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ORIGINAL ARTICLE

Computed Tomography Angiography Spot Sign as a Predictor of Hematoma Expansion and Outcome in Spontaneous Intracerebral Hemorrhage

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ABSTRACT

Background: Spontaneous intracerebral hemorrhage (sICH) accounts for10–30 % of acute stroke cases. Hematoma expansion (HE) has been accounted for 30% of patients introducing inside six hours of onset.

Aim: To examine the clinical significance of the CT angiographic spot sign as an indicator for early HE and its relationship with outcome of patients with sICH.

Subject and methods: This study was done at Stroke Unit of Neurology Department, Zagazig University Hospitals and included 50 patients with sICH, 22 of them were males and 28 were females, their age ranged from 45-86 years. They were diagnosed clinically and by brain imaging within 6 hours following stroke onset. Follow-up CT scan was performed within 48 hours after the baseline CT scan to detect early HE. Cerebral CTA was done within 12-24 hours of onset of symptoms to detect spot sign. Spot sign was defined as the presence of active contrast extravasations into the hematoma at the time of CTA. The Intra-cerebral hemorrhage (ICH) scale and Barthel index (BI) were performed to assess patients' outcome.

Results: Spot sign was observed on CTA in 30 (60%) of 50 patients with ICH. Hematoma expansion occurred in 27 patients (25 of cases with positive spot sign on CTA, while only two cases had negative spot sign). There was highly statistically significant association between spot sign and hematoma expansion, and also with the outcome of the patients.

Conclusion: The Spot Sign is a promising sign for predicting hematoma expansion and outcome of patients with acute sICH.

Keywords: Spot sign, CTA, HE, spontaneous intracerebral hemorrhage.

INTRODUCTION

Spontaneous intracerebral hemorrhage (sICH) is the second most common cause of stroke, after ischemic stroke and has been associated with high mortality and morbidity. Thirty day mortality for ICH has been reported to be 35–52 % and one-half of the deaths occur in the acute phase, especially within the first two days [1, 2]. Identifying predictors of early neurologic deterioration after ICH can help in the early management protocols and lead to more favorable outcomes [4]. In the past, several investigators tried to recognize the prognostic factors of outcome in patients with ICH [3, 4]. Previous studies had investigated great relations between clinical, laboratory and radiographic signs and outcome in patients with ICH [1, 5]. Early HE occurs in 18–38% of patients investigated within 3 hours of ICH onset, and more than 70% develop at least some extent of HE within 24 h of symptom onset, even in the absence of known dys-coagulopathy, suggesting an active bleeding progression in the hyperacute phase of ICH [6].Spot sign is one of the most important radiological factors predicting early HE [7]. Spot sign was defined as the presence of active contrast extravasation into the hematoma at the time of multi-detector CT angiography (MDCTA). It is a bright spot of 1 to 2 mm focus of enhancement within a hematoma. It is an indicator of active hemorrhage and has been associated with an increased risk of significant HE and mortality in

patients with ICH [7]. Using the spot sign to identify patients whose ICH is expected to grow is an excellent way of putting patients into interventions either medical or surgical one [8].

PATIENTS AND METHODS

Patients This study was done in Critical Care Unit and Stroke Unit of Neurology Department, Zagazig University Hospitals, during the period from August 2016 to August 2018. Fifty patients were included in our study, 22 of them were males and 28 were females, their age ranged from 45-86 years. The study included patients with acute primary ICH. The patients were diagnosed by history of important risk factors as hypertension, sudden onset of focal neurological deficit, symptoms of increased intracranial tension and the diagnosis was confirmed by CT brain done within six hours of symptoms. Patients were excluded from the study if they were: under the age of 18 years, with history of head trauma, recent surgical hematoma evacuation (within the past six months), on current anticoagulant therapy, had ischemic stroke, with aterio-venous malformations, with hemorrhagic transformation of ischemic stroke, with subarachnoid hemorrhage, with chronic liver or kidney disease, with malignancy and pregnancy.

