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REVIEW ARTICLE

Pathophysiology of transient neurological deficit in patients with chronic subdural hematoma: A systematic review

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Patients with chronic subdural hematoma (CSDH) can have transient neurological deficits deficit (TND) mimicking transient ischemic attacks. The prevalence of TNDs in CSDH varies between 1%–24%, depending on TND definition. Despite this high prevalence the pathophysiology of TND in CSDH is not clear in many cases. In this systematic review, we aim to unravel the responsible mechanism. Pubmed and Embase were searched for all articles concerning the pathophysiology of TND as a presenting symptom in patients with CSDH. There were no publication date restrictions for the articles in the search. Two reviewers independently selected studies for inclusion and subsequently extracted the necessary data. Out of 316 identified references, 15 met the inclusion criteria. Several articles mentioned multiple pathophysiological mechanisms. One of the proposed etiologies of TND was epileptic activity, stated by three articles. In contrast, three different studies stated that seizures are unlikely to cause TND. Five papers suggested that obstruction of blood flow, caused by the hematoma or subsequent swelling, might be the cause. Six articles made no definite statement on the responsible pathophysiological mechanism of TND. Different mechanisms have been proposed to be the cause of TNDs in patients with CSDH. Based on this review, the exact pathophysiology of TND remains unclear. We suggest that future studies on this topic should incorporate MRI of the brain (with diffusion-weighted imaging) and EEG, to provide better insight into TND pathophysiology. The knowledge resulting from future studies might contribute to better understanding of TND and optimal treatment in CSDH.

KEYWORDS
chronic subdural hematoma, pathophysiology, systematic review, transient neurological deficits

1 | INTRODUCTION

Chronic subdural hematoma (CSDH) is a frequent neurological and neurosurgical disorder which is most often present in the elderly and patients who use antithrombotic medication.[1] CSDH is usually preceded by a (minor) head trauma, and the incidence can be as high as 48/100.000/year in patients older than 65 years.[2]

Classicly CSDH results in (progressive) signs and symptoms such as headache, hemiparesis, cognitive deficits, and gait disturbances.[1] Less reported symptoms comprise seizures and extrapiramidal symptoms.[3] CSDH may mimic (sub) acute neurological deterioration and can therefore be mistaken for an (ischemic) stroke.[4,5] CSDH can also mimic a transient ischemic attack (TIA) when it presents with a transient neurological deficit (TND).[3] The prevalence of TND in CSDH patients has been reported to vary from 1% to 24% and TND clinical features most often consist of speech and/or language disorders, hemiparesis or hemisensory deficit.[3,6–8] "Classic" (transient) symptoms of a seizure such as loss of consciousness and/or clonic movements are as a rule not regarded as TND in the literature.[9,10]

Episodes of TND have also been described in the light of transient tumor attacks, amyloid spells (or more recently transient focal neurological episodes) and transient neurological attacks, all with different hypotheses of underlying pathophysiology.[11–13] Since the pathophysiological mechanism of TND in CSDH is unclear, the optimal treatment of TND remains difficult. Better understanding of the pathophysiology may aid clinicians in the management of CSDH patients with TND. For instance, if TNDs are caused by epileptic activity, this might require treatment with anti-seizure medication (ASM). However, ASM treatment might not have beneficial effects in case of a different pathophysiology than epilepsy or cortical spreading depression. Furthermore, ASM might even cause side effects like cognitive deficits. From the literature, we know that not all TNDs disappear after (surgical) treatment.[14,15] This is another argument to study the precise pathophysiology of TND, as alternative treatment modalities might be indicated in those circumstances.

The aim of our review was to provide a better insight in the pathophysiological mechanism(s) responsible for TND in CSDH, which consequently might contribute to more focused treatment of TND in CSDH and a better outcome for patients.

