td>
</tr>
</tbody>
</table>

+, slight; ++, moderate; ++++, severe. a DSM IV criteria.
between groups were performed with the t test, further transformed into the Z statistic. The resulting Z-maps were threshold at $P < 0.001$ cluster level corrected.

**Results**

VBM analysis revealed that grey matter concentration was significantly decreased in bilateral insula and bilateral lenticular nucleus in SMS subjects compared to normal subjects ($P < 0.05$ corrected, $df = 15$) (Table 2). No significant decrease of white matter concentration was observed. In addition, the comparison between SMS children and mentally retarded children revealed a significant decrease of grey matter concentration localized in the same insular and lenticular regions in SMS subjects ($P < 0.05$ corrected) (Table 3).

An ANCOVA analysis with age as nuisance variables was also performed to compare normal subjects and Smith Magenis children. The results are not modified by this variable. In addition, we

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### Table 2

<table>
<thead>
<tr>
<th>Anatomical regions</th>
<th>Z score</th>
<th>Talairach coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$x$</td>
<td>$y$</td>
</tr>
<tr>
<td>Left insula or lenticular nucleus</td>
<td>5.97</td>
<td>-27</td>
</tr>
<tr>
<td>Left lenticular</td>
<td>5.89</td>
<td>-18</td>
</tr>
<tr>
<td>Right insula</td>
<td>5.53</td>
<td>39</td>
</tr>
<tr>
<td>Right lenticular nucleus</td>
<td>5.38</td>
<td>15</td>
</tr>
</tbody>
</table>

Z-score as well as coordinates in Talairach stereotaxic space corresponds to local maxima; $x$ is the distance (mm) to the right (+) or left (-) of the midsagittal line; $y$ is the distance anterior (+) or posterior (-) to a vertical plane through the anterior commissure and $z$ is the distance above (+) or below, the intercommisural plane (anterior and posterior commissures).

*Brain regions displaying significant decrease of grey matter concentration ($P < 0.05$ corrected height threshold, $df = 15$) in five SMS children compared to normal children using MRI and optimized voxel-based morphometry.

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### Table 3

<table>
<thead>
<tr>
<th>Anatomical regions</th>
<th>Z score</th>
<th>Talairach coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$x$</td>
<td>$y$</td>
</tr>
<tr>
<td>Left insula</td>
<td>4.15</td>
<td>-54</td>
</tr>
<tr>
<td>Left lenticular</td>
<td>5.05</td>
<td>-26</td>
</tr>
<tr>
<td>Right insula</td>
<td>4.05</td>
<td>-16</td>
</tr>
<tr>
<td>Right lenticular nucleus</td>
<td>5.64</td>
<td>39</td>
</tr>
</tbody>
</table>

Z-score as well as coordinates in Talairach stereotaxic space corresponds to local maxima; $x$ is the distance (mm) to the right (+) or left (-) of the midsagittal line; $y$ is the distance anterior (+) or posterior (-) to a vertical plane through the anterior commissure and $z$ is the distance above (+) or below, the intercommisural plane (anterior and posterior commissures).

*Brain regions displaying significant decrease of grey matter concentration ($P < 0.05$ corrected height threshold) in five SMS children compared to normal children using MRI and optimized Voxel-based morphometry.
Table 4
PET hypoperfusion in five Smith Magenis children compared to mentally retarded children

<table>
<thead>
<tr>
<th>Anatomical regions</th>
<th>Z score</th>
<th>Talairach coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left insula or lenticular</td>
<td>4.07</td>
<td>–32 8 16</td>
</tr>
<tr>
<td>Left insula</td>
<td>3.93</td>
<td>–38 –6 22</td>
</tr>
<tr>
<td>Right insula</td>
<td>4.88</td>
<td>28 8 18</td>
</tr>
<tr>
<td>Right insula or lenticular</td>
<td>3.94</td>
<td>24 18 10</td>
</tr>
</tbody>
</table>

Z-score as well as coordinates in Talairach stereotaxic space corresponds to local maxima; \( x \) is the distance (mm) to the right (+) or left (−) of the midsagittal line; \( y \) is the distance anterior (+) or posterior (−) to a vertical plane through the anterior commissure and \( z \) is the distance above (+) or below the intercommissural plane (anterior and posterior commissures).

*Brain regions with significant hypoperfusion (\( P < 0.001, \text{df} = 9 \)) detected with PET in five SMS children compared to mentally retarded children.*

obtained exactly the same results by performing an additional analysis without the girls in the normal control group.

SPM analysis of PET images revealed a significant decrease in cerebral blood flow in the bilateral insula and bilateral lenticular nucleus of SMS individuals compared to mentally retarded children (\( P < 0.001 \) cluster level corrected, \( \text{df} = 9 \)) (Table 4, Fig. 1c).

