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Research Article

Long-Term Outcome of Acute Ischemic Stroke with Unruptured Intracranial Aneurysm Treated by Intravenous Thrombolysis

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ABSTRACT

Background: There are scarce data on long-term outcome of Acute Ischemic Stroke (AIS) with Unruptured Intracranial Aneurysms (UIAs) treated with Intravenous Thrombolysis (IVT). We studied the clinical characteristics of 10 Caucasians with AIS with UIAs treated IVT.

Methods: We analyzed data from a hospital-basedregistry. The standardized diagnostic work-up included: demographics; stroke risk factors; stroke etiology; stroke severity and treatment. Outcome measures were hemorrhagic complications, mRS on discharge, day 90 and up to 56 months.

On admission all participants had performed the radiological work-up, including Computed Tomography (CT) with and without contrast, perfusion CT, angio-CT of intra and extracranial vessels, and arch of aorta.

Results: We analyzed data from 362 patients; among them 330 had the standardized radiological work-up. Ten patients with UIAs were older as compared to others, and were more often females. UIA was located on the vessel affected by AIS in 2 cases; 1 patient developed brain hemorrhage not related to UIA;mRSon day 90 was as follows: 0 (n=3); 1 (n=2); 2 (n=2); 3 (n=1); 6 (n=2). Eight cases were alive up to 56 months. In 9 cases the aneurysm size varied from 2-6 mm; in one case-was 12 mm. Literature shows only 9 cases with the UIA sized >10 mm treated with IT.

Conclusion: Introducing expanded radiological diagnostic work-up before treatment decision of AIS in the era of different etiological treatment options, allows not only to detect the size of penumbra, clot location but also the presence of vascular malformations, including IUAs0.

Keywords: Acute ischemic stroke, Outcome; Unruptured intracranial aneurysm; Thrombolysis

INTRODUCTION

According to guidelines decision about introducing Intravenous Thrombolysis (IT) in Acute Ischemic Stroke (AIS) is primarily based on the time of stroke onset and the result of non-enhanced Computed Tomography (CT) examination. Epidemiological data show that the prevalence of Unruptured Intracranial Aneurysms (UIAs) in the population varies from 3% to 6% [1], and increases with age [2]; what means, that some patients with AIS, who may have aneurysm may also receive IT-the potentially harmful treatment. The current guidelines [3] accept IT for treatment of AIS, if a patient has UIA of the size of 10 mm or less.

Since the number of described cases with UIAs treated with IT is low, and very few are of Caucasian ancestry, we decided to study the clinical characteristics and long-term outcome of 10 patients of Caucasian ancestry with AIS with incidental UIAs treated with IT.

MATERIALS AND METHODS

We performed a retrospective analysis of prospectively collected data in the Krakow Stroke Data Bank [KSDB]. KSDB is a single center, hospital-based registry in which clinical, radiological and genetic data from the AIS cases are included. The systematic collection of data was started in 2007. The study design was approved by the Jagiellonian University Ethical Committee [(KBET 54/B/2007)]. Written informed consent was obtained from all participants in

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the study. The diagnosis of stroke was made according to the WHO definition [4].

The standardized diagnostic work-up included demographics; age and gender; stroke risk factors: hypertension, myocardial infarction, ischemic heart disease, atrial fibrillation, diabetes mellitus, history of stroke; clinical data: prestroke independence as measured by the modified Rankin Score (mRS) [5], stroke etiology according to the Trial of Org10172 in acute Stroke Treatment (TOAST) criteria [6], stroke severity on admission, on the next day morning and on the day of discharge assessed by National Institutes of Health Stroke Scale (NIHSS) [7].

The following biochemical data were collected on admission: international normalized ratio, glucose levels, white blood cells, platelets count, creatinine and hemoglobin levels.

The following information on treatment was also collected: prehospital treatment (antithrombotics, anticoagulants, antihypertensive treatment, antidiabetics); in-hospital treatment (intravenous thrombolysis, mechanical thrombectomy, antithrombotics, anticoagulants, antihypertensive treatment, antidiabetics, antibiotics); pharmacological secondary stroke prevention (antithrombotics, anticoagulants, antihypertensive treatment, antidiabetics). The following outcome measures were evaluated in each case: posttreatment hemorrhagic complications classified according to The European Cooperative Acute Stroke Study II (ECASS-2) classification [8], death form any cause during hospitalization, functional outcome assessed by the mRS[5] on discharge, and at day 90 after stroke (assessed by telephone call by a study nurse).

