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Original Article

# Incidence of Epilepsy and Associated Risk Factors in Perinatal Ischemic Stroke Survivors

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ABSTRACT

*INTRODUCTION:* Epilepsy is a serious and often lifelong consequence of perinatal arterial ischemic stroke (PAIS). Variable incidences and risk factors for long-term epilepsy in PAIS have been reported. To determine the incidence of epilepsy in PAIS survivors and report factors associated with the risk of developing epilepsy, a meta-analysis and systematic review of prior publications was performed.
*METHODS:* We examined studies on perinatal or neonatal patients ($\leq$28 days of life) with arterial ischemic strokes in which the development of epilepsy was reported. EMBASE and MEDLINE/PubMed databases were systematically searched in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
*RESULTS:* A meta-analysis of 10 studies revealed a summary incidence of epilepsy in PAIS patients of 27.2% (95% confidence interval 16.6% to 41.4%) over a mean study duration of 10.4 years (range 1.5 to 17). More recent studies generally reported a lower epilepsy incidence. A systematic review identified seven possible risk factors for epilepsy in PAIS patients: hippocampal volume reduction, infarct on prenatal ultrasound, a modified Alberta Stroke Program Early Computed Tomography score $\geq$9, family history of seizures, cerebral palsy, and initial presentation with cognitive impairment or seizures.
*CONCLUSIONS:* About a third of children with PAIS will develop epilepsy. While seven possible risk factors have been reported, further research is warranted to confirm the strength of their association with the development of epilepsy.


## Introduction

Perinatal arterial ischemic stroke (PAIS) is commonly defined as a cerebrovascular event that occurs on or before the 28th day of life with pathologic or radiographic evidence of a focal cerebral infarction in a discrete arterial territory.[1–3] PAIS occurs in an estimated one in 2300 to 4000 term births.[4,5] The most common presentation is seizure activity, seen in 75% to 90% of the

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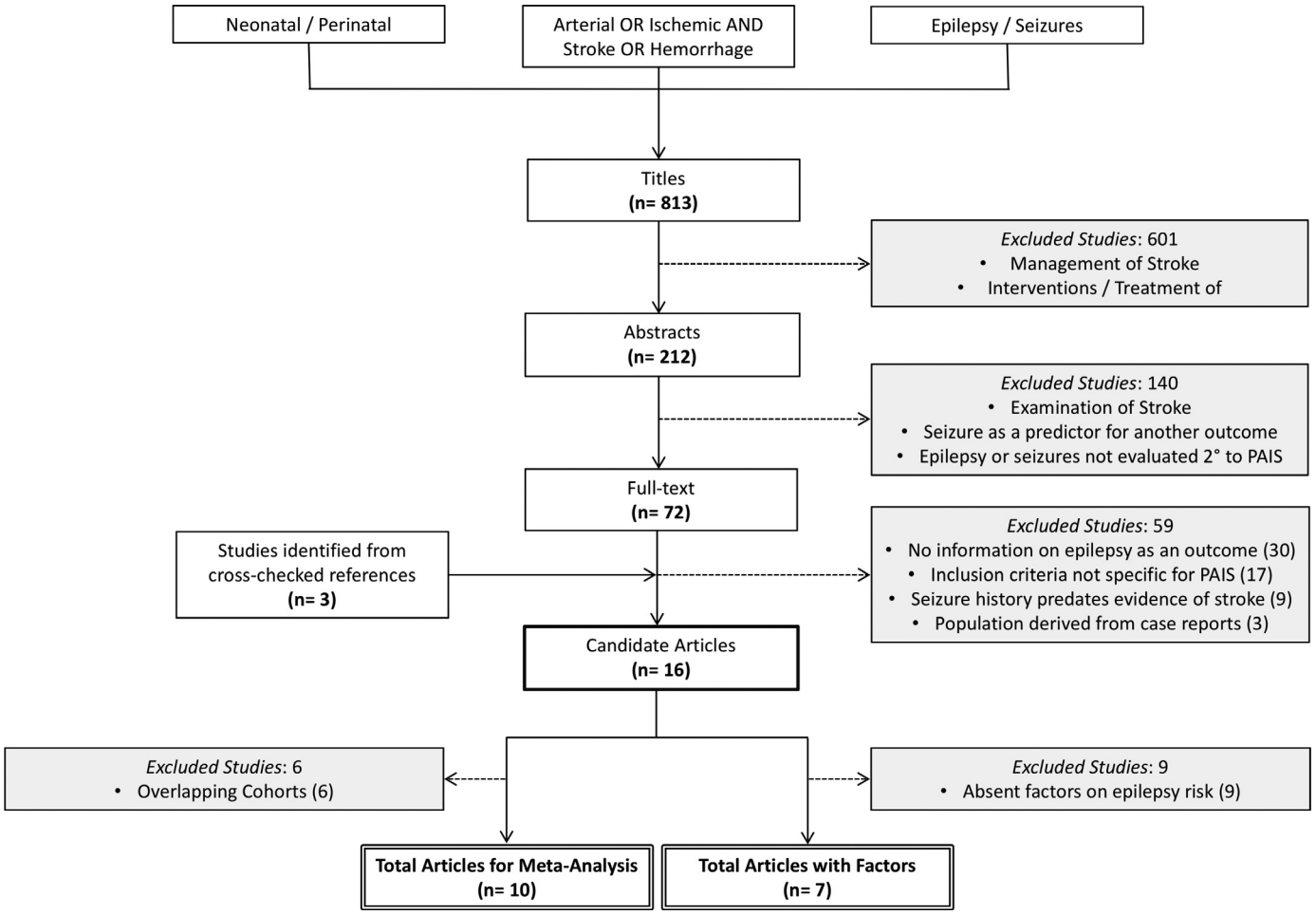


