DR MICHAELA ZALLMANN (Orcid ID : 0000-0002-1604-0547)

Article type : Review Article

Retrospective review of screening for Sturge-Weber syndrome with brain magnetic resonance imaging and electroencephalography in infants with high-risk port-wine stain

Authors: Michaela Zallmann, MBBS[1-2], Richard J. Leventer, MBBS, PhD, FRACP,[2-4] Mark T. Mackay, MBBS , PhD, FRACP, [2-4] Michael Ditchfield MBBS, MD, FRANZCR,[5-6] Philip S. Bekhor, MBBS, FACD[3] and John C. Su, MBBS, MA, MSt, MEpi, MBA, FRACP, FACD[1-5]

Authors' affiliation: [1]Department of Dermatology, Monash University, Eastern Health, Box Hill, Victoria, Australia

[2]Murdoch Children's Research Institute, Melbourne, Victoria, Australia

[3]Royal Children's Hospital, Melbourne, Victoria, Australia

[4]Department of Pediatrics, University of Melbourne, Melbourne, Victoria, Australia

[5]Monash University, Monash Health, Clayton, Victoria, Australia

[6]Diagnostic Imaging, Monash Health, Clayton, Victoria, Australia

Corresponding author: Dr Michaela Zallmann

Affiliation: Department of Dermatology, Eastern Health, 5 Arnold Street, Box Hill, Victoria, Australia 3128

Faculty of Medicine, Monash University, Clayton Campus, Victoria, Australia, 3168

Postal address: Department of Dermatology Outpatients
Box Hill Hospital
8 Arnold Street
Box Hill 3128
Victoria, Australia

Email: m.zallmann@gmail.com

Telephone: +61 402 618 352

Fax: +39351 0974

Declaration of publications/ submissions of related papers from the same study by any of the authors: None

Declarations of conflicts of interest by any of the co-authors None

Words: 2304

Abstract

BACKGROUND: A lack of consensus exists on how best to screen children with facial port-wine stain (PWS) for Sturge-Weber Syndrome (SWS). Many favor brain magnetic resonance imaging (MRI), and adjunctive electroencephalography (EEG) is increasingly used. However, the sensitivity/specificity, negative/positive predictive value of MRI/EEG and whether screening improves seizure recognition is unclear.

METHODS: A retrospective review of children with high-risk PWS presenting consecutively to the outpatient laser-clinic of a tertiary pediatric hospital between December 2015 and November 2016 was undertaken. Primary outcome measures were: yield, accuracy, age and protocols of screening MRI/EEG, type/age of presenting seizure and percent referred to neurology.

RESULTS: Of 126 patients with facial PWS, 25.4% (32/126) were high-risk (hemifacial and median forehead). 43.75% (14/32) underwent screening MRI. SWS was detected in 7.1% (1/14). False negative MRI's occurred in 23.1% (3/ 13) screened. Screening MRI had a sensitivity, specificity, positive and negative predictive value of 25%, 100%, 100% and 76.9% respectively for the detection of SWS. Only one-third of those with false negative MRI were referred to neurology. Mean age of first seizure in those with false negative screening MRIs was 28, versus 14 months in those not screened. Abnormal EEG signs were detected in the 2 infants who underwent presymptomatic EEG.

CONCLUSION: Findings from this small cohort of high-risk PWS suggest that children with positive screening MRI will almost certainly develop SWS, while negative screening MRI cannot exclude SWS (in up to 23.1% of cases). False negative MRI may delay seizure recognition. Seizure education, monitoring and consideration of adjunctive EEG are important irrespective of MRI findings.

Introduction

Certain facial port-wine stain (PWS) distributions have increased potential for neurological and ocular associations,[1, 2] a triad known as Sturge-Weber syndrome (SWS). Non-syndromic PWS and SWS are caused by a somatic activating mutation in *GNAQ*.[3] Hemifacial,[1] forehead[2] and median PWS phenotypes involve skin derived from the frontonasal placode which shares common progenitor cells with the brain.[1, 2] SWS risk increases significantly with these phenotypes (Figure 1).[1] Seizures occur in 75%-100% of patients with SWS.[4-6] Early recognition and treatment of seizures are crucial, as ongoing seizures in early childhood can adversely affect neurodevelopmental outcomes.[7]

Under the assumption that early detection will result in better neurological outcomes, magnetic resonance imaging (MRI) is commonly performed for screening of asymptomatic infants with facial PWS for cerebral capillary-venous malformations (leptomeningeal angiomatosis). At present, it is unclear whether screening MRI achieves this. MRI sensitivity/specificity in SWS is unknown and the optimal age at which the scan should be performed is not established.[1, 2, 8-10] Further data on MRI sensitivity/specificity at various ages are, therefore, essential to clarify the role of imaging in SWS. MRI, especially when performed early, may fail to detect SWS[10, 11], and false reassurance based on a negative MRI could, conversely, delay the recognition and treatment of SWS. Only 5 separate cases of false negative MRIs in SWS[10, 12] have been reported. We retrospectively examine a cohort of 132 infants with facial PWS to determine: 1. the yield and accuracy of screening MRI/EEG, 2. age at screening and repeat MRI, 3. whether screening resulted in earlier seizure detection, and 4. the number referred to neurology for assessment and counseling about seizure education.