In each case time of stroke onset, time of admission to the hospital and time of starting IT infusion were also recorded.

All patients admitted within 6 hours after stroke onset, excluding those with contraindications, had performed on admission the standardized radiological work-up including Computed Tomography (CT) with and without contrast, angio-CT of intra and extracranial vessels, and arch of aorta. 24 hours later all patients had non contrast CT. Other neuroimaging examinations were performed in case of indications. The presence of intracranial aneurysms, and other vascular malformations was recorded.

For the purpose of the presented study we analyzed data from participants of KSDB treated with IT from June 2014 to December 2018. Additionally, we analyzed the presence of UIAs. We classified them as either the saccular or fusiform type. In case of saccular UIAs, we analyzed their number (single or multiple), location, and the diameter (mm). All angiograms with aneurysms were evaluated retrospectively by an experienced, independent radiologist (P.B) while writing this paper. The size of one aneurysm was changed by P.B. from 10 to 12 mm during the reevaluation. We also studied the presence of subarachnoid hemorrhage (defined as bleeding in the subarachnoid space on CT imaging or magnetic resonance imaging or xantochromia in the cerebrospinal fluid) or subdural hematoma.

According to local protocol, based on AHA/ASA Guidelines [9] the presence of IA larger than 10 mm was considered as contraindication for IT. Intravenous thrombolysis was given within 4.5 hours after stroke onset. Inclusion and exclusion criteria were based on AHA/ASA Guidelines [9].

Statistical analysis

The patients were categorized into two groups according to the presence of UIAs on angio-CT. Clinical characteristics and

Table 1: Baseline characteristics of patients with and without intracranial aneurysms.

Patients characteristics	UIAs	No UIAs	P
Age, years (mean ± DSD)	75.2 ± 11.9	69.8 ± 13.3	0.2
Female gender, n (%)	8 (80)	145 (45.3)	0.03
Stroke risk factor profile			
Hypertension, n (%)	9 (90.0)	269 (84.0)	0.61
Diabetes mellitus, n (%)	4 (40.0)	93 (29.0)	0.55
Ischemic heart disease, n (%)	1 (10.0)	77 (24.1)	0.3
Atrial fibrillation, n (%)	4 (40.0)	91 (28.4)	0.63
Hypercholesterolemia, n (%)	3 (30.0)	105 (32.8)	0.85
BMI (mean ± DSD)	26.7 ± 4.5	27.4 ± 4.2	0.63
Smoking			
No, n (%)	4 (40.0)	205 (64.1)	
Current smoking, n (%)	4 (40.0)	55 (17.0)	
Smoking more than 6 month before stroke, n (%)	2 (20.0)	51 (15.9)	
No data, n (%)	0	9 (2.8)	
Stroke subtype			
Large artery disease, n (%)	2 (20)	43 (13.4)	
Small vessel occlusion, n (%)	0	3 (0.9)	
Cardioembolism, n (%)	5 (50)	103 (32.2)	0.06
Unknown, n (%)	2 (20)	157 (49.1)	
Rare, n (%)	1 (20)	14 (4.4)	
Neurological deficit			
NIHSSscoreon admission, (mean ± DSD)	12 ± 4.9	12.0 ± 7.0	0.83
NIHSS 24 hours after intravenous thrombolysis, (mean ± DSD)	6.6 ± 4.7	8.4 ± 7.9	0.47
NIHSS discharge from the hospital (mean ± DSD)	3.2 ± 3.1	8.1 ± 12.3	0.21
Modified Rankin score on discharge from hospital			
0 (n, %)	30 (30.0)	80 (25.0)	
1 (n, %)	4 (40.0)	92 (28.8)	
2 (n, %)	1 (10.0)	21 (6.6)	
3 (n, %)	1 (10.0)	29 (9.0)	0.8
4 (n, %)	1 (10.0)	29 (9.0)	
5 (n, %)	0	42 (13.0)	
6 (n, %)	0	27 (8.4)	
Modified Rankin score on day 90			
0 (n, %)	5 (50.0)	104 (32.5)	
1 (n, %)	2 (20.0)	80 (25.0)	
2 (n, %)	2 (20.0)	23 (7.2)	
3 (n, %)	1 (10.0)	13 (4.1)	0.2
4 (n, %)	0	19 (5.2)	
5 (n, %)	0	23 (7.2)	
6 (n, %)	0	42 (13.1)	
No data	0	15 (5.0)	

*Note: UIAs: Unruptured Intracranial Aneurysms; BMI: Body Mass Index; NIHSS: National Institutes of Health Stroke Scale.

outcomes between the groups were compared by the unpaired t student test or chi2 test, where appropriate. All statistics were performed by Statistica software version 13.3 (TIBCO software INC). P-value of <0.05 was considered statistically significant.

