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1. Review article

Calcified epidural hematoma after conservative treatment of acute epidural hematoma in the pediatric population: A systematic review

Short title: calcified epidural hematoma after conservative treatment of acute epidural hematoma.

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Abstract

Background: Acute traumatic epidural hematoma (EDH) is a complication in 2–3% of pediatric head injuries. Surgery is mandatory in symptomatic cases; otherwise, conservative treatment is a valid approach, especially in the pediatric population. Ossified epidural hematomas (OEHs) have been reported in the pediatric population as a rare complication of conservative EDH management, although the exact incidence remains unknown. The progressive increase in conservative management may lead to increases in OEH incidence over the next few years. Our study aimed to systematically review OEH incidence, management strategies, characteristics (thickness, inner/outer calcifications), complication rates, time to surgery after the EDH diagnosis, and clinical outcomes.
Summary: A systematic review was conducted in accordance with the PRISMA guidelines. Papers reporting diagnoses and clear descriptions of OEH after EDH in pediatric patients were considered eligible. Sixteen studies, including 18 pediatric patients aged 0–18 years, were included. Head trauma was the most common cause of OEH. Seven (38.8%) OEHs were treated less than 1 month after EDH diagnosis. Surgery was performed in 17 cases (94.44%), while 1 asymptomatic case (5.56%) was managed conservatively.
Key Messages: Surgery was the most commonly used treatment for OEH. Data for conservative treatment of OEH are limited. Magnetic resonance imaging or ultrasound within the first 2 months, to check for EDH resolution, may be crucial to rule out complications in pediatric patients.

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Introduction

Acute traumatic epidural hematoma (EDH) is a complication in 2–3% of pediatric head injuries [1,2]. Surgery is mandatory if symptomatic; otherwise, conservative treatment is a valid approach, especially in the pediatric population. Nevertheless, early surgical intervention has been advocated to prevent subsequent clinical deterioration in asymptomatic patients [1–9]. Ossified epidural hematomas (OEHs) have been reported as a rare complication of conservative management of EDH, although the exact incidence remains unknown [10–19]. Therefore, we performed a systematic review of the literature to shed light on OEH management, treatment options, characteristics (thickness of inner/outer calcifications), complication rates, time to surgery after EDH diagnosis, and clinical outcomes.

Study design

This systematic literature review was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Figure). Three different medical databases (PubMed-Medline, Cochrane library, and Embase) were searched, using "Ossified epidural hematoma", "calcified epidural hematoma", "calcification", "ossification", "children", and "conservative management" as keywords in combination with Boolean operators. The last search was conducted in December 2020.
Inclusion criteria: English-language papers that included pediatric participants (0–18 years old), a clear diagnosis and description of OEH, clinical and demographic data of the included patients, and descriptions of the treatments were eligible for the review.
Exclusion criteria: Studies with incomplete data on clinical symptoms, demographics, radiological features of OEH, and treatments used were excluded, along with editorials, reviews, and commentaries. The considered papers were cross-referenced (forward search) to allow inclusion of papers that were not detected during the initial search.

Methods

Demographic data (sex and age), preoperative and postoperative OEH-related symptoms (headache, intracranial hypertension, seizure, and loss of consciousness), radiological and anatomical locations of the OEHs, history of previous trauma, surgery, or shunt procedures, progressive OEH thickening on follow-up radiographs, time to surgery, surgical techniques, and final clinical outcomes (improved, stable, or worsened) were recorded for all patients.

Results

Literature review

The first literature search yielded 46 articles (Fig. 1). After duplicate removal and title/abstract screening, 33 papers were considered for eligibility. A further 17 papers were excluded due to unclear outcomes, lack of radiological findings, or the inclusion of adult patients. Finally, 16 studies (including 18 pediatric patients) matching the inclusion criteria were included in the review (Table 1). The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of the included papers and risk of bias (Supplementary Table).

Demographic and clinical characteristics

The demographic characteristics of the OEH patients are summarized in Table 2.
Among the 18 patients, 9 (50%) were males and 9 (50%) were females, ranging in age from 27 days to 18 years (mean age = 10 years).