**FIGURE 1.** PRISMA flow chart. Ten articles for meta-analysis and 7 that discussed factors associated with increased epilepsy risk were included from 813 titles.

patients.[6–9] Acute PAIS is defined as neurological symptoms (e.g., seizures) occurring in the newborn period, while delayed or presumed PAIS is diagnosed when children present with a focal neurological deficit (often early handedness in infancy) or seizures related to a chronic and/or remote arterial ischemic stroke on neuroimaging.[3] The history and imaging of the latter diagnosis are consistent with a prenatal or perinatal onset of infarction.[10] The majority of reported infarct cases are unilateral, involve the middle cerebral artery (MCA), and predominantly affect the left side.[11,12] PAIS often results in permanent neurological sequelae that leave the surviving children with significant disability.[5,13,14]

The development of epilepsy is one of the more morbid consequences of PAIS. Moreover, those with neonatal arterial ischemic stroke are at high risk for the development of poststroke epilepsy with equal risk for epilepsy in childhood when compared to other vascular stroke types.[15] However, the incidence of long-term epilepsy remains poorly defined with broad estimates ranging from 9.5% to 67.2%,[9,16] with few predictors of epilepsy risk identified; thus, prognostication and management remains a challenge. To this end, we sought to determine the incidence, as understood in terms of frequency or rate of new annual occurrences,[17] of epilepsy in PAIS survivors and to report factors associated with developing epilepsy through a meta-analysis and systematic review of prior publications.

## Methods

### *Systematic review*

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Fig 1).[18] We searched the EMBASE and NCBI/NLM PubMed databases from inception to March 1, 2018 using the following terms: “neonate” or “perinatal,” “arterial” or “ischemic,” “stroke” or “hemorrhage,” and “epilepsy” or “seizures.” Reviewers met and reached agreement on inclusion and exclusion criteria after independently reviewing a subset of studies, the authors (specifically, A.R., M.P., and S.R.) then commenced the review process by first screening English article titles and abstracts, before selecting candidate studies for full-text review. Full-text review of the screened articles was then performed (by A.R., J.L., M. P.) for selection of final set of studies.

Studies of both acute (presentation of neurological symptoms or other evidence of stroke ≤28 days of life) and delayed and/or presumed perinatal (neurologically symptomatic after the neonatal period with verified remote infarcts on contrast tomography [CT] or

magnetic resonance imaging [MRI] imaging) presentations of stroke were included.[3,19] Other inclusion criteria were studies implicitly or explicitly defining PAIS as an arterial ischemic stroke occurring on or before 28 days of life (neonatal); definition of epilepsy included having more than one unprovoked clinical or electrographic seizure after the neonatal period (as early as 14 days following a stroke) or those receiving anticonvulsant medication at or before follow-up. Studies implicitly defining PAIS or epilepsy were only included if the definitions used by study authors for PAIS and epilepsy were discernible from the data presented in the manuscripts. Exclusion criteria included studies that did not use an evident definition of epilepsy, PAIS, or lacked substantial data on epilepsy as an outcome or consisted of non-PAIS epilepsy patients. Further, studies whose population was derived from case reports and/or with narrow selection criteria (e.g., stroke in only one location, both venous and arterial infarcts) were excluded. All studies included in the meta-analysis were assessed for quality using the Newcastle-Ottawa Scale for Cohort Studies.[20]

Our systematic review initially yielded 813 articles, through a review of titles and abstracts, 741 articles were subsequently excluded. After a full-text review of 72 articles, a total of 16 studies met the inclusion and exclusion criteria.[5,8,9,14,16,19,21–30] Upon further review of the 16 studies, potential overlap of cohorts between studies was identified and further confirmed by personal communication with the senior authors of select studies.[8,9,21,23,26,27,29] Of the studies with overlapping cohorts, large PAIS cohorts with long study durations were favored for inclusion, with the exception of one study that did not report a study duration.[26] Ultimately, 10 studies were selected for meta-analysis.[9,14,16,22,23,25,26,28–30] Four studies omitted from the meta-analysis were included in the systematic review of factors associated with epilepsy development.[8,21,24,27] Figure 1 is a flow diagram of the systematic review search methodology.

