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PRE HOSPITAL AND IN HOSPITAL DELAYS AFTER THE ONSET OF ACUTE ISCHEMIC STROKE IN A SAMPLE OF EGYPTIAN PATIENTS

By

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ABSTRACT

Background: Cerebrovascular stroke (CVS) is the second most common cause of death after ischemic heart disease and the third most common cause of disability after ischemic heart disease and cancer.

Objective: Investigating the time lags and the factors causing pre hospital and in hospital delays after acute ischemic stroke.

Patients and Methods: This study included 70 patients recruited from the Neurology Department Al -Azhar University (Al Hussein Hospital) and El Sahel Teaching Hospital during the period from November 2018 to June 2019 with the diagnosis of acute ischemic stroke.

Results: The pre hospital time ranged from 6 to168 hours with mean 32.657 ± 32.838 hours. The laboratory time ranged from 48 to 70 minutes with mean 56.943 ± 4.943 minutes and computed tomography time ranged from 15 to 40 minutes with mean 27.271± 5.868 minutes. The results revealed that pre hospital delay was due to lake of awareness about stroke symptoms and signs, late decision to seek medical care and lake of transportation by Emergency Medical System, and revealed that in hospital delay due to delayed laboratory investigations and computed tomography completion time.

Conclusion: The time interval between the onset of symptoms and the decision to call for medical care was far from optimal in patients with acute stroke, and was the underlying cause of the prolonged pre hospital delay. The present study revealed that all patients arrived at our hospitals were too late to benefit maximally from the emerging stroke therapies.

Keywords: Cerebrovascular Stroke - Acute Ischemic Stroke - Intravenous Tissue Plasminogen Activator.

INTRODUCTION

Stroke is a clinical syndrome caused by focal or generalized brain injury that lasts more than 24 hours or lead to death and has no other cause than vascular. Stroke constitutes a big social and economic problem as it can lead to death or disability. In the highly developed countries stroke is the third most common cause of adult death, the second leading cause of dementia and the most common cause of disability *(Starostka et al., 2017)*.

The outcome of stroke can be made worse by failure to promptly start medical management as well as detect and deal adequately with the complications of stroke in the acute stage. Medical intervention has the ability to manage and

prevent complications of stroke, thereby improving the long term prognosis of acute strokes, It is important to note that prevention of stroke uses less resources compared to managing the complications of actual stroke when they occur *(Seremwe et al., 2017)*.

Successful outcome is based on early recognition of stroke, transportation to the hospital emergency department immediately after stroke, timely imaging, proper diagnosis and thrombolysis within 4.5 hours *(Badachi et al., 2015)*.

Despite the proven efficacy of intravenous tissue plasminogen activator (IV tPA) within the first 4.5h after the onset of symptoms, only a small proportion of stroke victims receive this medication .

Factors contributing to this delay are many and are influenced by awareness of stroke signs and symptoms, perception of the importance of early presentation for treatment, religious and cultural beliefs, educational level, geographical accessibility and technical factors such as the availability of diagnostic facilities and therapies *(Al Khathaami et al., 2018)*.

The present work aimed to investigate the time lags and the factors causing pre hospital and in hospital delays after acute ischemic stroke.

PATIENTS AND METHODS

The design of this study was a case series hospital-based, prospective observational study. Seventy patients with acute ischemic stroke (33 males “47.14%” and 37 females “52.86 %”) were studied ranging of age from 35 to 78 years.

All patients were recruited from Neurology Department of Al-Azhar University Hospital (Al Hussein), and El Sahel Teaching Hospital with signs or symptoms of acute ischemic stroke during the period from November 2018 to June 2019. Written informed consents were taken from all patients or their first-degree relatives.

Inclusion criteria:

1. Patients with age more than 18 years old.
2. Patients with acute ischemic stroke.

Exclusion criteria:

1. Patients with current intracranial hemorrhage.
2. Sub arachnoid hemorrhage.
3. Acute internal bleeding.
4. Recent head trauma.
5. Brain tumors.
6. Arterio venous malformation.
7. Cerebral venous sinus thrombosis.

