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Review Article

Pseudosubarachnoid hemorrhage: A systematic review of causes, diagnostic modalities, and outcomes in patients who present with pseudosubarachnoid hemorrhage

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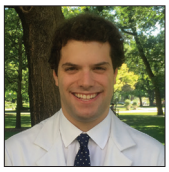

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ABSTRACT

Background: Patients with computed tomography (CT) findings consistent with subarachnoid hemorrhage without evidence of hemorrhage following autopsy or cerebrospinal fluid testing are termed to have pseudosubarachnoid hemorrhage (pSAH).

Methods: A systematic review of literature was conducted based on the preferred reporting items for systematic reviews and meta-analysis statement. Studies were evaluated for associated cause of pSAH, imaging modality used in assessment, method of confirmatory testing, and clinical outcome.

Results: Fifty studies were included in qualitative analysis including 197 cases of pSAH. Systematic review revealed 23 studies including 110 patients with pSAH attributed to hypoxic-ischemic brain injury following cardiac arrest. Three studies were included in meta-analysis that quantitatively analyzed differences in CT densities in patients with pSAH and true subarachnoid hemorrhage (true SAH). A random effects model meta-analysis showed a statistically significant decrease in densities in the Sylvian fissure in patients with pSAH compared to true SAH and a statistically significant decrease in densities in adjacent parenchyma in patients with pSAH compared to true SAH. Systematic review further revealed 32 patients with pSAH associated with spontaneous intracranial hypotension, 11 patients with pSAH related to infectious etiologies, 15 patients with pSAH associated with subdural hemorrhage, 20 cases of pSAH related to hyperhemoglobinemia, 2 cases related to valproate toxicity, and individual cases related to hyponatremia, diabetic ketoacidosis, sudden infant death syndrome, cerebellar infarction, and dialysis disequilibrium syndrome.

Conclusion: This study is the first systematic review of causes, diagnostic modalities, and outcomes in patients who present with pSAH. A diagnosis of pSAH may be considered following assessment of CT densities following cardiac arrest.

Keywords: Cardiac arrest, False subarachnoid hemorrhage, Pseudosubarachnoid hemorrhage, Systematic review

INTRODUCTION

Traumatic brain injury and aneurysmal rupture are the most common causes of subarachnoid hemorrhage; however, the differential diagnosis includes several etiologies. Computed tomography (CT) is the primary testing modality in the diagnosis of subarachnoid hemorrhage and has, with advances in technology, approached greater than 90% sensitivity and nearly 100%

specificity in the diagnosis of aneurysmal subarachnoid hemorrhage.[11,38,48] False positives include patients with nonaneurysmal causes of subarachnoid hemorrhage and those, despite positive CT findings, who have no evidence of hemorrhage following autopsy or cerebrospinal fluid (CSF) testing. This latter group, first identified by Spiegel *et al*. in 1986, has since been termed pseudosubarachnoid hemorrhage (pSAH) [Figure 1].[6,59]

Several etiologies of pSAH have been described including cerebral edema related to hypoxic-ischemic brain injury, meningeal infection, cerebral/cerebellar infarction, subdural hemorrhage, spontaneous intracranial hypotension, hyperhemoglobinemia, and iatrogenic causes following intrathecal, intravenous, or intra-arterial contrast administration.[37] Although the cause of the radiographic presentation of pSAH differs according to the etiology, it is hypothesized that the hyperdense appearance of the subarachnoid space in pSAH, related to hypoxic-ischemic injury, is related to the displacement of edematous parenchyma into the subarachnoid space, displacement of CSF, and engorgement of superficial pial veins.[6,23,37,69]

Several case reports and case series have been written concerning pSAH, however, there have been no significant reviews. This study is a systematic review of causes, diagnostic modalities, and outcomes in patients who present with pSAH as well as a meta-analysis comparing CT imaging characteristics of patients with pSAH secondary to hypoxic-ischemic brain injury and true subarachnoid hemorrhage (true SAH).

MATERIALS AND METHODS

This study includes a systematic review of literature conducted based on the preferred reporting items for systematic reviews and meta-analysis statement.[43] Online databases PubMed, the Cochrane Library, and Scopus were used to identify clinical studies evaluating patients with pSAH. Specific MeSH terms and key words including "pseudo" and "subarachnoid hemorrhage" were used in various combinations to identify studies of interest. Additional manual searches through cited references were performed.