Subjects and methods

We conducted a retrospective chart review of children with facial PWS who presented consecutively to the outpatient laser clinic of the Royal Children's Hospital (RCH), a tertiary pediatric facility in Melbourne, Australia, between December 2015 and November 2016. Records of all children with facial PWS who had adequate clinical photography were reviewed. The following information was collected: PWS distribution, age at screening MRI

(defined as MRI performed before the onset of neurological signs/symptoms of SWS including seizures and/or neurodevelopmental abnormalities) or age of first MRI (if already symptomatic at initial MRI), age of screening EEG, outcome of screening MRI (SWS detected or not) and/or EEG (presence of rhythm asymmetry, attenuation of normal background rhythms or epileptiform activity to suggest SWS), age at first seizure, whether a neurology referral was made, age and outcome of any repeat MRI/EEG, and neurodevelopmental status at last review (presence or absence of neurodevelopmental delay or any neurological deficits, such as hemiplegia, cognitive impairment or learning difficulties that were attributed to SWS). Facial PWS were classified according to one of six PWS patterns observed by Dutkiewicz et al.[1] based on best fit (Figure 2). This classification system was chosen because it is the most recent and was derived from a prospective study. PWSs were categorized from clinical photographs based on which PWS phenotype best matched the clinical distribution. PWSs were classified as high-risk if they involved any aspect of the hemifacial or median distributions defined by Dutkiewicz et al. (Figure 2).[1] Six patients were excluded because they did not have adequate clinical photography.

Results

Between December 2015 and November 2016, 126 patients with facial PWS presented to the outpatient laser-clinic of our institution (Figure 3). Of these, 25.4% (32/126) had high-risk PWS. Nine patients developed SWS, defined as the association of a facial PWS with a capillary-venous malformation of the eye, and/or of the brain/leptomeninges (Table 1). The PWS phenotypes observed in the 9 patients with SWS were, hemifacial (7 patients), frontotemporal (1 patient), and isolated cheek and canthus (1 patient) (Figure 2). Of these 9 children with SWS, 5 had bilateral facial PWS (i.e. crossing the midline).

Fourteen patients with high-risk PWS were screened. SWS was detected on MRI in 1/14 patients screened (Figure 3). This child subsequently developed seizures at 10 weeks of age (true positive). Of those with a negative screening MRI, 23.1% (3/ 13) were false negative (Table 2.). All false negative MRIs were performed in children younger than 9 weeks. In our

cohort, MRI screening for SWS in asymptomatic infants with predominantly high-risk PWS had a sensitivity, specificity, positive and negative predictive value of 25%, 100%, 100% and 76.9% respectively.

Two of three false negative MRIs occurred in infants scanned within the past 5 years (2015, 2013 and 2009) (Table 3). Screening MRI's in the 3 infants with false negative scans were performed with bean bag immobolization which is prone to movement artifact (patient 6) and may limit completion of the MRI protocol, especially the administration of contrast (Table 3). The screening MRI in patient 3 was performed without contrast and with limited sequences (Table 3). A prominence of draining cortical veins was deemed to be a normal variant on the report. The infant was referred to RCH where, neurological examination performed by an experienced pediatric neurologist detected a right visual hemi-field defect at 2 months of age. The initial MRI was reviewed by experienced pediatric neurologists/neuroradiologists who concluded that these findings were suggestive of SWS. Prophylactic aspirin was offered.

Neurological referral was not made in 2/3 (66.7%) of infants with false negative MRI. These patients/families received no counseling about seizure recognition before their first seizure. The mean age of first seizure documentation in those with false negative screening MRIs was 28 months compared to 14 months in those with no screening MRI (Table 2). First seizure presentation was with focal seizures, both with and without impaired consciousness. Patient 3 presented in status epilepticus (focal at onset). Patients 2 and 5 (Table 1) presented with unilateral limb jerking and ipsilateral eye deviation and mouth twitching and contralateral head deviation, typical of focal motor seizures, without loss of consciousness. Patients 4, 6 and 7 had features of impaired consciousness (unresponsiveness, staring episodes, not responding to questions/commands) in addition to motor features (Table 1). Patients 1, 4 and 7 had seizures before screening MRI could be undertaken, presenting with focal seizures with impaired consciousness (patients 4 and 7). The type of presenting seizure in patient 1 was not described. Patients 1,4 and 7 all had leptomeningeal angiomatosis detected on subsequent post-seizure MRI.