2 | METHODS

A literature search was performed by searching Pubmed and Embase for all articles considering transient symptoms in patients with CSDH. This systematic review was conducted following the PRISMA rules. For the exact search terms, see Table 1. The search was last updated on January 1, 2022, and went as far back as data was available. Studies were included in full text reviewing if they: (1). Studied patients with CSDH, (2). Focused on TND as a presenting sign/symptom (pre-treatment), (3). Reported on possible pathophysiological mechanisms for the TND, and (4). Were written in English or Dutch. All transient neurological symptoms were included, including seizure-like symptoms such as clonic movement and loss of consciousness. Articles only reporting on headache, nausea and/or vomiting as TND were excluded, as fluctuation of these symptoms cannot be determined objectively. Also, articles were excluded if CSDH was not confirmed by intra-operative findings or imaging with CT and/or MRI.

2.1 | Review process

Abstracts and titles of all articles identified through the database searches were independently screened by two reviewers (JB and JvZ), blinded to the authors and journal titles. If needed, the articles were discussed with one of the senior authors (BJ). Articles were excluded if they did not meet inclusion criteria. Articles without abstracts were automatically passed into the full text-screening phase. After title and abstract screening, the full text of all remaining articles was studied and the studies meeting the inclusion criteria for this review were selected. The references of included articles were scrutinized for additional relevant articles.

2.2 | Data extraction

The following data were retrieved from the included articles: number of patients with TND, together with their age and sex, localization of the CSDH, treatment modality, effect of treatment, EEG characteristics, type of neurological signs/ symptoms, duration of each TND episode, and the number of episodes. Finally, we extracted the

TABLE 1 Search terms for literature search in PubMed and Embase

PubMed	Embase
"Hematoma, Subdural, Chronic"[Mesh] OR ("Hematoma, Subdural"[Mesh:NoExp] AND chronic*[tw]) OR csdh[tiab] OR (chronic*[tiab] AND (subdural-hematoma*[tiab] OR subdural-haematoma*[tiab] OR extra-axial-hematoma*[tiab] OR extraaxial-hematoma*[tiab] OR extra-axial-hemorrhage*[tiab] OR extra-axial-haemorrhage*[tiab] OR extraaxial-hemorrhage*[tiab])) OR subdural-bleed*[tiab] OR subdural-hemorrhage*[tiab] OR subdural-haemorrhag*[tiab]) AND (transient[tiab] OR intermitt*[tiab] OR passing[tiab] OR temporar*[tiab])	(('subdural hematoma'/exp AND chronic*:ab,ti,kw) OR csdh:ab,ti,kw OR (chronic* NEXT/3 (subdural OR extraaxial OR 'extra-axial') NEXT/3 (hematoma* OR haematoma*)):ab,ti,kw OR ((subdural OR extraaxial OR 'extra-axial') NEXT/3 (bleed* OR hemorrhag* OR haemorrhag*)):ab,ti,kw) AND (transient OR intermitt* OR passing OR temporar*):ab,ti,kw

(postulated) pathophysiological mechanism(s) stated in the article and grouped them accordingly. If multiple mechanisms were noted, all different mechanisms were scored. If an article mentioned a most likely or unlikely mechanism, this was also registered.

2.3 | Citation network

When conducting the review, it was found that the included articles frequently cited one another on the assumed pathophysiological processes, sometimes without referring to the primary or original article. To assess and visualize overlapping citations, a citation network analysis was conducted using the "igraph" package of R.

3 | RESULTS

The online search of databases identified 457 studies of which 320 remained after removal of duplicates (Figure 1). An additional ten studies were identified by examining the references of the included studies resulting in a total of 330. After screening of abstracts and titles, 249 studies were excluded. The full texts of the remaining 81 studies were studied, after which another 63 were excluded. Of three studies, no full text but only abstracts or scientific meeting notes were available. Also after repeated requests from library to the interlibrary loan system, full texts could not be retrieved. Finally, 15 studies met all inclusion criteria. In these 15 studies, a total of 34 CSDH patients with TND were reported (Table 2).

3.1 | Demographics and clinical features of patients in the included studies

Of the 34 included patients, 25 (74%) were male, with a mean age of 70 years (±12.9 SD) (Table 3). Aphasia/dysphasia and weakness/hemiparesis were the most common transient symptoms, present in 21 and 20 patients (62% and 59%), respectively. Hypesthesia was reported in 15 patients (44%) and paresthesia in 5 patients (15%). Although we did not exclude classic seizure symptoms, such as loss of consciousness or clonic movements, there were no articles including these symptoms.