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The main etiologies of OEH were previous head trauma (n = 9; 50%), previous shunting (n = 4; 22.22%), and cranial surgery for tumor or arachnoid cyst (n = 3; 16.66%). One case had an unidentifiable cause, and in one case OEH was diagnosed after cesarean section in another. Among the selected articles, the duration of symptoms before OEH diagnosis ranged from 7 days to 3 years, with a mean of more than 9 months (278 days). Seven of the eighteen OEHs were treated less than 1 month after the trauma, tumor resection, or shunting that triggered EDH.
Computed tomography (CT) was the most common imaging modality used for OEH diagnosis; X-rays and magnetic resonance imaging (MRI) were used in one (5.55%) and three (16.65%) cases, respectively.
There were five (27.5%) parietal, four (22.2%) bifrontal, three (16.66%) frontal, and one (5.5%) temporal OEH, while in two cases (6.24%) the exact location of the OEH was not specified.
The most common clinical symptoms/signs at diagnosis were intracranial hypertension (papilledema, nausea, vomiting, and/or sensorium alterations; seven cases, 38.85%), headaches (four cases, 22.2%), and seizures (one case, 5.5%), while in three cases (16.65%) OEH was diagnosed incidentally during imaging for another issue (Table 2).
Anatomical characteristics of OEH were reported in 12 papers. In seven cases (54.85%), the calcification was predominantly located on the inner surface of OEH, while in 6 cases (46.15%) calcifications were present on both OEH surfaces. OEH was h histologically confirmed in all cases.
After radiological confirmation of OEH, surgical treatment (craniotomy or burr hole) was performed in 17 cases (94.44%), while 1 case (5.56%) was treated conservatively.
Among the 17 patients who underwent surgery, 15 recovered completely and the final outcome of 2 cases (11.11%) was not reported. One patient underwent conservative treatment and was asymptomatic at the last follow up.

DISCUSSION

To the best of our knowledge, this was the first systematic review of the clinical/radiological characteristics and clinical outcomes of pediatric OEH patients.
There has been a progressive increase in the number of EDH diagnoses in asymptomatic patients after minor trauma because of extensive use of CT [6–9]. When symptomatic, an emergent craniotomy and evacuation of the EDH are routinely performed, while asymptomatic patients are treated conservatively with serial clinical and radiological follow-up using CT or MRI [6–20].
EDHs in pediatric patients are unusual, accounting for less than 3% of pediatric hospitalizations for head trauma. The strong dura-skull fibrovascular attachments seen in pediatric patients weaken with age and growth, making toddlers (1–3 years old) more susceptible to EDHs compared to infants (< 1 year old) [20]. In a series of 35 traumatic pediatric EDHs by Rocchi et al., temporal EDHs were extremely rare because the middle meningeal artery in children is not strongly connected to the temporal bone [21]. The marked diploic and dural vascularization of skull bones seen in the pediatric population might explain the varied EDH locations and higher rate of venous hemorrhage reported in the literature. In combination, these two factors might play a fundamental role in slow EDH growth and minor symptoms, as 60% of children and 85% of infants with EDHs show no signs of deterioration at the time of injury and are frequently diagnosed with a chronic form. Conservative management of EDH in asymptomatic children relies on the above-mentioned pathophysiological mechanisms [13,21].
Balmer et al. (2006) reported a series of 13 asymptomatic EDHs (thickness range: 1–4 cm). Twelve of the patients were successfully managed conservatively, indicating the safety of conservative treatment in such cases. It was concluded that size alone is not an indication for surgical treatment [3]; Champagne et al. (2017) confirmed this in a series of 16 conservatively managed traumatic EDHs more than 15 mm thick, achieving an overall success rate of 88% [3,4].
Calcified and ossified EDHs after conservative treatment, and EDHs diagnosed as an incidental finding several years after trauma, have been reported, but the exact incidence is unknown, in the pediatric population due to the risks of imaging radiation exposure [10–12].
Due to the increasing interest in conservative management of EDH, we believe that the incidence of OEH may increase in the coming years.
The exact mechanism of EDH calcification, and the timing thereof, are still a matter of debate [13,22–39]. Ergodan et al. reported early signs of calcification around an EDH 10 days after the trauma, suggesting a role for the acute inflammatory response in EDH calcification [13,27]. The inner layer of the EDH, which is strongly connected to the dural surface, might represent the origin of active ossification [13]; Greenwald et al. in 2000 demonstrated the

