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Screening for Sturge-Weber syndrome: A state of the art review

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Abstract

Infants with high-risk distribution port-wine stain (PWS) are commonly screened for Sturge-Weber syndrome (SWS) using brain magnetic resonance imaging (MRI). Currently, there is no consensus about which PWS phenotypes to screen, optimal timing, screening sensitivity and whether presymptomatic diagnosis improves neurodevelopmental outcomes.This state of the art review examines the evidence in favour of screening for SWS based on its impact on neurodevelopmental outcomes, agaist the risks and limitations of screening MRI and electroencephalography (EEG). A literature search of Pubmed/MEDLINE was conducted between January 2005- May 2017 using key search terms. Relevant articles, published in English were reviewed. 34 papers meeting the search criteria were analysed according to the following outcome measures: neurodevelopmental outcome benefit of screening MRI/EEG, diagnostic yield, financial costs, procedural risks and limitations. At present, there is no available evidence that presymptomatic SWS diagnosis with MRI results in better neurodevelopmental outcomes. EEG screening is also unestablished. In SWS, neurodevelopmental outcome is dependant on prompt recognition of neurological red-flags and early seizure control. Our findings are limited by small numbers and a lack of prospective randomized controlled trials. For infants with PWS involving skin derived from the frontonasal placode (forehead and hemi-facial phenotypes), we recommend early referral to a pediatric neurologist for parental education/counselling/monitoring for neurological red-flags, seizures and consideration of EEG, regardless of whether MRI is performed and irrespective its findings.

Manuscript Text

Screening for Sturge-Weber syndrome: a state of the art review.

Sturge-Weber syndrome (SWS) is a rare sporadic congenital neurocutaneous syndrome, characterised by cutaneous capillary malformations (port-wine stain (PWS)) typically involving the forehead, cerebral capillary-venous malformations (leptomeningeal angiomatosis), and/or glaucoma. [1-3] It occurs in 1:20,000-1:50,000 births and usually has a progressive course in early childhood characterised by seizures. [4-6] The majority of cases of non-syndromic PWS and SWS are caused by a somatic activating mutation in *GNAQ*. [7] Limiting the neurodevelopmental complications of SWS is central to SWS management and involves minimizing epileptic seizures and normalizing electroencephalography (EEG), especially in infants.[8]

Many authors recommend magnetic resonance imaging (MRI) screening of asymptomatic infants with at-risk PWS for SWS. However, several questions remain unclear, regarding which PWS phenotypes to screen, when to screen, the sensitivity of imaging, and whether presymptomatic diagnosis of SWS improves neurodevelopmental outcomes. [2, 6, 8] This paper reviews the role of MRI and EEG in asymptomatic infants with high-risk distribution facial PWS, through analysis of the following outcome measures: diagnostic yield, financial costs, procedural risks and the limitations of respective screening modalities (including those related to false negative results). The clinical value of screening for SWS is also considered by examining the evidence for presymptomatic treatment and whether screening improves neurodevelopmental outcomes.

Methods

Six separate searches of Pubmed/MEDLINE were conducted to target the primary study objectives (Appendix 1). Searches were restricted to papers published between the 1st January 2005 and 1st May 2017. The following key search terms were used: port wine stain/nevus flammeus, Sturge-Weber Syndrome, magnetic resonance

imaging, leptomeningeal angioma/tosis, screening, electroencephalography, neurodevelopment/neurocognitive/developmental outcome, pediatric anesthesia/anaesthetic, distress/mortality/morbidity/cardiac arrest/contrast reaction/allergy, prophylactic/presymptomatic aspirin/antiepileptic. A total of 85 papers matched the search criteria across 6 searches. Following analysis of abstracts, 71 were excluded because they did not meet the study objectives (Appendix 1.). Twenty papers meeting the aims of the paper were found on cross-referencing. Thus a total of 34 papers were included for final analysis. The Medicare benefits schedule, a schedule of fees for medical services set by the Australian Government, was used to determine costs of MRI, EEG and general anesthesia.

Results of literature review

i Which infants to scan for SWS

Recently identified as a form of somatic mosacism, PWS phenotypes involving specific embryonic facial prominences (Figure 1a), have been determined to better predict risk of SWS than involvement of the trigeminal V1 dermatome. [3, 9] Waelchli et al. described "forehead" region involvement (Figure 1b) as the strongest predictor of SWS. [3] Of 103 infants retrospectively studied with involvement of any part of the forehead, 83 (80.6%) had SWS; odds ratios for neurodevelopmental disability, seizures and glaucoma were 247, 158 and 144 respectively. [3] Compared with the general population, their cohort selected for more severely affected patients.[3] A similar but prospective study by Dutkiewicz et al., described 6 facial PWS phenotypes in 11 infants with SWS. [9] Of these, two patterns showed significant correlation with SWS: complete hemi-facial involvement (Figure 1b), of which 47% developed SWS (OR 7.70, P=0.003), and median PWS involvement (Figure 1b), of which 27% developed SWS (OR 17.08, P = .008). [9] PWS involvement of certain independent sites also conferred higher-risk of SWS. These included the upper midline, temporal, nose areas [9] and upper eye-lids (affected in virtually all cases of