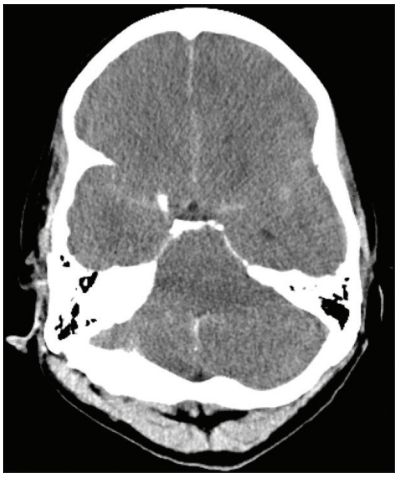

Figure 1: Computed tomography demonstrating diffuse hyperdensity within the subarachnoid space in a patient with pseudosubarachnoid hemorrhage.

Case reports, case series, comparative studies including randomized controlled trials, prospective/retrospective cohort, and case–control studies were included in further analysis. Non-English publications, editorials, conference abstracts, errata, and book chapters were excluded. Only studies including patients with radiographic and clinical findings concerning for possible subarachnoid hemorrhage, that were later ruled nonsubarachnoid hemorrhage, were included in further analysis. Patients with true SAH of aneurysmal or nonaneurysmal origin were excluded from the study. Cases of patients with pSAH following iatrogenic administration of contrast including patients with postprocedural contrast neurotoxicity or gadolinium encephalopathy were excluded from the study. Studies that were not available to be read in entirety were excluded from the study. Studies were evaluated for associated cause of pSAH, imaging modality used in assessment, method of confirmatory testing, and clinical outcome.

A standardized mean difference and 95% confidence interval were calculated for continuous outcomes that were then pooled by random effects model meta-analysis. All statistical tests were performed using RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). An I^2 test was performed for each comparison to test statistical heterogeneity with I^2 values exceeding 25%, 50%, and 75% indicating a low, moderate, and high degree of heterogeneity, respectively. For all meta-analyses, outcomes were pooled with weights calculated by the inverse-variance method. $P < 0.5$ was used to assess statistical significance.

RESULTS

In total, 169 abstracts were reviewed of which 30 were excluded. Several studies were excluded as full manuscripts were unable to be obtained. One hundred and thirty-nine full text articles were assessed of which 89 were excluded. Several studies of iatrogenic pSAH were excluded.[4,21,36,41,45,50,52,53,62] Individual cases of iatrogenic pSAH within included manuscripts were excluded.[24,49] Studies were excluded for not specifying associated causes of pSAH, for including only patients with postmortem radiography, or for including patients without pSAH.[6,55,57] One study of a patient with pSAH was excluded as both history and imaging findings were clearly concerning for leukemic leptomeningitis and not concerning for a diagnosis of subarachnoid hemorrhage.[26] Overall, 50 studies were

included in qualitative analysis including 197 cases of pSAH. Cases were further stratified by associated causes. Three studies were further analyzed in quantitative synthesis.[2,14,69] A flowchart of study inclusion and exclusion is shown in [Figure 2].

Systematic review revealed 23 studies of patients with pSAH following hypoxic-ischemic injury. Two individual patients were excluded from included studies for having initial CT scans following cardiac catheterization.[24,49] Overall 110 patients with pSAH following hypoxic-ischemic injury were included [Table 1].[1-3,10,14,17,23,24,30,33,34,39,40,46,49,56,60,63,64,66,68-70] Cases attributable to hypoxic-ischemic injury occurred following cardiac arrest with return of spontaneous circulation. All patients were evaluated with CT scans of the brain revealing pSAH. Patients were further evaluated with CT angiography (CTA) in two studies and with a diagnostic cerebral angiogram in one study.[1,24,66] In studies reporting confirmatory testing, the method employed included lumbar puncture (LP) in five studies, autopsy in nine studies, and external ventricular drainage (EVD) in one study. In studies reporting outcomes of patients with pSAH following hypoxic-ischemic injury, the mortality rate was 77%.

Three studies were included in meta-analysis that quantitatively analyzed differences in CT densities in patients with pSAH and true SAH.[2,14,69] Densities for high-density areas (HDAs) were measured in Hounsfield units (HU) taken from the Sylvian fissure, whereas densities for parenchyma were measured in HU taken from brain parenchyma adjacent to the Sylvian fissure.

