

Early stroke-related deep venous thrombosis: risk factors and influence on outcome

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Abstract Deep venous thrombosis (DVT) is a serious complication of various medical conditions including acute stroke. Our aim was to identify the occurrence of early stroke-related DVT, risk factors for its development and the influence on outcome. The study involved consecutive patients admitted to our center due to acute ischaemic ($n = 278$) or haemorrhagic ($n = 12$) stroke during a 16-month period. We collected data on their pre-stroke health status, neurological deficit on admission and baseline serum CRP and fibrinogen level. Ultrasonographic imaging was performed at the 3rd (IQR: 2–4) and 9th (IQR: 8–9) day after stroke. Patients thrombosis occurring between the first and second examination comprised the newly developed early stroke-related DVT group. We found DVT in 8.0% (24/299) of patients at initial evaluation. Newly developed DVT was present in 3.0% (9/299) of patients, and was predominantly distal (7 of 9 cases). It was associated with elevated serum CRP level (OR 8.75; 95%CI: 1.61–47.6), which was verified in a model adjusted for stroke severity and pre-stroke dependency (3–5 pts. in mRS). In a multivariate model, newly developed DVT significantly increased the risk of 3-month mortality (OR 12.4; 95%CI: 1.72–89.4), without affecting the combined risk of dependency and death (OR 2.57; 95%CI: 0.39–17.0). Early stroke-related DVT is an infrequent complication. However, it may be an independent risk factor for 3-month mortality. Increased serum CRP

level combined with normal fibrinogen level seems predictive for development of DVT. It may be reasonable to provide those patients with additional DVT prophylaxis.

Keywords Deep vein thrombosis · Stroke · Epidemiology · Risk factors · Outcome

Introduction

Deep vein thrombosis (DVT), including pulmonary embolism (PE) as a sequel, is a serious complication of various medical conditions including stroke. It is considered to develop mostly within 2 weeks post-stroke [1]. The incidence in immobilized post-stroke patients ranges from 10 to 75%, depending on the diagnostic method and time of evaluation [1–5]. According to the literature, the major risk factors of post-stroke DVT are older age [6], atrial fibrillation [7] and limb paresis [8].

Most studies addressing the issue of DVT and stroke tend to focus on patients with lower limb paresis and search for in-hospital DVT. The initial ultrasound examination is usually performed after 7 days from stroke onset, and the second one 2–5 weeks after stroke. Such an approach is sufficient to evaluate the incidence of DVT in those patients. However, it does not allow to distinguish between early stroke-related and late onset DVT, nor with DVT probably present before. We assume this difference is of particular importance, as the late onset DTV is mainly associated with prolonged immobility, and the early onset DVT may be more likely a direct consequence of the ischaemic cerebrovascular event.

The aim of our study was to establish the occurrence of early stroke-related DVT, risk factors for its development and the influence on 3-month outcome.

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Materials and methods

We recruited consecutive patients admitted to our department due to acute stroke from December 2007 to May 2009, excluding the period from May to August 2008. The diagnosis of stroke was based on clinical symptoms and brain CT imaging.

Neurological deficit on admission was measured with the National Institutes of Health Stroke Scale (NIHSS). Stroke severity was categorized as mild (NIHSS ≤ 7 pts.), moderate (NIHSS 8–14 pts.) or severe (NIHSS >14 pts.). Pre-stroke disability was measured with Modified Rankin Scale (mRS). Information about pre-existing comorbidities and oral anticoagulation or heparins was obtained from patients medical records, patients themselves or their proxies if necessary. We also collected data on serum routine CRP level (immuno-turbidimetric method, Synchron CX 7, Beckman Coulter) and serum fibrinogen level (Claus method, Synchron CX 7, Beckman Coulter) measured within 24 h from hospital admission.

The follow-up examination was provided 3 months after stroke onset by a physician blinded to the patient's DVT status during a routine outpatient visit or by phone.

Primary outcome measures were overall mortality, and combined death or dependency (3–6 pts. in mRS).