Methods

1. Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University.
2. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.
3. Full history taking, stressing on vascular risk factors including hypertension, diabetes mellitus, dyslipidemia, smoking and previous stroke.
4. General and neurological examination with assessment of level of consciousness on admission using Glasgow Coma Score (GCS) [9], the body temperature on admission was recorded orally or rectally. 5. Applying the Intra-Cerebral Hemorrhage (ICH) scale [10] at admission and after one week to detect short term outcome. It is used for assessment of severity and expected mortality of cases. The range of score is from 0 up to 6 points with each point predicts the percentage of expected short term mortality (0=0%, 1=13%, 2=26%, 3=72%, 4=97%, 5=99% and 6=100%).
6. Applying the Barthel index (BI); which is the measure of dependency of patients; at admission, after one week and after one month to detect short term outcome. The maximum possible score is **100** which indicates excellent functional outcome and the minimum possible score is **zero** which indicates poor functional outcome. Neurological outcome of patients was classified according to BI as independent (score: 100), mildly dependent (score: 60–95), moderately dependent (score: 40–55), severely dependent (score: 20–35) and totally dependent (score: <20), [11].
7.Laboratory assessment including complete blood count with special stress on the total leukocytic count, Blood glucose level, Liver function tests, kidney function tests and lipid profile.
8. Computerized Tomography: CT brain was done within 6 hours of onset of symptoms and after 48 hours of initial CT for all patients with stress on hematoma location; hematoma volume which was measured on initial brain CT scans by the formula *ABC*/2, where *A* is the greatest hemorrhage diameter by CT, *B* is the diameter 90° to *A*, and *C* is the approximate number of CT slices with hemorrhage multiplied by the slice thickness [29]. and they were classified according to the ICH volume into < 30 cm^3 & ≥ 30 cm^3. In addition to the hematoma growth (which indicates expansion or increase in its volume about 33% or 6 ml in subsequent follow up after 48hours), [12].
9. Computed Tomography Angiography (CTA) brain was done using Multi- detector CT Angiography within 12-24 hours of onset of symptoms. Its aim was detection of spot sign (whether present or not). Spot sign was defined as a focus of any size and morphology, discontinuous from normal or abnormal vasculature adjacent to ICH, ≥ One focus of contrast pooling within ICH and Hounsfield unit density at least 120 HU[7] .

Statistical Analysis: All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows. Continuous variables were expressed as the mean ± SD & median (range), and the categorical variables were expressed as a number (percentage). All tests were two sided. P-value < 0.05 was considered statistically significant (S), P-value < 0.001 was considered highly statistically significant (HS), and p-value > 0.05 was considered statistically insignificant (NS).

RESULTS

The included patients in our study were 50 patients with acute spontaneous ICH, 22 of them were males and 28 were females. Their age ranged from 45-86 years (mean 61.92±9.24 years). Hypertension was a major risk factor in the studied patients (96% of cases) followed by diabetes mellitus (50%) and lastly smoking (30%).

Glasgow coma scale (GSC) mean among patients at admission was12.5±2.03 and after one week was 11.46±3.5. Barthel index (BI) mean among patients at admission was 28.8±15.2, after one week was 34.88±22.39 and after one month was 51.47±21.2. Intracranial hemorrhage score (ICH score) mean at admission was1.36±1 and after one week was 1.76±1.9 (table 1).Cases with hematoma volume ≤ 30 cm^3 at admission were 29 and those with

hematoma volume >30 cm³ were 21 patients. Volume of hematoma in initial CT brain was 42.48±39.23 and in follow up CT brain was 56.21±63.98. Hematoma expansion of the studied patients occurred in 27 patients (54% of cases), (table 2).Spot sign was positive in 30(60%) of cases and negative in 20(40%) of cases (figure 1).