Of the patients not screened with MRI, 5 developed SWS (patients 1,4,7,8 and 9). Patients 1, 4 and 7 already had epilepsy by the time they were first referred to our institution. Subsequent MRI's at 4 years, 17 months and 4 months, respectively, were positive for intracranial features of SWS (Table 2). Patients 8 and 9 were treated for glaucoma with drainage techniques and 5-fluorouracil (5-FU) injection; they were not imaged, but remain seizure free up to ages 11 and 25 years, respectively. Of the remaining 13 infants without screening MRI, 8 were first seen after the age of 3 years and MRI was not performed because the absence of seizures or neurodevelopmental concerns by this age made SWS highly unlikely.[5, 6] The remaining 5 patients not screened with MRI were monitored clinically. Four had not developed seizures or neurodevelopmental concerns on last review (at ages 3, 4.5, 5.5 and 6 years, respectively). One patient was diagnosed with autism spectrum disorder but had not shown any clinical manifestations of SWS on last review at age 11 years.

Screening 16-channel scalp electroencephalography (EEG) was performed in the standard clinical fashion with International 10–20 electrode placement and 256 Hz sampling rate in patients 3 and 5. Both were abnormal, with sub-clinical seizures detected in patient 3, 2 months before onset of clinical seizures. Posterior quadrant focal slowing was detected in patient 5.

Discussion

Many authors agree that, when screening infants with high-risk PWS, a negative MRI cannot be considered conclusive if performed early.[8, 10] However, no consensus exists on who to screen or the age at which a negative scan can reliably exclude SWS.[7, 8, 13] To our knowledge, this is the first review to quantify the reliability of screening MRIs in a population of children with high-risk PWS and to highlight practical considerations in the management of infants at risk of SWS.

Of the 9 patients with SWS in our cohort, 7 were classified as high-risk according to the Dutkiewicz et al.[1]criteria. The patient with a frontotemporal PWS, not considered high-risk by Dutkiewicz et al.,[1] would be classified as high-risk according to Waelchli et al.[2] criteria.

Forehead,[2] hemifacial[1] and median[1] phenotypes contain skin derived embryologically from the frontonasal prominence, which shares common neural crest progenitor cells with the cerebral cortex.[14] Therefore, involvement of any structures emanating from this prominence raise the possibility of SWS.

In our cohort, 23.1% (3/ 13) with negative screening MRI were false negatives. The sensitivity and negative predictive value of detecting SWS on screening MRI in asymptomatic children with high-risk PWS were therefore low (25% and 76.9% respectively). Conversely, the specificity and positive predictive value of screening MRI were 100%. These findings suggest that, children with a positive screening MRI will almost certainly develop SWS, while negative screening MRI cannot exclude SWS (in up to 23.1% of our cases).

Several factors can increase the probability of false negative screening MRI for SWS, including early scanning, inappropriate or suboptimal imaging protocols and inexperience of the reporting radiologist. All false negative MRIs in our cohort occurred in infants imaged under the age of 9 weeks. Similarly, the majority of false negative scans published in the literature were reported in infants under 7 months of age, suggesting that MRI sensitivity is reduced when imaging is done before this age.[9, 10, 12] Screening practices and protocols vary among authors in the literature. The majority recommend early imaging (without clear definitions of timing) with the caveat that repeat MRI may be required after 1-2 years of age in uncertain cases.[1, 2, 8] In contrast, Priram et al.[10] advocate for neuroimaging at any age if seizures occur, but after 1 year of age for asymptomatic children, while Melancon et al.[9] monitor clinically and image only if seizures develop. Currently, there is no consensus regarding the age at which a negative MRI can reliably exclude SWS.[7, 10, 11] While later imaging may have improved sensitivity for SWS detection, 75% of infants with SWS will have already had their first seizure by 12 months of age.[5, 6] Conversely, early scanning (before 3 months of age) may increase pre-symptomatic SWS detection and typically avoids the need for general anesthesia (GA) or intravenous sedation, but these benefits are offset by the risk of lowered sensitivity with early MRI.

MRI practices, protocols and the experience of the reporting radiologist also affect SWS detection. To maximize detection, MRI protocols should include thin slice pre and post-contrast T1-weighted volume acquisitions, 3-plane T2-weighted and fluid-attenuated inversion-recovery (FLAIR) images and axial susceptibility weighted imaging (SWI).[15, 16] While, our findings that early screening reduce MRI sensitivity are consistent with the literature, we cannot exclude the possibility that newer 3 Tesla MRIs may be more sensitive in detecting earlier, more subtle cerebral angiomatosis/dilated cortical veins. Prospective studies are required to substantiate this. When possible, images should be reported by radiologists experienced in pediatric neuroimaging. Infants under the age of three months can usually be immobilized for the time required to complete an MRI using feed and swaddle techniques. This is favored by many authors because it avoids the need for and the risks associated with GA or sedation. [17] The mortality rate for pediatric anesthesia is estimated at 0.1-1.2 cases per 10,000 anesthetics delivered. [18] This figure probably overestimates risk for infants with PWS who lack many of the comorbidities contributing to the mortality in this study.[19] The benefit of avoiding GA or sedation must be balanced against the potential for movement artifact (from sub-optimal immobilization with feed and swaddle techniques), which may limit SWS detection.