Yuzawa *et al*. measured densities bilaterally and included 18 hemispheres in the pSAH group for both HDA and parenchymal measurements, 14 hemispheres in the true SAH group for HDA measurements, and 16 hemispheres in the true SAH group for parenchymal measurements.[69] Only one patient in the pSAH group had an autopsy confirmation of pSAH. The remainder of patients was defined as pSAH based on the absence of the following characteristics: intraventricular hemorrhage, "clumped" HDA in the ventricles or sulci, and typical clinical presentation of SAH including sudden headache with impaired consciousness. Patients were also added to the pSAH group if they had interval development of HDA on a second CT which was not evident on the presenting CT.[69] Measurement of densities of

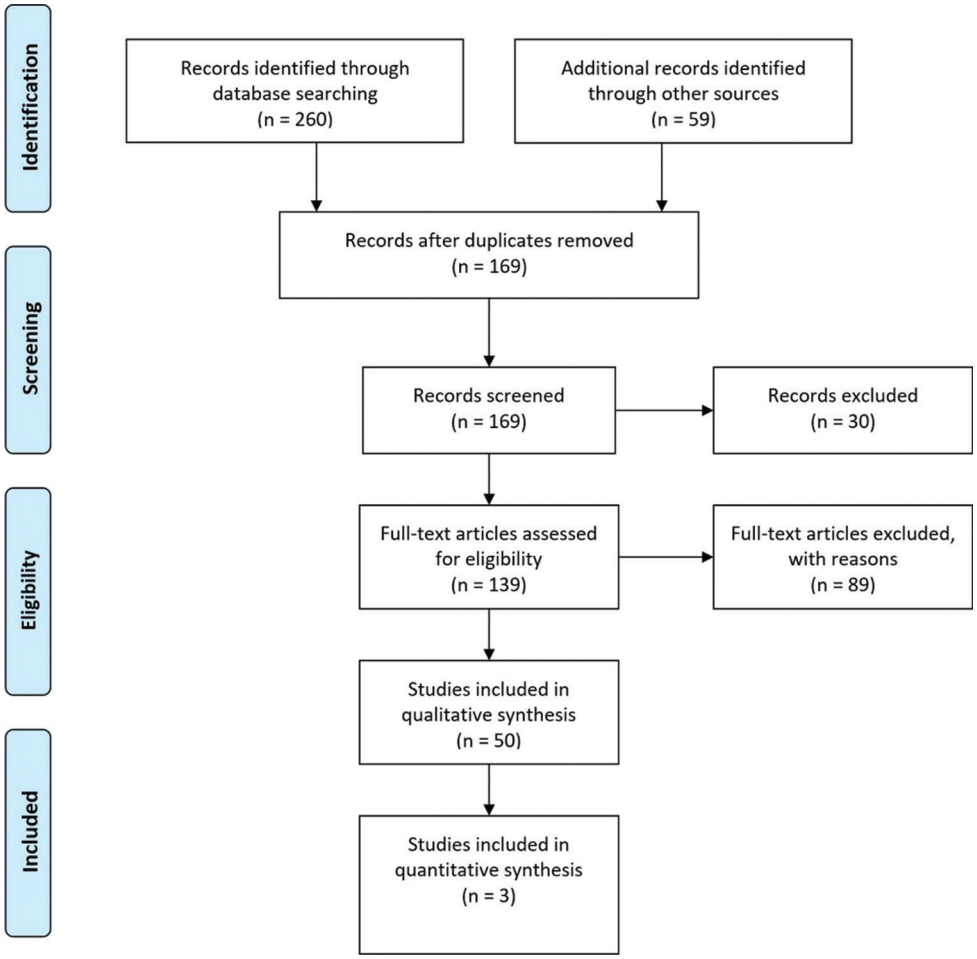

Figure 2: A flowchart of study inclusion and exclusion.

Table 1: Cases of pseudosubarachnoid hemorrhage related to hypoxic-ischemic injury.