In-hospital mortality represented 6 (12%) cases. Mildly dependent represented 15 (30%) cases, while moderately and severely dependent represented 18 (36%) and 11 (22%) cases respectively.There was high significant association between spot sign and hematoma expansion (P value 0.001**), with sensitivity 92.6% and specificity 78.3%. Spot sign was positive in 30 cases (25 cases had hematoma expansion). While, only two cases with negative spot sign had HE, (table3). Sensitivity of spot sign to detect HE= N of spot sign positive patients among total N of patients with HE= 25/27*100= 92.6%. Specificity of spot sign to detect HE= N of spot sign negative patients among total N of patients without HE= 18/23*100= 78.3%.There was a significant association between hematoma expansion and outcome of the patients (P value was 0.002*). All dead cases (6 cases) had hematoma expansion and 21 patients with hematoma expansion were moderately to severely dependent (table 4).

Spot sign was highly significantly associated with patient's outcome (P value was 0.001*).All dead cases (12% of cases) had positive spot sign and 23 cases with positive spot sign were moderately to severely dependent (table 5

Table 1: Glasgow coma scale, ICH score and BI of studied patients.

Scale		On admission	After one week	After one month
GCS	Mean± SD	**12.5±2.03**	**11.46±3.50**	
	Range	**7 – 15**	**4 – 15**	
ICH scale	Mean± SD	**1.36±1.0**	**1.76±1.93**	
	Range	**Zero – 3**	**Zero – 4**	
BI	Mean± SD	**28.8±15.20**	**34.88±22.39**	**51.47±21.20**
	Range	**25 – 70**	**30 – 80**	**35 – 90**

GSC=Glasgow Coma Scale BI= Barthel index ICH scale=Intracerebral Hemorrhage scale.

Table 2: Changes in hematoma volume and expansion in computed tomography scan

Volume of hematoma ≤ 30ml	**N**	**29**
	%	**58%**
Volume of hematoma >30ml	**N**	**21**
	%	**42%**
Volume of hematoma in initial CT brain(ml)	Mean± SD	**42.48± 39.24**
	Range	**6.75 – 216**
Volume of hematoma in follow up CT brain(ml)	Mean± SD	**56.21± 63.99**
	Range	**3.75 – 315**
Hematoma expansion	**Yes N (%)**	**27 (54%)**
	No N (%)	**23 (46%)**

Table (3): Association between spot sign and hematoma expansion

			Spot Sign		Total	X^2	P
			Negative	positive			
Hematoma expansion	NO	N	**18**	**5**	**23**	**25.98**	**0.001****
		%	**90.0%**	**16.7%**	**46.0%**		
	YES	N	**2**	**25**	**27**		
		%	**10.0%**	**83.3%**	**54.0%**		
Total		N	**20**	**30**	**50**		
		%	**100%**	**100%**	**100%**		

Sensitivity of spot sign to detect HE= N of spot sign positive patients among total N of patients with HE= 25/27*100= 92.6%.
Specificity of spot sign to detect HE= N of spot sign negative patients among total N of patients without HE= 18/23*100= 78.3%.

Table (4): Association between hematoma expansion and outcome of the patients

Outcome	Hematoma expansion		X^2	P
	Yes	No		
In-hospital mortality	6 (22.2%)	0 (0.0%)	20.59	0.002*
Independent	0 (0%)	0 (0%)		
Mildly dependent	0 (0.0%)	15 (65.2%)		
Moderately dependent	12 (44.4%)	6 (26.1%)		
Severely dependent	9 (33.3%)	2 (8.7%)		
Totally dependent	0 (0%)	0 (0%)		
Total	27 (100%)	23 (100%)		

Table (5): Association between spot sign and outcome of patients

Outcome	Spot sign		X^2	P
	Positive	Negative		
In-hospital mortality	6 (20%)	0 (0.0%)	22.59	0.001**
Independent	0 (0%)	0 (0%)		
Mildly dependent	1 (3.33%)	14 (70%)		
Moderately dependent	13 (43.33%)	5 (25%)		
Severely dependent	10 (33.33%)	1 (5%)		
Totally dependent	0 (0%)	0 (0%)		
Total	30 (100%)	20 (100%)		