While positive screening may facilitate more judicious education and monitoring of seizures, currently there is no evidence that it improves neurodevelopmental outcomes. Evidence for the use of prophylactic aspirin and anticonvulsants is currently limited .[20] At present, our institution does not routinely offer prophylactic anticonvulsants. Likewise, prophylactic aspirin is not systemically offered for everyone with positive screening, but is considered on an individual basis. Conversely, in our cohort, a negative screening MRI had little clinical value, since the post-test probability of SWS in those with negative screening MRIs was 25%, which approximates the risk of SWS in infants with high-risk PWS based on phenotypic risk stratification. Therefore, infants with high-risk PWS require ongoing neurodevelopmental assessment, seizure education, and monitoring, regardless of screening outcome. In our cohort, 66.7% (2/3) of those with false negative scans were not referred to a neurologist for education about seizures. Presentation typically involved focal motor seizures, both with and without impaired consciousness. In addition to the typical signs of focal motor seizures (unilateral limb jerking with ipsilateral eye and contralateral head deviation), they

can also present with subtle automatisms (lip smacking, chewing and stereotyped movements of the limbs, such as picking/fumbling) and staring episodes or unresponsiveness. Of the infants with SWS, the mean age of first seizure documentation in those with false negative MRIs was 29 months compared to 14 months in those without screening MRI and 10 weeks in those with positive screening. False negative MRI may have provided false reassurance, leading to a delayed recognition of seizures. Our cohort is too small to exclude the influence of confounding factors, such as discrepancies in the severity of brain involvement, on the delayed seizure recognition in those with false negative MRI.

The use of EEG as a non-invasive screening tool for SWS is so far unvalidated. However, studies have demonstrated decreased amplitude and frequency of electrocerebral activity (slowing of dominant background rhythms) over the affected hemisphere. Sub-clinical epileptiform activity and posterior quadrant focal slowing were observed on EEG in patients 3 and 5 (respectively), 2 months before seizures became clinically apparent. EEGs are subject to sampling error (miss the seizure) and are highly operator dependant.[21-23] In SWS, the rhythm asymmetry may not be detectable early on.[21-23]

This study is subject to several limitations including small numbers, retrospective data ascertainment, variable follow-up, and heterogeneity in the MRI protocols employed. Based on the relatively high rate of false-negative screening MRIs in our cohort, we suggest that infants with hemifacial and median PWS should be referred to a pediatric neurologist early for seizure education, counselling, monitoring and consideration of adjunctive EEG, regardless of the decision to pursue MRI, or of its outcome. Where MRI screening is performed under the age of 6 months, patients/families should be informed about the possibility of false-negative scans and counseled about seizures by a neurologist. Adjunctive EEG may have a future role in screening for SWS brain involvement, but this requires prospective study. We suggest more prospective studies in this important area with larger cohorts, and if available, looking at MRI results from different ages and with both older and newer 3 Tesla scanners, possibly as a multi-institution collaboration.

References

1. Dutkiewicz AS, Ezzedine K, Mazereeuw-Hautier J et al. A prospective study of risk for Sturge-Weber syndrome in children with upper facial port-wine stain. J Am Acad Dermatol 2015;72:473-480.

2. Waelchli R, Aylett SE, Robinson K et al. New vascular classification of port-wine stains: improving prediction of Sturge-Weber risk. Br J Dermatol 2014;171:861-867.

3. Shirley MD, Tang H, Gallione CJ et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in *GNAQ*. N Engl J Med 2013;368:1971-1979.

4. Jagtap S, Srinivas G, Harsha KJ et al. Sturge-Weber syndrome: clinical spectrum, disease course, and outcome of 30 patients. J Child Neurol 2013;28:725-731.