All the following data collected from the patients, family members, witnesses and medical records.

1. Review of the demographic characteristics .
2. Clinical assessment of patients.
3. Imaging assessment: Computed Tomography, Magnetic Resonance Imaging, and Magnetic Resonance Angiography (MRA) was visualized for the presence of intracranial stenosis or occlusion. Significant intracranial stenosis was assumed if $\geq 50\%$.
4. Laboratory assessment: The laboratory investigations including random blood

sugar (RBS) at the time of admission, total leucocyte count (TLC), International Normalize Ratio (INR), erythrocyte sedimentation rate (ESR), glycated hemoglobin (HB), and lipid profile (total cholesterol, low density lipoproteins [LDL], high density lipoproteins [HDL] and triglycerides).

All patients were subjected to estimation of the duration of neurological consultation time, CT completion time, ECG completion time and laboratory investigations time.

The study was approved by the Research Ethics Committee in faculty of medicine, Al Azhar University, Cairo, Egypt.

Statistical analysis:

The collected data were coded, tabulated and subjected to statistical analysis using descriptive statistics: Means, standard deviations, numbers and percentages were computed.

Mean to measure a central value for a group of data.

Standard deviation SD to measure the degree of difference between two samples means.

Chi-square testing was used to compare qualitative data.

ANOVA was used to compare quantitative data .

All statistical analysis was performed using SPSS 19 for windows.

In all statistical tests, P value < 0.05 was considered significant.

RESULTS

Patient's demographics characteristics

The mean age was 63 years, 33(47.14%) patients were males and 37(52.86%) patients were females. Forty two (60%) patients were illiterate, 20(28.57%) patients had moderate education, and 8(11.43%) patients had high education. Twenty one (30%) patients were urban, and 49 (70%) patients were rural. Only 9 (12.86%) patients were transported by emergency medical system (EMS), 54(77.14%) patients transported by non EMS, and 7(10%) patients referred from other medical facilities. A history of previous stroke was reported in 11(15.71%) patients. Ten (14.29%) patients lived alone. The mean driving time from the onset place to the first hospital was 42.429 minutes, the mean pre hospital time was 32.657 hours, the mean neurological consultation time was 20.429 minutes, the mean CT completion time was 27.271minutes, and the mean laboratory completion time was 56.943 minutes **(Table 1)**.

Table (1): The socio demographics characteristics of patients and Descriptive Statistics

Age of patients	**N**	**%**
<65 Years	33	47.14
>65 Years	37	52.86
Total	70	100.00
Sex of patients	**N**	**%**
Males	33	47.14
Females	37	52.86
Total	70	100.00
Level of education	**N**	**%**
Illiterate	42	60.00
Moderate	20	28.57
High	8	11.43
Total	70	100.00
Place of attack	**N**	**%**
Urban	21	30.00
Rural	49	70.00
Total	70	100.00
Transportation	**N**	**%**
EMS	9	12.86
Non EMS	54	77.14
Referral	7	10.00
Total	70	100.00
Previous stroke	**N**	**%**
Yes	11	15.71
No	59	84.29
Total	70	100.00
Living alone or not	**N**	**%**
Yes	10	14.29
No	60	85.71
Total	70	100.00

Descriptive Statistics						
	Range			**Mean**	**±**	**SD**
Age	35	-	87	63.157	±	12.545
The driving time from the onset place to the first hospital (Minutes)	15	-	90	42.429	±	18.819
Pre hospital time (Hours)	6	-	168	32.657	±	32.838
Neurological consultation time (Minutes)	10	-	35	20.429	±	5.154
CT Completion time (Minutes)	15	-	40	27.271	±	5.868
ECG time (Minutes)	10	-	30	20.571	±	5.444
Laboratory time (Minutes)	48	-	70	56.943	±	4.943

