Early magnetic resonance imaging to detect presymptomatic leptomeningeal angioma in children with suspected Sturge–Weber syndrome

CLAIRE BAR1,2,3 | JEAN-MICHELE PEDESPAN3 | OLIVIA BOCCARA4 | NICOLAS GARCELON2,5,6 | RAPHAEL LEVY7 | DAVID GRÉVENT7 | NATHALIE BODDAERT7 | RIMA NABBOUT1,2,5

1 Department of Paediatric Neurology, Hôpital Necker-Enfants Malades, Reference Centre for Rare Epilepsies, APHP, Bordeaux; 2 Imagine Institute UMR 1163, Paris; 3 Department of Paediatric Neurology, Hôpital des Enfants, CHU Bordeaux, Bordeaux; 4 Department of Paediatric Dermatology, Hôpital Necker-Enfants Malades, Paris; 5 Paris Descartes University, Sorbonne Paris Cîte, Paris; 6 Centre de Recherche des Cordeliers, INSERM, UMR 1138 Equipe 22, Paris; 7 Department of Paediatric Radiology, Hôpital Necker-Enfants Malades, Paris, France.

Correspondence to Rima Nabbout, Department of Paediatric Neurology, Reference Centre for Rare Epilepsies, Necker Enfants Malades Hospital, 149 rue de Sèvres, 75015 Paris, France.
E-mail: rimanabbout@yahoo.com

AIM We aimed to evaluate the contribution of early magnetic resonance imaging (MRI) for the presymptomatic diagnosis of Sturge–Weber syndrome (SWS) in infants with a facial port-wine birthmark (PWB).

METHOD Asymptomatic infants with a facial PWB who performed a first MRI scan before 3 months and a second MRI scan after 9 months were included in this study. Leptomeningeal enhancement on T1-weighted imaging and four indirect signs of leptomeningeal angioma (choroid plexus enlargement, cerebral atrophy, signal inversion of the white matter with T2 hypointensity, and T1 hypersignall) were screened on the first MRI scan and correlated with clinical and/or radiological diagnosis of SWS.

RESULTS Thirteen of 30 included patients had SWS with leptomeningeal angioma. Eleven had a leptomeningeal enhancement on the first MRI scan and 10 had associated indirect signs. The presence of a direct or at least one indirect sign of leptomeningeal angioma on the first MRI scan confirmed the diagnosis of SWS with a sensitivity of 100 per cent (95% confidence interval 75–100%) and a specificity of 94 per cent (71–100%).

INTERPRETATION Early diagnosis of SWS is possible on contrast-enhanced MRI performed in asymptomatic infants with a facial PWB before the age of 3 months. This early detection would help to select patients who may benefit from early neuroprotective intervention.

Sturge–Weber syndrome (SWS) is a congenital neurocutaneous syndrome defined by the association of a facial capillary malformation named port-wine birthmark (PWB) with ipsilateral leptomeningeal angioma and inconstant ipsilateral glaucoma. Isolated PWB and SWS have a common genetic etiology with a somatic mosaic mutation that has been recently identified in the guanine nucleotide-binding protein alpha-q gene.1 Only patients with a facial PWB on the forehead and/or the upper eyelid are at risk of SWS2,3 (Fig. 1). Although no epidemiological data are available, this risk is estimated to be between 10 and 20 per cent.4

The prognosis of SWS is mainly related to the neurological complications that develop often during the first year of life.5,6 Seizures occur in 75 to 85 per cent of patients with SWS, with an onset before 1 year of age in 75 per cent of patients.6,7 The cognitive outcome of patients with SWS is highly variable and is correlated to the early onset of seizures and to the degree of pharmacoresistance.5,6 In addition to neurological complications, 40 to 60 per cent of patients with SWS will develop glaucoma.6,7 Sixty per cent of glaucoma cases occur before the age of 1 year and can lead to early visual impairment.6 Therefore, early diagnosis of SWS is needed to accurately identify the infants at risk, to educate parents to properly identify and manage seizures, and to organize consequent medical follow-up. Moreover, preventive therapy with antiepileptic drugs and low-dose aspirin might decrease the seizure frequency and result in improving the cognitive outcome.8,9 Hence, criteria helping to establish presymptomatic diagnosis are essential to help to select patients with facial angioma having SWS.