glaucoma in SWS).[3, 10] These regions all originate from the frontonasal prominence, so patients with PWS affecting skin derived from this embryological precursor are most at risk of SWS (Figure 1a).[11] Larger area of PWS involvement may indicate earlier mutation and a more severe phenotype. Children with SWS had complete hemifacial and median involvement in the Dutkiewicz et al. cohort. Waelchli et al. selected patients with any involvement of the forehead but stated that their cohort had severe PWS phenotypes.

ii Modalities available for screening

Electroencephalography (EEG)

Electroencephalography (EEG) may help identify infants with cerebral involvement.[12] Background abnormalities, (i.e. decreased voltage amplitudes or attenuation of normal background dominant rhythms) suggest increased likelihood of cerebral cortical involvement of SWS. [13] Virtually all patients with SWS have involvement of the cerebral cortex ipsilateral to their PWS, usually with unilateral involvement (90% of cases). [14] Therefore, rhythm and voltage asymmetry may be an important EEG marker of SWS and is captured much more frequently than epileptiform abnormalities such as sharp waves or spike/wave discharges which are associated with an increased risk of clinical or subclinical seizure activity.[12, 15, 16] Five studies in the last 10 years have examined the role and reliability of EEG to detect or screen for SWS (Table 1)[12, 15, 16]. All patients examined with EEG had confirmed SWS on MRI and nearly all (145/151, 94%) were symptomatic at the time of initial EEG. There was a large discrepancy in mean age at first EEG between studies; 38,[17] 24,[16] 6[12] and 121[15] months respectively and the proportion with abnormal EEG in those with SWS ranged between 52-100% across studies. In two studies examining qualitative EEG, 52-55%[17] and 80%[14, 16] of infants with SWS had EEG abnormalities suggestive of cerebral involvement. Abnormal EEG findings tended to be seen in older infants (mean age of those with abnormal EEG was 68[17] and 82[16] months and compared with a mean age of 45[17] and 24[16] months for normal EEGs). However, Pascual-

Castroviejo et al. found that EEG abnormalities were evident from the first few months of life.[14]

Data on the clinical relevance of abnormal EEG findings is limited, but some correlation has been reported. Bosnyak et al. found a statistically significant correlation between EEG severity scores and global intelligence quotient scores on longitudinal study.[17] All 44 patients in the Pascual-Castroviejo et al. cohort with EEG abnormalities had seizures, whereas 8/11 (73%) patients with normal EEG remained seizure free over the 40 year study duration. By contrast, no clinical correlation was demonstrated by Kossoff et al. between EEG severity scores and SWS neuroscores (composite scores of seizure frequency, hemiparesis, cognition, and visual deficit).[16]

Quantitative EEG (qEEG), performed in 2 studies,[12, 15] used power values of selected raw EEG data generated by commercial analysis soft-wear to calculate mean Laterality Scores (LS) for each cerebral hemisphere. [15] EEG laterality scores attempt to provide an objective measure of EEG asymmetry through quantification of mean interhemispheric and regional EEG power discrepancy.[12, 15] Ewan et al. reported that a discrepancy in LS by ≥ 0.2 between hemispheres reliably discriminated between infants with and those without SWS in their initial and validation cohorts. [12] In their study of 5 infants with SWS on MRI, qualitative EEG interpretation by a fellowship trained, board-certified, pediatric electroencephalographer gave a sensitivity of 80% for SWS detection whilst quantitative EEG had a sensitivity of 100%.[12] The mean age at first EEG was 6 months and 2 of 5 infants were asymptomatic.[12]

Neuroimaging

Magnetic resonance imaging (MRI) may help establish the diagnosis of SWS and evaluate the extent of intracranial involvement, but no consensus exists regarding who to screen, the optimal timing of imaging, the sensitivity of MRI, or the overall benefit in identifying high risk vascular anomalies in asymptomatic infants. [2, 18]

Four studies reported neuroimaging findings in children with high-risk PWS being investigated for SWS in the last 10 years (Table 2).[3, 9, 19, 20] Two studies were excluded from analysis; one only included patients with confirmed leptomeningeal

angiomatosis on MRI [14] and the other was a single case-report.[21] Definitions of high-risk PWS differed across studies. [3, 9, 19, 20] Dutkiewicz et al.[9] and Waelchli et al.[3] classified hemifacial, median and forehead PWS phenotypes as high-risk, whereas Piram et al.[20] and Adams et al.[19] used old definitions based on involvement of the first division of the trigeminal nerve (V1). MRI features suggestive of SWS were detected in 43-73% of patients with high-risk PWS (mean of 56%) who underwent neuroimaging (predominantly MRI) (Table 2). Of the patients imaged whose facial PWS did not meet the criteria for high-risk, MRI features suggestive of SWS were only detected by Dutkiewicz et al. in 11/66 (17%) patients.