5. Pascual-Castroviejo I, Pascual-Pascual SI, Velazquez-Fragua R et al. Sturge-Weber syndrome: study of 55 patients. Can J Neurol Sci 2008;35:301-307.
6. Sujansky E , Conradi S. Outcome of Sturge-Weber syndrome in 52 adults. Am J Med Genet 1995;57:35-45.
7. Sudarsanam A , Ardern-Holmes SL. Sturge-Weber syndrome: from the past to the present. Eur J Paediatr Neurol 2014;18:257-266.
8. Lo W, Marchuk DA, Ball KL et al. Updates and future horizons on the understanding, diagnosis, and treatment of Sturge-Weber syndrome brain involvement. Dev Med Child Neurol 2012;54:214-223.
9. Melancon JM, Dohil MA, Eichenfield,LF Facial port-wine stain: When to worry? Pediatr Dermatol 2012;29:131-133.
10. Piram M, Lorette G, Sirinelli D et al. Sturge-Weber syndrome in patients with facial port-wine stain. Pediatr Dermatol 2012;29:32-37.
11. Comi AM. Update on Sturge-Weber syndrome: diagnosis, treatment, quantitative measures, and controversies. Lymphat Res Biol 2007;5:257-264.
12. Mentzel HJ, Dieckmann A, Fitzek C et al. Early diagnosis of cerebral involvement in Sturge-Weber syndrome using high-resolution BOLD MR venography. Pediatr Radiol 2005;35:85-90.
13. Comi AM. Presentation, diagnosis, pathophysiology, and treatment of the neurological features of Sturge-Weber syndrome. Neurologist 2011;17:179-84.
14. Odaci E. Face embryology. In: A.D. Meyers, Talavera, F. editor: Medscape; 2013. https://emedicine.medscape.com/article/844962-overview. Updated October 19, 2016. Accessed January 8, 2017.
15. Griffiths PD, Coley SC, Romanowski CA et al. Contrast-enhanced fluid-attenuated inversion recovery imaging for leptomeningeal disease in children. AJNR Am J Neuroradiol 2003;24:719-723.
16. Hu J, Yu Y, Juhasz C et al. MR susceptibility weighted imaging (SWI) complements conventional contrast enhanced T1 weighted MRI in characterizing brain abnormalities of Sturge-Weber Syndrome. J Magn Reson Imaging 2008;28:300-307.
17. Serafini G , Zadra N. Anaesthesia for MRI in the paediatric patient. Curr Opin Anaesthesiol 2008;21:499-503.

18. Bhananker SM, Ramamoorthy C, Geiduschek JM et al. Anesthesia-related cardiac arrest in children: update from the Pediatric Perioperative Cardiac Arrest Registry. Anesth Analg 2007;105:344-350.
19. van der Griend BF, Lister NA, McKenzie IM et al. Postoperative mortality in children after 101,885 anesthetics at a tertiary pediatric hospital. Anesth Analg 2011;112:1440-1447.
20. Zallmann M, Leventer RJ, Mackay MT et al. Screening for Sturge-Weber syndrome: A state-of-the-art review. Pediatr Dermatol 2018;35:30-42.
21. Bachur CD , Comi AM. Sturge-weber syndrome. Curr Treat Options Neurol 2013;15:607-617.
22. Ewen JB, Kossoff EH, Crone NE et al. Use of quantitative EEG in infants with port-wine birthmark to assess for Sturge-Weber brain involvement. Clin Neurophysiol 2009;120:1433-1440.
23. Kossoff EH, Bachur CD, Quain AM et al. EEG evolution in Sturge-Weber syndrome. Epilepsy Res 2014;108:816-819.

Table 1: Clinical characteristics of those with SWS and the timing and accuracy of screening investigations (MRI and EEG)

Patient no.	PWS phenotype and extent (%)	Bilateral PWS (Y/N)	Age & year at screening MRI (+/- SWS)	Age & year of first MRI (+/- SWS)	False negative screening MRI (age)	Age of screening EEG	Age of first seizure	Age of SWS detection on follow-up MRI
1	Hemifacial (90%)	Y	NP	4yr (+) (2005)	No	NP	3yr	_
2	Hemifacial (95%)	Y	2wk (+) (2011)	_	No	NP	10wk	_
3	Hemifacial (75%)	Y	4d (-)[a] (2015)	_	Yes (4d)	2 m[b]	14m[c]	4m
4	Hemifacial (75%)	N	NP	17m(+) (1999)	No	NP	2m	_
5	Frontotemporal (75%)	Y	7wk (-) (2009)	_	Yes (7wk)	34 m[d]	3yr	3yr
6	Hemifacial (75%)	N	8wk (-) [e] (2013)	_	Yes (8wk)	NP	3yr[f]	3yr [g]
7	Isolated cheek & canthus (100%)	N	NP	4m (+) (2010)	No	NP	4m	_
8	Hemifacial (80%)	N	NP	NP	_	NP	N/A[h]	_
9	Hemifacial (80%)	Y	NP	NP	_	NP	N/A[h]	_

yr: years; m: months; wk: weeks; d: days; NP: Not performed; Bilateral PWS: PWS that crosses the midline; Screening MRI: MRI performed before the onset of neurological signs/symptoms of SWS; First MRI: Initial MRI in patients already symptomatic with SWS; [a] MRI performed with limited sequences and without contrast. Prominence of the draining cortical veins was reported but deemed a normal variant. Review of the images by pediatric neurologists/neuroradiologists, concluded that the the prominent veins were suggested of SWS; [b] Epileptiform activity detected; [e] Right visual hemi-field defect detected at 2 months of age ; [d] Posterior quadrant focal slowing; [e] Capillary-venous malformation localised to orbit. No cerebral/leptomeningeal involvement reported; [f] Problematic glaucoma requiring surgery manifest before seizures; [g] Leptomeningeal angiomatosis on MRI following first seizure; [h] Glaucoma

Table 2: Age of first recognised seizure, abnormal electroencephalography and counselling in those with false negative screening brain magnetic resonance imaging