Data availability statement

Anonymized data will be shared on request from any qualified investigator.

RESULTS

During the study period 1209 patients agreed to participate in the KSDB and 362 (29,9%) received IT. Among them 330 (91,1%) had performed standardized radiological work-up. Unruptured intracranial aneurysm was found in 10 patients (3,0%). Patients with UIA as compared to others did not differ in respect to age, stroke risk factor profile, neurological deficit as measured on admission, 24 hours later and on discharge. They presented with similar profile of stroke etiology and outcome as measured by mRS on discharge and on day 90. Interestingly, there were significantly more females in the group of patients with UIA (Table 1).

All identified UIAs were saccular. Their size varied from 2 to 12 mm (mean: 4,3±3,0; minimum 2 mm-maximum: 12 mm).

Table 2: The list of patients with unruptured intracranial aneurysm who received intravenous thrombolysis.

No	Age (years)	Sex	NIHSS before rtPa	Vascular territory of stroke	Location of aneurysm	Size of aneurysm (mm)
1	79	F	20	R't MCA	R't MCA	2
2	80	F	16	L't MCA	R't MCA	3
3	60	M	14	L't MCA	Ant. com. a.	3
4	92	F	12	R't MCA	Ant. com. a.	2
5	72	M	8	L't ACA	BA	5
6	87	F	19	L't MCA	L't ACA	2
7	71	F	13	L't MCA	R't ICA	12
8	83	F	6	L't MCA	Ant. com. a.	4
9	75	F	7	L't MCA	R't ICA	6.2
10	53	F	10	R't MCA	L' t ACA	4

Abbreviations: M: Male; F: Female; NIHSS: National Institutes of Health Stroke Scale; r-tPA: Recombinant Tissue Plasminogen Activator Treatment; R: Right; L: Left; MCA: Middle Cerebral Artery; PCA: Posteriori Cerebral Artery; BA: Basilar Artery; ACA: Anterior Cerebral Artery; Ant Com A: Anterior Communicating Artery; ICA: Internal Carotid Artery.

Table 3: Outcome measures of patients with unruptured intracranial aneurysms treated by intravenous thrombolysis.

No	ICH	mRS on discharge	mRS day 90	Duration of the follow-up (months)	Final mRS
1	No	3	2	16	5
2	Yes	4	3	17	3
3	No	2	2	28	1
4	No	1	1	35	3
5	No	0	0	Death 14 months after stroke	6
6	No	1	0	48	0
7	No	0	0	50	0
8	No	1	1	56	1
9	No	0	0	Death 21 months after stroke	6
10	No	1	0	51	1

Abbreviations: ICH: Intracranial Hemorrhage; mRS: modified Rankin Scale

Table 4: Patients with unruptured intracranial aneurysm >10 mm described in the literature.

Paper	Sex	Age (years)	Knowledge about aneurysm before rtPa iv.	Size of aneurysm (mm)	ICH	SAH	NIHSS on admission	NIHSS on discharge
Desai, 2011 [31]	M	54	Yes	16	No	No	9	1
Ganesalingam 2013 [30]	F	45	Yes	20	Yes	No	10	8
Goyal, 2015 [12]	N=3	N=3	NK	>/= 10	NK	No	NK	NK
	NK	NK						
Kim, 2012 [13]	M	33	No	12	No	No	9	1
Ritter, 2003 [18]	M	72	No	15	No	Yes	8	death
Sheth,2012 [15]	NK	No	No	26	Yes	No	NK	NK
Xu, 2014 [32]	M	59	Yes	17	No	No	6	0

Note: NK: Not Known

Interestingly, only in two cases the UIA were located in the same vascular territory as AIS and two-on the same side. One patient developed intracranial hemorrhage not related to UIA during hospitalization and no one developed subarachnoid hemorrhage (Table 2). We were able to follow-up the patients with UIAs from 14 to 56 months. During that time only 2 patients died, 14 and 21 months, respectively after stroke. Unfortunately, we were not able to find out the reason of their death. The survivals were followed from 16 to 56 months. The details of their outcome measures are shown in Table 3. One patients with the aneurysm sized of 12 mm was followed for 50 months and he scored 0 on mRS at that time.