Fig. 1 shows the similar topography of grey matter decrease and cerebral blood flow hypoperfusion using either MRI-VBM study or PET in SMS subjects compared to two distinct control groups.

Finally, clinical review of anatomical MRI showed a retrocerebellar posterior fossa cyst in 4/5 SMS children as previously reported with CT scans (Greenberg et al., 1996). All five SMS children had a moderate dilatation of the lateral ventricles.

**Discussion**

In this study, we show that a voxel-by-voxel analysis of high-resolution functional and anatomical images detected localized cortical brain anomalies in SMS. Indeed, 3D-MRI and optimized-VBM analysis revealed a bilateral decrease of grey matter concentration in insulo-lenticular regions. The topography of these anatomical anomalies overlapped with insulo-lenticular hypoperfusion areas detected by PET. The consistency of bilateral insulo-lenticular anomalies using two brain-imaging methods is striking. Moreover, current visual CT or MRI analyses only found nonspecific cystic posterior fossa anomalies and failed to detect any structural intracerebral anomalies.

However, the present study has some methodological limitations, mostly concerning the age of SMS patients and controls and needs to be replicated in a larger population.

Bearing in mind the neurobehavioral phenotype of SMS, it is tempting to hypothesize that anatomical or functional anomalies of insulo-lenticular regions in SMS account at least in part for several behavioral features including pain insensitivity, self-injury, aggressive behavior and hyperactivity or attention deficit.

In fact, several lines of evidence support the involvement of insula in the complex processes associated with pain (Bushnell et al., 1999; Rainville et al., 1997). Peyron et al. (2000) have reported a meta-analysis of 34 functional imaging experiments in response to pain in normal subjects and showed a consistent activation of insula in response to noxious stimuli. Moreover, the involvement of insula in thermosensory processes has recently been emphasized by functional studies showing a significant activation of insula by cooling stimuli and its linear correlation with stimulus intensity, strongly supporting the view that insula represents a discriminative thermal sensation area (Craig et al., 2000). In keeping with this, SMS children have low sensitivity to cold and warmth. For example, they can swim in very cold water and their mothers have to use a thermostatic control in the shower to avoid burns. In addition, they also have low sensitivity to pain, breaking arms or legs without complaint. They display autoaggressivity, onychotillomania, self-injury and bite or bang themselves against walls. Part of their behavioral problems of self-injury could therefore be related to increased tolerance to pain in SMS. On one hand, congenital insensitivity to pain in humans is generally not associated with self-injury, and reduced sensitivity to pain is not necessarily associated with self-injury. On the other hand, striatal anomalies suggest dopaminergic dysfunction in SMS children. Such dopaminergic dysfunction could underlie the aggressive and self-injury behavior as it is assumed to Lesch–Nyhan disease. Indeed, positron emission tomography scanning in Lesch–Nyhan disease has indicated dopamine transporter deficiency (Ernst et al., 1996).

Attention-deficit and hyperactivity are almost consistent features in SMS. One might associate attention-deficit or hyperactivity to the anatomical or functional involvement of lenticular nucleus reported here. The striatum has long been considered to be involved in attention-deficit or hyperactivity disorder (ADHD) and an alteration of corticostriatal circuits has been suggested in patients with ADHD. Indeed, functional and anatomical brain imaging studies have reported striatal abnormalities in children with ADHD (Castellanos et al., 2001; Ernst et al., 1997; Hendren et al., 2000). More recently, functional MRI studies using relaxometry have shown a bilaterally reduced perfusion of lenticular nucleus in ADHD children (Teicher et al., 2000). Thus, involvement of the two lenticular nucleus reported here could be related to hyperactivity and attention deficit in SMS.

Finally, all SMS children have severe sleep disturbances and major anomalies in their circadian rhythm of melatonin (De Leersnyder et al., 2001; Potocki et al., 2000). Melatonin, a hormone produced by the pineal gland during the night, influences circadian and seasonal rhythms, particularly the sleep–wake cycle (Zisapel, 2001). An antiodopaminergic activity of melatonin has been demonstrated in the striatum (Escamés et al., 1996).

Future neurotransmitter PET studies will hopefully help to determine the dopaminergic activity in SMS.

In conclusion, we present here anatomical and functional evidence of bilateral insulo-lenticular involvement in SMS, and we speculate that these features are relevant to behavioral disorders in SMS. Insular abnormalities might be related to increased tolerance to pain, self-injury and thermosensory processes, while hyperactivity or attention-deficit could be related to the lenticular anomalies. More generally, we feel that analyses of brain structure in genetic syndromes using up-to-date imaging tools might be helpful to link genetic and behavioral abnormalities in severe developmental disorders.
Acknowledgments

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References