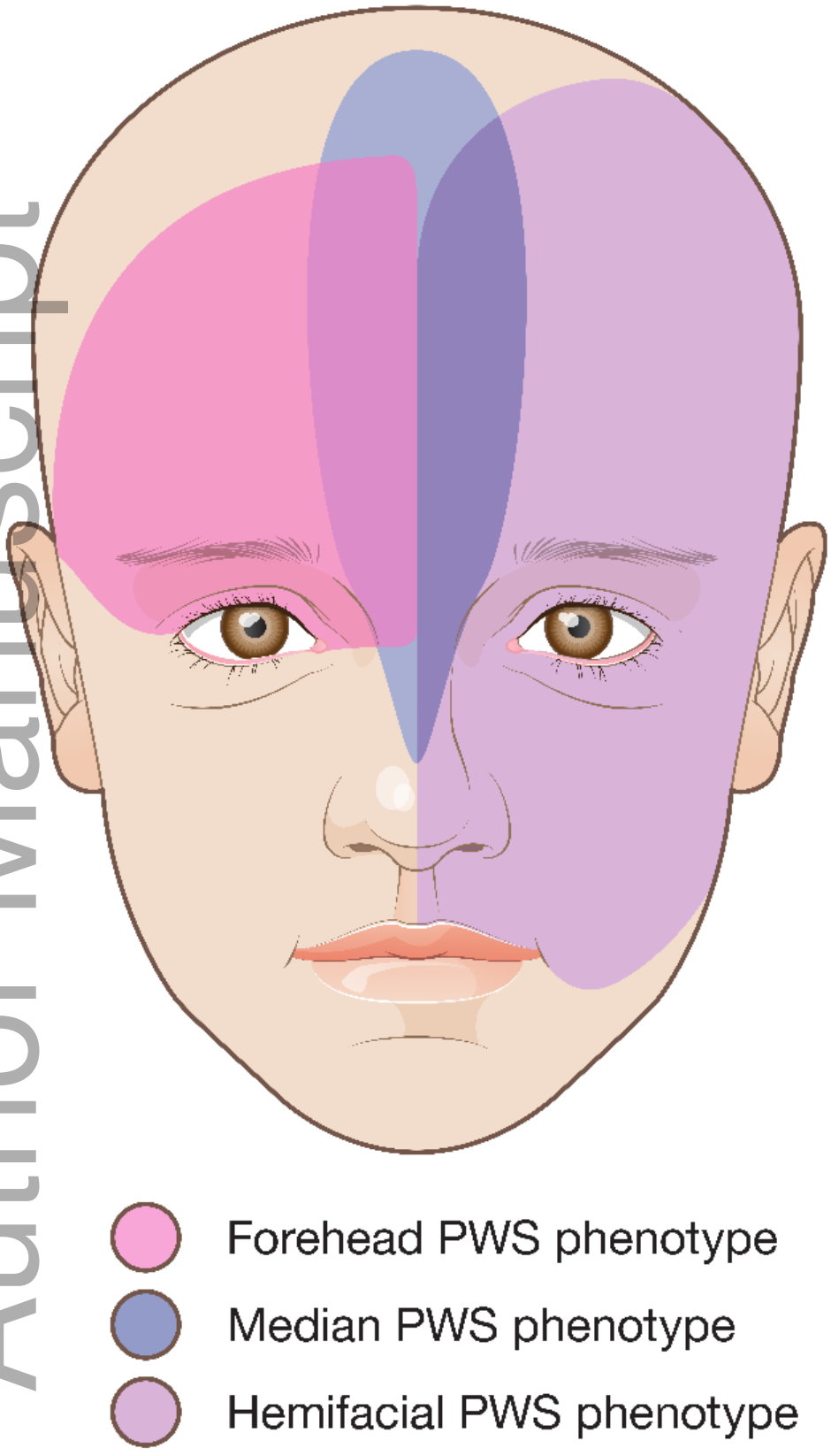
Patient no.	PWS phenotype (% involvement)	Age of false - MRI	Age of first abnormal EEG	Seizure recognition counselling	Age of first recognised seizure (clinical)	First seizure presentation
3	Hemifacial (75% and bilateral)	4 d	2 m[a]	Yes	14 m[b]	Status epilepticus
5	Frontotemporal (75%)	7 wk	34 m[c]	No	34 m	Focal motor seizure
6	Hemifacial (75%)	8 wk	NP	No	36 m	Focal with impaired awareness

d: days; wk: weeks; m: months; [a]: Epileptiform activity detected; [b]: Right visual hemi-field defect detected at 2 months of age on full neurological examination performed by an experienced pediatric neurologist; [c]: Posterior quadrant focal slowing detected