DISCUSSION

Our study shows that IT in AIS with the presence UIA does not affect the stroke outcome, as measured by brain hemorrhage or subarachnoid hemorrhage on the CT scanning on the day after stroke, mRS on discharge, mRS on day 90 and finally several months after the event. Our findings are in line with the results of previousstudies [2,10,11-17], which became the basis for the current guidelines [3].

We present data from the Polish patients of Caucasian origin. Based on the literature we would like to highlight that there are only very few case reports of single patients with UIAs treated with IT who are citizens of Europe (in total=6), described so far [18-22]. Interestingly, in the United States, with a very heterogeneous population, many authors did not indicate the ancestry of their patients [11,12,14,15,23,24]. To the best of our knowledge, the literature search showed that total number of cases with the UIA treated by IT was low (n=209); 85 were of Asian ancestry, 118 were citizens of the United States with no indication of their ancestry and 5 citizens of Europe [18-22] also with no indication of their ancestry and one patient of Afro-Caribbean ancestry living in London [25].

The prevalence of UIAs in the population is high and varies from 3%-6.6% [26]. Some data indicate that the prevalence of UIAs may vary between the populations; from 1.8% in the European population- based prevalence study [27] to 7% in a cross-section study in China [28].

Unfortunately, available data do not allow comparing the outcome of patients with UIAs treated with IT in respect of their ancestry.

In contrast to the most studies on this topic [2,10,13,15-17,19,23,24,29] we were aware of the presence of the UIA before introducing IT. In our center we use complex radiological diagnostic protocol before treatment decision in AIS patients. It allows detecting not only the size of penumbra or clot location but also the presence of malformations, including IUAs. This approach improves certainty of the decision about individual treatment strategy (IT or mechanical thrombectomy or both). Our protocol also helps to exclude contraindications that are not showed on standardized non contrast CT, i.e. larger aneurysms, brain tumors, etc. [3].

Nowadays, it becomes a common procedure in Stroke Centers, maximally saving time from stroke onset to treatment, that IT is introduced in a CTlab concomitantly with introducing contrast for vessel imaging or perfusion CT. That is why performing complex radiological procedure before making decision about stroke treatment should not be considered as an obstacle for getting optimal outcome.

It is well known that older age, female gender, location in posterior circulation and larger size (≥10mm) of the aneurysm increase the risk of aneurysm rupture [30]. In our case series aneurysms were found mostly in women (80%), in the most cases the size of UIA was lower than 5 mm (80%), and only one UIA was located on the basilar artery. It means, that UIAs detected in our case series were of lower risk of rupture. What is more, in our case series brain area affected by stroke was different as compared to the location of aneurysms in 8 cases. Unfortunately, in the literature the question concerning the relationship between UIA and stroke locations was not discussed widely. The detailed location of the UIA was shown in 76 out of 209 described cases and in 54 (71%) of them UIAs were located on the site of stroke, what is not in line with our findings.

In our case series we present one patients with UIA sized more than 10 mm. Its final size was reestablished retrospectively by an independent radiological evaluation of the cases included into this study. This UIA was located on the opposite site of stroke. The patient was followed by 50 months and at that time he scored 0 on mRS. In the literature we were able to identify only 9 cases who received IT since AIS with UIA larger than 10 mm. [12,13,15,18,30,31,32]. Unfortunately, detailed clinical information and outcome measures are available only for 6 cases (Table 4).

The presented studies have some limitations. First, it is a retrospective analysis of prospectively collected data; however, our data are solid since they were reviewed by an experience radiologist. The selection bias was related to the fact that only patients who agreed and who were able to sign the informed consent during hospitalization (mean 9 days) participated in this study. What is more, the number of patients with UIAs is small, what may lead to the type II error.

CONCLUSION

We present the largest case series with UIAs treated with IT due to AIS of the European ancestry described so far. We also reviewed all described cases that had UIAs sized >10 mm and who received IT. The 10 mm cut-off for decision making about qualification of patients with AIS for IT, is based on a scarce data on the efficacy of this procedure in patients with UIAs sized >10 mm. In our opinion, it is important to encourage neurologists to share their experience on IT of AIS cases with UIAs with the community, what may affect the extension of the indications for the IT in patients with UIAs.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurologu.org for full disclosures.

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