The criteria for MRI diagnosis of SWS were not well defined and varied among studies. (Table 2) The presence of leptomeningeal angiomatosis was considered a direct feature of SWS (typically involving the posterior parietal/occipital cortex ipsilateral to the PWS), however, a spectrum of indirect findings were deemed suggestive (Table 2). Dutkiewicz et al. and Adams et al. defined direct and indirect MRI features of SWS.[9, 19] Patients were classified as having SWS based on the presence of leptomeningeal angiomatosis on MRI and/or indirect MRI signs with seizures or other neurodevelopmental disorder.[9] Those with indirect MRI features who remained neurologically asymptomatic were classified as suspicious of SWS.[9] Other authors diagnosed SWS based on the presence of facial PWS and at least one direct or indirect finding on MRI.[3, 20] The mean age of MRI was 55 months (range from 4-32 months) across all 4 studies. The percentage of patients already symptomatic at the time of initial MRI was not reported. Patients were followed-up for a mean of 116 months based on the 2 studies in which follow-up was reported.[3, 9]

Few studies specifically recorded false negative neuroimaging for SWS.[3, 19-21] In these, initial neuroimaging was negative in 3-6% (mean 5%) of infants with PWS imaged (Table 3).[19, 20] Of the 7 infants in whom false negative imaging was reported, 4 were under the age of 6 months (range 4-24 months, mean 10 months).[19-21] This paper, therefore, defines early MRI as those occurring before 6 months of age. Adams et al.[19] reported 2 infants in whom pial enhancement was not apparent until after 25 and 33 months respectively and a third infant with obvious leptomeningeal

angiomatosis on post-mortem examination which was not detected on serial MRI (up to 32 months of age). In those with negative initial imaging, the mean age at which features of SWS were first reported on repeat MRI was 32 months (range from 12-56 months). No data on the sensitivity/specificity of MRI for the detection of SWS has been published.

Gadolinium enhanced MRI (Gd-MRI) of the brain was used to screen/diagnose SWS in all but one patient who had brain computerised topography (CT) with contrast. .[19-21] Imaging protocols were not consistently described (Table 3). Mentzel et al. reported the use of standard Gd-MRI sequences and conventional arterial and venous magnetic resonance angiography (MRA).[21] Adams et al. used standardised brain MRI protocols in a 1.5 Tesla MRI scanner.[19] For infants under 24 months of age, they used axial dual-echo short tau-inversion-time inversion recovery (STIR) with T1WI axial, coronal, and sagittal sequences post-gadopentate dimeglumine. Older patients were imaged with axial T2-weighted (T2WI) sequences.[19] Whether MRI was conducted with sedation/general anaesthesia or bean-bag immobilisation was not described.

iii Financial costs of MRI/EEG

In a public hospital, MRI brain examination with contrast costs US$643.[22] In children aged 3 months to 4-6 years, general anesthesia is usually required at a cost of US$229.23.[22, 23] Findings from our retrospective chart-review (under concurrent *Pediatric Dermatology* review) demonstrate that to detect 1 asymptomatic patient with SWS, 14 MRIs were performed, costing US$11,768.31. By contrast, EEG costs US$87.01, for a routine outpatient study.[24]

iv Risks

In children not anesthetised for MRI, 30-50% report considerable distress. [25] General anesthesia (GA) performed on infants in the MRI suite is considered very safe; with low, but not negligible, risks of adverse events. [26] Death rate attributable to pediatric anesthesia is estimated at 0.1 to 1.2 cases per 10,000 anesthetics delivered. [27] GA-related deaths occur almost exclusively in patients with comorbidities and more

commonly in neonates, therefore, anesthesia related mortality in asymptomatic infants with PWS is highly unlikely.[28] Maintaining peri/intra-operative seizure control is of particularly importance.[29] The potentially proconvulsant properties of anaesthetics also require consideration, but are rarely a problem clinically.[29] Provision of a dedicated anesthetics team can minimise rates of serious adverse effects. [26] A weak association, between adverse neuro-cognitive outcome and exposure to anesthetic in infancy, has been reported in epidemiological studies (hazard ratio < 2). [30] However, a recent multinational randomised control trial found no such association.[31]

Gadolinium contrast increases MRI sensitivity. However, its administration can wake non-sedated infants, compromising image quality and increasing the need for GA. Some centres omit the use of gadolinium, at the expense of sensitivity. Gadolinium-related adverse reactions, usually immediate hypersensitivity reactions, are rare (incidence of 0.004% to 0.22%), but may be life-threatening, [32] The renal immaturity of neonates places them at higher risk of nephrogenic systemic fibrosis (NSF), otherwise rare in infants.[33] Current guidelines advise against the administration of high-risk gadolinium agents (gadodiamide and gadoversetamide) to neonates and recommend caution in infants. [33]

