Epilepsy & Behavior 92 (2019) 57–60

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Brief Communication

Brain MRI abnormalities in patients with infantile spasms and Down syndrome

Sara K. Trowbridge [a], Christopher J. Yuskaitis [b,1], Nicole Baumer [a,c], Mark Libenson [b], Sanjay P. Prabhu [d,*], Chellamani Harini [b]

[a] Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[b] Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[c] Down Syndrome Program, Developmental Medicine Center, Boston Children's Hospital, Boston, MA, USA
[d] Neuroradiology Division, Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 9 November 2018
Revised 14 December 2018
Accepted 15 December 2018
Available online 4 January 2019

Keywords:
Infantile spasms
Down syndrome
Neuroimaging
MRI

ABSTRACT

Introduction: Infantile spasms (IS) are the most frequent epilepsy syndrome in children with Down syndrome (DS). In DS, cellular (synaptic/dendritic changes) and molecular mechanisms are believed to contribute to epileptogenesis, rather than gross structural anomalies. Neuroimaging is a standard part of the evaluation of newly diagnosed infantile epilepsy including IS and, in this age group, often requires sedation. It is unclear if neuroimaging provides additional clinically useful etiologic information in IS associated with DS.
Methods: We conducted a retrospective chart review and detailed neuroimaging review in 36 patients (24 males) with IS and DS, cared for at Boston Children's Hospital.
Results: Incidental imaging abnormalities were common (42%), but potentially relevant etiologic abnormalities were rare (16%). Structural congenital or acquired abnormalities were associated with ongoing antiepileptic drug (AED) use ($p = 0.02$), as well as refractory epilepsy ($p = 0.04$). However, neuroimaging did not alter the treatment plan for any of these patients.
Conclusions: Clinicians must carefully weigh the benefits and risks of neuroimaging in infants with DS and IS, as neuroimaging did not lead to any changes in clinical management in our patients but may offer information regarding prognosis.

1. Introduction

Infantile spasms (IS) represent the most common form of infantile epilepsy [1], with an overall poor prognosis [2]. Down syndrome (DS) accounts for five to 6 % of IS cases [3,4], and IS are the most common epilepsy syndrome seen in children with DS [5,6].

Brain magnetic resonance imaging (MRI) is recommended in new onset IS to aid in identifying the underlying etiology [2–4], but clinicians do not undertake MRI routinely in IS associated with DS, as DS is a recognized genetic etiology for IS [4]. Nevertheless, available information from the literature shows that neuroimaging is obtained in many patients with DS who have presented with IS [7,8]. No study to date has systematically addressed the clinical utility of neuroimaging in children with IS who have DS. Here, we detail the MRI findings in IS associated with DS in a single-center cohort and examine the clinical relevance of the observed neuroimaging abnormalities.

2. Methods

This study was approved by the Boston Children's Hospital (BCH) Institutional Review Board. We identified patients with IS and DS seen at BCH between 2001 and 2016 using the Informatics for integrating Biology and the Bedside (i2b2) based clinical research tools [9]. Patients with DS and IS were included if they were followed primarily at BCH and had MRI scans available for review ($n = 36$) and excluded if they did not have MRI ($n = 9$) or MRI scans were not available for review ($n = 7$). Retrospective chart review confirmed the IS diagnosis and identified timing, indication, and type of imaging. Clinical variables collected include demographics, medical comorbidities, IS/epilepsy history, and IS treatment response. Refractory epilepsy was defined as ongoing seizures at last follow-up despite a trial of two antiepileptic medications at appropriate doses.

All available neuroimaging and sequences were independently reviewed by a board-certified pediatric neuroradiologist specializing in epilepsy blinded to the prior MRI reports. At a minimum, sagittal T1

Abbreviations: IS, infantile spasms; DS, Down syndrome; AED, antiepileptic drug.

* Corresponding author at: Neuroradiology Division, Department of Radiology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA.
E-mail address: sanjay.prabhu@childrens.harvard.edu (S.P. Prabhu).

[1] Contributed equally.

https://doi.org/10.1016/j.yebeh.2018.12.013
1525-5050/

or sagittaly acquired volumetric T1-weighted (sagittal) images, axial T2-weighted, and axial T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR) sequences acquired on either 1.5 Tesla (1.5 T) or 3 Tesla (3 T) MRI scanner were reviewed. Where available, multiplanar reformats of the volumetric T1-weighted (coronal/axial) and coronal T2-weighted images were also reviewed. Based on MRI findings, scans were classified as normal/normal variant or abnormal (Table 1). Abnormal scans were subdivided into (1) acquired structural abnormalities; (2) relevant or potentially relevant congenital structural abnormalities; (3) nonspecific abnormalities. Note that incomplete inversion of the hippocampus was classified as a normal variant since none met the criteria for hippocampal malrotation [10].