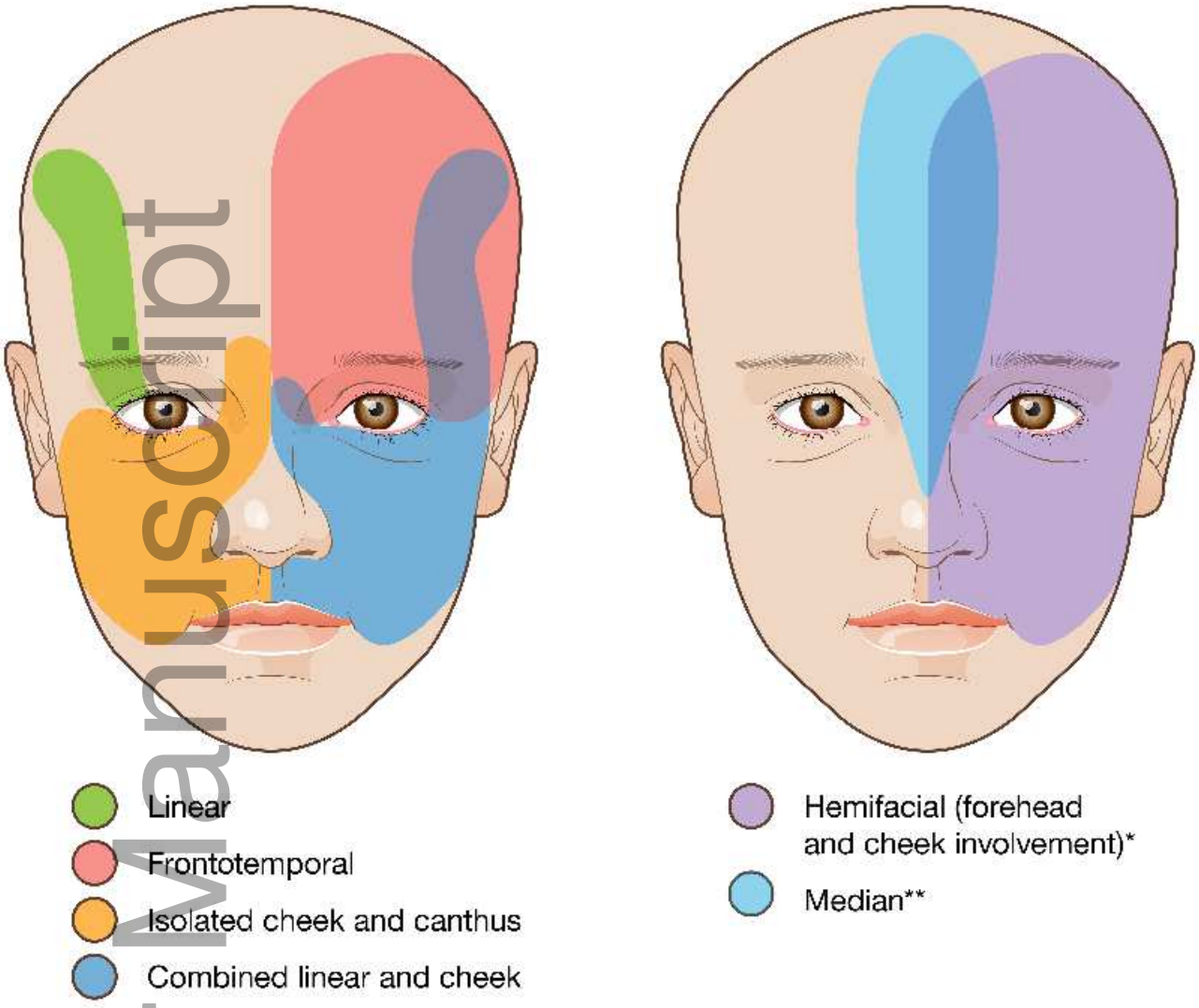
Table 3. MRI protocols and age of SWS detection in those with false negative screening MRIs

	Patient # 3	Patient # 5	Patient # 6
Age of false negative screening MRI and (year performed)	4 d (2015)	7 wk (2009)	8 wk (2013)
MRI protocol at screening	Limited sequence pre-and post-contrast T1 and T2 weighted MRI. Bean bag immobilisation.	Axial T2, fat-sat T2, SWI, DWI, T1 pre-and post-contrast; coronal T2; TOF MRA. Bean-bag immobilisation	T2, DWI, SWI and pre-and-post contrast volumetric T1-weighted MRI, acquired at 3 Tesla. Bean-bag immobilisation
Age at positive repeat MRI	3 m	3 yr	3 yr
MRI protocol on repeat scan	Pre-and post-contrast T1 volume acquisitions with multiplanar reconstructions; 3 plane T2; axial DTI and SWI. TOF MRA of the COW with multi-planar MIP reconstructions. GA	Multiplanar multi-sequence pre-and post-contrast MRI brain and COW MRA. GA	T2, DWI, SWI and pre-and post-contrast volumetric T1-weighted MR images acquired at 3 Tesla. GA
Age at first seizure	14 m[a,b]	3 yr	3 yr[a]

d: days; wk: weeks; m: months; yr: years; T1: T1-weighted MRI; T2: T2-weighted MRI; DWI: Diffusion weighted imaging; TOF MRA: Time of flight magnetic resonance angiography; SWI: Susceptibility weighted imaging; DTI: Diffusion tensor imaging ; MIP: Maximum intensity projection; GA: General anesthesia;
[a] Counselled about possibility of false negative MRI; [b] Counselled about seizure recognition before onset seizures/neurology