Author	Year	*n*	Imaging for diagnosis	Confirmatory test	Outcome
Opeskin *et al.*	1998	5	CT	Autopsy	Death
Al-Yamany *et al.*	1999	1	CT	Autopsy	Death
Phan *et al.*	2000	1	CT	NR	Death
Given *et al.*	2003	2	CT	LP×1, autopsy×1	Death
Lowenthal *et al.*	2004	1	CT	LP	Death
Thomas *et al.*	2007	1	CT	Autopsy	Death
You *et al.*	2008	1	CT	NR	NR
Yuzawa *et al.*	2008	9	CT	Autopsy×1	NR
Agha *et al.*	2011	1	CT, cerebral angiogram	LP	Death
Wong *et al.*	2011	2	CT	Autopsy	Death
Ahn *et al.*	2012	12	CT	Autopsy/EVD	NR
Westwood *et al.*	2012	1	CT	NR	NR
Bedford *et al.*	2013	1	CT	Autopsy	Death
Choi *et al.*	2013	28	CT	NR	Death×26
Tekelioglu *et al.*	2013	1	CT, CTA	NR	Death
Zhang *et al.*	2015	1	CT	LP	Death
Kim *et al.*	2017	1	CT	NR	Death
Lee *et al.*	2017	32	CT	NR	Death×16
Lewis *et al.*	2017	3	CT	LP×1, autopsy×1	Death×2
Coulier *et al.*	2018	1	CT	NR	Death
Faeez *et al.*	2018	1	CT	NR	Death
Hasan *et al.*	2018	3	CT, CTA	NR	Death×2
Schreyer *et al.*	2018	1	CT	NR	NR

CT: Computed tomography, CT: Computed tomography angiography, NR: Not reported, LP: Lumbar puncture, EVD: External ventricular drain

HDA revealed a mean density and standard deviation of 37.6 ± 3.3 HU (range 30.0–42.0 HU) in patients with pSAH and a mean density and standard deviation of 56.6 ± 7.8 HU (range 41.0–67.0 HU) in patients with true SAH.

Ahn *et al*. also measured densities bilaterally and included 12 patients (24 hemispheres) in each pSAH and true SAH group. They defined patients as pSAH following negative confirmatory testing (LP or autopsy) or through clinical characteristics similar to Yuzawa *et al*. Patients defined clinically and those defined through confirmatory testing did not have a statistically significant difference in averaged measured densities.[2] Measurement of densities of HDA revealed a mean density of 37.3 ± 3.1 HU in patients with pSAH and a mean density of 50.5 ± 4.0 HU in patients with true SAH. Unlike in the other two studies included in quantitative synthesis, the true SAH cohort was not taken from patients diagnosed following cardiac arrest. Choi *et al*. did not report if densities were measured bilaterally thus for the sake of comparison, the number of patients was used as the number of hemispheres. Again, they defined patients as pSAH following negative confirmatory testing (LP) or through clinical characteristics similar to Yuzawa *et al*.[14,69] Measurement of densities of HDA revealed a mean density of 38.5 ± 5.1 HU in patients with pSAH and a mean density of 58.4 ± 7.3 HU in patients with true SAH.

In comparing densities in HDA, 70 hemispheres were included in the pSAH group and 73 hemispheres were included in the true SAH group. Mean densities ranged from 37.3 to 38.5 HU in the pSAH group and 50.5 to 58.4 HU in the true SAH group. A random effects model meta-analysis was carried out which showed a statistically significant decrease in densities in HDA in patients with pSAH compared to true SAH (SMD −3.27; 95% CI −3.79, −2.76; $P < 0.00001$; $I^2 = 0$) [Figure 3]. In comparing densities in adjacent parenchyma, 46 hemispheres were included in the pSAH group and 51 hemispheres were included in the true SAH group. Mean densities ranged from 26.8 to 27.4 HU in the pSAH group and 30.0 to 30.8 HU in the true SAH group. A random effects model meta-analysis was carried out which showed a statistically significant decrease in densities in adjacent parenchyma in patients with pSAH compared to true SAH (SMD −1.22; 95% CI −1.66, −0.79; $P < 0.00001$; $I^2 = 0$) [Figure 4].