2.1. Statistical analysis

Data were analyzed with Graphpad Prism version 7.0 for Mac, (GraphPad Software, La Jolla California USA). Chi-square tests were used to compare categorical variables across three groups, and one-way ANOVA was used for continuous variable with post-hoc Tukey's test performed to adjust for multiple comparisons. Analyses used two-sided p-values <0.05 for statistical significance.

3. Results

Sixty-nine patients were screened, with 52 confirmed to have DS and IS, of which 43 (83%) had a brain MRI. Magnetic resonance imaging scans were available for review in 36 of the 43 patients (84%) included in the study. The patients included in the study ($n = 36$) did not differ from the excluded patients ($n = 16$) in gender, age at IS onset, response to treatment, or refractory seizure status at follow-up. Of these, most ($n = 19$) were obtained at the time of diagnosis, and the rest ($n = 12$) were obtained a median of two months (interquartile range (IQR): 5 months) after diagnosis of IS. In total, 41 scans were available (multiple scans in four patients), 27 acquired on a 1.5 T magnet, and 14 on a 3 T magnet.

3.1. Clinical characteristics

Among the cohort of 36 patients, 24 (67%) were male. Median age at IS diagnosis was seven months (IQR: 6 to 10 months), and median age at follow-up was five years (IQR: 2 to 9 years). Congenital cardiac disease was present in 20 patients (56%), of whom seven patients (19%) required cardiac surgery. Five patients (14%) had congenital gastrointestinal abnormalities, all requiring surgical intervention.

Electroencephalogram (EEG) demonstrated hypsarrhythmia or modified hypsarrhythmia in 30 patients (83%) and was not present or not clearly documented in the remainder ($n = 6$). Twenty-four patients (69%) were treated with standard therapy (hormonal therapy or vigabatrin). Eleven patients (31%) were initially treated with nonstandard therapy, of which six later received standard therapies. One patient (3%) did not have clearly documented initial therapy.

Thirty-five patients had a follow-up visit with a neurologist or developmental medicine physician. At last follow-up, 14 of the 35 patients (40%) had refractory epilepsy. Among these, four patients (29%) had ongoing epileptic spasms in addition to other seizure types, seven patients (50%) had ongoing seizures but no spasms, and three patients (21%) did not have clearly documented follow-up information about epileptic spasms. Nineteen of the 35 patients (54%) were on antiepileptic drugs (AEDs) at last follow-up with seven patients (20%) on one to two AEDs, and 13 patients (34%) on at least three or more AEDs.

Table 1
Imaging findings for each category.

Category	Imaging findings
Normal or normal variant	Pars intermedia cyst
	Mega cisterna magna
	Small anterior pituitary gland
	Incomplete inversion of the hippocampus[a]
Nonspecific abnormalities	Prominence of extra-axial spaces and/or Sylvian fissures
	Isolated inferior vermian hypoplasia
Potentially relevant congenital structural abnormalities (all patients had multiple findings)	Hypoplastic pons
	Undersulcation of the inferior frontal lobes
	Shallow pontomedullary sulcus
	Thinned or thickened callosum
	Simplified gyral pattern
	Gray matter heterotopia
Acquired structural abnormalities	Hypoxic ischemic injury

[a] None met criteria for hippocampal malrotation [10].

3.2. MRI findings in patients with IS/DS

On detailed review of brain MRIs ($n = 36$ patients, 41 scans), 15 patients (42%) had normal scans or findings classified as normal variants, 15 patients (42%) had nonspecific abnormalities, and 6 patients (17%) had abnormal findings (Table 1). Magnetic resonance imaging did not identify surgically remediable focal epileptogenic lesions nor did the imaging findings lead to any documented change in medication selection. Vigabatrin-related MRI changes were seen in one patient, and this finding did not alter management.

Of those with abnormal MRIs, two patients had acquired abnormalities consistent with hypoxic–ischemic damage identified on neuroimaging prior to IS onset and histories compatible with hypoxic–ischemic injury. Eleven percent (4 of 36 patients) had multiple dysmorphic features that were classified as potentially etiologically relevant congenital abnormalities. These included gray matter heterotopia, callosal or brainstem abnormalities, and undersulcation or simplified gyral patterns. These four patients also showed evidence of volume loss with either ventriculomegaly or prominence of extra-axial spaces. Fifteen patients (42%) had nonspecific imaging findings. The majority of these patients had prominence of the extra-axial spaces and/or Sylvian fissures. One patient had abnormal T2 signal in the bilateral globi pallidi and thalami, determined subsequently to be vigabatrin-related changes.