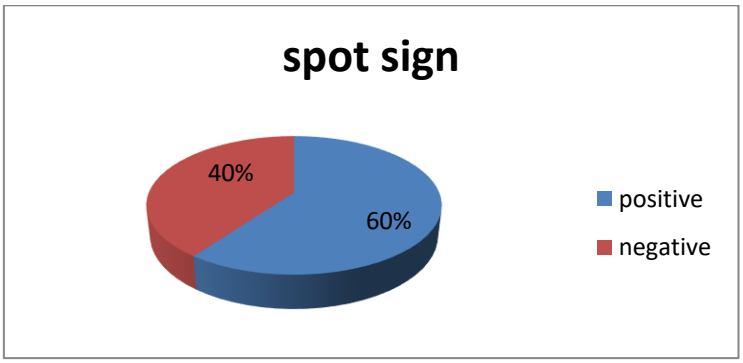

Figure 1: Spot sign distribution of studied patient

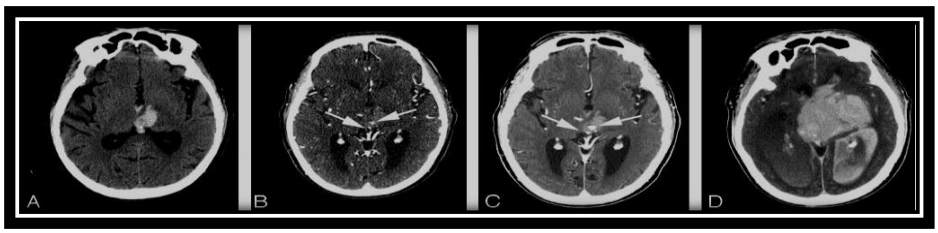

Figure 2: 69-year-old hypertensive man underwent imaging 2 hours following onset of right-sided paralysis. (*A*) Admission NCCT demonstrates left thalamic hematoma with extension of hemorrhage into the third ventricle.
After 24hours CTA (*B*) and CECT (*C*), respectively,were done and showed 2 foci of active extravasation (*arrows*); **postive spot sign.**
*(D)*Follow-up NCCT 48 hours later shows marked hematoma growth with hemorrhage in both lateral ventricles and severe hydrocephalus.

DISCUSSION

Spontaneous intracerebral hemorrhage is the most devastating type of stroke, with mortality up to 40% at 30 days after ictus and only one-fifth of the survivors could live independently after 6 months [13]. Many ICHs still expand at the time of initial emergency department assessment, causing increased risk of death or disability. Therefore, HE is a promising potential treatment target to improve prognosis of ICH [13]. Spot sign was reported as a risk factor for hematoma expansion and poor outcome after ICH [14].In our present study, we included 50 patients diagnosed with spontaneous ICH, their mean age 61.92±9.24 years and ranged from 45-86 years. Males were 44% and 56% were females. The hematoma volume varied between our patients. While patients with hematoma volume ≤ 30 cm^3 are 29 patients (58%), those with large hematoma volume >30 cm^3 are 21 patients (42%). These results were in agreement with that of **Broderick et al.**[15], whom found that patients with hematoma volume >30 cm^3 were 71 out of 188 patients (37.76%) and those with hematoma volume ≤ 30 cm^3 were 117 out of 188 patients (62.23%). Recently **Murthy et al.**[16], found nearly correlated results with ours, that patients with hematoma volume ≤ 30 cm^3 are (75.7%) and those with hematoma volume >30 cm^3 are (24.3%) but the difference in the proportions of the two groups of hematoma volume in our study and that of **Murthy et al.,** may be due the larger sample size (596 patients).Initial hematoma expansion following spontaneous acute ICH is an important marker of poor prognosis, increased mortality, and longer hospital stay [17]**.** Therefore, HE is a promising potential treatment target to improve prognosis of ICH [14].We defined HE in our study as an increase in hematoma volume>33% or >6 ml from the baseline CT scan [12]. Hematoma expansion occurred in 27 cases (54% of patients) of whom 6 patients died within the first week after admission and outcome of the rest of cases was assessed by GCS, Barthel Index and ICH score.Spot sign which was the target of our study was positive in 60% of the cases. **Morotti et al.** [18] studied 90 patients of whom spot sign was found in 67.8% of the patients. The result of their study can be explained by usage of a new technique for detection of spot sign which was a phantom based calibration of CTA images. Prevalence of spot sign, also, depends on scan time. Study done by **Tsukabe et al.** [19] proved that idea; the result of this study found that spot sign was present in 24.1% of the patients in the early phase of imaging (spot sign before 23.13 seconds of start of scan) and in 53% of the patients in the late phase of imaging (spot sign after 23.13 seconds). On the other hand **Dowlatshahi et al.** [20] found that spot sign was positive in 37% of the patients. This result can be explained by the smaller sample size (35 patients) in this study.Our study proved that there was a high significant association between spot sign and HE, with sensitivity 92.6% and specificity 78.3%. Spot sign was positive in 30 (60%) of 50 cases with ICH. Hematoma expansion occurred in 27 patients (25 of cases with positive spot sign on CTA). Two meta-analysis studies done by **Xu et al.** [14] **and Sporns et al.** [21] showed that there high significant association between spot sign and HE with sensitivity 62%,53% respectively and specificity 88% in both studies. **Zheng et al.** [13] performed, also, a study on 115 patients to detect accuracy of spot sign in predicting HE in primary intracerebral hemorrhage patients and found that the sensitivity and the specificity of the spot sign for predicting hematoma expansion were 57.14%, 89.66% respectively.The results of our study showed that there was a significant association between hematoma expansion and outcome of the patients. Most cases of HE were moderately to severely dependent on family members during performance of daily activities and all dead cases had HE. These results matched with **Li et al.** [22]**, Miyahara et al.** [23] and **Lim et al.** [24] whom found that HE was significantly associated with poor functional outcome in patients with primary ICH. **Miyahara et al.** used non contrast CT brain of primary ICH patients and created a new