Ultrasonographic examination

Patients were examined for both proximal (popliteal, femoral and common femoral vein) and distal (peroneal and tibial veins) DVT. The first ultrasonographic examination was performed within the first 7 days and then 8–10 after stroke onset by a trained physician (JB) blinded to patients' baseline health status in order to identify patients in whom DVT occurred early in the course of stroke. We used Vivid 7 Dimension (GE, USA) with the 7–10 Hz linear probe. The diagnosis of DVT was based either on presence of a non-compressible segment (compression ultrasound test—CUS) or the flow impairment on color Doppler imaging. This method is recognized as sufficiently sensitive and specific, especially in proximal DVT detection [9].

DVT prevention

None of DVT prevention methods were used routinely. Patients at high risk of developing DVT received low molecular weight heparins (LMWH) at physician's discretion. Patients diagnosed with DVT were treated with full dose LMWH.

Ethics committee approval

The study protocol was approved by the local Ethics committee. As DVT screening with Doppler USG is non-invasive and safe, we did not collect patients written consent for the examination. The follow-up outpatient visit after 3 months is a routine element of post stroke care in our department.

Statistical methods

Categorical variables were presented as ratio with number of valid observations, and continuous variables as median with interquartile range (IQR). Proportions were calculated with exclusion of unknown values from the denominator. In basic comparative statistics we applied chi square test or two sided exact Fisher's test, and Mann–Whitney *U* test, for categorical and continuous variables, respectively.

Multivariate logistic regression was adjusted for all independent outcome predictors. To avoid variable selection caused by spurious correlations, only variables showing a relationship to the outcome (defined $P < 0.10$ in the univariate model) were included as potential predictors. We identify the final multivariate model for each major outcome using a backward stepwise approach with the $P < 0.05$ of the likelihood ratio test for exclusion of excess factors.

We considered P value < 0.05 statistically significant. Analyses were conducted in STATISTICA 8.0 (StatSoft, Inc. 2008).

Results

During the recruitment period of 16 months a total of 425 acute stroke patients were admitted to our stroke unit. We excluded 102 patients who were not able to undergo initial USG evaluation due to early transfer to another hospital, death or unstable general condition not allowing to transfer the patients to the USG laboratory. We also excluded 24 patients who were lost from the follow-up USG due to reasons similar as mentioned above.

Patients excluded from the study had more severe neurological deficit at baseline, and more frequently decreased level of consciousness. 39 (31%) of them died during the hospital stay at a median of 2 days (IQR: 2–4). A detailed description of both groups is presented in Table 1.

The final analysis involved 299 Caucasian patients with acute ischaemic (92.8%) and haemorrhagic (7.2%) stroke. The initial and follow-up USG examinations were performed at the 3rd (IQR: 2–4) and 9th (IQR: 8–9) day after stroke, respectively. The median gap between examinations was 6 (IQR: 4–7) days.

Table 1 Comparison of the study group and patients not included in the study

	Not included		Included		<i>P</i>
	N	Observed (%)	N	Observed (%)	
Age (median, IQR)	126	72 (62–81)	299	75 (64–82)	0.162
Female sex	126	62 (49.2%)	299	159 (53.2%)	0.454
Arterial hypertension	126	89 (70.6%)	288	214 (74.3%)	0.438
Congestive heart failure	123	32 (26.0%)	290	72 (24.8%)	0.799
Atrial fibrillation	123	30 (24.4%)	290	61 (21.0%)	0.452
Diabetes	124	16 (12.9%)	297	54 (18.2%)	0.185
Smoking status					
Current smokers	123	28 (22.8%)	298	74 (24.8%)	0.652
Past smokers	122	55 (45.1%)	296	140 (47.3%)	0.680
Oral anticoagulants	125	14 (11.2%)	296	21 (7.1%)	0.163
Pre-stroke disability					
mRS 0–1 pt.	126	85 (67.5%)	299	218 (72.9%)	0.257
mRS 0–2 pts.	126	95 (75.4%)	299	246 (82.3%)	0.104
Stroke severity (median, IQR%)	126	8 (3–20)	299	5 (2–9)	<0.001
NIHSS ≤7 pts.	126	59 (46.8%)	299	205 (68.6%)	<0.001
NIHSS 8–14 pts.	126	20 (15.9%)	299	52 (17.4%)	0.703
NIHSS >14 pts.	126	47 (37.3%)	299	42 (14.0%)	<0.001
Decreased consciousness					
Not present	126	78 (61.9%)	299	256 (85.6%)	<0.001
1 pt. in NIHSS	126	24 (19.0%)	299	30 (10.0%)	0.011
≥2 pts. in NIHSS	126	24 (19.0%)	299	13 (4.3%)	<0.001