### *Meta-analysis*

A meta-analysis was conducted to calculate a summary rate of epilepsy secondary to PAIS. A pooled, random effects, inverse, weight-based rate of epilepsy was generated from frequencies reported in the studies using the Comprehensive Meta-Analysis software version 2.2 (Biostat Inc., Englewood, NJ, USA) for Microsoft Windows operating system, which also accounted for methods of moments analysis. All analyses assumed random-effects. The pooled estimate of incidence was reported with a 95% confidence interval (CI). Publication bias was assessed by generating a funnel plot and testing for Egger's regression intercept.[31] Heterogeneity among the frequencies reported in the studies was quantitatively measured by calculating the $I^2$ value. If the value suggested significant heterogeneity (i.e., $I^2 > 75\%$), then the heterogeneity was explored using metaregression to probe for a correlation of incidence (in logit scale where logit [x] = ln [x/{1-x}]) with another variable, specifically the year of publication of study.

## Results

### *Study characteristics*

Ten studies were identified for inclusion (Table 1);[9,14,16,22,23,25,26,28–30] six were based in North America (United States = 4, Canada = 2), three in Europe, and one was an international study. Seven studies were retrospective, and three were prospective. Six were multicentered studies, and the remaining was single-center. All studies were deemed to be of sufficient quality on the Newcastle-Ottawa Scale (Supplementary Table 1). The mean study duration was 10.2 years (range 1.5 to 17) with the number of studied PAIS patients averaging 73.3 (range 27 to 230) and epilepsy averaging 18 patients (range three to 41). A cumulative meta-analysis for temporal assessment has been provided as a supplement (Supplementary Figure 1). Limitations and considerations for each study, including follow-up information, are included in Table 1.

Eight studies explicitly defined PAIS as occurring on or before 28 days of life with symptoms (acute PAIS), while two studies relied on imaging alone to diagnose PAIS. The definition of epilepsy in these studies was heterogeneous and included: seizure(s) occurring more than 14 days after the PAIS event, a score of greater than 1 on the modified Engel scale which indicates that the patient has not been seizure-free for six months (score of 2) or poorer seizure control,[23,32] or initiation of anticonvulsant medication. All studies utilized either clinical or electrographic criteria to diagnose epilepsy (Table 1).

### *Incidence of epilepsy*

In total, these studies contained 733 patients who suffered a PAIS. Of these, 180 developed epilepsy (24.6%). Based on the meta-analysis of these 10 studies (Table 1), the summary incidence of epilepsy was 27.2% (95% CI 16.6% to 41.4%) (Fig 2A, Table 2) without obvious evidence for publication bias by visual inspection of the funnel plot or by Egger's regression intercept ($P = 0.77$), illustrated in Figure 2B. However, the meta-analysis displayed a high amount of heterogeneity ($I^2 = 65\%$); therefore, a metaregression was performed. Metaregression analysis demonstrated a correlation between the year in which the study was published and the frequency of epilepsy; the epilepsy frequency decreased with recently published studies in a linear fashion (slope = $-0.12 \pm 0.02$, $P < 0.0001$) (Fig 2C). Additionally, a subsequent metaregression analysis demonstrated a correlation between the nine studies with available study duration data and the frequency of epilepsy, namely the frequency of epilepsy increased in a linear fashion with longer study durations (slope = 0.05 +/− 0.02, $P < 0.01$) (Fig 2D).

### *Factors associated with epilepsy development*

Following the systematic review, seven studies reported statistically significant data on factors associated with risk of epilepsy development following PAIS.[8,9,21,23,24,26,27] A summary of these factors and other considerations for each study are outlined in Table 3.

#### *History, presentation, and prognostic factors*

Whether the neonatal seizures at presentation is associated with development of epilepsy in PAIS patients is unclear. Although two studies identified such correlations,[23,24] another two studies did not.[8,9] One study found cognitive impairment, defined by developmental level and educational requirements as clinically documented, correlated with a risk of persistent epilepsy at last follow-up.[23] Additionally, Golomb et al. also noted that a prior family history of epilepsy was associated with a development of seizures at least six months after a stroke diagnosis.[9]

The diagnosis of cerebral palsy (CP) plays a unique role in epilepsy risk prediction in PAIS patients, requiring