The median duration of an episode was 30 min (range 1–120 min), and patients experienced a median of five episodes (range 1–35). In four patients, an EEG was performed. All four EEGs showed non-specific possible (post)ictal abnormalities. Specific epileptic EEG findings such as spikes or sharp waves were not present on any of the EEGs. The majority of patients had a left-sided hematoma (25%, 74%), four patients a right sided hematoma (12%) and five a bilateral hematoma (15%).

3.2 | Treatment modality and effect of treatment

A total of 33 of the included 34 patients were treated surgically (Table 2). In one patient, antithrombotic drugs were discontinued, and close observation was performed. Of the surgically treated patients (n = 33), one patient received ASM treatment. Two patients were treated with agents to decrease edema (mannitol, dexamethasone). One patient was initially treated with antiplatelet medication because of the suspicion of a TIA. After CT showed a CSDH in that patient, the antiplatelet medication was discontinued, and surgery was performed. After treatment, 29 patients (85%) had no further TND episodes (Table 3).

3.3 | Proposed etiology

All included articles discussed pathophysiological considerations for the occurrence of TND. We grouped the postulated mechanisms in the included papers into four possible mechanisms:

3.3.1 | Epileptic activity

The hematoma acts as an irritative lesion producing (focal) epileptic discharges. The neurological deficit should then be considered as postictal cortical suppression or an active (focal) seizure.[16]

3.3.2 | Obstruction of blood flow

The mechanical pressure of the CSDH could compress the surrounding vessels, leading to an impairment of blood flow and eventually cerebral ischemia. The intermittent nature of the symptoms could be explained by differences in head position or performance of the Valsalva maneuver, as a result of changes in intracranial pressure. On turn, these changes in intracranial pressure can influence the degree of blood flow impairment.[16,17]

3.3.3 | Cortical (spreading) depression

Mechanical stimulation of the cortex as a result of a cerebral mass lesion could lead to a depression of spontaneous electrical activity over the cortex.[18] In turn, the cortex becomes (temporarily) unexcitable to electrical stimulation, causing TND.[16]

3.3.4 | Repeated hemorrhaging

Repeated hemorrhaging in the subdural space. This pathophysiological mechanism was suggested in an article reporting that repeated hemorrhage comprises about 10% of the total hematoma volume in CSDH. However, no explanation how this results in TND is given.[19]

Some articles reported on multiple mechanisms, and in several cases listed different unlikely causes, rendering the total mentioned pathophysiological mechanisms higher than 15. Six articles mentioned all the aforementioned mechanisms, but gave no opinion about the

