American Journal of Emergency Medicine 37 (2019) 2079–2083

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Misdiagnosis of acute subarachnoid hemorrhage in the era of multimodal diagnostic options

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ARTICLE INFO

Article history:
Received 17 January 2019
Received in revised form 28 February 2019
Accepted 2 March 2019

ABSTRACT

Objective: Patients suffering from aneurysmatic Subarachnoid Hemorrhage (SAH) may present with a variety of symptoms. The aim of this study is to evaluate the spectrum of misdiagnoses and to analyze the significance of delay of correct diagnosis on the clinical outcome.
Methods: The data was collected prospectively from 2003 to 2013. Patients diagnosed with disease different from aneurysmal SAH by the initially treating physician, and admitted to our department with a delay of at least 24 h after the beginning of the symptoms, were included in this study. We analyzed the various diagnoses that were ascertained instead of SAH and which medical specialty had provided them.
Results: Overall 704 patients were treated with acute SAH. The inclusion criteria were matched in 76 patients (13.7%). Eleven specialties were involved in the initial patients' treatment. The time interval between initial symptoms and neurosurgical admission varied enormously. Statistically, higher Hunt & Hess score did not lead to an earlier diagnosis ($p = 0.56$) nor did localisation of the aneurysm ($p = 0.75$). Lower Fisher score was led to delayed diagnosis ($p = 0.02$). Delay of diagnosis was not significantly associated with the outcome ($p = 0.08$) whereas Hunt & Hess grade on admission was a strong predictor for bad outcome ($p = 0.00001$) as was cerebral vasospasm on the first angiogram ($p < 0.05$).
Conclusion: A straightforward diagnosis of SAH despite diffuse and unspecific symptoms is crucial for the successful treatment of these patients, especially with high grade SAH.
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1. Introduction

1.1. Background

Aneurysmal Subarachnoid hemorrhage (SAH) might be a devastating neurovascular emergency with high mortality and morbidity. Among the factors that negatively influence the overall mortality, the most important one is rebleeding from an untreated aneurysm [1,2,3]. Its incidence is described up to 19,3%, whereas a recent study of a small cohort showed that up to 41,3% of the patients experienced rebleeding within the first 24 h [1]. It is accepted that SAH treatment and especially securing of the symptomatic aneurysm should take place as early as possible. Clinical course, the occurrence and incidence of delayed cerebral ischemia (DCI) and neurological outcome are associated with the severity of the early brain injury (EBI) [4,5]. The phase of EBI is considered to take place in the first 72 h after aneurysm rupture [4-7]. These facts highlight the importance of the early recognition and diagnosis of SAH. In the era of interdisciplinary emergency treatment and readily available multimodal diagnostic options, it should therefore be self-evident that the numbers of misdiagnosis are small.

1.2. Objectives

One aim of the analysis was to evaluate the number of patients who were not diagnosed with SAH in the acute phase of early brain injury as well as on the delay and which other diagnoses were attributed to their symptoms. The other aim of the study was to investigate if the delayed diagnoses of SAH lead to a worse clinical outcome. In order to do that we compared the group of the misdiagnosed patients with the ones who to our clinic on day 0.

2. Materials and methods

This is a retrospective observational analysis of our prospective SAH data database.

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https://doi.org/10.1016/j.ajem.2019.03.001
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All patients who were admitted to our university hospital with the diagnosis of a SAH between 2003 and 2013 were retrospectively evaluated. Inclusion criteria were age > 18 years old and the diagnosis of SAH in the computed tomography (CT) or lumbar puncture (LP). Patients without the angiographic confirmation of a ruptured aneurysm were excluded. Demographic data such as gender, age, as well as comorbidities were evaluated. The initial Hunt and Hess (HH) score and Fisher score were documented. Patients were dichotomized into good grade (H& H 1–2) and poor grade (H & H 3–5) SAH.