**TABLE 1.** PAIS Studies Included in Meta-analysis

| Author | Year | Country | Population Pool | Study Period | Study Duration (Years) | PAIS Patients (Sample Size) | Epilepsy (Cases) | Study Scale | Study Design | Epilepsy Definition | PAIS Definition | Limitations & Considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Billinghurst | 2017 | USA | Children's Hospital of Philadelphia | 2006 to 2014 | 8.8 | 113 | 25 | SC | Retrospective | ≥2 unprovoked seizures ≥24 hrs apart occurring ≥30 days after PAIS | ≥37 wks gestation to 28 days of life with acute neonatal encephalopathy and infarction in arterial territory on MRI; presumed PAIS: normal perinatal neurological histories who developed neurological issues >28 days with remote focal infarction in arterial territory on MRI | Median follow-up for NAIS was 3.4 yrs (range 1.5 to 5.8) and PAIS was 5.3 yrs (range 2.5 to 7.5); time to epilepsy onset: NAIS was 12.2 yrs (range 5.8 to 48.4) and PAIS was 21.7 yrs (range 6.3 to 67.7) |
| Chabrier | 2016 | France | Regional* | 2003 to 2006 | 3 | 80 | 12 | MC | Prospective | ≥2 afebrile unprovoked seizures occurring after PAIS, or in the case of a single afebrile unprovoked seizure, initiation of anticonvulsant treatment (classified by International League Against Epilepsy terminology and classification scheme) | Birth to 28 days of life | Birth closed-cohort study, only term newborns included; assessment conducted at age 7 |
| Fitzgerald | 2007 | USA | Riley Hospital for Children neurology stroke clinic | 1999 to 2004 | 5 | 45 | 17 | SC | Retrospective | Modified Engel's score >1 | Delayed presentation, but confirmed remote infarct on imaging | Median age at last follow-up was 58 mos (range 7 to 259), median length of follow-up was 49 mos (range 2 to 207) |

(*continued on next page*)

**TABLE 1** (*Continued*)

| Author | Year | Country | Population Pool | Study Period | Study Duration (Years) | PAIS Patients (Sample Size) | Epilepsy (Cases) | Study Scale | Study Design | Epilepsy Definition | PAIS Definition | Limitations & Considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fox | 2017 | International | Multi-site | 2011 to 2012 | 1.5 | 28 | 3 | MC | Retrospective | Treatment with maintenance anticonvulsant at 1 year follow-up in children with ≥1 remote seizure | Birth to 28 days of life | Cohort included neonatal and adolescent stroke (≥37 wks gestation and <18 yrs); all had acute neurological deficit or seizure consistent with stroke; epilepsy assessment at 1 yr follow-up |
| Gold | 2014 | USA | University of California, San Diego | - | - | 27 | 15 | MC | Retrospective | Epilepsy occurring >28 days of life | Birth to 28 days of life | Case-control study |
| Golomb | 2007a | USA | Riley Hospital for Children (Indianapolis, IN) | 1990 to 2007 | 17 | 61 | 41 | SC | Retrospective | Presence of clinical or electrographic seizures, with <6 mo seizure-free off medication | 20 wks gestation to 28 days of life | ≥ 6 months of follow-up; median age at last follow-up 43 mos (range 9 to 179) |
| Grunt | 2015 | Switzerland | Multi-site | 2000 to 2010 | 11 | 74 | 7 | MC | Prospective | Received anticonvulsant medication; seizures were either antecedent to infantile spasms or symptomatic epilepsy with focal or generalized seizures | Birth to 28 days of life | Mean follow-up 23.3 mos (SD 4.3) after birth |
| Sreenan | 2000 | Canada | University of Alberta and Royal Alexandra Hospitals | 1983 to 1997 | 15 | 46 | 21 | MC | Retrospective | Seizure disorder, clinically diagnosed, occurring after PAIS requiring re-institution of anticonvulsant medication | Birth to 28 days of life | Pts were at term (≥37 wks gestation); mean follow 42.1mos (range 18 to 164); diagnosis made via reading neonatal CT scan |
| Van Buuren | 2013 | Netherlands | Wilhelmina Children's Hospital, Utrecht | 1991 to 2005 | 14 | 29 | 7 | SC | Retrospective | Occurring >2.5 yrs of life; included simple partial seizures, secondary generalized seizures, symptomatic multifocal seizures, or EEG findings | Specific range not included but methods state all patient had PAIS verified by imaging in neonatal period | 1° study outcome: cognitive; 3 patients were recruited from VU University Medical Centre; Developed epilepsy at median of 6.5 yrs (range 2.5 to 13) |

(*continued on next page*)

**TABLE 1** (*Continued*)

| Author | Year | Country | Population Pool | Study Period | Study Duration (Years) | PAIS Patients (Sample Size) | Epilepsy (Cases) | Study Scale | Study Design | Epilepsy Definition | PAIS Definition | Limitations & Considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| de Veber | 2017 | Canada | Multi-site | 1992 to 2008 | 16 | 230 | 32 | MC | Prospective | Included seizures occurring >14 days post-stroke not considered a presenting symptom of stroke event | Birth to 28 days of life | Of 230 neonates, 47 died or did not have available data prior to follow-up; long-term outcome data (n = 183); mean follow-up interval from stroke = 3 yrs, (IQR: 2.8 to 3.2) and ranged ≥13 yrs |

Abbreviations:
CT = Computed tomography scan
EEG = Electroencephalogram
IQR = Interquartile Range
MC = Multi-center
mos = months
NAIS = Neonatal Arterial Ishcmic Stroke
PAIS = Perinatal Arterial Ischemic Stroke
PB = Population-based
Pts = patients
SC = Single-center
SD = Standard Deviation
USA = United States of America
wks = weeks
yrs = years
* In this study, authors report that children were recruited from 39 participating neonatal units in France.