Eight (11.43%) patients awake with symptoms. Initial symptoms were limb weakness in 53 (75.71%) patients, speech disturbance in 38 (54.29%) patients, dizziness and vertigo in 32 (45.71%) patients, and limb numbness in 28 (40%) patients. Among the stroke risk factors, 57 (81.43%) patients had hypertension, 42 (60%) patients had diabetes, 35 (50%) patients had hyperlipidemia, 18 (25.71%) patients had arrhythmia, 23(32.86%) patients had smoking as a risk factor, and 16 (22.86%) patients had valvular heart diseases. Thirty five (50%) patients had knowledge about stroke, and 35 (50%) patients had not knowledge about stroke. Twelve 17.14%) patients were able to recognize the problem as a stroke, and 58 (82.86%) patients were not able to recognize the problem as a stroke. Eight (11.43%) contacted their relatives, 28 (40%) gave aspirin, and 34 (48.57%) acted nothing. Diurnal onset of acute ischemic stroke was observed in 59 (84.29%) patients, while the stroke onset

was nocturnal in 11 (15.17%) patients **(Table 2)**.

Table (2): Ischemic stroke patient's of risk factors, awakening with symptoms, initial symptoms, knowledge of stroke, recognizing the problem as a stroke, patients initial reaction when symptoms first occurred and stroke onset

		N	%
Risk factors	**Hypertension**	57	81.43
	Diabetes	42	60.00
	Hyperlipidemia	35	50.00
	Arrhythmia	18	25.71
	Smoking	23	32.86
	Valvular heart diseases	16	22.86
Awakening with symptoms	**Yes**	8	11.43
	No	62	88.57
	Total	70	100.00
Initial symptoms	**Limb weakness**	53	75.71
	Speech disturbance	38	54.29
	Dizziness, Vertigo	32	45.71
	Limb numbness	28	40.00
Knowledge of stroke	**Yes**	35	50.00
	No	35	50.00
	Total	70	100.00
Recognizing the problem as a stroke	**Yes**	12	17.14
	No	58	82.86
	Total	70	100.00
Patients initial reaction when symptoms first occurred	**Contact relatives**	8	11.43
	Giving aspirin	28	40.00
	Nothing	34	48.57
	Total	70	100.00
Stroke Onset	**Diurnal**	59	84.29
	Nocturnal	11	15.71
	Total	70	100.00

Chi-square analysis showed that the level of education ($\chi 2$ p= 0.038) was the factor significantly associated with pre-hospital delay, the mode of transportation ($\chi 2$ p=0.612), previous stroke ($\chi 2$ p=0.217), lived alone ($\chi 2$ p=0.330), place of attack ($\chi 2$ p=1.000). Patients initial reaction when symptoms first occurred ($\chi 2$ p=0.549), and recognition the problem as a stroke ($\chi 2$ p=0.110) were associated with pre-hospital delay. ANOVA test (0.016*), and post hoc analysis (0.003**) showed that the laboratory completion time was the factor significantly associated with pre-hospital delay **(Table 3)**.

Table (3): Pre hospital time delay and characteristics of patients.