Although SWS is easily suspected at birth because of an upper facial PWB, the diagnosis should be confirmed by the visualization of leptomeningeal enhancement on T1-weighted magnetic resonance imaging (MRI).4 This direct sign of the leptomeningeal angioma can be, however, absent on early MRI, and other radiological signs are thought to provide indirect evidence of the leptomeningeal angioma: ipsilateral choroid plexus enlargement, cerebral atrophy, and signal inversion of the white matter.
(hyposignal on T2 and hypersignal on T1-weighted imaging).\textsuperscript{10,11} The sensitivity of these abnormalities on early MRI is still debated so that no consensus exist regarding the age at which the MRI should be performed.

The aim of this study was to evaluate to what extent early MRI can confirm the diagnosis of SWS in presymptomatic neonates and infants with a facial PWB. Our goal was to establish MRI diagnostic criteria at an early stage before the onset of neurological complications.

METHOD

Participants

This study was performed at the University Hospital of Paris Necker-Enfants Malades among children presenting at the paediatric dermatology clinic for a clinical suspicion of SWS from January 2001 to February 2016. Following our institution protocol for the diagnosis of SWS, these children are referred to the child neurologist from the dermatology or neonatology department. Early MRI is performed at the first consultation and confirmatory MRI is usually performed around the age of 1 year, repeated later if the diagnosis is still uncertain. Using the full text search engine of the Necker Hospital Data Warehouse,\textsuperscript{12} we included patients who fulfilled the following criteria: (1) children with a facial PWB covering at least one part of the forehead and/or eyelid; (2) no neurological sign on a first clinical examination before 3 months of age; (3) availability of a first MRI scan performed before the age of 3 months; (4) availability of a second MRI scan performed after the age of 9 months; and (5) clinical follow-up available until at least the age of 2 years for asymptomatic children. Because of MRI scheduling, some patients had the second MRI scan a few months before turning 1 year of age, so we choose 9 months as the cut-off for the inclusion. Patients were excluded from the study if the MRI revealed a pathology different from a leptomeningeal angioma. For each patient included, we collected information from medical charts regarding the age, sex, PWB distribution, clinical and ocular findings at the first consultation, use of prophylactic treatment, along with follow-up data regarding neurological and ocular manifestations.

The study protocol was approved by the ethical board of our hospital as part of the good care practice and written informed consent for participation and publication was obtained from parents.

Test methods

The early MRI performed before 3 months of age was considered as the index test and was compared to the second MRI conducted after 9 months of age along with the clinical follow-up, as the reference standard. The routine MRI protocol of a child with a suspicion of SWS included 3D T1-weighted sagittal and axial images, T2-weighted axial and coronal images, and a postgadolinium 3D T1-weighted acquisition. All the patients of this study had this MRI protocol. For the patients seen after 2010, the protocol included a cube postgadolinium T1-weighted acquisition with fat saturation. MRI scans were performed on a 1.5T magnetic resonance scanner before 2015 and on a 3T magnetic resonance scanner after 2015. To avoid movement artifacts, some children were sedated using intrarectal pentobarbital (5mg per kilogram of the child’s weight <20kg), as is the protocol of our radiology department.

Two paediatric neuroradiologists (NB and RL) reviewed independently the brain images of each child, blinded to clinical information except for the side of the PWB. The early MRI was evaluated for the presence of a leptomeningeal enhancement on postcontrast T1-weighted imaging as the direct sign of a leptomeningeal angioma. We additionally screened for associated signs already described in the literature: white matter abnormalities with a T1 hypersignal or a T2 hyposignal, an asymmetry of the choroid plexus, or a localized cerebral atrophy.\textsuperscript{11,13,14}

On the second MRI performed after 9 months of age, the presence or absence of a leptomeningeal enhancement was screened for in each child. The diagnosis of SWS was then confirmed if a leptomeningeal enhancement was
visible on the second MRI scan and/or if the child developed a neurological disorder. The diagnosis was ruled out if the second MRI scan was normal and there was no neurological sign on the clinical examination after the age of 2 years.