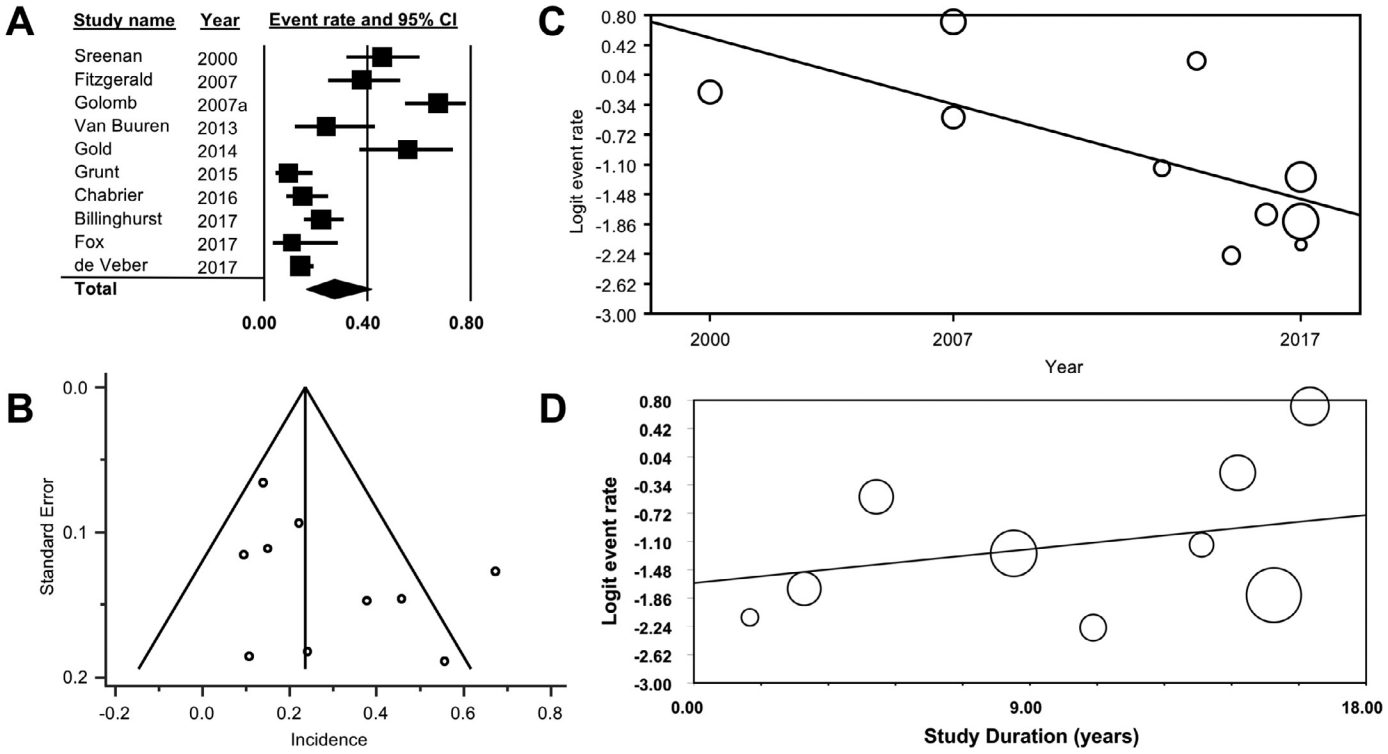


**FIGURE 2.** (A) Meta-analysis of the incidence of epilepsy in PAIS patients. CI, confidence interval. (B) Funnel plot of standard error by incidence of epilepsy for evaluation of publication bias in the incidence of epilepsy meta-analysis. Open circles indicate studies included in the meta-analysis. Diagonal lines represent 95% confidence intervals. (C) Meta-regression of publication year of studies with the logit of the incidence of epilepsy. Size of the circle representing each study is proportional to that study's weight in the meta-analysis. The straight diagonal line represents best line of regression. (D) Meta-regression of study duration on logit of incidence of epilepsy. Size of the circle representing each study is proportional to that study's weight in the meta-analysis. The straight diagonal line represents best line of regression.

additional investigation. In patients with acute PAIS, the subsequent diagnosis of CP (especially tri/quadriplegic CP) was significantly associated with epilepsy in the future.[27] In contrast, children with CP who presented with delayed and/or presumed PAIS did not have an increased epilepsy risk.[23] Finally, a significant association has been noted between children with CP delivered via Caesarean section who had an acute PAIS and with the later onset of epilepsy.[27]

Finally, in a series of hippocampal volume measurements following unilateral ischemic stroke via MRI images of all participants, Gold et al. noted that in patients who eventually developed seizures, hippocampal volume was markedly reduced compared to the control group.[26]