Moreover, factors taken into consideration were the initial presentation of cerebral vasospasm, the localization of the aneurysm, whether or not there were multiple aneurysms and how they were treated, surgically or interventionally. All patients who had a thunderclap headache 1 to over 15 days before admission were included. The day of the initial symptoms was assessed either by asking the patient on admission or her/his family members. Many of them consulted different medical specialists asides from their general practitioner. The activity during which the headache occurred was documented. The outcome was assessed via the Glasgow Outcome Score (GOS) upon discharge to a rehabilitation center. In 36,06% of patients the outcome was re-evaluated 6 months ago.

A matched pair cohort was extracted from the same prospective data in order to see if the patients who had the same mean Hunt and Hess score and came to our clinic at the time of their initial symptoms did have a better clinical outcome compared to the ones who were admitted 1 or more days later.

2.1. Statistics

This is a retrospective observational study. To investigate the association of delayed admission with the variables such as different false diagnoses univariately, we used a chi-square-test. The association of delayed admission status with dichotomized variables such as good or bad Hunt and Hess scores was tested by chi-square test. For the association of delayed admission status with continuous or ordinal variables or clinical outcomes (age, H&H grade, localization of the aneurysm), Wilcoxon Mann Whitney Test was used.

3. Results

3.1. Baseline characteristics

Overall 704 patients had the diagnosis of SAH. In 555 of them one or more intracerebral aneurysms were diagnosed. In 149 patients the SAH was of unknown origin despite 6 vessel angiography which was initially made as well as in a short interval. In 76 of them (13,69%), the diagnosis of SAH was made with delay of >24 h. There was a female predominance (n = 56 to 20). The age span was 29 to 84 years of age with an average age of 51 years old. The female population was not significantly older as the male population. In 52 patients one aneurysm was diagnosed whereas in 24 patients multiple aneurysms were detected. The time interval between initial symptoms and admission varied enormously (1–122 days, mean: 17,85, median:11) (Table 1). Sixty three of the patients were admitted to our emergency department up to day 8, whereas 29 of them came within the first 2 days. Thirty six of the 76 patients were consulted on an outpatient basis, 26 were treated in hospitals, whereas 14 patients were initially seen in the ambulance and then admitted to a nearby hospital.

Looking at the group who was diagnosed with delay, statistically, higher H&H score was not associated with an earlier diagnosis (p = 0.56) nor was localization of the aneurysm (p = 0.75). Lower Fisher score was associated with a more delayed diagnosis (p = 0.02).

Table 1
Time interval between initial symptoms and admission to our clinic.

Timepoint to our clinic (d)	Number of patients
1	19
2	10
3	9
4	5
5	3
6	7
7	4
8	6
9	0
10	2
11	1
12	1
13	2
14	1
15	1
18	1
26	1
56	1
122	1
Median	11

More than half of the patients had a H&H grade 1–2 SAH. These two groups retained a good grade SAH i.e. although the diagnosis of SAH was not made at the proper time, their clinical status remained stable without deterioration of their vigilance. 42,1% of the patients however had a H&H grade 3–5 SAH, which should be considered as a deterioration of their initial clinical status, or else it should be assumed that the correct diagnosis would have been made initially.

A probable cause of deterioration could be either rebleeding, vasospasm, especially after day 4 or hydrocephalus. This was documented upon admission to our clinic. Of the 76 patients, 13 patients had local vasospasm in one intracranial artery, whereas 11 had vasospasms in more than one artery. On the other hand, 44 of the patients revealed hydrocephalus and were treated with implantation of an external ventricular drain. Since the interval between initial symptoms and admission to our clinic varied a lot, there could not be an exact documentation of whether the symptoms were ongoing or ceased and presented again, in order for a rebleeding to be assumed.

3.2. Characterization of the initial treatment: involved specialists and (false) diagnoses

Overall, doctors from eleven different specialties were involved in the patients' initial treatment. The majority of them were general practitioners followed by emergency doctors who treated the patients at home. A considerable number of medical doctors were neurologists, but there were also many internists and especially cardiologists involved (Table 2). Statistically, neurological

Table 2
Different specialties involved in the initial management.