Parameters \ Pre hospital time		6 - <12 Hours		12-24 Hours		>24 Hours		Total		Chi-Square	
		N	%	N	%	N	%	N	%	X^2	P-value
Level of education	Illiterate	14	70.00	15	50.00	13	65.00	42	60.00	10.163	0.038*
	Moderate	3	15.00	14	46.67	3	15.00	20	28.57		
	High	3	15.00	1	3.33	4	20.00	8	11.43		
	Total	20	100.00	30	100.00	20	100.00	70	100.00		
Place of attack	Urban	6	30.00	9	30.00	6	30.00	21	30.00	0.000	1.000
	Rural	14	70.00	21	70.00	14	70.00	49	70.00		
	Total	20	100.00	30	100.00	20	100.00	70	100.00		
Transportation	EMS	4	20.00	3	10.00	2	10.00	9	12.86	2.685	0.612
	Non EMS	13	65.00	24	80.00	17	85.00	54	77.14		
	Referral	3	15.00	3	10.00	1	5.00	7	10.00		
	Total	20	100.00	30	100.00	20	100.00	70	100.00		
Previous stroke or MI	Yes	3	15.00	7	23.33	1	5.00	11	15.71	3.056	0.217
	No	17	85.00	23	76.67	19	95.00	59	84.29		
	Total	20	100.00	30	100.00	20	100.00	70	100.00		
Patients initial reaction when symptoms first occurred	Contact relatives	2	10.00	5	16.67	1	5.00	8	11.43	3.050	0.549
	Giving aspirin	10	50.00	11	36.67	7	35.00	28	40.00		
	Nothing	8	40.00	14	46.67	12	60.00	34	48.57		
	Total	20	100.00	30	100.00	20	100.00	70	100.00		
Risk factors	Hypertension	18	90.00	25	83.33	14	70.00	57	81.43	2.771	0.250
	Diabetes	9	45.00	22	73.33	11	55.00	42	60.00	4.306	0.116
	Hyperlipidemia	9	45.00	17	56.67	9	45.00	35	50.00	0.933	0.627
	Arrhythmia	3	15.00	8	26.67	7	35.00	18	25.71	2.119	0.347
	Smoking	8	40.00	8	26.67	7	35.00	23	32.86	1.025	0.599
	Valvular heart diseases	5	25.00	7	23.33	4	20.00	16	22.86	0.149	0.928
Living alone	Yes	3	15.00	6	20.00	1	5.00	10	14.29	2.217	0.330
	No	17	85.00	24	80.00	19	95.00	60	85.71		
	Total	20	100.00	30	100.00	20	100.00	70	100.00		
Recognizing the problem as a stroke	Yes	6	30.00	5	16.67	1	5.00	12	17.14	4.409	0.110
	No	14	70.00	25	83.33	19	95.00	58	82.86		
	Total	20	100.00	30	100.00	20	100.00	70	100.00		

		Pre hospital time									ANOVA	
		6 - < 12 Hours			12-24 Hours			>24 Hours			F	P-value
Age	Range	35	-	83	36	-	85	40	-	87	0.196	0.823
	Mean ±SD	64.600	±	11.232	62.833	±	12.649	62.200	±	14.066		
Neurological consultation time (Minutes)	Range	12	-	35	15	-	30	10	-	30	0.668	0.516
	Mean ±SD	20.950	±	6.493	20.833	±	4.227	19.300	±	5.017		
CT Completion time (Minutes)	Range	15	-	40	18	-	36	18	-	40	1.081	0.345
	Mean ±SD	26.600	±	6.142	26.633	±	5.209	28.900	±	6.480		
Laboratory time (Minutes)	Range	50	-	67	50	-	70	48	-	65	4.416	0.016*
	Mean ±SD	57.850	±	4.848	58.100	±	4.936	54.300	±	4.207		

Post hoc analysis by LSD		
6 - < 12 Hours Vs **12-24 Hours**	**6 - < 12 Hours** Vs **>24 Hours**	**12-24 Hours** Vs **>24 Hours**
0.401	0.115	**0.003****

DISCUSSION

Acute ischemic stroke (A I S) is characterized by the sudden loss of blood circulation to an area of the brain, typically in a vascular territory, resulting in a corresponding loss of neurologic function *(Mozaffarian et al., 2015)*. Ischemic stroke is the most common type of stroke occurs as a result of insufficient or interrupted blood flow to an area caused by blockage of an artery. According to data released by the American Heart Association (A H A) 87% of stroke are classified as ischemic *(Roger et al., 2012)*. The time is brain is a concept introduced more than two decades ago, encapsulates the crucial importance of time in treating acute stroke, this has become more pertinent since the advent of thrombolysis treatment using tissue plasminogen activator and endovascular therapy *(Furlan, 2015)*. We aimed to investigate the time lags and the factors caused pre hospital and in hospital delays after acute ischemic stroke.