*Vascular factors*

Vascular or infarct-related factors, typically identified at presentation, associated with increased epilepsy risk in the PAIS population include presence of infarction on prenatal ultrasound[9] and lesion (infarct) size.[8] The presence of an infarct on prenatal ultrasonography indicated a shorter time to seizures after at least six months of age when compared to children without an evidence of

**TABLE 2.** Meta-analysis of the Incidence of Epilepsy Secondary to PAIS

| Study Name | Year | Study Duration (years) | Statistics for Each Study | | | | |
|---|---|---|---|---|---|---|---|
| | | | Total | Event Rate | Lower Limit | Upper Limit | Relative Weight (%) |
| Sreenan | 2000 | 15.0 | 21/46 | 0.457 | 0.320 | 0.600 | 10.36 |
| Fitzgerald | 2007 | 5.0 | 17/45 | 0.378 | 0.249 | 0.526 | 10.29 |
| Golomb | 2007a | 17.0 | 41/61 | 0.672 | 0.546 | 0.778 | 10.50 |
| Van Buuren | 2013 | 14.0 | 7/29 | 0.241 | 0.120 | 0.427 | 9.42 |
| Gold | 2014 | - | 15/27 | 0.556 | 0.369 | 0.728 | 9.76 |
| Grunt | 2015 | 11.0 | 7/74 | 0.095 | 0.046 | 0.185 | 9.69 |
| Chabrier | 2016 | 3.0 | 12/80 | 0.150 | 0.087 | 0.246 | 10.25 |
| Billinghurst | 2017 | 8.8 | 25/113 | 0.221 | 0.154 | 0.307 | 10.75 |
| Fox | 2017 | 1.5 | 3/28 | 0.107 | 0.035 | 0.284 | 8.07 |
| de Veber | 2017 | 16.0 | 32/230 | 0.139 | 0.100 | 0.190 | 10.92 |
| Total | | | 180/733 | 0.272 | 0.166 | 0.414 | 100.0 |

**TABLE 3.** Factors Associated with Epilepsy Development Secondary to PAIS

| Author | Study Year | Study Duration | Study Design | Study Scale | PAIS Cases | Epilepsy Cases | Major Findings | Significance | Limitations & Considerations |
|---|---|---|---|---|---|---|---|---|---|
| History, Presentation, and Prognosis | | | | | | | | | |
| Fitzgerald et al. | 2007 | 5 | Retrospective | SC | 45 | 17 | Initial presentation with seizures (RR = 3.2) | Significant | 15/17 children with epilepsy were on medication at last follow-up |
| | | | | | | | Cognitive impairment | Significant | |
| | | | | | | | CP association to epilepsy | NA | |
| Fox et al. | 2016 | 14 | Retrospective | MC | 87 | 24 | Neonatal seizures associated with epilepsy later in childhood (HR = 2.6) | Significant | Stroke registry; clinical presentation consistent with stroke such as hemiparesis, encephalopathy, or seizures; active epilepsy at last follow-up (median 7.1 yrs) |
| Golomb et al. | 2007a | 17 | Retrospective | SC | 61 | 41 | Family history of epilepsy associated with time to seizure $>6$ mo | Significant | Univariate and multivariate showed different significances; only univariate analysis log-rank test of time to seizure $\geq 6$ mos was reported |
| | | | | | | | Initial presentation with seizures | NA | |
| Golomb et al. | 2007b | 17 | Retrospective | SC | 111 | 47 | In acute PAIS, CP associated with epilepsy | Significant | 1° objective: cerebral palsy as an outcome; perinatal stroke registry |
| | | | | | | | Neonatal presentation and Caesarean section associated with epilepsy development in CP patients | Significant | |
| | | | | | | | Tri/Quadripleglic CP associated with epilepsy or cognitive impairment (OR of 9.18) | Significant | |
| Wusthoff et al. | 2011 | 5 | Retrospective | SC | 46 | 6 | Initial presentation with seizures | NA | Factors associated also included 5 patients who had single seizure episodes in analysis |
| Gold et al. | 2014 | - | Retrospective | MC | 27 | 15 | Hippocampal volume reduction | Significant | 1° study outcome: hippocampal volume and memory performance post-neonatal strokes; no clear definition of seizures |

(*continued on next page*)

