Recommendations for structural magnetic resonance imaging in infants with first afebrile seizure or new onset epilepsy: evidence-based recommendations from the ILAE Neuroimaging Task Force (Supplementary Materials)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg 3,4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg 4,5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pg 4, Suppl. Tables 1-3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 5,6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N.A.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pg 5,6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg 5,6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg 5,6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg 5,6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N.A.
	13f	Describe any sensitivity analyses conducted to assess robustness of the	N.A.

Section and Topic	Item #	Checklist item	Location where item is reported
		synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg 5,6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig 1
Study characteristics	17	Cite each included study and present its characteristics.	Pg 7, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl. Table 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pg 7-11, Table 1, Suppl. Tables 7,8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg 7-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N.A.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N.A.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N.A.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg 8,10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pg 8,10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg 12-15
	23b	Discuss any limitations of the evidence included in the review.	Pg 12-15
	23c	Discuss any limitations of the review processes used.	Pg 12-15
	23d	Discuss implications of the results for practice, policy, and future research.	Pg 12-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Pg 4-5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	18
Competing interests	26	Declare any competing interests of review authors.	18
Availability of data, code	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
and other materials		for all analyses; analytic code; any other materials used in the review.	

Supplementary Table 1. Ovid MEDLINE(R) ALL 1946 to April 13, 2023

	Searches	Results
1	exp Magnetic Resonance Imaging/	529100
2	(mr* adj2 (scan* or imag*)).ab,ti.	197229
3	(mri or Magnetic Resonance Imaging).ab,ti.	449413
4	1 or 2 or 3	708369
5	((recent* or new* or first or afebrile) adj3 (epilep* or seizure*)).ab,ti.	11231
6	4 and 5	1584
7	exp Infant/	1245199
8	(infant* or child*).ab,ti.	1919373
9	7 or 8	2502993
10	6 and 9	571
11	limit 10 to case reports	163
12	10 not 11	408

Supplementary Table 2. Embase Classic + Embase 1947 to 2023 April 13

#	Searches	Results
1	exp Magnetic Resonance Imaging/	1216453
2	(mr* adj2 (scan* or imag*)).ab,ti.	288545
3	(mri or Magnetic Resonance Imaging).ab,ti.	710858
4	1 or 2 or 3	1291294
5	((recent* or new* or first or afebrile) adj3 (epilep* or seizure*)).ab,ti.	18757
6	4 and 5	3738
7	exp Infant/	1307802
8	(infant* or child*).ab,ti.	2655127
9	7 or 8	3289062
10	6 and 9	1313
11	(case adj3 report*).ab,ti.	967914
12	10 not 11	1065
13	(case adj2 series).ab,ti.	150797
14	10 not 12	248
15	13 and 14	4
16	12 or 15	1069

Supplementary Table 3. WOS Core Collection, April 13, 2023

#	Search Query	Results
1	TI=(Magnetic Resonance Imaging OR "mri") OR AB=(Magnetic Resonance Imaging or "mri")	516718
2	TI=((("mr" OR "mri") NEAR/2 (scan* or imag*))) OR AB=((("mr" OR "mri") NEAR/2 (scan* or imag*)))	207146
3	#1 OR #2	549234
4	TI=(((recent* or new* or first or afebrile) NEAR/3 (epilep* or seizure*))) OR AB=(((recent* or new* or first or afebrile) NEAR/3 (epilep* or seizure*)))	14091
5	#3 AND #4	1426
6	(infant* or child*) (Title) OR (infant* or child*) (Abstract)	2100791
7	#5 AND #6	446
8	(TI=((case NEAR/3 report*) NOT (Case NEAR/3 serie*)) OR AB=((case NEAR/3 report*) NOT (Case NEAR/3 serie*)))	671388
9	(#7) NOT #8	390