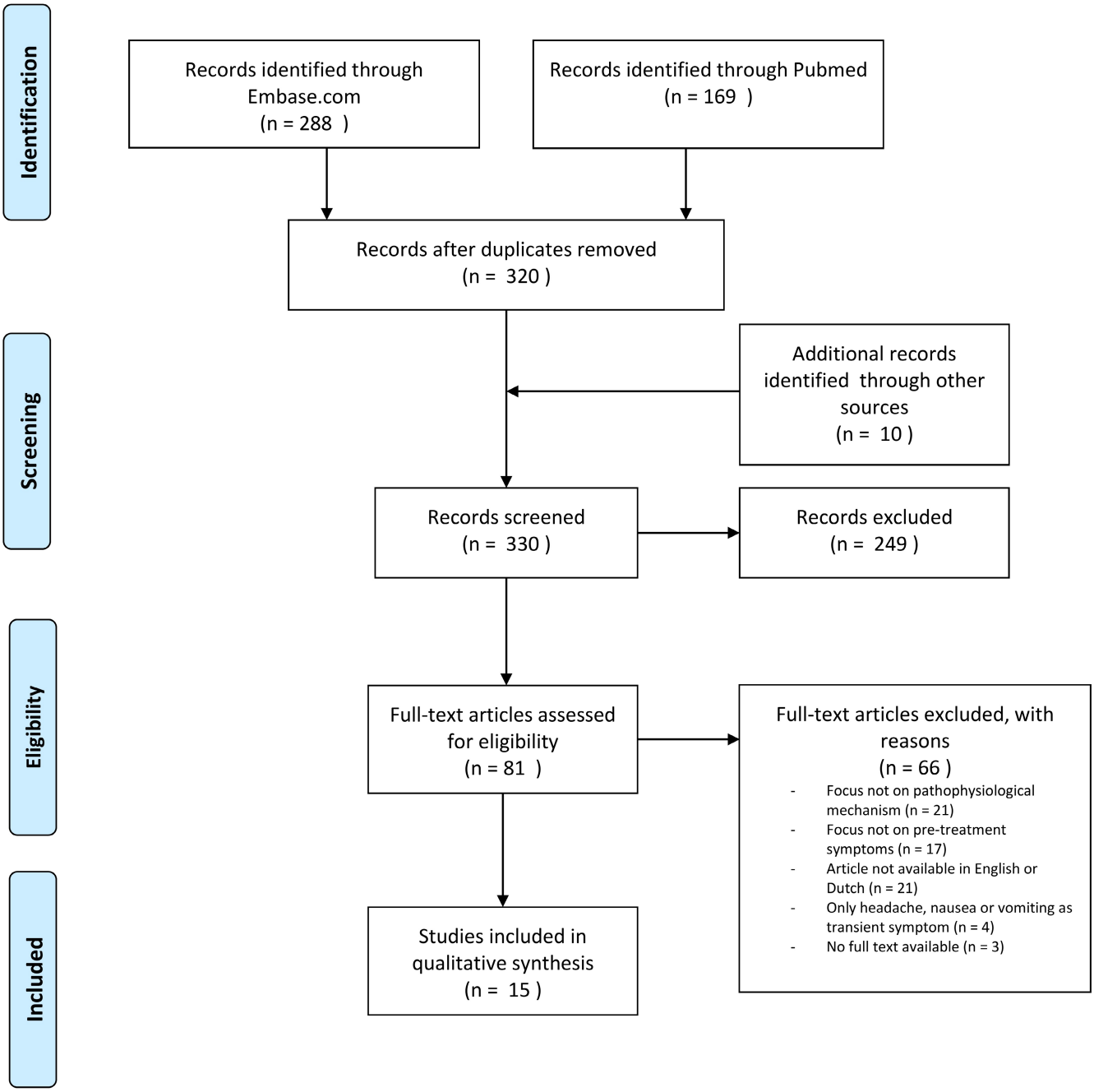

FIGURE 1 Flowchart of the literature search

most likely one (Table 2).[16,20–24] Three articles stated that epileptic activity might be the cause of the TNDs in CSDH patients.[15,25,26] However, three other articles suggested that the TNDs were not caused by epileptic activity at least in their patients because of the absence of epileptic characteristics on EEG.[7,14,27] Obstruction of blood flow was named in five articles, with different hypotheses.[17,25,27–29] The authors of two papers postulated temporarily increased parenchymal swelling, or edema, resulting in reduced cerebral blood flow (CBF) as the most plausible etiology for TND.[27,29] One article suggested intermittent mechanical pressure causing CBF impairment, as a result of failing vascular tonus.[28] Another article focused on the role of decreased CBF but did not provide an explanation for the decreased CBF.[17]One article suggested that focal compression of an entire cerebral region (not only the arteries) leading to cortical dysfunction to be a possible cause.[25] Finally, cortical spreading depression is considered a possible cause for TND in the discussion of one article without correlation to a patient.[16]

3.4 | Citation network

The assessment of the references in the included articles showed that most articles refer to either Melamed et al.[16] (ten in total), McLaurin[30] (six in total), or Moster et al.[7] (five in total) for the pathophysiological process (Figure 2). Melamed et al. based their pathophysiological