**TABLE 3** (*Continued*)

| Author | Study Year | Study Duration | Study Design | Study Scale | PAIS Cases | Epilepsy Cases | Major Findings | Significance | Limitations & Considerations |
|---|---|---|---|---|---|---|---|---|---|
| Vascular Distribution, Location, and Size of Infarct at Presentation | | | | | | | | | |
| Ballantyne et al. | 2007 | 10 | Retrospective | SC | 28 | 11 | Relationship between seizure status and lesion severity (single versus multilobe) | NA | 1° study outcome: language post-stroke |
| Fitzgerald et al. | 2007 | 5 | Retrospective | SC | 45 | 17 | MCA infarction | NA | See above |
| | | | | | | | Large-branch MCA infarction | NA | |
| Gold et al. | 2014 | - | Retrospective | MC | 27 | 15 | Lesion severity and presence of seizures | NA | Bilateral lesions were excluded; no clear definition of seizures |
| Golomb et al. | 2007a | 17 | Retrospective | SC | 61 | 41 | Infarct on prenatal ultrasonography associated with time to seizure $>6$ mo | Significant | See above |
| | | | | | | | Presence of bilateral infarcts | NA | |
| | | | | | | | MCA infarction in large branch | NA | |
| Wusthoff et al. | 2011 | 5 | Retrospective | SC | 46 | 6 | modASPECT score $\geq 9$ increased incidence of seizures by 6.2 times when compared to lower score group | Significant | Factors associated also included 5 patients who had single seizure episodes in analysis |
| | | | | | | | Bilateral versus unilateral involvement | NA | |
| EEG Findings at Presentation | | | | | | | | | |
| Fitzgerald et al. | 2007 | 5 | Retrospective | SC | 45 | 17 | Initial abnormal EEG | NA | See above |
| Golomb et al. | 2007a | 17 | Retrospective | SC | 61 | 41 | Abnormal neonatal ICU EEG | NA | See above |

Abbreviations
CP = Cerebral Palsy
EEG = Electroencephalogram
HR = Hazard Ratio
ICU = Intensive Care Unit
MC = Multicenter
MCA = Middle Cerebral Artery
mos = months
modASPECT = modified Alberta Stroke Program Early Computed Tomography score
NA = No association to epilepsy development or recurring seizures; not significant
OR = Odds Ratio
PAIS = Perinatal Arterial Ischemic Stroke
RR = Relative Risk
SC = Single-center
yrs = years

prenatal infarct.[9] A lesion size score of greater than or equal to nine on the modified Alberta Stroke Program Early Computed Tomography (modASPECT) was also positively predictive of a higher seizure frequency when compared to a group with lower scores.[8] Of note, Fitzgerald et al. observed that size and location of the infarct were not associated with epilepsy development.[23] Several studies have reported no correlation between epilepsy risk and lesion severity,[21,26] or the presence of bilateral infarcts.[8,9]

*Electroencephalography factors*

Studies on electroencephalography (EEG) indicators of future epilepsy secondary to PAIS are sparse. Two articles included in this meta-analysis reported that initial abnormalities on EEG were not associated with epilepsy.[9,23]

## Discussion

We aimed to review the incidence and risk factors of epilepsy development after PAIS. In this review, the summary incidence of epilepsy after PAIS was 27.2% at a mean duration of 10.4 years (range 1.5 to 17), and 7 possible risk factors for epilepsy following PAIS were identified (Table 3). In comparison to the included 10 studies, the highest incidence was reported by Golomb et al. who reported that 67.2% of PAIS patients developed epilepsy across a study duration of 17 years with at least six months of follow-up (median age at last follow-up: 43 months, range 9 to 179 months).[9] The lowest value was reported almost a decade later by Grunt et al., noting that 9.5% of PAIS patients developed epilepsy across an 11-year study duration (mean follow-up of 23.3 months).[16]

In a meta-regression analysis, we also noted a negative correlation between study year and epilepsy frequency, i.e., the frequency of epilepsy was lower in more recent studies. While this may be coincidental, one possibility may be that the detection of arterial ischemic strokes has increased secondary to a more heightened level of suspicion or pretest probability, subsequently increasing the sample size of PAIS patients. Further investigation may be warranted to assess whether improvement in and increasing use of technology have impacted the sensitivity or specificity of diagnosing epilepsy.[33] For instance, in earlier studies such as Sreenan et al. epilepsy was diagnosed clinically on patient history and physical findings.[14] On the other hand, more recent studies such as Suppiej et al. and Laugeaar et al. technological adjuncts, such as EEG, were used to aid with diagnosis.[15,34]

In a subsequent meta-regression of incidence versus study duration, a significant positive trend was observed between increasing duration and an increased incidence of epilepsy. This observation could be interpreted as a corroboration of previous findings suggesting longer study duration or follow-up length generally allowed for the identification of delayed and/or late onset of seizures.[8,29,35–37] When compared to the 10.4 year study duration of our meta-analysis, Fox et al. (excluded from the meta-analysis due to overlapping cohort) reported that 24 of the 87 children who developed active epilepsy secondary to PAIS were on anticonvulsant maintenance treatment, reporting a ten-year cumulative incidence of 40% (CI 27% to 55%).[24] On the other hand, a single-center study by Billinghurst et al. reported that by two years, cumulative incidence of epilepsy was 11% and 19% in the acute and presumed PAIS cohorts, respectively.[29] Despite differences in study duration, the CI associated with our incidence estimate included Fox et al.'s estimate of 40%, but only included Billinghurst et al.'s presumed PAIS value. Thus, study duration arguably accounted for the partial variability in epilepsy frequency over time in addition to the aforementioned variations in diagnostic methods and increased suspicion for stroke.