Supplementary Table 4. Evidence synthesis – PICO 1

Study ID	Country	Inclusion criteria	Infants		
			Total, N°	Undergoing MRI, N° (%)	With abnormal MRI, N° (%)
Al-Shami 2016	QAT	Age: <14 years; First afebrile seizure	26 (<2y)	26 (100)	14 (53.9)
Ali 2022	PAK	Age: 1m-18y; New-onset afebrile seizures	83 (<1y)	N.R.	N.R.
Aprahamian 2014	USA	Age: 1m-18y; First time non-febrile seizure with focal manifestations	72 (<18m)	N.R.	N.R.
Berg 2000	USA	Age: 1m-15y; New diagnosis of epilepsy	N.R.	N.R.	N.R.
Berg 2009	USA	Age: 1m-16y; New diagnosis of epilepsy	N.R.	113 (N.A.)	30 (N.A.)
Cornelius 2023	IND	Age: <12 years; New-onset seizures (due to inherited metabolic disorder)	32 (<1y)	N.R.	N.R.
Coryell 2019	USA	Newly diagnosed early life epilepsy; First seizures <3 year; Established epilepsy diagnosis <42 months	N.R.	N.R.	N.R.
Dirik 2018	TUR	Age: 1-18y; New diagnosis of epilepsy	N.R.	N.R.	N.R.
Eltze 2013	GBR	Age: 1-24m; New diagnosis of epilepsy	57	51 (89.5)	37 (72.5)
Gattamaneni 2022	IND	Age: 1m-5y; New-onset seizures*	46	N.R.	N.R.
Gowda 2019	IND	Age: 1m-1y; First afebrile seizure	121	N.R.	36 (N.A.)
Hourani 2021	LBN	Age: 6m-18y; New-onset unprovoked seizure(s)	169 (<2y)	169 (100)	82 (48.5)
Hsieh 2010	USA	Age: 1-24m; New-onset afebrile seizures	317	182 (57.4)	104 (57.1)
Kasap 2023	TUR	Age: 1m-18y; First focal seizure*	15 (<1y)	N.R.	3 (N.A.)
Stödberg 2020	SWE	New diagnosis of epilepsy with first seizure <2y	116	57 (49.1)	37 (64.9)

Trowbridge 2019	USA	Down Syndrome + Infantile Spasms who had MRI	36	36 (100)	21 (58.3)
Vecchi 2016	ITA	Age: 1m-13y; Diagnosis of symptomatic epilepsy due to acquired and developmental etiologies and presumed symptomatic focal epilepsy	119 (<3y)	119 (100)	74 (62.2)

***** A proportion of the infants in this study had a febrile seizure etiology; however, the study was retained as it also includes infants within the target population of interest (first afebrile seizure or new-onset epilepsy).

Note: Country codes refer to the country of origin of each study, based on ISO 3166-1 alpha-3 codes. Full names: QAT = Qatar; PAK = Pakistan; USA = United States; IND = India; TUR = Türkiye; GBR = United Kingdom; LBN = Lebanon; SWE = Sweden; ITA = Italy.

Supplementary Table 5. Evidence synthesis – PICO 2

Study ID	Country	Inclusion criteria	Infants			
			Total, N°	Abnormal N.E., N° (%)	Abnormal EEG, N° (%)	Abnormal pregnancy/delivery, N° (%)
Al-Shami 2016	QAT	Age: <14 years; First afebrile seizure	26 (<2y)	N.R.	N.R.	N.R.
Ali 2022	PAK	Age: 1m-18y; New-onset afebrile seizures	83 (<1y)	N.R.	N.R.	N.R.
Aprahamian 2014	USA	Age: 1m-18y; First time non-febrile seizure with focal clinical manifestations	72 (<18m)	N.R.	N.R.	N.R.
Berg 2000	USA	Age: 1m-15y; New diagnosis of epilepsy	N.R.	N.R.	N.R.	N.R.
Berg 2009	USA	Age: 1m-16y; New diagnosis of epilepsy	N.R.	N.R.	N.R.	N.R.
Cornelius 2023	IND	Age: <12 years; New-onset seizures (due to inherited metabolic disorder)	32 (<1y)	N.R.	N.R.	N.R.
Coryell 2019	USA	Newly diagnosed early life epilepsy; First seizures <3 year; Established epilepsy diagnosis <42 months	N.R.	N.R.	N.R.	N.R.
Dirik 2018	TUR	Age: 1-18y; New diagnosis of epilepsy	N.R.	N.R.	N.R.	N.R.
Eltze 2013	GBR	Age: 1-24m; New diagnosis of epilepsy	57	25 (43.9)	N.R.	N.R.
Gattamaneni 2022	IND	Age: 1m-5y; New-onset seizures	46	N.R.	N.R.	N.R.
Gowda 2019	IND	Age: 1m-1y; First afebrile seizure	121	85* (70.2)	N.R.	46# (38.0)