By contrast, EEG is safe, minimally invasive and can be easily repeated. EEG analysis, however, is highly operator dependent.[12, 16]

v Potential therapeutic benefits of screening

Prophylactic treatment of seizures

Evidence supporting the use of prophylactic anticonvulsants in presymptomatic patients with SWS is limited. Pascual-Castroviejo et al. reported an association between seizures and neurocognitive deterioration over-time in a study of 55 SWS patients followed over 40 years, and suggested that levetiracetam offered best seizure control. [14] In their cohort, however, anti-epileptics were not used prophylactically.[14] Another study reported that prophylactic phenobarbital was associated with better cognitive outcomes, compared with those treated after seizure

onset. [34] However, the presymptomatic-treated group had less severe brain involvement and the age at seizure onset in the two groups was not described. [34] In tuberous sclerosis, another neurocutaneous syndrome associated with epilepsy, emerging evidence suggests that presymptomatic treatment with vigabatrin may result in better neurodevelopmental outcomes and patients are increasingly screened with regular EEGs when young. [35]

Aspirin

Since venous congestion, stasis and thrombosis predispose SWS infants to ischaemia-related progressive brain injury, low-dose aspirin may theoretically offer benefit.[6] Two small case series have reported fewer strokes in children with SWS treated with aspirin. [36, 37] However, no such benefit was observed in a third case-series examining presymptomatic aspirin. [38] These studies possess several limitations, including retrospective designs, small numbers, and the use of other SWS populations as control groups.[38] Evidence on the safety of aspirin use in SWS is also limited. A questionnaire-based study reported that 39% of SWS patients treated with aspirin had mild adverse effects (bruising and gum/nose bleeding). [39] Allergic reactions and haematemesis have been rarely reported. [38] Given the lack of prospective randomized controlled trials demonstrating efficacy and safety, aspirin use is not routine in SWS. [2, 5, 6]

Seizure recognition

No existing publications examined whether detection of presymptomatic SWS cerebral involvement results in earlier seizure detection. Seizures associated with SWS are focal and may manifest as behavioural change, staring episodes, change in posture, eye deviation or automatisms affecting the mouth (i.e. lip smacking, chewing, swallowing) or upper extremities (i.e. fumbling, picking). [6] These features can be very subtle in newborns/infants and require a high degree of education and vigilance for detection.

Prognostication

Assessment of the localisation and extent of brain involvement in SWS may assist prognostication and the early identification of patients that could benefit from epilepsy surgery for drug-resistant seizures, which are common in SWS.[8] Neurodevelopmental outcomes in SWS depend on aggressive treatment of seizures and normalisation of epileptiform EEG in young children. [6] No data exists to verify whether presymptomatic diagnosis of SWS improves outcomes. Early negative MRI, particularly within the first 6-12 months of life cannot reliably exclude SWS.[3, 19-21] The impact of false negative scans on seizure detection and neurodevelopmental outcomes is hitherto undescribed.

Discussion

Infants with hemi-facial and forehead PWS phenotypes are at highest risk for SWS (45-80%). [3, 9] Seizures are the earliest presenting neurological feature, [2, 4, 6] having potentially significant consequences for neurodevelopment, so early recognition and treatment is vital. [2, 6, 8, 9] Most authors favour presymptomatic MRI. However, there is no current evidence that screening MRI, costing US$11,768.31 to identify one asymptomatic patient with SWS, improves neuro-developmental outcomes. In clinical practice, MRI may be performed for other reasons, including parental expectations, anxieties, or discomfort with diagnostic uncertainty. Inadequate data concerning optimal timing, limited sensitivity, repeat scanning, costs and risks have led to a lack of consensus on the place of imaging of asymptomatic infants with high-risk PWS. [2, 3, 9, 18, 20]

Imaging before the age of 3 months usually does not require GA. However, the sensitivity of MRI to detect SWS is lowest before the age of 6-12 months.[3, 19-21] Visualisation of leptomeningeal enhancement on MRI may be delayed in SWS as late as 48 months.[19] Furthermore, subtle indirect MRI findings may be the only features of SWS on early imaging.[9, 19] As isolated findings, these are not specific for SWS and can be easily missed without a high degree of suspicion from the radiologist.[19] Data on the sensitivity and specificity of MRI to detect SWS, the degree to which sensitivity is reduced with early imaging, and whether newer 3 Telsa (3T) MRI's overcome these limitations, is not available. We recommend that SWI and FLAIR

sequences, easily added to conventional T1-Gd MRI, be incorporated into standard protocols for SWS imaging. Scans should be reported by experienced pediatric neuroradiologists where possible.