3.3. MRI findings and clinical outcomes

Thirty-five of the 36 patients had information on clinical follow-up, with only one of the patients with a normal MRI lost to follow-up. We compared clinical characteristics across the groups of patients with normal/normal variant MRIs, nonspecific abnormalities, and abnormal scans with acquired/congenital structural abnormalities. The age at IS onset and diagnosis were not significantly different across the three groups ($p = 1.0$). Gender varied significantly across the groups with seven males of 14 (50%) with normal/normal variant scans, 14 males of 15 (93%) with nonspecific abnormalities, and 2 males of 6 (33%) with acquired/congenital structural abnormalities (chi-square: $p = 0.009$).

Refractory epilepsy at last follow-up was significantly different across all three groups ($p = 0.035$; Fig. 1a). When compared with the normal/normal variant group, patients with acquired structural or potentially relevant congenital structural abnormalities were more likely to have refractory epilepsy (3 of 14 in normal/normal variant group versus 5 of 6 in acquired/congenital structural abnormality group, adjusted for multiple comparisons $p = 0.03$, Fig. 1a). We confirmed this finding by assessing the number of AEDs patients were on at last follow-up (Fig. 1b). Individuals with normal/normal variant MRIs were on an average of one AED (median = 0, IQR: 0–1.5) while those with nonspecific abnormalities were on an average of two AEDs (median = 1, IQR: 0–3), and those with potentially relevant abnormalities were on an average of three AEDs (median = 3, IQR: 2–5). The number of AEDs patients were prescribed at last follow-up was significantly different across the groups (one-way ANOVA, $p = 0.0137$) with the difference primarily

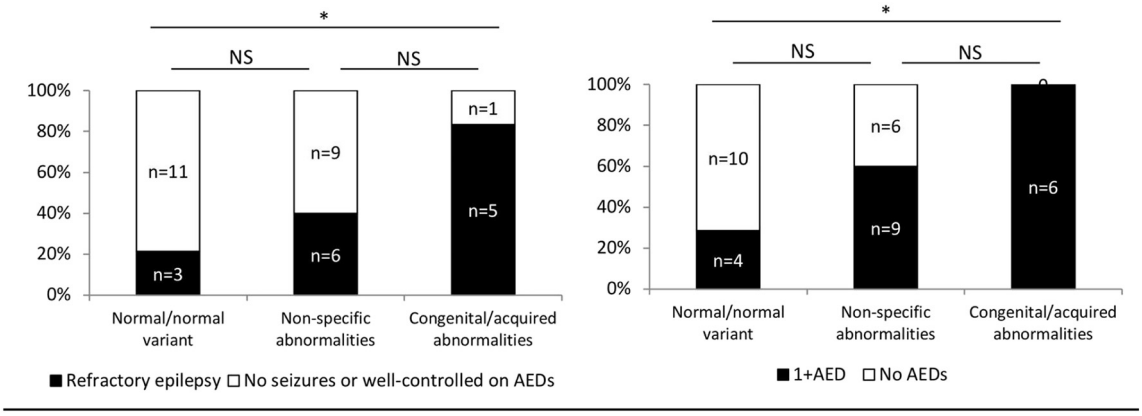

Fig. 1. Patients with congenital/acquired abnormalities were significantly more likely to have (A) refractory epilepsy (normal vs congenital/acquired, adjusted chi-square *p = 0.03) and to be on (B) multiple AEDs at last follow-up (normal vs congenital/acquired, adjusted Fisher's exact test *p = 0.032), as compared with patients with normal imaging.

between the normal group and the potentially relevant abnormalities group (Tukey's post-hoc p = 0.01).

4. Discussion

In this single-center retrospective study neuroimaging was abnormal in 21 (58%) of the 36 patients with scans available for review, but identified abnormalities were nonspecific and not felt to be explanatory of the patients' epilepsy in 15 patients (42%). However, six patients (16%) had acquired or potentially relevant structural congenital abnormalities, suggesting an additional or compound etiology for the epilepsy. The presence of these potentially relevant congenital or acquired abnormalities was associated with later refractory epilepsy, but none of the identified abnormalities influenced medical treatment.

The findings noted on MRI in our study patients are consistent with brain abnormalities previously reported in patients with DS. Specifically, the frequent finding of prominent extra-axial space or Sylvian fissures, vermian hypoplasia, and frontal lobe abnormalities in our population is in line with prior neuroimaging studies in patients with DS [11,12]. Furthermore, children and neonates with DS are found to have congenitally small brainstems [13]. Therefore, some of the MRI findings in our patients may be intrinsic developmental neuroanatomic findings related to DS, whether or not associated with epilepsy. In the absence of an imaged control group of infants with DS without epilepsy, the significance of our macrostructural findings in the context of epileptogenesis requires further study.