Hourani 2021	LBN	Age: 6m-18y; Diagnosis of ≥1 unprovoked seizure	169 (<2y)	136* (80.5)	N.R.	N.R.
Hsieh 2010	USA	Age: 1-24m; New-onset afebrile seizures	317	34 (10.7)	105[£] (33.1)	30[$] (9.5)
Kasap 2023	TUR	Age: 1m-18y; First focal seizure	15	N.R.	N.R.	N.R.
Stödberg 2020	SWE	New diagnosis of epilepsy with first seizure <2y	116	46* (39.7)	73 (62.9%)	18[$] (15.5)
Trowbridge 2019	USA	Down Syndrome + Infantile Spasms who had MRI	36	36 (100)	30 (83.3)	N.R.
Vecchi 2016	ITA	Age: 1m-13y; Diagnosis of symptomatic epilepsy due to acquired and developmental etiologies and presumed symptomatic focal epilepsy	119 (<3y)	42 (35.3)	110 (95.7)	N.R.

***** Cases reporting evidence of developmental delay at neurological assessment were included under the category of abnormal neurological examination.

[#] A significant history of perinatal insult was included under the category of abnormal pregnancy/delivery.

[$] Low birthweight and preterm birth were included under the category of abnormal pregnancy/delivery.

[£] EEG was performed in 90.3% of the sample; the reported percentage of abnormal findings refers to this subset.

Note: Country codes refer to the country of origin of each study, based on ISO 3166-1 alpha-3 codes. Full names: QAT = Qatar; PAK = Pakistan; USA = United States; IND = India; TUR = Türkiye; GBR = United Kingdom; LBN = Lebanon; SWE = Sweden; ITA = Italy.

Supplementary Table 6 – Risk of Bias assessment

	Inclusion criteria	Subjects and setting	Exposure measure	Condition criteria	Confounding factors identified	Confounding factors dealt	Outcome measurement	Statistical analysis
Ali 2022	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Al-Shami 2016	Yes	No	Unclear	Yes	No	No	Unclear	Yes
Aprahamian 2014	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Unclear
Berg 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Berg 2009	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Cornelius 2023	Yes	Yes	Unclear	Yes	Unclear	No	Not applicable	Yes
Coryell 2019	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Dirik 2018	Yes	No	Yes	Yes	No	No	Yes	Unclear
Eltze 2013	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Gattamaneni 2022	Yes	No	Unclear	Yes	No	No	Yes	Yes
Gowda 2019	Yes	No	Unclear	Yes	No	No	Yes	Unclear
Hourani 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hsieh 2010	Yes	Unclear	Yes	Yes	Unclear	Unclear	Not applicable	Yes
Kasap 2023	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes
Stödberg 2020	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Trowbridge 2019	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes
Vecchi 2016	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes

Note: Risk of bias was assessed using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (https://jbi.global/sites/default/files/2020-08/Checklist_for_Analytical_Cross_Sectional_Studies.pdf)

Question: What is the effectiveness of brain MRI performed in both emergency and non-urgent settings in identifying the underlying cause of seizures in infants with a first afebrile seizure or new-onset epilepsy?
Setting: Emergency and non-urgent settings