**Analysis**

Descriptive statistics were used to analyse the characteristics of the study population. To determine test performance characteristics, the results of the early MRI (the index test) were illustrated in a cross tabulation according to the clinical and/or radiological diagnosis of SWS (the reference standard). We estimated the sensitivity, the specificity, and the positive post-test probability using standard methods, along with corresponding confidence intervals (CIs) of 95 per cent.

**RESULTS**

Thirty-two patients were eligible for the study, but two patients were excluded because of a final diagnosis of megalencephaly capillary malformation. Therefore 30 patients were included in this study.

**Baseline demographic and clinical characteristics of participants**

The diagnosis of SWS was confirmed in 13 out of 30 patients. Main clinical and follow-up data of the study population are detailed in Table I.

Thirteen patients received prophylactic antiepileptic drugs, 11 of them were treated with valproate, and two of them with carbamazepine at usual therapeutic doses. Among these 13 patients receiving a prophylactic treatment, eight had a confirmed diagnosis of SWS. Nine patients developed epilepsy during the follow-up period, among whom five had received prophylactic antiepileptic drugs. None of the study patients received prophylactic aspirin. First seizure occurred at a median age of 6 months (range 2–8mo). All children presenting epilepsy had an associated leptomeningeal angioma confirmed by the second MRI scan. The first seizures were reported as focal in all patients, contralateral to the leptomeningeal angioma. In three patients, the first seizure evolved to status epilepticus. Another three patients later developed status epilepticus at 6 months, 13 months, and 5 years of age respectively. Three patients underwent surgery for refractory epilepsy, two had a hemispherotomy at 15 months, and one a lobectomy at 17 months. The eight patients who had developed hemiparesis during the course of the disease had epilepsy.

**MRI results**

The median age at the first MRI scan was 2 months (range 0–3mo) and 12 months at the time of the second MRI scan (range 9–36mo). Thirteen patients had a confirmed diagnosis of SWS. Out of these 13 patients, 11 had a leptomeningeal contrast enhancement on the first MRI scan. Postcontrast T1-weighted images with and without fat saturation have been performed in seven. For two children, the leptomeningeal enhancement was comparable on both sequences while it was more visible on sequences with fat saturation in the five other patients (Fig. 2a). In the group showing visible leptomeningeal enhancement on the first MRI, 10 out of 11 also had indirect signs of leptomeningeal angioma on the first MRI scan. A signal inversion of the white matter with T1 hypersignal and/or T2 hyposignal were reported most often, both found in nine patients (Fig. 2b,c). The two remaining patients did not have visible leptomeningeal contrast enhancement but presented at least one indirect sign of leptomeningeal angioma: one with all four indirect signs and the other with an isolated choroid plexus asymmetry. In all patients with SWS, a visible enhancement of the leptomeningeal angioma was visible on the second MRI confirming the diagnosis (Fig. 2d). The diagnosis of SWS was ruled out in 17 patients. In 16, the first MRI scan was negative for both direct and indirect signs of leptomeningeal angioma and radiologists reported a high suspicion of direct visualization of leptomeningeal angioma in only one patient (Fig. 2e,f). This patient was followed up until 10 years of age and did not develop a neurological disorder.

Table I shows the diagnostic accuracy of the early MRI for the diagnosis of SWS. We considered three situations for the positive diagnosis of SWS on the early MRI, according to the presence of the direct and/or indirect signs. If we considered the early MRI positive for the diagnosis of SWS with one indirect sign, even without a direct sign, it allowed all the patients with SWS in our study to be detected (‘Direct or ≥1 indirect sign’, sensitivity 100% CI 75–100%). On the other hand, having one direct sign associated with at least one indirect sign on the first MRI confirmed the diagnosis of SWS with a specificity of 100 per cent (‘Direct and ≥1 indirect sign’, CI 80–100%).