Medical specialty	Number of patients
General practitioner	27
Emergency specialist	20
Neurologist	16
Internist	15
Radiologist	14
Cardiologist	7
Orthopedic surgeon	4
Psychiatrist	1
Ophthalmologist	1
ENT	1
Traumatologist	1

involvement in the initial diagnostic phase did not lead to a shorter delay of the diagnosis ($p = 0.93$).

Twenty three different diagnoses were assessed. Since the major symptoms of the patients was headache, the most popular diagnosis was a headache (32,07%) of variable forms such as tension headaches or migraine attacks, especially in patients with a history of migraines. Other patients (9,43%) were diagnosed for degenerative disease of the cervical spine or shoulder pathologies. The next popular diagnosis was meningitis (9,43%), whereas a significant number of patients (14,15%) were treated for cardiac pathologies such as myocardial infarction or cardiac arrhythmias. (Table 3).

3.3. Neurological outcome

The clinical outcome was assessed on discharge using the (GOS) (Table 4).

In 22 of them (36,06%) the GOS was re-evaluated after 6 months. The overall in hospital mortality in the delay group was 19,73%. The causes of in- hospital mortality are listed in Table 5.

Hunt & Hess grade on admission was a strong predictor for worse neurological outcome ($p = 0.00001$) as was cerebral vasospasm on the first angiogram ($p < 0.05$).

Surprisingly, the extent of delay of diagnosis was not significantly associated with the outcome ($p = 0.08$).

In order to find out, if the delayed diagnosis of SAH affected the outcome of the patients, a statistical analysis with ANOVA was performed comparing the outcome of these patients opposed to those who reached medical attention in our clinic on day 0. This matched-pair analysis was done with a cohort of patients with similar mean H&H score (2,67). The results of this comparison showed that patients with poor grade SAH on admittance had a better outcome than misdiagnosed and delayed patients. Vice versa, outcome was not worse comparing good grade SAH patients.

3.4. Aneurysm localization and type of occlusion in the patients with delayed admission

We also looked into the localization of the aneurysms of the patients who were misdiagnosed as well as into the treatment that was performed. The most common aneurysm location was the middle cerebral artery (31) followed by the anterior cerebral artery (29) and the internal carotid artery (24). Aneurysms of the posterior circulation were as expected not so common (15). Twenty three patients had more than one aneurysm.

Regarding the treatment modality 37 of the aneurysms were clipped and 33 were coiled. One aneurysm was treated via both methods. In 5 patients no therapy was admitted due to very poor clinical status and restriction of therapy through the family due to old age.

Table 3
The different false diagnoses initially assessed.

Misdiagnosis	N=
Headaches	30
Cervical syndrome, disc herniation	10
Meningitis	10
Myocardial infarction	9
Head injury	7
Hypertensive crisis, heart rhythm irregularities	6
Brain tumor	5
Migraine	4
Drug abuse complication	4
Seizures	2
Transient Ischemic attack	2
Encephalitis	2
Sinus thrombosis	2
Intracerebral hemorrhage	2
Vasculitis	2
A. subclavia-A. vertebralis stenosis	2
Borreliosis	1
Gastrointestinal infection	1
Hemorrhage of the retina	1
Cetoacidosis	1
Uremic coma	1
Lung embolism	1
Sinus infection	1
Overall	106

4. Discussion

Aneurysmal subarachnoid hemorrhage is an acute neurovascular emergency which requests immediate diagnosis and initiation of therapy [8]. Its incidence has remained stable over the years and is around 9/100.000 person- years. Around 12% of the patients die immediately, whereas the chance of a patient surviving a SAH has increased over the 3 last decades and is around 65% because of improved diagnostic as well as treatment methods [9,10]. Since it affects a significantly younger population compared to ischemic and hemorrhagic stroke with a mean age of occurrence of 55 years, the importance of correct initial diagnosis becomes imperative, since studies have shown that delayed transport to a specialized neurovascular center are associated with worse clinical outcome [11].