The results of our study found that the pre hospital delay among ischemic stroke patients was considerable, in the present study the pre hospital time ranged from 6 to 168 hours with mean 32.657± 32.838 hours. These results explained by lack of awareness of patients and their relatives to recognize stroke symptoms and signs as a medical emergency, lack of awareness about thrombolysis, lack of public awareness, non-availability of ambulance services and contacted with local general practitioner, non-affordability, location of stroke onset and lived alone were the most important barriers associated with pre hospital delay after acute ischemic stroke. *Badachi et al. (2015)*, found that the mean time to reach nearest primary healthcare hospital was 18.02 ± 26.98 hrs., 34 patients reached nearest primary healthcare hospital between 6 and 24 hrs., 16 patients reached between 24 and 72 hrs., and two patients reached beyond 72 hrs., Seven patients arrived within 6 h after stroke onset at a tertiary care hospital where thrombolysis facility was available, 52 patients reached between 6 and 24 hrs., 15 patients reached between 24 and 48 hrs., 13 patients reached between 48 and 72 h, and 13 patients reached beyond 72 hrs. Median time to reach tertiary care hospital was 40.87 ± 45.17 hrs. Thirty patients arrived at the nearest primary healthcare hospital within 3 hrs. and three patients arrived between 3 and 4.5 hrs., 15 patients reached between 4.5 and 6 hrs.. *Ashraf et al. (2015)* found that the median delay from onset of symptoms to hospital arrival was 12 hours, only 67 (25.3%) patients arrived within 4 hours, while 74.7% arrived after 4 hours (21.6%) within 6 hours, 20.5% within 24 hours, and 32% more than 24 hours) . *Wasay et al. (2010)* found that the mean time interval between stroke onset and arrival to emergency room was 49 min (range 15–110 min) .They explained their results by increased awareness of patients and relatives of stroke symptoms and signs, transport by EMS, stroke severity, lowered consciousness, sudden onset of stroke, and not live alone.

In the current study 60% of patients were illiterate, 28.57% were moderately educated, and 11.43% were highly educated. Our study found significant delay of illiterate patients. These results might be explained by patients with high educational level may know basic informations about stroke symptoms and

importance of early stroke intervention. *Springer and Labovitz (2018)* found that patients with higher or highest educational level have higher probability to arrive within the first 6 hrs. than those with only basic educational background.

In the present study, we found only 12.86% of patients were transported by EMS, 77.19% of patients transported by non EMS, 10% of patients referred from other medical facilities. These results may be explained by lack of EMS, most patients lived in remote and rural areas, absence of stroke call system in the EMS, and non-recognition when call EMS. This was consistent with *Zhao et al. (2019)* found poor awareness in using EMS was one of the major factors in prolonged pre hospital delay, less than 15% of people in India used EMS, due to lack of EMS itself, In some developing countries, EMS is not well developed and does not have enough ambulances, they found that there were a very limited number of operational ambulances in India that actually provide pre hospital care.

In the present study we found the CT completion time ranged from 15 to 40 minutes. Our results found that considerable delay in CT completion time. These results explained by lack of staff to transport patients, distance between ED and CT room, shortage of radiologists, radiographers, not enough CT scanners, lack of priority for patients in performance CT and lack of stroke team. *Ogbole et al. (2015)* found that the mean presentation time for CT imaging was 70 hours. Only 31% of all stroke patients presented for CT imaging within 12 hours, and none, within 3 hours. Forty-six percent did not present within 24 hours of symptom onset. In contrast, the study of *Jeon et al. (2017)* found that the median door-to-CT time was 13 minutes. *Huang et al. (2016)* found the median time from door to CT was 24 (16_29) minutes. *Zinkstok et al. (2016)* found that the median time from door to CT was 6 (4_10) minutes. Their results explained by introduced ambulance pre notification, updated the thrombolysis protocol, specified time limits for each step, applied Point of care system (POCT), changed their MRI screening system to CT-plus-MRI screening, introduced a computerized physician order entry system for thrombolysis candidates, relocated a new MRI machine beside the ER, Direct transfer onto CT-table upon hospital arrival, administered tPA on the CT table.