<table>
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<tr>
<th>Table I: Demographic, clinical, and follow-up data of the population according to the presence or absence of a leptomeningeal angioma</th>
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<tbody>
<tr>
<td>Age at first examination, d*</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Side of PWB</td>
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<tr>
<td>Right</td>
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<tr>
<td>Left</td>
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<tr>
<td>Bilateral</td>
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<tr>
<td>Prophylactic AE treatment</td>
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<td>Follow-up</td>
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<td>Age at last examination, y;mo*</td>
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<tr>
<td>Epilepsy</td>
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<td>Hemiparesis</td>
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*Median and interquartile range. SWS, Sturge–Weber syndrome; PWB, port-wine birthmark; AE, antiepileptic.
DISCUSSION
This study assessed the diagnostic performance of a routine MRI protocol in the detection of leptomeningeal angioma before the age of 3 months in asymptomatic infants with a facial PWB. A presymptomatic diagnosis of SWS remains a major challenge with regards to establishing a prognosis for the families, identifying patients at risk of seizures, and proposing possible preventive therapeutic strategies.

Our data suggest that cerebral MRI with gadolinium enhancement has a high diagnostic accuracy for the early detection of leptomeningeal angioma in neonates with a facial PWB. The presence of a leptomeningeal enhancement on the early MRI confirmed the diagnosis of SWS with a sensitivity of 85 per cent (95% CI 55–98%) and a specificity of 94 per cent (95% CI 71–100%). Screening of indirect signs increased the sensitivity up to 100 per cent (95% CI 75–100%) and permitted, when associated with the direct sign, to confirm the diagnosis of SWS with a specificity of 100 per cent (95% CI 80–100%). Only one recent study evaluated the reliability of early MRI in a population of 14 asymptomatic children with high-risk PWB. While they also found a high specificity of 100 per cent, they reported a low sensitivity of 25 per cent as three children had a false negative early MRI. However, there was no pre-established protocol for MRI performing and interpretation so that two out of the three false negative patients did not have adequate sequences. Moreover, the definition of the reference standard chose for the diagnosis of SWS is not detailed in this paper.

We found white matter abnormalities in almost 80 per cent of cases (T1 hypersignal and T2 hyposignal). Described for the first time by Jacoby et al. in 1987, these abnormalities are thought to be related to an accelerated myelination process as suggested by the hyperperfusion visualized in the same area on single photon emission computed tomography imaging and the increase of the fraction of anisotropy with a decrease of the apparent diffusion coefficient in diffusion-tensor imaging. However, these abnormalities are rarely reported, as most imaging series involve older children whose MRI pattern changes after the occurrence of the neurological complications. Enlargement of the choroid plexus is a well-recognized feature of SWS, first described on computed tomography scans. This sign was not constant in our study since it was found in nine out of 13 patients, emphasizing the superiority of the MRI already reported in previous

Table II: Diagnostic accuracy of the early magnetic resonance imaging (MRI) according to the presence of the radiological markers (95% confidence interval)

<table>
<thead>
<tr>
<th>Early MRI</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Post-test probability</th>
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<tbody>
<tr>
<td>Direct sign</td>
<td>85 (55–98)</td>
<td>94 (71–100)</td>
<td>68</td>
</tr>
<tr>
<td>Direct or ≥1 indirect sign</td>
<td>100 (75–100)</td>
<td>94 (71–100)</td>
<td>72</td>
</tr>
<tr>
<td>Direct and ≥1 indirect sign</td>
<td>77 (46–95)</td>
<td>100 (80–100)</td>
<td>100</td>
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Estimated pretest probability 15%.
studies. Its pathophysiology remains unclear, but could be related to a vascular engorgement of the choroid plexus upstream from the leptomeningeal angioma. More common in later stages of the disease because of chronic hypoperfusion and hypoxia, cortical atrophy was rare on the early MRI, but was highly specific (100% associated with an underlying leptomeningeal angioma).

Although the diagnostic performance of the routine MRI protocol used in this study seems quite sensitive, some more specific MRI sequences that have not been done here might further improve the early detection of brain involvement in these patients. For instance, the gradient Echo T2* sequence was not included in our protocol as it was used to detect microcalcification, usually not visible early in life. However, it has been shown that T2* sequence or similar sequences such as susceptibility weighted imaging may detect enlarged transmedullary veins in infants before the appearance of typical leptomeningeal enhancement. Other reports suggest that gadolinium-enhanced fluid-attenuated inversion-recovery imaging may also increase the sensitivity for detecting leptomeningeal disease when compared with routine contrast-enhanced T1-weighted imaging. Since these data mainly come from adult studies, this postcontrast fluid-attenuated inversion-recovery sequence was not part of our initial routine MRI protocol for neonates with a suspicion of SWS. However, we now recommend including both T2* and postcontrast fluid-attenuated inversion-recovery sequences in early screening MRI of these children.