The age at which a negative MRI can reliably exclude SWS is unknown. Most clinicians accept that an early negative scan cannot exclude SWS and recommend repeat neuroimaging after one year of age in cases with uncertainty. [2] However, in clinical practice, it is not clear which infants should have repeat MRI, or when. For infants imaged early, the benefit of early scanning is offset by both the risks of GA in subsequent MRIs [23] and inability to provide conclusive relief to parents. [8, 18, 20, 40] Conversely, in older patients, the potential improvements in detection are counteracted by the diminished clinical value of screening MRI with advancing age, since most affected children would have demonstrated symptoms by this time. [41]

By contrast, EEG is cheap, minimally invasive and can be easily repeated. However, its ability to reliably diagnose SWS cerebral involvement in asymptomatic patients remains to be validated. The age at which reduced background voltages and rhythm asymmetry can first be detected on EEG is unknown, however, results from some cohorts suggest that features may be evident from the first 3-6 months of age.[12, 14-17] Electroencephalographers with specialised experience in SWS and pediatric EEG are not readily available and so subtle asymmetry, particularly in bilateral involvement, or rare spikes may be missed. Quantitative EEG may help overcome this in the future. Currently, both qualitative and quantitative EEG require further validation in higher powered studies on both asymptomatic and symptomatic infants with and without SWS. The standardization of EEG interpretation through use of grading systems such as the spike frequency scores and EEG severity score will assist comparisons across studies and generalizability.

Although some advocate that presymptomatic diagnosis of SWS allows for better parental education, more judicious clinical monitoring and earlier introduction to specialist services, no evidence currently exists to verify this. If optimal education and clinical monitoring were standard practice for all asymptomatic infants with high-risk PWS, diagnosing presymptomatic brain involvement (to facilitate earlier seizure

detection) would be of less value. Recognition of seizures may be enhanced by adjunctive EEG, although this requires prospective study. The benefits of presymptomatic treatment with aspirin and anticonvulsants have not been established.

In high-risk PWS phenotypes, we advocate for early referral to a pediatric neurologist (or otherwise the most experienced pediatrician) for parental education and counselling, to optimise neurological red-flag/symptom recognition and early management of seizures. regardless of the decision to image. Red-flags include onset of visual field deficits, early hand preference, automatisms, nystagmoid movements or concerns about developmental delay or plateau. The presence of these in any infant with PWS, requires urgent neurological review and exclusion of seizures. Ongoing vigilance to detect seizures/neurological red flags is paramount. Prompt seizure recognition can be facilitated by provision of this information to parents in written form to give to medical service providers involved in the care of their child.

Conclusions

Infants with PWS affecting skin derived from the frontonasal placode (i.e. forehead, hemi-facial or median phenotype) should be referred to a pediatric neurologist early for parental education, counselling and monitoring. Currently, there is no available evidence to verify that early MRI (before 6 months) results in better neurodevelopmental outcomes for infants with SWS. Diagnostic utility of early EEG in presymptomatic SWS is possible but presently unestablished. Demonstrating brain involvement on MRI in infants with high-risk PWS may facilitate more judicious counselling and monitoring, but given the potential for false negatives, a negative MRI does not obviate the need for neurological counselling and monitoring. Allaying anxiety about diagnostic uncertainty is not achieved by a scan, but through detailed education, appropriate clinical monitoring and nuanced reassurance. [42] Prospective studies are required in high-risk PWS to clarify SWS neurodevelopmental outcomes in infants screened with MRI, EEG and those only given early neurological assessment/education/monitoring. This will allow determination of the optimal

screening/monitoring strategy.

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Conflicts of interest

Declaration of a conflict of interest by any of the authors involved in the authorship and acknowledgements of the manuscript: None

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	Bosnyák et al.	Kossof et al.	Ewan et al.	Hatfield et al.	Pascual-Castroviejo et al.
No. of patients	33	44[d]	5	14	55
Mean age at initial EEG (months)	38	24	6	121	NR[j]
Presymptomatic SWS at time of EEG	3/33	0/44	2/5[f]	0/14	NR
Type of EEG	Qual	Qual	Qual[g] and Quant[h]	Qual[g] and Quant[h]	Qualitative[k]
% abnormal EEGs in those with SWS ; mean age (months)	55[a] and 52[b];68	80[a]; 47	Qual: (80; 7) Quant:(100; 6)	Quant:[i] 79; 114	80[l]; NR
% abnormal EEGs in presymptomatic SWS; mean age (months)	67; 39[c]	NR	100[g,h]; 6	NR	NR
EEG Sen/Spec	55[a]/NR and 52[b]/ NR	80/NR	Qual: 80/100 Quant: 100/100	Quant: 79/NR	80/NR
Significant clinical correlation	Yes: between EEG severity scores[a,b] and GIQ	No: between severity of EEG findings and SWS neuroscores[e]	Yes: reliably discriminated between infants with SWS vs. no-SWS	Yes: between qEEG power asymmetry and clinical severity	Yes: 100% abnormal EEG had szs. 73% (8/11) normal EEG had szs[m]