Systematic review revealed nine studies of 32 patients with pSAH associated with spontaneous intracranial hypotension [Table 2].[7,8,15,22,24,29,31,54,67] All patients were evaluated with CT scans of the brain revealing pSAH. Patients were further evaluated with magnetic resonance imaging (MRI) in six studies, CTA in one study, and diagnostic cerebral angiograms in two studies. Confirmatory testing was done in three studies utilizing lumbar puncture, including one study,

Yokota *et al*., in which the CSF results, showed evidence of xanthochromia, leukocyte pleocytosis, and increased protein.[67] All studies that reported outcomes reported complete resolution of symptoms following treatment. Conversely, pSAH is also associated with pseudotumor cerebri and has been demonstrated in two single patient case reports.[18,23] Both patients were diagnosed on CT with one patient additionally having a MRI. Both patients had lumbar punctures for confirmatory testing and were discharged following inpatient stays.

Eleven patients with pSAH related to infectious etiologies were discovered across 10 manuscripts [Table 3].[12,13,16,18,20,23,25,32,44,65] The most common infectious etiologies included pneumococcal meningitis in three patients, cryptococcal meningitis in two patients, and viral meningoencephalitis in two patients. Radiographic investigations besides CT included CTA, CT perfusion, MRI, MR angiography, and MR venography, as well as one case in which a diagnostic cerebral angiogram was utilized.[20] Confirmatory testing included CSF sampling in all patients and brain biopsy in one patient.[44] Death occurred in 27% of cases.

Systematic review further revealed 15 cases of pSAH associated with subdural hemorrhages.[5,51,58] Two of three studies included cases that involved diagnostic cerebral angiograms and one study included a patient who underwent clipping of an incidental aneurysm that was preoperatively presumed to have caused a ruptured subarachnoid hemorrhage.[51,58] Additional studies included 20 cases of pSAH related to hyperhemoglobinemia, 2 cases related to valproate toxicity, and individual cases related to hyponatremia, diabetic ketoacidosis, sudden infant death syndrome, cerebellar infarction, and dialysis disequilibrium syndrome.[9,19,23,28,35,42,47,61]

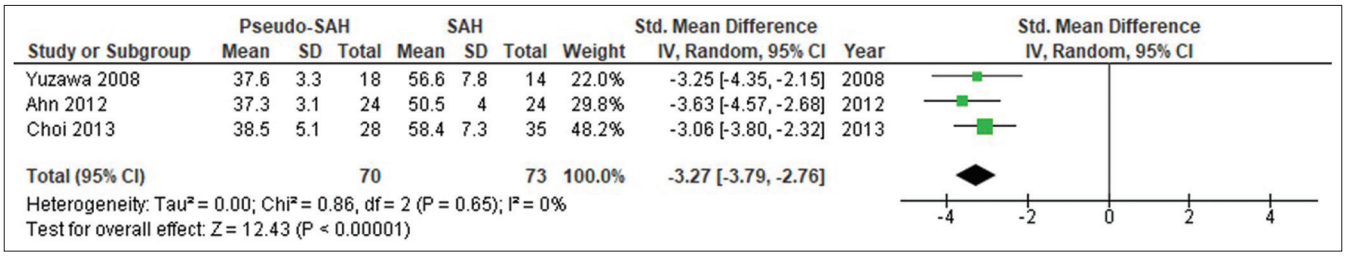

Figure 3: A random effects model meta-analysis comparing densities in high-density areas in patients with pseudosubarachnoid hemorrhage and true subarachnoid hemorrhage. IV: Inverse variance, CI: Confidence interval, SD: Standard deviation.

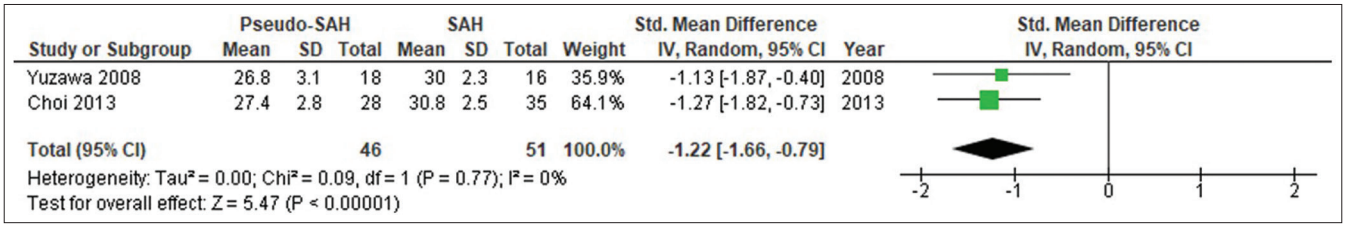

Figure 4: A random effects mode meta-analysis comparing densities in adjacent parenchyma in patients with pseudosubarachnoid hemorrhage and true subarachnoid hemorrhage. IV: Inverse variance, CI: Confidence interval, SD: Standard deviation.