More recent MRI techniques such as diffusion tensor imaging could identify microstructural white matter damage associated with the leptomeningeal vascular malformation. Functional imaging based on glucose metabolism with positron emission tomography or cerebral perfusion by single photon emission computed tomography provide complementary information to the conventional MRI. New techniques like arterial spinal labelling which quantifies cerebral blood flow without the need for contrast injection could provide information on the leptomeningeal angioma diagnosis and the progression of the disease. Diagnostic accuracy of these sequences is not yet fully assessed in presymptomatic children.

Although neurodevelopmental prognosis of patients with SWS has been well correlated with the neurological complications, especially with early and severe epilepsy, there is no reliable data in the literature supporting that early intervention could change the clinical course in children with a presymptomatic diagnosis of SWS. Performing contrast-enhanced MRI in newborn infants cannot be considered completely risk-free, considering the sedation that is often required or the gadolinium injection whose long-term consequences are not yet well known. However, some retrospective reports suggest a protective effect of preventive treatment with antiepileptic drugs or low doses of...
aspirin on the neurological development of children with SWS. Given the known side effects of these treatments, we thought that the benefit of early SWS diagnosis should outweigh the potential risk of this strategy. Prospective, controlled, and randomized studies are needed to confirm the potential benefit of these preventative strategies and presymptomatic diagnosis of SWS is essential for the conceptualization of such trials. A proposal for a diagnostic approach is summarized in Figure 3. The radiologist should be aware of the lateralization of the facial PWB to carefully look for an ipsilateral leptomeningeal enhancement. The presence of a gadolinium enhancement (direct sign) is usually considered enough to affirm the diagnosis of SWS. However, one patient in our study had a false positive early MRI with a suspicion of gadolinium enhancement. Given the consequences for the patient and their family, we prefer to qualify this situation as ‘SWS suspected’ and advise to control the MRI around the age of 1 year. Screening for ipsilateral indirect signs is also essential for raising the diagnostic suspicion if the leptomeningeal angioma is not seen and to reinforce the suspicion in case of visible leptomeningeal enhancement.

Our study has several limitations. The number of children included was limited by the low prevalence of the disease so that a multicentric prospective study would be necessary to confirm these results. MRI scans were analysed by neuroradiologists of a tertiary medical centre, who could have overestimated the presence of the indirect signs because of the frequently associated visualization of the leptomeningeal angioma. No consensus exists regarding the age at which a normal MRI can reliably rule out the diagnosis of SWS. Therefore, we had to choose a criterion standard to evaluate the performance diagnostic of early MRI. Based on clinical experience, it is suggested that the diagnosis of SWS can be excluded in a child with a normal clinical examination, no history of seizures, and a normal MRI with gadolinium injection after the age of 1 year. In our study, five patients had their second MRI scan between 9 months and 1 year of age because of the MRI scheduling agenda. We cannot completely exclude the possibility of later presentation. However, we believe that we minimized this risk of missed diagnosis as we included a follow-up beyond the age of 2 years for asymptomatic patients. Among these 17 children, the median follow-up was 5 years with 13 out of 17 whose last examination was made after the age of 4 years. Finally, we were not able to establish the benefit of preventive therapy because of the small number of patients in both groups, with and without preventive therapy.

CONCLUSION
We showed that early diagnosis of SWS is possible on a contrast-enhanced MRI performed in asymptomatic neonates with facial PWB through reliable radiological markers detecting the leptomeningeal angioma. Recognition of presymptomatic brain involvement is essential to identify the population at risk of neurological complications, to help families with the prognosis and organizing subsequent medical follow-up. This early presymptomatic diagnosis might facilitate the development of clinical trials to evaluate the safety and efficacy of current and future neuroprotective strategies for SWS.

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REFERENCES