Table 1: Summary of studies examining EEG diagnosis of Sturge-Weber syndrome

NR: Not reported; Qual: Qualitative EEG; Quant: Quantitative EEG; Sen: sensitivity; Spec: specificity; szs: seizures; LS: Laterality score (mean power asymmetry between cerebral hemispheres); GIQ . Global intelligence quotient; [a] Using the EEG severity score, adopted from Kossoff et al. where any score other than 0 is considered abnormal where 0= normal EEG; 1=focal voltage asymmetry [with or without slowing] without epileptiform discharges; 2=sporadic, unilateral epileptiform activity [10/minute]; 3=frequent epileptiform activity [>10/minute]; [b] Using the spike frequency score where: 0= Normal EEG; 1=Rare spikes [<1/min]; 2= Occasional [1-10/ minute] and 3=Frequent [>10/minute]); [c] 2 of 3 asymptomatic infants remained free of seizures up a follow of up 3.4 and 10.3 years respectively. However, they did have mild cognitive impairment; [d] Bilateral cerebral involvement on MRI in 10/44; [f] A composite score of seizure frequency, hemiparesis, cognition, and visual deficit. In both presymptomatic

infants, EEG's were interpreted as abnormal via both qualitative EEG analysis (fellowship trained pediatric board-certified electroencephalographer) and quantitative analysis; [g] 30–40 min, 16-channel scalp EEG, collected in the standard clinical fashion with International 10–20 electrode placement and 256 Hz sampling rate. Standard visual clinical EEG interpretation for rhythm slowing, asymmetry and/or spike waves was performed by a fellowship trained, board-certified pediatric electroencephalographer. Asymmetry in dominant background rhythms was the most common abnormal finding.[h] Commercial analysis soft-wear generated power values from selected raw EEG data. A mean Laterality Score (LS) was generated for each cerebral hemisphere where laterality score = (ipsilateral − contralateral) / (ipsilateral +contralateral) for pairs of symmetrical bipolar channels. A separate cohort was examined to compare laterality scores in cerebral hemispheres of patients with SWS cerebral involvement compared to those without. A discriminating laterality threshold was derived, allowing separation of patients with SWS (i.e., those diagnosed with SWS) from those without SWS. This threshold was validated on another cohort, demonstrating its ability to discriminate between those SWS and non-SWS patients. Regional mean laterality scores were obtained from an average of laterality scores derived from pairs of bipolar channels reflecting brain activity in that region; [i] Qualitative data not reported. Authors stated that Quantitative EEG power asymmetry correlated strongly with clinical SWS severity and MRI asymmetry and this correlation was stronger than that of a qualitative read of the EEGs;[j] The EEG abnormality was seen from the first few months of life; [k] EEG was performed in the first few months of life, where possible. Frequent EEG's were conducted if the type of seizures changed or the response to the medication was poor. Otherwise EEGs were repeated 12 monthly; [l] 44 of 55 EEGs were abnormal. The abnormal EEGs consisted of asymmetric voltage (observed in most patients), with low-voltage ipsilateral to the affected hemisphere. 15 patients had additional ipsilateral focal paroxysmal discharges and 7 had contralateral paroxysmal discharges. Isolated contralateral focal paroxysms occurred in four patients and hypsarrhythmia in three. Six of the seven patients with bilateral leptomeningeal angiomas showed a greater severity in one hemisphere, with a predominance of low-voltage focal discharges in the ipsilateral hemisphere; [m] Of the 11 children with normal EEG, 8 did not develop seizures over a 40 year period despite cerebral involvement on MRI

Table 2: Summary of papers examining the MRI diagnosis of Sturge-Weber Syndrome in high-risk distribution port-wine stain

	Dutkiewicz et al.	**Waelchli et al.**	**Priram et al.**	**Adams et al.**
Study design	Prospective recruitment Retrospective MRI analysis	Retrospective	Cross-sectional	Retrospective review
Inclusion criteria	Infants < 12 m with upper facial PWS (SA ≥1cm^2) MRI within the 1 yr age	Infants with facial PWS seen sequentially at dermatology and neurology O/P clinics[e]	Patients with a facial PWS seen at a vascular anomalies or pediatric dermatology clinic[i]	Patients with PWS of the upper face and eyelids referred to neuro-radiology for T1-Gd MRI
% high-risk PWS in those with facial PWS (no.)	20% (13/66)[a]	49% (94/192)[f]	32% (83/259)[j]	63[n] (Only high-risk PWS were referred)
% with MRI features of SWS in those with high risk PWS (no.)	54% (7/13)[a]	73% (69/94)	43% (15/35)[k]	52% (32/62): Definitive leptomeningeal angiomatosis 16% (10/62): Other suggestive findings[o]
% SWS in high-risk PWS(no.)	65% (11/17)[b]	80% (83/104)	18% (15/82)[k]	52% (32/62)[p]
% with MRI features SWS in non high-risk facial PWS (no.)	17% (11/66)[c]	0% (0/4)[g]	0% (0/177)[l]	Only high-risk PWS were referred
Mean age of MRI (m)	4 (SWS) 5 (No SWS)	NR	32	11.5
% Symptomatic at time of MRI	NR	NR	NR	NR
% false –ve MRI	NR	NR	NR	6% (4/62)[q]
Mean follow-up(m)	40	192	None	NR
Imaging recommendations	Routine MRI brain for infants with hemi-facial and	MRI brain before 3 months of life. If negative but neurological	PWS with any V1 involvement should have ophthalmologic	Gd-T1W1 MRI. +/- SWI, post-contrast FLAIR and BOLD MR venography (masy