Interestingly, imaging abnormalities (congenital/acquired) are a known risk factor for refractory epilepsy, and we found a similar association in patients with DS. Whether this is related to other genetic or anatomic variables remains to be determined. In general, it is believed that patients with DS and IS have better outcomes as compared with IS with other etiologies [6], and further phenotyping may help clarify outcomes in children with DS and IS. The reasons for differential outcomes in patients with DS versus other patients remain unclear. It would also be interesting to do functional connectivity studies, to better evaluate connectivity abnormalities as a potential prognostic indicator. This would, of course, be challenging to obtain in many patients, as it could require additional sedation time for functional magnetic resonance imaging (fMRI). However, improving technologies could speed up data acquisition and make such studies possible.

The clinical relevance of neuroimaging is an important consideration, as imaging usually requires general anesthesia, and the population with DS is known to be a higher risk group for general anesthesia [14]. Magnetic resonance imaging utility in our cohort is relatively low, but abnormal MRI appears to offer some prognostic information. The anesthesia risk, although somewhat higher with DS, is still relatively low, affecting <5% of patients [15]. For some clinicians, this could be an argument in favor of deferring imaging while others might prefer to obtain neuroimaging at time of IS diagnosis or with refractory IS.

Limitations of our study are the retrospective study design, small cohort, lack of control data, and shorter duration of follow-up. The strengths include blinded neuroimaging review with the majority of scans occurring on the same MRI scanners.

Overall, our study provides the first detailed review of neuroimaging findings in a cohort of patients with DS with IS. We find that neuroimaging did not significantly alter treatment course. We demonstrate an association between refractory epilepsy and potentially relevant congenital structural abnormalities in a significant minority of DS–IS. Further prospective studies would be helpful to clarify this finding.

Acknowledgments

Funding from the Fred Lovejoy House-staff Research and Education Grant. We thank Kimberly Levitt for her contribution in data formatting and manuscript review.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

[1] Wilmshurst JM, Gaillard WD, Vinayan KP, Tsuchida TN, Plouin P, Van Bogaert P, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE Commission of Pediatrics. Epilepsia 2015;56:1185–97.
[2] Pellock JM, Hrachovy R, Shinnar S, Baram TZ, Bettis D, Dlugos DJ, et al. Infantile spasms: a U.S. consensus report. Epilepsia 2010;51:2175–89.
[3] Wirrell EC, Shellhaas RA, Joshi C, Keator C, Kumar S, Mitchell WG, et al. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia 2015;56:617–25.
[4] Osborne JP, Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, et al. The underlying etiology of infantile spasms (West syndrome): information from the United Kingdom Infantile Spasms Study (UKISS) on contemporary causes and their classification. Epilepsia 2010;51:2168–74.
[5] Arya R, Kabra M, Gulati S. Epilepsy in children with Down syndrome. Epileptic Disord 2011;13:1–7.
[6] Stafstrom CE, Konkol RJ. Infantile spasms in children with Down syndrome. Dev Med Child Neurol 1994;36:576–85.
[7] Sanmaneechai O, Sogawa Y, Silver W, Ballaban-Gil K, Moshé SL, Shinnar S. Treatment outcomes of West syndrome in infants with Down syndrome. Pediatr Neurol 2013;48:42–7.
[8] Saltik S, Kocer N, Dervent A. Magnetic resonance imaging findings in infantile spasms: etiologic and pathophysiologic aspects. J Child Neurol 2003;18:241–6.
[9] Murphy SN, Weber G, Mendis M, Gainer V, Chueh HC, Churchill S, et al. Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2). J Am Med Inform Assoc 2010;17:124–30.

[10] Cury C, Toro R, Cohen F, Fischer C, Mhaya A, Samper-González J, et al. Incomplete hippocampal inversion: a comprehensive MRI study of over 2000 subjects. Front Neuroanat 2015;9:160.
[11] Carducci F, Onorati P, Condoluci C, Di Gennaro G, Quarato PP, Pierallini A, et al. Whole-brain voxel-based morphometry study of children and adolescents with Down syndrome. Funct Neurol 2013;28:19–28.
[12] Pinter JD, Brown WE, Eliez S, Schmitt JE, Capone GT, Reiss AL. Amygdala and hippocampal volumes in children with Down syndrome: a high-resolution MRI study. Neurology 2001;56:972–4.
[13] Fujii Y, Aida N, Niwa T, Enokizono M, Nozawa K, Inoue T. A small pons as a characteristic finding in Down syndrome: a quantitative MRI study. Brain Dev 2017;39:298–305.
[14] Lewanda AF, Matisoff A, Revenis M, Harahsheh A, Futterman C, Nino G, et al. Preoperative evaluation and comprehensive risk assessment for children with Down syndrome. Paediatr Anaesth 2016;26:356–62.
[15] Borland LM, Colligan J, Brandom BW. Frequency of anesthesia-related complications in children with Down syndrome under general anesthesia for noncardiac procedures. Paediatr Anaesth 2004;14:733–8.