Table 2: Cases of pseudosubarachnoid hemorrhage related to spontaneous intracranial hypotension.

Author	Year	*n*	Imaging for diagnosis	Confirmatory test	Outcome
Schievink *et al.*	2005	4	CT, MRI	LP×4	Resolution
Chung *et al.*	2006	9	CT	NR	NR
Balgera *et al.*	2008, 2009	1	CT, MRI, cerebral angiogram	None	Resolution
Koh *et al.*	2011	1	CT, CTA, MRI, cerebral angiogram	LP	Resolution
Ferrante *et al.*	2013	10	CT, MRI	None	Resolution
Yokota *et al.*	2016	1	CT, MRI	LP	Resolution
Hasan *et al.*	2018	1	CT	NR	NR
Kim *et al.*	2019	5	CT, MRI	NR	NR

CT: Computed tomography, CTA: Computed tomography angiography, NR: Not reported, LP: Lumbar puncture, EVD: External ventricular drain, MRI: Magnetic resonance imaging

Table 3: Cases of pseudosubarachnoid hemorrhage related to infectious etiologies.

Author	Year	*n*	Associated cause	Imaging for diagnosis	Confirmatory test	Outcome
Chatterjee *et al.*	2003	1	Pneumococcal meningitis	CT, MRI, MRA, MRV	LP	Discharged
Given *et al.*	2003	1	Septic shock	CT	LP	Death
Cucchiara *et al.*	2004	2	Viral meningoencephalitis×1 herpes zoster vasculitis×1	CT, MRI	LP	Discharged
Coady *et al.*	2011	1	Cryptococcus meningitis	CT, CTA, MRI	EVD	Death
Lang *et al.*	2013	1	Pneumococcal meningitis	CT	EVD	Discharged
Nakae *et al.*	2013	1	Cryptococcus meningitis	CT, MRI	LP, Brain Biopsy	Discharged
Dredla *et al.*	2016	1	Ehrlichia meningitis	CT, CTA, cerebral angiogram	LP	Resolution
Xin *et al.*	2016	1	Viral meningoencephalitis	CT	LP	Resolution
Ho *et al.*	2018	1	Pneumococcal meningitis	CT, CTA, CTP, MRI	EVD	Death
Camacho *et al.*	2019	1	Staphylococcus meningitis	CT, CTA, MRI	LP	Resolution

CT: Computed tomography, CTA: Computed tomography angiography, NR: Not reported, LP: Lumbar puncture, EVD: External ventricular drain, MRI: Magnetic resonance imaging, MRA: Magnetic resonance angiography, MRV: Magnetic resonance venography, CTP: Computed tomography perfusion

DISCUSSION

Early recognition of aneurysmal subarachnoid hemorrhage following presentation is essential to improving patient outcomes.[38] pSAH is a diagnosis of exclusion once aneurysmal rupture and other causes of true SAH are ruled out. Several causes of pSAH have been reported in the literature to date. On presentation, history can provide significant clues as to the etiology of pSAH and can help rule out true SAH.[24,37] Cases of iatrogenic pSAH following contrast injected procedures are some of the most straightforward cases to rule out based on procedural history and thus were not included in this systematic review.[4,21,36,41,45,50,52,53,62] Cases of pSAH related to hypoxic-ischemic injury following cardiac arrest, conversely, can be extremely difficult to rule out from high-grade aneurysmal subarachnoid hemorrhage.[27]

All of the 197 cases of pSAH revealed in systematic review had CT scans that revealed HDA within the subarachnoid space. Compared with patients with true SAH, meta-analysis has shown patients with pSAH, associated with hypoxic-ischemic injury, to have significantly decreased densities in HDA and adjacent parenchyma [Figures 3 and 4]. The previous studies have hypothesized that the hyperdense appearance of the subarachnoid space in pSAH is related to displacement of edematous parenchyma into the subarachnoid space, displacement of CSF, and engorgement of superficial pial veins.[6,23,37,69] Although the results of this meta-analysis can be used to help differentiate pSAH from true SAH in patients with hypoxic-ischemic injury, they cannot be generalized to all causes of pSAH. These results are, however, useful as they are a tool to differentiate pSAH from high-grade subarachnoid hemorrhage which can have nearly identical presentations however highly different treatment pathways and outcomes.