pde_13598_f1.tiff



pde_13598_f2.tiff

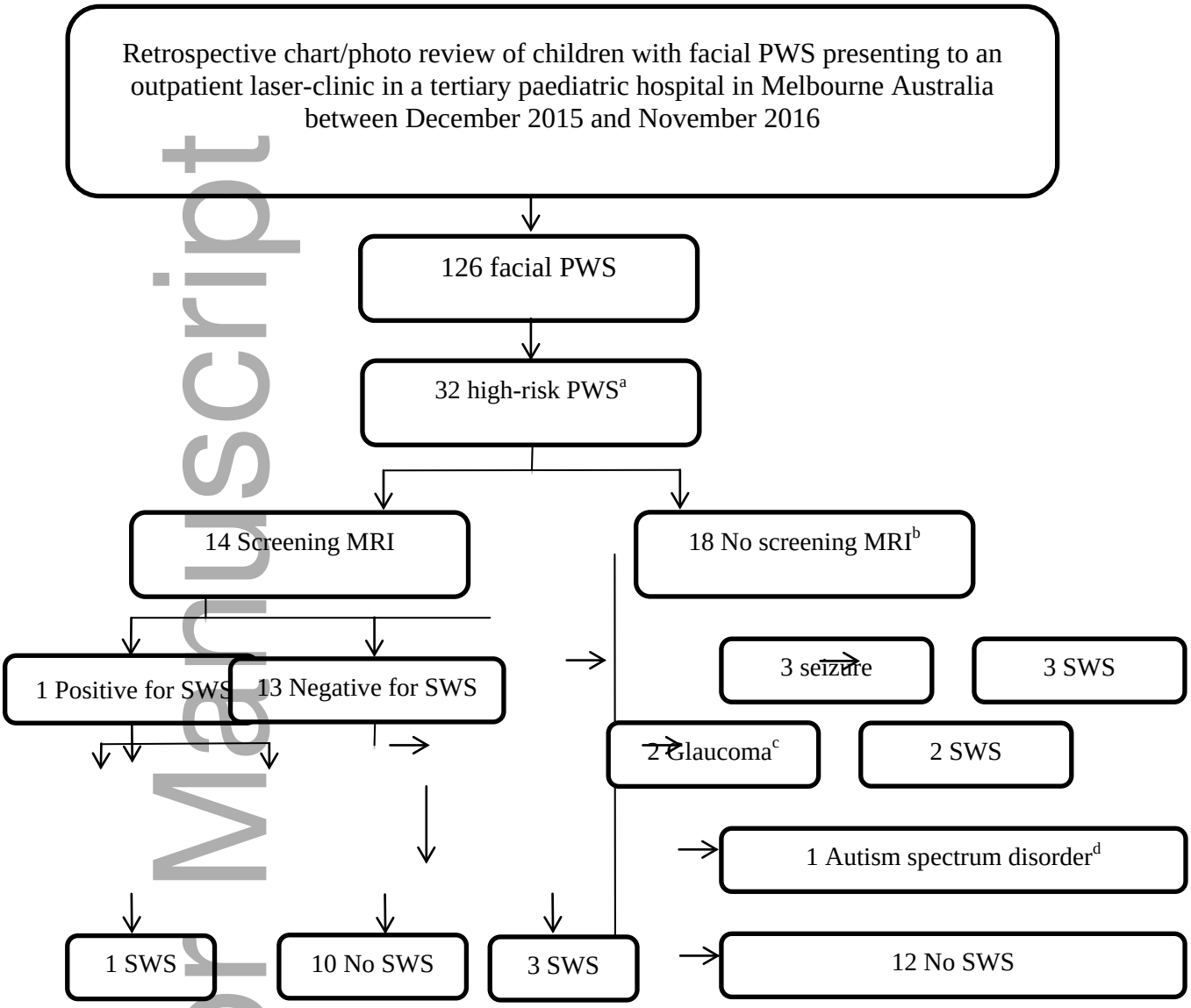


Figure 3: Outcomes of infants with high-risk port-wine stain with and without screening magnetic resonance imaging

[a]High risk was defined as a PWS involving any portion of the hemifacial or median phenotypes as classified by Dutkiewitcz et al.
[b] Of the 18 that did not have MRI: 3 presented with seizure before MRI could be performed, 2 had glaucoma but no seizures, 1 patient was diagnosed with autism spectrum disorder. All 12 other patients remain free of seizures/ neurodevelopmental abnormalities at a minimum age of 17 months (age range 33 months – 25 years).
[c] Meet diagnostic criteria for SWS defined as a facial PWS with associated cerebral or ocular capillary-venous malformation and associated clinical features (seizures/neurodevelopmental impairment and/or glaucoma)
[d] No features of seizures on last review up to the age of 11 years