Supplementary Table 7. Summary of Findings for PICO 1 (GRADE assessment)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic yeld									
17	non-randomised studies	not serious	not serious	very serious[a]	serious[b]	none	• 17 studies were analyzed, including 1209 infants who met the inclusion criteria. • 753 infants underwent brain MRI, with the percentage of MRI utilization ranging from 49.1% (*Stödberg 2020*) to 100.0% (*Al-Shami 2016, Hourani 2021, Trowbridge 2019, Vecchi 2016*). • MRI abnormalities were identified in 438 infants, with the percentage of abnormal findings ranging from 48.5% (*Hourani 2021*) to 72.5% (Eltze 2013). • 4 studies did not report the total number of infants evaluated (*Berg 2000, Berg 2009, Coryell 2019, Dirik 2018*), leading to potential underestimation of the true sample size. • 9 studies lacked explicit data on the number of infants who underwent MRI (*Ali 2022, Aprahamian 2014, Berg 2000, Cornelius 2023, Coryell 2019, Dirik 2018, Gattamaneni 2022, Gowda 2019, Kasap 2023*), preventing precise calculation of MRI utilization rates in those cases. • The reporting of MRI abnormalities was also incomplete, with 8 studies failing to specify the number of abnormal findings in infants (*Ali 2022, Aprahamian 2014, Berg 2000, Cornelius 2023, Coryell 2019, Dirik 2018, Gattamaneni 2022, Kasap 2023*).	⊕◯◯◯ Very low[a,b]	9

Explanations

a. Variability in MRI protocols, inclusion criteria, and the classification of abnormalities limits the direct applicability of findings to all clinical settings. Some studies do not distinguish between clinically significant and incidental findings.

b. Confidence in effect estimates is limited by incomplete data reporting, wide variability in diagnostic yield across studies, and differences in neuroradiologists' expertise. While some findings are based on small sample sizes, substantial variability is also observed within these cohorts.

Question: Which clinical features in infants with a first afebrile seizure or new-onset epilepsy are associated with MRI-detected abnormalities that explain the cause of seizures?
Setting: Emergency and non-urgent settings

Supplementary Table 8. Summary of Findings for PICO 2 (GRADE Assessment)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Clinical predictors									
17	non-randomised studies	serious[a]	not serious	very serious[b]	serious[c]	none	• 17 studies were analyzed, including 1209 infants who met the inclusion criteria. • 404 infants had abnormal neurological examinations, with the percentage ranging from 10.7% (*Hsieh 2010*) to 100.0% (*Trowbridge 2019*). • 318 infants had abnormal EEG findings, with the percentage ranging from 33.1% (*Hsieh 2010*) to 95.7% (*Vecchi 2016*). • 94 infants had abnormalities related to pregnancy or delivery, with the percentage ranging from 9.5% (*Hsieh 2010*) to 38.0% (*Gowda 2019*). • 4 studies did not report the total number of infants evaluated (*Berg 2000, Berg 2009, Coryell 2019, Dirik 2018*), potentially leading to an underestimation of the sample size. • 10 studies lacked explicit data on abnormal neurological examinations (*Al-Shami 2016, Ali 2022, Aprahamian 2014, Berg 2000, Berg 2009, Cornelius 2023, Coryell 2019, Dirik 2018, Gattamaneni 2022, Kasap 2023*) • 13 studies did not provide data on abnormal EEG findings (*Al-Shami 2016, Ali 2022, Aprahamian 2014, Berg 2000, Berg 2009, Cornelius 2023, Coryell 2019, Dirik 2018, Eltze 2013, Gattamaneni 2022, Gowda 2019, Hourani 2021, Kasap 2023*) • 14 studies failed to report abnormalities related to pregnancy or delivery (*Al-Shami 2016, Ali 2022, Aprahamian 2014, Berg 2000, Berg 2009, Cornelius 2023, Coryell 2019, Dirik 2018, Eltze 2013, Gattamaneni 2022, Hourani 2021, Kasap 2023, Trowbridge 2019, Vecchi 2016*).	⨁◯◯◯ Very low[a,b,c]	CRITICAL

Explanations

a. Many studies lack complete reporting on the total number of infants evaluated, the presence of abnormal neurological examinations, EEG findings, and perinatal complications. This increases the risk of selection and reporting bias, potentially skewing the associations between clinical features and MRI abnormalities.
b. Variability in the definitions of clinical features (e.g., focal vs. generalized seizures, abnormal neurological exams), inconsistencies in EEG interpretations and abnormal neurological examination reporting, and the lack of standardized population descriptions limit the direct applicability of findings. Additionally, some studies do not account for confounders that may influence MRI findings, further reducing the strength of the associations observed.
c. The limited sample sizes, along with missing, non-standardized data on clinical features and reporting inconsistencies, reduce confidence in the precision of effect estimates.