The second most common employed imaging modality in patients with pSAH is MRI. It is especially helpful in patients with pSAH associated with spontaneous intracranial hypotension where it may show dense pachymeningeal enhancement along the tentorium as well as brain sagging with obliteration of the basilar cisterns and Sylvian fissures.[15,22,29,54] The utility of MRI in clinching the diagnosis of pSAH associated with infection is less clear as some reports have shown MRI to aid in ruling out subarachnoid hemorrhage and others have shown it to not be helpful.[12,13,18,25] Ho *et al*. showed utility of MRI in a case of pSAH associated with pneumococcal meningitis and reported gradient recalled echo sequences showed absence of hemorrhage within the cisterns and sulcal spaces previously seen as HDA on CT.[25] They further reported increased hyperintensity within CSF spaces on FLAIR imaging likely related to the increased protein content and inflammatory response related to breakdown of the blood–brain barrier.[25]

The confirmatory test of choice in patients with pSAH remains CSF sampling through LP or EVD. Its utility is not only in ruling out aneurysmal subarachnoid hemorrhage but also in potentially identifying the cause of pSAH. CSF sampling is especially important in cases of central nervous system infection as it can be used to rule out subarachnoid hemorrhage and identify the causative pathogen. Performing a LP to rule out aneurysmal subarachnoid hemorrhage is also controversial, especially regarding the interpretation of CSF results and xanthochromia.[38] Interpretation of CSF sampling in cases of pSAH is also prone to failure as evidence by a case of pSAH associated with spontaneous intracranial hypotension that revealed xanthochromia.[67] There is also a risk in performing lumbar punctures in patients who present following hypoxic-ischemic brain injury as these patients may have increased intracranial pressure which increases the risk of downward herniation during the procedure.

Individual laboratory testing tailored to the presumed cause of pSAH has also been shown to be effective. In cases of hyperhemoglobinemia, the previous studies have found hematocrit levels to range from 62.3 to 74.8%.[28,47] In a case–control study, Li *et al*. found that a significantly higher proportion of patients with hyperhemoglobinemia had pSAH with hemoglobin ≥210 g/L than with lower hemoglobin levels. They further showed a significant correlation between pseudo-SAH and hyperhemoglobinemia.[35] In regard to cases of pSAH related to valproate toxicity, patients presented with serum valproate levels of 637–1270 μg/mL.

Outcomes following pSAH vary greatly according to the underlying etiology. In studies reporting outcomes of patients with pSAH following hypoxic-ischemic injury, the mortality rate was 77%, however, in studies reporting outcomes of patients with spontaneous intracranial hypotension, the mortality rate was 0% with 100% of patients having complete resolution of symptoms following treatment. In studies reporting outcomes of patients with pSAH related to central nervous system infection, the mortality rate was 27%. In patients who present following cardiac arrest, pSAH has further been identified as a significant predictor of increased in-hospital mortality and poor neurologic outcome compared to patients who present following cardiac arrest without evidence of pSAH.[33,69] The presence of pSAH in patients following cardiac arrest is also shown to be a predictor of worse 3-month survival compared to patients with true SAH following cardiac arrest.[14]

Given the results of this systematic review and meta-analysis, we have proposed the following theoretical diagnostic protocol in patients with CT findings of HDAs within the subarachnoid space following resuscitation from cardiac arrest [Figure 5]. First, pSAH remains a diagnosis of exclusion. Any concern for aneurysmal subarachnoid hemorrhage including clinical or typical radiologic findings should precipitate workup and treatment of that condition. In patients without typical history or CT findings of subarachnoid hemorrhage, we suggest measurement of density of HDA. A value of 41 HU was the minimum density within HDA reported in true SAH patients in Yuzawa *et al*.[69] This value was also greater than two standard deviations away from the mean in patients with true SAH in Ahn *et al*. and Choi *et al*. We thus recommend consideration of a diagnosis of pSAH in patients with densities less than 41 HU in HDA. Before this protocol can be put into action, further studies would be required to test its validity.