prediction score for detecting short term outcome of patients. This new score was called HEAVN score (heterogeneity, Peripheral edema, anticoagulant use, volume of hematoma >30 mL on initial CT, niveau formation).The study also proved that, spot sign was highly significantly associated with patient's outcome (P value was 0.001*). All dead cases (12% of cases) had positive spot sign and 23 cases with positive spot sign were moderately to severely dependent according to BI. These results were in agreement with **Zhang et al.** [25] whom found that the spot sign was an excellent independent predictor for bad outcome of patients but they followed the patients for three months outcome and mortality. The results revealed that there was a significant association between spot sign and mortality of the patients. Dead cases represented 12% of the cases (6 patients), and all dead cases had positive spot sign. The sensitivity of spot for predicting of mortality was100% and the specificity was 45.5%. These results did not go in the same line with **Morotti et al.** [26] whom found that in-hospital mortality was higher in spot sign-positive versus spot sign-negative subjects but the specificity of spot sign for predicting in-hospital mortality was 95%. This result may be explained by knowing that **Morotti et al.** studied the CT angiography spot sign, HE, and outcome in primary pontine intracerebral hemorrhage only and excluded other sites and types of hemorrhage from the study. **Li et al.** [27] did a prospective study of 139 cases on spot sign , contrast extravasation on computed tomography angiography and clinical outcome in primary intracerebral hemorrhage and their results showed the sensitivity of spot for predicting of in-hospital mortality was 60% and the specificity was 81.4 %. **Goldstein et al.** [28] results showed sensitivity 73% and specificity 50% of spot sign for predicting in-hospital mortality of patients.

CONCLUSION

The Spot Sign is a potentially promising sign for predicting hematoma expansion and outcome of patients with acute primary ICH. This sign may play a role in patient selection for clinical trials of acute haemostatic therapy or surgical interventions aimed at minimizing hematoma growth.

RECOMMENDATIONS

CT Angiogram should be done immediately after an acute intracerebral hemorrhage and the spot sign should be specifically looked for in a CT angiogram. The Clinicians should be aware of the Spot Sign and its mimics. Presence of Spot Sign predicts poor outcome and such patients should be vigorously treated.

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