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fundamental capacity of the immature dura to induce and regulate calvarial ossification [38]. Chang et al. suggested that the process of ossification starts within the periphery of the inner EDH surface and then proceeds towards the center; this hypothesis was based on the intraoperative presence of thicker calcifications near the dural peripheral borders of the EDH [25].

Our literature review revealed a lack of any established clinical-radiological follow-up protocol to detect calcifications of conservatively managed OEHs. Only three studies [27–28, 31] identified the early signs of OEH calcification during radiological follow-up, based on CT scans performed on the first day after EDH diagnosis, and then at 1 week and 1 month. The vast majority of cases had an acute OEH presentation, demonstrating the lack of effective radiological screening.

This review retrieved data on 18 pediatric patients. EOHs were most common in frontal and parietal locations, followed by a bifrontal location (4 cases); a temporal location was rare (1 case), confirming the results of Rocchi et al. [21].

The most common symptoms at diagnosis were headaches, intracranial hypertension, and seizures; these were seen in over 70% of the cases., and suggest that OEH compresses the underlying parenchyma (although three cases were completely asymptomatic) (Table 2).

Surgical treatment of OEH was preferred (94.44%); conservative treatment was performed in only 1 case (5.56%) [28]. Good clinical outcomes were reported in 15 patients treated surgically, while in 2 cases the final clinical outcomes were not reported.

Because of the increase in conservative management of EDHs, we recommend that conservatively managed EDHs be followed up via imaging studies until radiological resolution of EDH, as signs of EDH calcification (especially on the inner layer surface) have been reported just 7–10 days after trauma. In our series, calcified inner surfaces of OEHs were reported by several studies, suggesting its potential role in OEH detection.

According to our literature review, surgical management of OEH is the most common approach in symptomatic patients with persistent headaches and intracranial hypertension, as well as in asymptomatic cases (to avoid late complications such as seizures, which were reported in > 20% of cases). Notably, four patients had a previous history of shunting; malfunction of the shunting system must be carefully evaluated in these cases and a strict radiological follow up should be performed in order to avoid EDH recurrence after surgery.

To rule out any radiological risk, MRI or ultrasound may be preferable within the first 2 months due to the high rate of precocious inner layer calcifications, especially in the pediatric population.

This systematic review had several limitations. First, the available data were observational, nonrandomized, and non-comparative. Moreover, the data were collected retrospectively, and all of the included studies were case reports or retrospective short case series, due to the rarity of the phenomenon. Therefore, there is a risk of bias due to the poor quality of the available literature studies (over 60% of the included articles had NOS scores < 3). Larger series may be required for validation.

Conclusion

OEH is a rare complication of conservative EDH management in the pediatric population. Surgery is the most common treatment, but it is difficult to compare outcomes given the relative lack of patients. MRI or ultrasound within the first 2 months to confirm EDH resolution may be crucial to avoid such complications. CT scans could be reserved for doubtful cases, especially in the pediatric population. Given the increase in conservative management, the incidence of OEH may also increase in the coming years.

Statement of ethics

This paper was exempt from ethical committee approval as it was a systematic review of currently available literature.

Conflict of interest statement

The authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest.

Funding sources

No funding was received for this study.

Author contributions

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Marcello D'Andrea and Lorenzo Mongardi wrote the manuscript; Francesco Cultrera and Dalila Fuschillo conceived the study; Simone Peraio, Antonio Musio, and Paul Roblot performed the data analysis; and Luigino Tosatto, Flavio Giordano, and Paul Roblot were responsible for the overall direction and planning of the research. All authors provided critical feedback on the research plan, analysis, and manuscript.

Data availability statement

All data generated and analyzed during this study are included in the article. Further inquiries can be directed to the corresponding author.

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Fig. 1 Flow chart of study inclusion.