TABLE 2 Characteristics of the 15 studies included in our literature review

Author	Included patients (total $n = 34$)	Transient neurological deficit symptoms	Proposed pathophysiological mechanism	Treatment
Melamed (1975)[16]	1	Paresthesia, aphasia	Mentions different mechanisms but no statement about the most likely one	Surgical evacuation
Williams (1979)[15]	1	Aphasia, hemiparesis, paresthesia	Epileptic activity	Surgical evacuation
Welsh (1979)[17]	4	Weakness (2), dysphasia (4), paresthesia (1)	Mentions different mechanisms, with the most attention for decreased CBF	Surgical evacuation
Herskowitz (1982)[26]	1	Dysphasia	Epileptic activity or focal compression of a cerebral region	Surgical evacuation
Hilt (1982)[27]	1	Paresthesia	Epileptic activity	Surgical evacuation +ASM
Russell (1982)[21]	1	Weakness, hypoesthesia	Mentions different mechanisms but no statement about the most likely one	Surgical evacuation
Moster (1983)[7]	15	Aphasia (9), weakness (8), hypoesthesia (8), dysarthria (3), visual loss (1)	Mentions different mechanisms but no statement about the most likely one, however epileptic activity is stated to be unlikely	Surgical evacuation
Russell (1985)[22]	1	Weakness, hypoesthesia, dysarthria, ataxia	Mentions different mechanisms but no statement about the most likely one	Initially antiplatelet medication because of the suspicion of TIA, later surgical evacuation
Lazzarino (1989)[28]	1	Weakness, aphasia	Temporarily increased parenchymal swelling most likely cause. Epileptic activity unlikely	Mannitol and surgical evacuation
Kaminski (1992)[14]	3	Aphasia (2), weakness (2), hypoesthesia (2), ataxia (1)	Mentions different mechanisms, but no statement about the most likely one, however epileptic activity is stated to be unlikely	Surgical evacuation
Root (1993)[29]	1	Weakness, hypoesthesia, paresthesia	Intermittent mechanical pressure causing impairment of cerebral blood flow	DXM +surgical evacuation
Mishriki (1999)[30]	1	Aphasia, weakness, hypoesthesia	Mentions different mechanisms. Impairment of CBF due to temporarily increased parenchymal swelling most likely	Surgical evacuation
Khealani (1999)[23]	1	Weakness, hypoesthesia, dysarthria	Mentions different mechanisms, but no statement about the most likely one	Surgical evacuation
Guptha (2001)[24]	1	Weakness	Mentions different mechanisms, but no statement about the most likely one	Surgical evacuation
Coutts (2003)[25]	1	Weakness, dysphasia	Mentions different mechanisms, but no statement about the most likely one	Observation and cessation of antithrombotic agents

Abbreviations: ASM(s), anti-seizure medication(s); CBF, cerebral blood flow; DXM, dexamethasone; TIA, transient ischemic attack.

considerations on previous findings in the literature, but did not always provide a literature reference. Moster et al. based their findings on a single patient in which the symptoms disappeared after verticalization, inducing the idea that cerebral pressure is related to TND in CSDH. Their statement that epileptic activity is unlikely is supported by the observed length of the episodes and the absence of Jacksonian symptoms. No EEG examination was performed to support their hypothesis.

Remarkably, McLaurin et al.[31] did not report on any patients with TND but refer to an article by Browder and Rabiner. In this article, the authors investigate brain swelling in a postmortem study of 600 patients with subdural hematomas. However, it was not reported which patients had an acute or chronic subdural hematoma. In addition, regarding TND they did not provide prevalence figures. They proposed that transient symptoms could be caused by systemic dehydration and that the hematoma would decrease in size as a result of the patient not being able to eat or drink caused by the neurological symptoms of the CSDH. After resolution of the symptoms caused by dehydration, consecutive eating and drinking would allow the hematoma to grow again.

TABLE 3 Clinical characteristics of transient neurologic deficits (TND) in patients with CSDH included in the literature search

Variable	*n* (%)
Sex (male)	25 (74)
Age (years ± SD)	70 (±12.9)
Type of Transient Neurological Deficit (TND)	
Aphasia/ dysphasia	21 (62)
Weakness/ hemiparesis	20 (61)
Dysarthria	5 (15)
Sensory - Hypoesthesia	15 (45)
Sensory - Paresthesia	5 (14)
Ataxia	2 (6)
Visual loss	1 (3)
Location of CSDH	
Left	25 (74)
Right	4 (12)
Bilateral	5 (15)
Duration in minutes, median (range)	30 (1–120)
Number of episodes, median (range)	5 (1–35)
Findings on EEG ($n = 4$)	
Delta waves	2 (50)
Slowing abnormalities	2 (50)
Symptoms permanently improved after treatment	29 (85)

Abbreviation: SD, standard deviation.