	median PWS[d]	symptoms develop, assume a false-negative scan. Repeat later if SWS suspicion remains[h]	Ex. MRI for Infants with V1 and: ophthalmologic or neurologic abnormalities[m] or extension PWS to superior eyelid, V2/V3, or contralateral hemiface[m]	increase sensitivity). MRI visualization of leptomeningeal angiomatosis may be delayed; the absence of pial enhancement does not exclude the diagnosis of SWS, especially if other features of SWS present

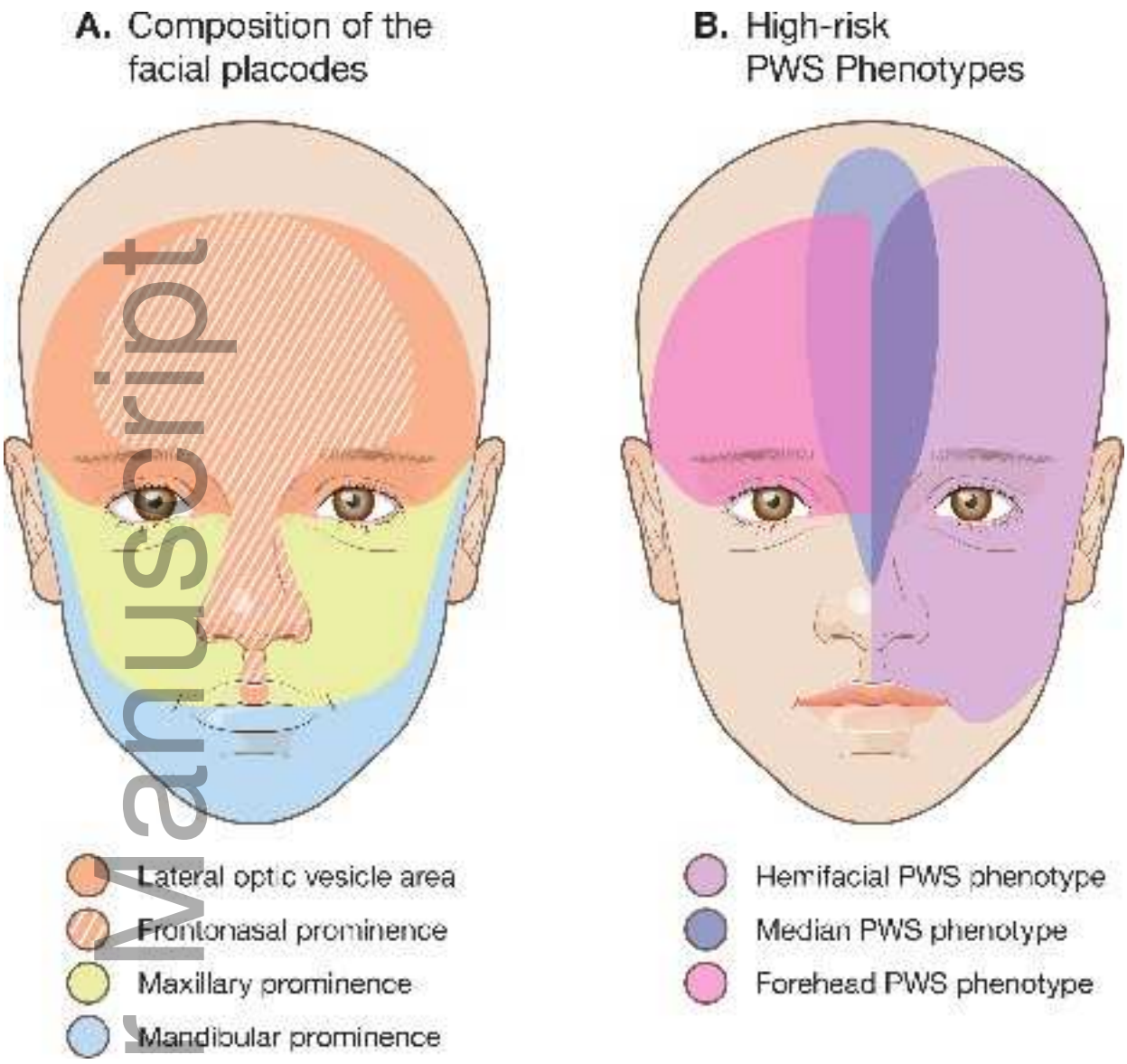
NR: Not reported; T1-Gd: T1 weighted gadolinium enhanced; SWI: Susceptibility weighted imaging MRI; FLAIR: fluid-attenuated inversion recovery sequences
a Involvement of the hemi-facial and median PWS phenotypes considered high-risk; b SWS defined as a patient with a facial PWS and an MRI demonstrating leptomeningeal angiomatosis (direct MRI criteria) OR demonstrating 2+ indirect criteria (increased myelination OR increased ventricular size OR anomalies of venous drainage OR enlargement of the choroid plexus OR atrophy OR specific unilateral abnormalities); cAny facial PWS other than hemi-facial and median distributions considered non high-risk PWS; dThe authors do not define at what age imaging should take place or whether repeat imaging should be undertaken and at what age; e Of the Great Ormond Street Hospital (GOSH), a pediatric tertiary referral centre; f PWS involvement of any aspect of the forehead considered high-risk; g Any facial PWS other than forehead considered non high-risk PWS; h MRI performed before 3 months may avoid the need for GA. The age for repeat scan is not defined. The authors highlight that appropriate information on the use of gadolinium enhancement in young children should be provided to families; i At a tertiary teaching hospital in Tours France; j High-risk considered as PWS involving any aspect of the first division of the trigeminal nerve (V1); k Of the 35 infants with high-risk PWS with neuroimaging, 8 had MRI and 7 had CT. The majority of those with SWS on MRI had extension of their PWS to V2 and or V3 or some degree of midline crossing of the PWS; l Not involving any aspect of V1; m The authors recommend neuroimaging should be performed early if seizure occurs. If not, neuroimaging should be performed after the age of 1 year
n The criterion for referral was the presence of a High-risk facial PWS involving, but not necessarily restricted to, the distribution of V1
[o] Leptomeningeal angiomatosis (supratentorial, typically occipital and posterior parietal. Involvement of the occipital lobes is also recognized) is the diagnostic hallmark of SWS, considered a direct finding of SWS. In the absence of direct findings, the following features were considered suggestive of SWS: Infratentorial pial angiomatosis, prominence of deep veins, cortical atrophy and sub-cortical calcification, globe enlargement +/-choroidal hemangioma
[p] Of these, 3 had no pial enhancement or angioma on MRI on serial imaging up to 48 months of age. Leptomeningeal enhancement was not visible on serial MRI in the fourth patient until 56 months of age. In 2 additional patients only subtle infratentorial pial enhancement was observed. This may be easily missed if not actively sought.