In the present study, we found the laboratory completion time ranged from 48 to 70 minutes with. Our results found that significant delay in the time of laboratory investigations ($p = 0.016$). Waiting for laboratory results was a major barrier of in hospital delay after AIS, due to central hospital laboratory consumed long time for (routine tests, hematology and coagulation profile) due to time for registration, centrifugation, analyses, and validation, time for electronic data processing. Lak of point of care system, and lack of technicians. Our results consistent with the study of *Huang et al. (2015)* who found that the door to laboratory time was 84 (67–103) minutes, among the specific causes of time intervals, 177 (87.6%) of patients of delay DTLs were due to blood biochemistry tests with ($P < 0.001$) were positively associated with severe in-hospital delay, they found that excessive abnormal values of laboratory results

were cause of in hospital delay, they revealed time delays spent on laboratory tests were important elements of in-hospital delay and blood biochemistry tests played key roles.

In the current study the age of patients ranged from 35 to 87 years. Our study found that patients ≥ 65 years of age were likely to arrive earlier than patients < 65 years of age. These results might be explained by older patients were more likely to perceive stroke symptoms as a serious occurrence based on personal experience or exposure to stroke patients in their communities, consistent with the study of *Papapanagiotou et al. (2011)*. In contrast, the study of *Eleonora et al. (2014)* found that advanced age was significantly associated with increased delay time, they explained their results by negative previous experiences with hospital treatment, and patients ≥ 65 years of age have been reported to be less likely to know a symptom of stroke than their younger counterpart.

CONCLUSION

The time interval between the onset of symptoms and the decision to call for medical care is far from optimal in patients with acute stroke and is the underlying cause of the prolonged pre hospital delay. The present study revealed that all patients arrived at our hospitals too late to benefit maximally from the emerging stroke therapies, This may be due the failure to recognize the signs and symptoms and the lack of awareness of potential treatment benefits, the non-recognition of the characteristic symptoms of stroke or the late perception of these symptomatology corresponds to the main factor of pre hospital delay.

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التأخير قبل دخول المستشفي وداخل المستشفي بعد السكتة الدماغية الحادة لدي عينة من المرضي المصريين

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خلفية البحث: تعد السكتة الدماغية السبب الثاني للوفاة بعد أمراض القلب الإفقارية؛ والسبب الثالث الأكثر شيوعا بعد السرطان وأمراض القلب الإفقارية.

الهدف من البحث: حساب وقت التأخير قبل دخول المستشفي وحساب الوقت داخل المستشفي وأسباب التأخير.

المرضي وطرق البحث: تم تجميع المرضي من قسم طب المخ والأعصاب في مستشفي الحسين الجامعي التابعة لجامعة الأزهر ومستشفي الساحل التعليمي وعددهم 70مريض بالسكتة الدماغية الإفقارية وهذا البحث أظهر التأخير قبل دخول المستشفي وداخل المستشفي في الفترة من شهرنوفمبر2018 إلي يونيو 2019.

النتائج: الوقت المستغرق قبل دخول المستشفي تراوح من 6 الي 168 ساعة بمتوسط زمني قدرة 32 ساعة ووقت إنتظار نتائج التحاليل الطبية تراوح من 48 الي 70 دقيقة بمتوسط زمني قدرة 65 دقيقة ووقت عمل الأشعة المقطعية تراوح من 15 الي 40 دقيقة بمتوسط زمني 27 دقيقة وفسر هذا التأخير بقلة وعي المريض بأعراض وعلامات السكتة الدماغية والتأخير في إتخاذ قرار العلاج وقلة الإنتقال بسيارات الإسعاف وإنتظار نتائج التحاليل والأشعة المقطعية.

الإستنتاج: الوقت المستغرق من بداية الأعراض والتأخير في إتخاذ قرار العلاج والوصول للمستشفي بعيدا عن الوقت المثالي للوصول وأيضا التأخير داخل المستشفي في إنتظار نتائج التحاليل الأشعة المقطعية أدي إلي التأخير وعدم تلقي العلاج المناسب.