The citation network visualizes that most articles refer to one another, and ultimately, the gathered pathophysiological evidence relies on the findings of three studies (from 1965, 1975, and 1983) that did not provide objectively substantiated evidence for their own findings.

4 | DISCUSSION

Our systematic review demonstrates that there are different hypotheses on the pathophysiological mechanism of TND in patients with CSDH. Most included articles mentioned several mechanisms but made no decisive statement about the most plausible etiology in their patients. Furthermore, the articles that did provide a hypothesis often failed to support it with diagnostic methods, such as EEG or MRI. Also, most included articles in this review were fairly outdated, being published in 1970–1990. A limited number of studies reporting on the pathophysiology of TND in CSDH have been published since then. Nevertheless, given the recent renewed interest on this topic and the importance of understanding the pathophysiology of TND to ensure optimal patient care, it remains a relevant topic in CSDH care.[32,33]

4.1 | Epileptic activity

In the papers included in our review, epileptic activity was an often-stated cause of TND, classified as the responsible mechanism in three articles. Nevertheless, none of the included articles present EEG findings that confirmed this hypothesis. The only EEG abnormalities that are reported show non-specific prominent delta activity and/or low voltage slow activity.[25,26] However, the absence of epileptic activity on EEG does not rule out epilepsy, as the diagnosis heavily depends on timing of EEG examination.[34] Furthermore, these articles[25,26] describe patients with transient paresthesia, which consequently would have to be interpreted as somatosensory seizures causing the TND. However, somatosensory seizures in general are most often caused by the presence of intraparenchymal tumors.[35] Also, the duration of the TNDs in the patients included in our review (median of 30 min) were much longer than the average focal seizure time (longest mean duration of 2 min), also making a (focal) epileptic origin less likely.[36] An epileptic origin is also thought to be unlikely because the TNDs rarely progress to generalized seizures. The low number of patients ($n = 4$) with EEG examination and the absence of typical epileptic activity on these EEGs combined with the timing of EEG in these patients (after the episode) do not provide sufficient information for an underlying pathophysiological explanation. To provide more insight in this matter, future studies should perform EEG examination in all CSDH patients with TND. An EEG could also aid clinicians in management of TND, regarding whether to start ASM treatment or not.

4.2 | Obstruction of blood flow

Next to epilepsy, several causes of obstructed blood flow were provided as the pathophysiological mechanism for TND. In one article, a temporarily decreased local CBF as a result of parenchymal swelling was mentioned as a pathophysiological mechanism for TND.[27] One of the reasons for this hypothesis is the improvement of TNDs after administration of edema decreasing agents, like mannitol. Transient symptoms could then be explained by temporary decrease of the edema/ swelling caused by (relative) dehydration.[31] A second article supporting this hypothesis has shown that the neurological symptoms of CSDH can be caused by regional cerebral edema, visualized by carotid arteriography.[30] The authors reported that the swelling, measured by the location of the anterior cerebral artery, leads to a displacement of arteries although the extent of displacement does not correlate with clinical severity of the TND. Temporary increase of mechanical pressure caused by the hematoma itself on the neighboring cerebral vessels might also cause impairment of CBF. It is suggested that TND could represent plateau waves or acute loss of local cerebral autoregulatory vascular tone.[28] Autoregulatory vascular tone is the autonomous ability of the brain to maintain and/or adjust perfusion pressure.[37] As a result of loss of autoregulatory tone, cerebral perfusion pressure (CPP) decreases, with subsequent lower CBF causing (relative) ischemia. The transient symptoms in this case could be related to changes in position (recumbent to supine), performance of the Valsalva maneuver or use of antihypertensive medication.[7,29] However, results from studies in which the role of CBF in CSDH patients was investigated are inconsistent. Some authors reported a clear correlation between reduced CBF (and therefore CPP) and (persistent) neurological deficits,[38,39] whereas others stated that the effect of the hematoma on regional CBF is minimal and cannot cause neurological deficits.[40,41] CBF