Table 3: False negative neuroimaging for Sturge-Weber Syndrome in infants with facial port-wine stain

	Piram et al.	**Mentzel et al.**	**Adams et al.**
No. (%) with false negative imaging in all those imaged	2/59 (3%)	1/1 (100%)[b]	4/62 (6%)[d]
Mean age at false negative scan (m)	i._5 ii. 6	4	23
Imaging modality (protocol)	i.Gd-MRI[a] ii.CT-C+[a]	Gd-MRI, standard sequences + conventional arterial and venous MRA[c]	Standardized brain MRI protocol (1.5T scanner). Before 24 months of age: axial dual-echo STIR with T1WI axial, coronal, and sagittal sequences post-gadopentate dimeglumine. After 24 months of age: dual-echo replaced by an axial T2-weighted (T2WI) sequence
Mean age (m) on positive repeat scan	i._28 ii._48	12	32
Findings on repeat scan	i._Focal cortical atrophy and calcification (CT) ii. Leptomeningeal angiomatosis	Strong leptomeningeal enhancement, prominent medullary, subependymal and deep veins. Early cortical atrophy and calcification	Abnormal leptomeningeal enhancement overlying parieto-occipital region, subtle loss of parenchymal volume and hypointensity within the subcortical white matter on T2WI sequences. Subtle infratentorial pial enhancement. Subtle infratentoria pial enhancement only appreciated post-mortum
Age (m) first seizure	i._5 ii._48	12	NR

m: Months; Gd: Gadolinium; C+: Contrast enhanced; MRA: Magnetic resonance angiography; STIR: short tau-inversion-time inversion recovery; T1WI: T1-weighted imaging MRI; T2WI: T2-weighted imaging MRI; [a] No other protocol information provided; [b] Case report

[c] Application of Blood-oxygen-level-dependent (BOLD) venography i.e. a high-resolution T2*-weighted, rf-spoiled 3D gradient-echo sequence with first-order flow compensation to the initial (normal) MRI demonstrated distinctly abnormal deep venous vessels in the left occipital lobe[d] 3 had no pial enhancement or angioma on MRI on serial imaging up to 48 months of age. In one of these, leptomeningeal enhancement was not visible until 56 months of age in the 4th patient. In 2 additional patients only subtle infratentorial pial enhancement was observed. This is an infrequent finding in SWS and may be easily missed if not actively sought



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