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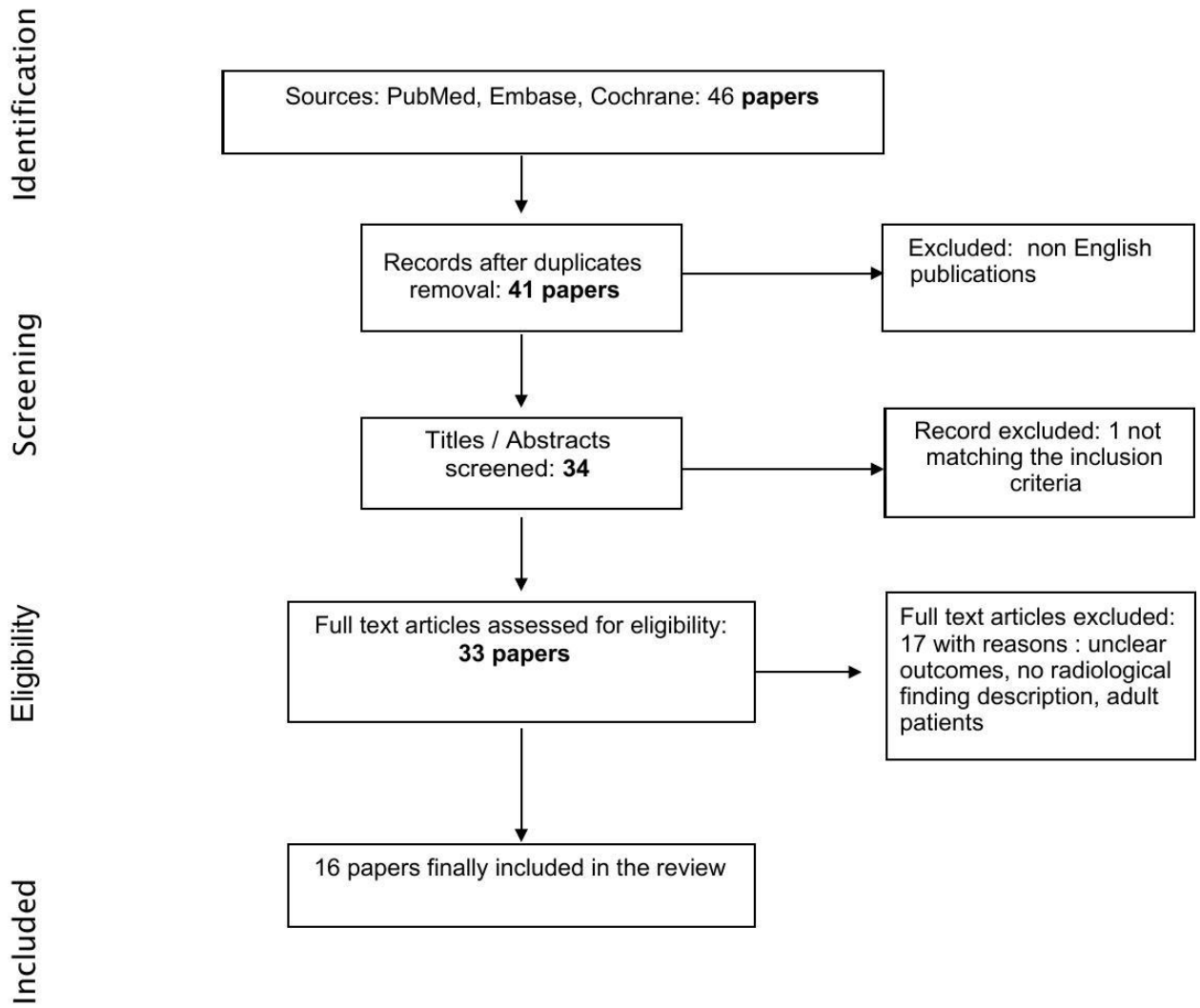
Identification
Screening
Eligibility
Included
Sources: PubMed, Embase, Cochrane: 46 papers
Records after duplicates removal: 41 papers
Excluded: non English publications
Titles / Abstracts screened: 34
Record excluded: 1 not matching the inclusion criteria
Full text articles assessed for eligibility: 33 papers
Full text articles excluded: 17 with reasons : unclear outcomes, no radiological finding description, adult patients
16 papers finally included in the review