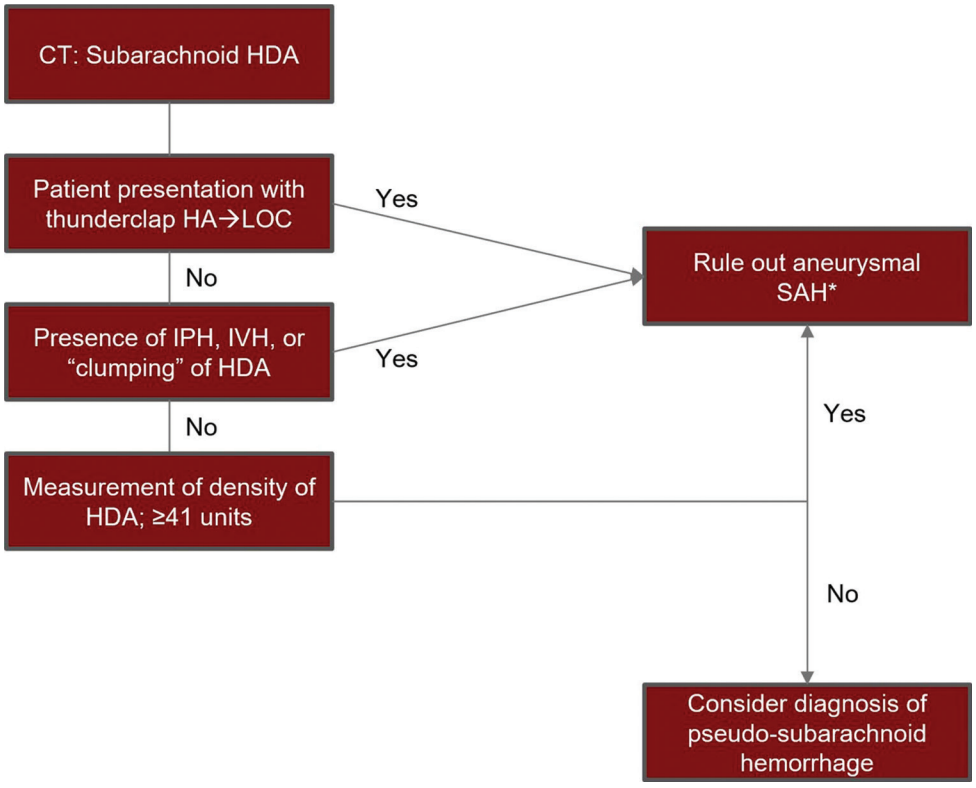

Figure 5: A flowchart of a theoretical diagnostic protocol to differentiate cases of pseudosubarachnoid hemorrhage from aneurysmal subarachnoid hemorrhage in patients who present following cardiac arrest with high-density areas on computed tomography. *Ruling out subarachnoid hemorrhage to be done per individual hospital policy which may include further vascular imaging or confirmatory testing, HAD: High-density areas, HA: Headache, LOC: Loss of consciousness, IPH: Intraparenchymal hemorrhage, IVH: Intraventricular hemorrhage.

Limitations

There are several limitations to this study. Following systematic review, 50 studies were included in qualitative analysis, however, only three studies met inclusion criteria for quantitative analysis. Although all studies were directly comparative in nature, studies defined patients as pSAH mostly from clinical presentation and radiologic findings, not through confirmatory testing. This study was also limited by heterogeneity within the true SAH group, and low patient samples and incomplete reported data.

CONCLUSION

This study, to the best of our knowledge, is the first systematic review of causes, diagnostic modalities, and outcomes in patients who present with pSAH. This study is also the only meta-analysis comparing CT imaging characteristics of patients with pSAH related to hypoxic-ischemic brain injury and true SAH. Although aneurysmal subarachnoid hemorrhage must always remain at the top of a differential when a patient presents with HDAs within the subarachnoid space, a diagnosis of pSAH may be considered following assessment of CT densities in a patient that presents following cardiac arrest. Furthermore, patient history is essential to diagnose other causes of pSAH and can be aided by targeted diagnostic tests including MRI to assess for cases of spontaneous intracranial hypotension, CSF analysis to assess for central nervous system infection, and specific laboratory tests including hemoglobin/hematocrit to assess for hyperhemoglobinemia and valproate levels to assess for valproate toxicity.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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