4.1. Main results

In our study there was a strong tendency of a better outcome of the patients who came on day 0 to our clinic rather than later on. This surprisingly did not reach statistical significance. This result may have to do with the fact, that more than half of the patients had a good grade SAH on delayed admission. On the other hand we found that higher grade SAH patients (H&H 3–5) who did not come immediately showed a worse outcome compared to the ones who presented after the initial symptoms.

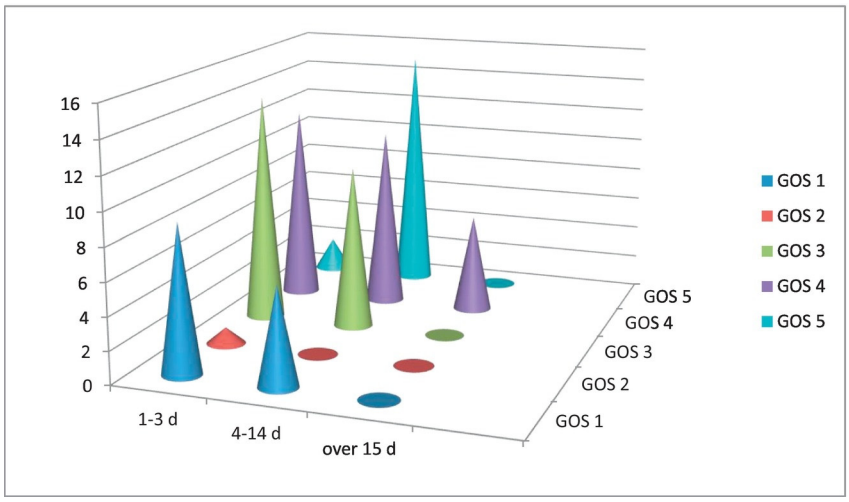
At this point a significant detail has to be mentioned. Our study included only patients who reached the hospital albeit delayed. We know however for a fact that a considerable number of patients with SAH do not manage to reach medical attention because they do not survive the high intracranial pressure i.e. hydrocephalus and eventually succumb. This number of patients could have crucially influenced the results of our study. This leads to the logical conclusion that a number of patients after the initial bleeding could have been saved if they were admitted on time.

In our series the three most common diagnoses were, as expected, various types of headaches, cervical spine syndrome and meningitis.

Since the initial symptoms could only be limited to headaches with an almost normal neurological status, the assessment of correct diagnosis can be complex. A false diagnosis can have severe consequences since the risk of rebleeding from an untreated aneurysm is high in the first 24 h [8].

The paramount symptom of SAH is the thunderclap headache i.e. an acute, severe headache "for the first time in one's life". The pain radiates to the nuchal region and is commonly associated with symptoms of high intracranial pressure or deterioration of consciousness up to coma. In these cases the diagnosis of SAH can be easily assumed. The problem that usually occurs is failing to make the correct diagnosis in patients with headaches, which do not always have an acute onset and in patients with normal neurological examination. In a very detailed review of Edlow et al. aimed at emergency physicians in year 2008, four elements were thought to play a major role in regards to the history of the

Table 4
GOS according to time delay.



patients; onset, severity, quality and associated symptoms. But acute headache can also have other causes which do not primarily come from brain pathologies such as temporal arteritis, cervicocranial artery dissections, acute narrow angle closure glaucoma or even carbon monoxide poisoning [12]. In our series there were 2 patients diagnosed with vasculitis and also two others diagnosed with stenosis of the subclavian- vertebral artery junction. One patient was diagnosed with an acute vitreous body hemorrhage, which has also been described as a complication of SAH (Terson's syndrome). A recent study by Bäuerle et al. showed indeed that ocular sonography identifies SAH-related preretinal and vitreous hemorrhages with high accuracy [13].