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	N° of patients	M/F	Age	L/R	Location	X Rays	CT	MRI	Calcification inner border	Calcification outer border	Calcification both sides	Main cause of OEH	Progressive thickening Of OEH during Radiological follow up	Interval Of Between Cause and diagnosis	Presentation symtpoms	Treatment	Outcome (improved,stable, worsened)	Complications
Trivedi 2010 [22]	2	F	6y6m	L	parietal		x				x	Cerebellar astrocitoma resection	none	6m	headache	craniotomy	improved	none
		F	9y	bilat	bifrontale		x				x	trauma	none	5m	Intracranial hypertension symptoms	craniotomy	improved	none
Kotil 2006 [23]	1	M	6y	l	frontal		x					none	none	nn	none	craniotomy	improved	none
Kawata 1994 [24]	2	M	9y		nn		x					Trauma	None	4m	Unknown	Craniotomy	Unknown	Unknown
		M	12y		nn		x					trauma	none	12d	unknown	craniotomy	Unknown	unknown
Hee CHang 2002 [25]	1	F	13y	r	frontal		x		x			trauma	6 weeks	4w	Headache, nausea, vomit	craniotomy	improved	none
Erdogan 2003 [27]	1	M	8y	r	parietale		x		x			trauma	none	10d	Intracranial hypertension	craniotomy	improved	none
Kim 2014 [28]	1	M	5y	l	Temporoparietal		x		x			trauma	decreased	14d	none	conservative	improved	none
Yoshida 1985 [29]	1	M	14y	r	parietal	x	x				x	Shunt	none	3y	headache	craniotomy	improved	none
Pankaj 2013 [31]	1	M	18y	r	Fronto temporo parietal		x		x			trauma	none	20d	Intracranial hypertension	craniotomy	improved	none
Seyithanogiu 2010 [33]	1	F	17y	bilat	bifrontal		x	x			x	shunt	none	3y	headache	craniotomy	improved	none
Mishra 2014 [34]	1	M	18y	r	parietal		x					shunt	none	3m	Headache, altered sensorium	craniotomy	improved	none
Chao Hung 2015 [35]	1	F	8y	l	Fronto parietal		x		x			Asportation of tumor	none	6m	Seizure, disorientation	craniotomy	improved	none
Kumar 2014 [3]9	1	f	10y	r	temporal	x	x		x			Trauma	none	3y	Swelling	craniotomy	improved	none
Bayri 2009 [37]	1	F	3y	bilat	bifrontal		x	x			x	Asportation of craniopharyngioma and shunt	none	1om	none	craniotomy	improved	none
Oliveira 2008 [30]	1	m	12y	l	parietal		x		x			trauma	none	1m	Headache, nausea, vomit	craniotomy	improved	none
Clayborne 2015 [13]	1	F	2y	bilat	bifrontal		x				x	Masupialization of cyst	none	unspecified	Headache, calvarian deformity	Craniotomy	improved	none
Yu 2008 [36]	1	F	27days	r	frontal		x	x				Cesarian section	none	26days	Hypotonia, drowsiness	Burr hole	Improved	none

Tab.1: review of the Literature.

Tab 2: demographic characteristics of the OEH patients.

	Pediatric pupulation
Number of patients	18
Sex	9m; 9f
Laterality	Left 5 Right 7 Unknown 2 Bilateral 4
Diagnosis	Rx 1 Ct 18 Mri 3
Calcification	Inner border 7 Outer border 0 Both 6
Cause	Trauma 9 Surgery 3 Shunt 4 None 1 Others 1
Surgery vs conservative	Surgery 17 Conservative 1
Clinical presentation	Headache 4 Intracranial hypertension 7 None 3 Uwknown 2 Seizure 1 Others 1 Calvarian defects 1
Outcome	Improved 16 Stable 0 Worsened 0 Death 0 Unreported 2

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