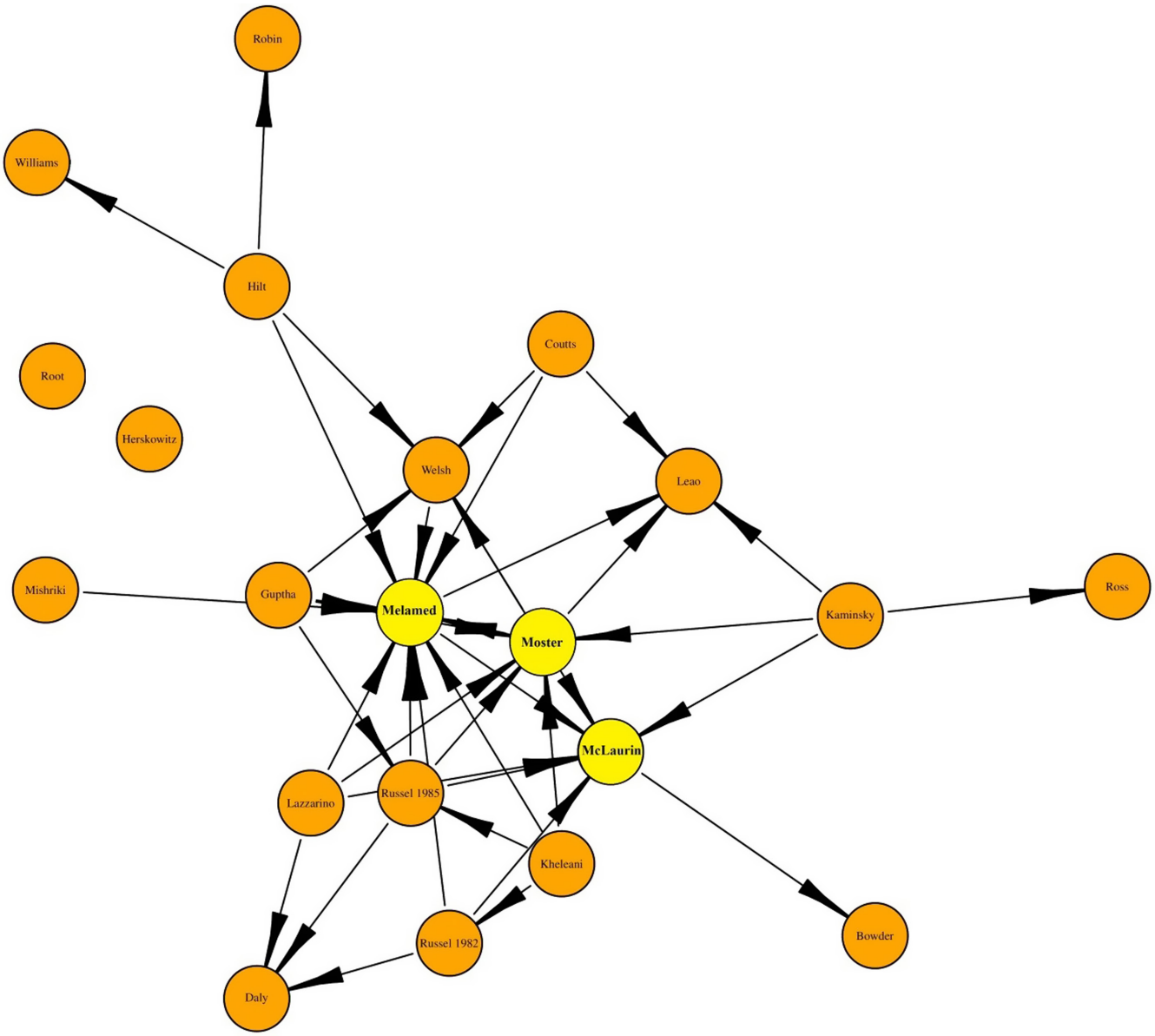

FIGURE 2 Visualization of the citation network analysis, the three most often cited papers are colored in yellow

in these studies was measured with perfusion CT,[39] and inhalation,[38,40] or intra-arterial injection of 133-Xenon.[41] To determine the role of the (relative) ischemia in TND (caused by lowering of CBF/ CPP), future studies should incorporate MRI (including DWI/ ADC to assess for diffusion restriction) and/or perfusion CT imaging. The differentiation between an ischemic origin and other pathophysiological causes may also be useful for the clinician, as ischemia requires a different treatment approach.