Of the seven possible factors associated with risk of developing epilepsy, two were radiographic (hippocampal volume, ModASPECT) while the remaining were clinical risk factors. The weakest evidence existed for the clinical finding of seizures initially presenting at birth. This finding was both positively and negatively associated with later onset of epilepsy.[8,9,15,23,24] While seizures at presentation have been largely considered a marker of acute brain injury in the setting of PAIS,[24,34] their role in the development of epilepsy remains unclear.

Evaluating the strength of associated factors in context of the study's inclusion and/or exclusion criteria, sample size, and design is important. For example, hippocampal volume reduction as a risk factor was based on a PAIS sample size of 27 (smallest study analyzed),[26] while CP as correlative factor was based on 111 PAIS patients.[27] While the studies considered herein cumulatively provide the best available data to clinicians for prognostication, we admire the ongoing efforts of others to identify stronger correlations between and risk factors associated with PAIS and poststroke epilepsy.[15,38]

While there has been debate about the role of stroke size and location in determining future epilepsy risk, three recent studies have supported the importance of stroke size. Wusthoff et al. found that a high modASPECT score (corresponding to large stroke size) was correlated with increased risk of developing epilepsy.[8] Trauner et al., including both hemorrhagic and ischemic stroke patients, also reported size to be a risk factor.[39] A recent study on various vascular stroke subtypes also found an association between large lesions involving multiple lobes and an increased risk for the development of epilepsy.[15]

Stroke location as a factor remains unresolved. Fitzgerald et al. and Golomb et al. found no significant association between MCA involvement in PAIS and subsequent increased risk for epilepsy.[9,23] Similarly, Trauner et al. noted no significance of location and epilepsy risk.[39] However, in a study by Suppej et al. that only included symptomatic PAIS patients presenting with acute seizures in the neonatal period, increased epilepsy risk was found to be associated with involvement of the right MCA and multiple infarcts.[34] Kirton et al. included both arterial and venous ischemic strokes and noted cortical involvement as a predictor of epilepsy.[10] Recent work also suggested stroke location including the cerebral peduncle as a factor in the frequency of poststroke epilepsy.[38] Left-sided strokes, cortical involvement, and the involvement

of the thalamus, and/or parietal and temporal lobes have also been recently implicated in increasing epilepsy risk.[15] Finally, single versus multilobe involvement as an independent variable does not seem to increase epilepsy risk,[21] nor do findings of bilateral lesions.[8,9,26]

EEG results following PAIS were not a predictor of epilepsy risk. However, EEG activity may be a useful predictor in older children. Specifically, in patients less than 18 years of age with a history of stroke (including neonates), abnormal slowing on acute EEG was associated with a 10-fold increased risk for active epilepsy.[25]

A major limitation of this review is the size and heterogeneity of included studies. Studies were small and retrospective with variability in: study duration, follow-up length, focus on epilepsy predictors, measures of features (e.g., infarct volume and/or size), and diagnosis of epilepsy. Of note, only three of 10 included studies had sample sizes of 80 or greater participants.[22,29,30] Further studies would ideally be large prospective perinatal stroke studies primarily reporting epilepsy incidence. Additionally, strict adherence to diagnostic definitions established by the National Institute of Neurological Disorders and Stroke[3] or other similar institutions[40] is recommended for generalizability.

More research with clear diagnostic criteria and larger sample sizes is required to improve the estimation of epilepsy risk in children with PAIS. Nonetheless, this work represents the first study to aggregate the best available data to accurately calculate epilepsy incidence secondary to PAIS and also provide clinicians with contextualized factors associated with epilepsy risk to better inform their management and family counseling. As more studies are published,[15,38] larger sample sizes may allow further meta-analysis toward a better incidence estimate of epilepsy secondary to PAIS and increased understanding of associated risk factors.

## Conclusions

We report an incidence of epilepsy following PAIS of 27.2% (95% CI 16.6% to 41.4%) at a mean duration of 10.4 years (range 1.5 to 17) and identified seven possible risk factors worthy of consideration when evaluating risk of epilepsy onset. Further studies are warranted to evaluate the strength of these potential risk factors.

## Author Contributions

Mr. Rattani conceptualized and designed the study, acquired data, carried out the initial data analysis and interpretation, drafted the initial manuscript, critically reviewed and revised the manuscript for important intellectual content.

Dr. Mistry designed the study, performed the meta-analysis, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content.

Dr. Lim, Dr. Prablek, and Dr. Roth acquired data, and critically reviewed and revised the manuscript for important intellectual content.

Dr. Jordan substantially contributed to the analysis and interpretation of data, and critically reviewed and revised the manuscript for important intellectual content.

Dr. Shannon and Dr. Naftel conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content.

All authors approved of the final version of the manuscript and report no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pediatrneurol.2018.08.025.

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