Thus, there were out of a total of 107 false diagnoses 15 ones suggesting myocardial infarction, atrial fibrillation, or other arrhythmias. This fact should not come to our surprise since SAH has long been known to be associated with electrocardiogram changes [14]. The reason for these remains to a large extent unknown. The reported prevalence ranges from 27% up to even 100% [15], the most common being ST-T changes as well as rhythm abnormalities such as sinus bradycardia, possibly also in the context of Cushing's reflex, sinus tachycardia, wandering atrial pacemaker or atrial fibrillation [16]. If one also takes into consideration that many of patients with SAH present with an acute loss of consciousness due to a possible early brain injury, it is not unremarkable that many are further assigned to a cardiologist. As Suwatcharangkoon et al. published recently, loss of consciousness was significantly associated with cardiopulmonary arrest in a retrospective evaluation of 1460 patients with spontaneous SAH [17]. This misdiagnosis has unfortunately potentially deleterious implications since these patients receive a catheter angiography of the coronary vessels and antiplatelet agents which could rapidly worsen the clinical status in case of an unsecured aneurysm.

But even if the clinical diagnosis of a SAH is suspected, the emergent of the situation seems not to be clear enough. This issue could be due to the normal neurological examination of patients with Hunt and Hess grade 1 to 2. Except from meningismus, these patients show no other focal neurological deficits. In our series 14 of our patients received a CT scan; 7 of them were actually in a hospital unit, but no SAH was diagnosed. This could be attributed to Fisher grade 1 SAH, where no blood is detected in the CT scan or due to the fact that the patients presented several days after initial symptoms. A large Canadian study suggested that CT without contrast medium within 6 h of symptom onset approached 100% sensitivity when interpreted by an experienced radiologist; at 4 days the sensitivity would only be 50% [18]. Mitchell et al. demonstrated that beyond day 4 the FLAIR MRI sequence would have a 100% sensitivity up to day 14 [19].The question that thereupon arises, is what diagnostic modality should be performed. This matter was addressed by Farzad et al. in an evidence- based debate among emergency medicine physicians. Among the combination of CT and lumbar puncture, MRI and MRA or CT and CT Angiography, there was concluded that CT/LP has the highest sensitivity of the three. The MRI/MRA should be used in younger patients with delayed presentation after symptom onset and CTA in severe, obvious cases of SAH [20] Malhotra et al. also suggested LP after CT scan as the most cost-effective strategy for evaluation of thunderclap headache [21]. Even if after CT and LP no SAH is diagnosed, other differential diagnoses could then be evaluated such as for example reversible cerebral vasoconstriction syndrome, pituitary apoplexy, arteriovenous malformations, dural arteriovenous fistulas, posterior reversible leukoencephalopathy syndrome (PRES) and cerebral sinus venous thrombosis. But the acute diagnosis of the potentially life-threatening SAH would have already been excluded [22].

Table 5
In-hospital mortality causes.

In-hospital mortality causes	Number of patients
Vasospasm/DCI with multiple infarcts and refractory ICP	5
Primary hypoxia	5
Cardio-pulmonary complication/multiorgan failure	5

5. Limitations

Our study is a retrospective observational one with all the corresponding limitations. The data of the patients were however collected prospectively and the therapy was the same regardless of diagnosis been made on day 0 or after day 1. To strengthen the results of the study a matched pair analysis was performed. Another practical limitation as mentioned before is the fact that an unknown number of patients could have died after the initial misdiagnosis without never reaching our clinic for receiving therapy.

6. Conclusion

Acute SAH is a life threatening neurosurgical emergency which can present in different clinical forms from mild to severe. We opt to stimulate the awareness of all specialties physicians to recognize the symptoms of SAH on time in order to optimize the patients' outcome. In the era of multimodal diagnostic options at short notice, the delay of diagnosis of SAH through misdiagnosis, should be minimized to the smallest possible percentage.

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