4.3 | Cortical spreading depression

One of the other mechanisms causing TNDs in CSDH might be cortical spreading depression (CSD). CSD is a slow spreading wave of altered brain activity that includes changes in neuronal, glial, and vascular function, and might be caused by local mechanical stimulation or injury.[18,42] It is described in a variety of neurological conditions such as migraine, traumatic brain injury, and more recently also in CSDH.[33,42–44] Although several articles in our review mentioned this etiology, none of the articles in our literature review substantiated this with valid arguments. This may be the direct result of the invasive method of demonstrating the presence of CSD, such as placement of electrodes directly on the exposed cortex.[45] CSD has been demonstrated in postoperative TND in CSDH, but it is not known if the preoperative TNDs share this pathophysiology.[43] Considering the ethical consequences of diagnosing preoperative CSD, establishing the role of CSD in patients with TNDs and CSDH will remain a challenge.

4.4 | Repeated hemorrhaging

The last pathophysiological mechanism of TND that has been hypothesized is the presence of small repeated hemorrhages within the subdural

space and granulation tissue encapsulating the hematoma.[19] Although micro-bleeding has been described to be part of the development of CSDH, it is not known how it would lead to TND.[46] Histopathological data are scarce, but intramembranous hemorrhagic foci and hypertrophy that might have been caused by repeated hemorrhages have been described in a patient with transient hemiparesis, hypesthesia, and dysarthria.[47] Given the complex pathophysiology of CSDH, it remains unclear whether this is the unifying explanation for TND in these patients. In order to support this hypothesis, future studies should perform histopathological examination of the hematoma membranes.

4.5 | Strengths and limitations

This is, to our knowledge, the only systematic review concerning the pathophysiology of TND in CSDH. Whereas previous studies regarding TNDs most often focused on the importance of not starting antithrombotic drugs,[7,14] we have focused on the pathophysiological mechanisms underlying temporary neurological signs and symptoms in CSDH. However, due to the methodology and scope of the included studies, this proved to be difficult. For instance, most articles lacked diagnostic EEG and MRI examination of the TND patients, not allowing for more definite statements about the suggested pathophysiology. This might partly result from the publication date of the included studies, since almost all studies have been published over 25 years ago. Also, we could only include a very limited number of studies (15 out of 320) with an even more limited number of patients experiencing TND. Therefore, generalizing our data to all CSDH patients (with TND) is difficult. Another shortcoming of most studies is that they do not provide arguments for their different pathophysiological considerations but refer to previously hypothesized mechanisms. This is further demonstrated by our citation analysis, showing that most articles cite the same three papers. As a result, it is debatable whether we truly analyzed 15 articles, or only studied these three "original" papers. Additionally, these three "original" papers report on a total of 38 patients, in whom TND was only present in 16 patients. The authors of these papers derived the pathophysiology of TND predominantly from their own hypotheses without providing clear diagnostic evidence of the origin of TND. Therefore, where in most systematic reviews the references of the included studies are scrutinized for other eligible reports, we suggest that also a citation network analysis as we have done, should be performed, to assess where and how the scientific evidence included in the review is generated.

5 | CONCLUSION

Different mechanisms have been proposed to be the cause of TNDs in patients with CSDH. However, based on our results, the exact pathophysiology of TND remains unclear. This finding is a result from the difficulty of providing evidence of the suggested mechanisms by a diagnostic method, mostly of the lack of EEG and MRI examinations. We believe that future studies on this topic should at least involve MRI (with diffusion-weighted imaging) or perfusion CT and EEG, to provide better insight in the possible pathophysiology. This knowledge might contribute to better understanding and more optimal treatment of CSDH patients with TND.

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CONFLICT OF INTEREST

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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