We found DVT in 24 (8.0%) patients at initial and in 32 (10.7%) patients at follow-up examination. In one case, the clot resolved before the second examination. Therefore, newly developed DVT was present in nine (3.0%) patients, and was predominantly distal (7 cases).

Patients with newly developed DVT despite a trend for younger age (median 68 vs. 75; $P = 0.429$) tended to have higher ratio of pre-existing diabetes (33.3 vs. 17.7%; $P = 0.213$) and congestive heart failure (44.4 vs. 24.2%; $P = 0.233$). There was also a trend for higher stroke severity (median NIHSS score 8 vs. 5; $P = 0.090$), including more frequently decreased consciousness (33.3 vs. 13.8%; $P = 0.125$). Patients with DVT had significantly higher ratio of elevated serum CRP level (77.8 vs. 32.6%; $P = 0.008$) with a strong inverse trend for elevated serum fibrinogen level (44.4 vs. 73.6%; $P = 0.067$). Detailed characteristic of the study population is presented in Table 2.

In a multivariate model, development of early stroke-related DVT was associated with elevated serum CRP concentration and not-increased serum fibrinogen concentration. There was also a positive trend for pre-stroke diabetes. Pre-stroke dependency and stroke severity did not show significant association, nor trend for increased risk of DVT. Detailed OR for early stroke-related DVT are presented in Table 3.

Patients with early stroke-related DVT had significantly higher 3-month mortality (42.9 vs. 9.2%, $P = 0.03$), and slightly more frequently developed death or dependency (57.1 vs. 41.1%, $P = 0.45$). In multivariate logistic regression early stroke-related DVT was associated with increased risk of death at 3 months (OR 12.4; 95%CI: 1.72–89.4), after adjusting for the independent predictors (i.e. older age, use of oral anticoagulants, stroke severity and elevated CRP concentration) (Table 4).

Early stroke-related DVT did not significantly influence 3-month death or dependency. After adjusting for the independent predictors (i.e. stroke severity and pre-stroke disability level), the OR in early stroke-related DVT was 2.57 (95%CI: 0.39–17.0). It also did not influence the outcome in survivors. After adjusting for the independent predictors (i.e. age, stroke severity and pre-stroke disability level), the OR for dependency in survivors (mRS 2–5 pts.) in early stroke-related DVT patients was 1.83 (95%CI: 0.17–20.1) (Table 4).

Discussion

Our findings show, that the frequency of DVT in acute stroke patients reaches 10.7%. However, in 8% of cases it may have developed before the stroke, while only in 3%

Table 2 Baseline characteristics of the study population and 3-month outcomes

	Newly developed DVT group		Old DVT or non-DVT group		P
	N	Observed (%)	N	Observed (%)	
Age (median, IQR)	9	68.0 (63–79)	290	75 (65–82)	0.429
Female sex	9	5 (55.6%)	290	154 (53.1%)	1.000
Arterial hypertension	9	7 (77.8%)	279	207 (74.2%)	1.000
Congestive heart failure	9	4 (44.4%)	281	68 (24.2%)	0.233
Atrial fibrillation	9	2 (22.2%)	281	59 (21.0%)	1.000
Diabetes	9	3 (33.3%)	288	51 (17.7%)	0.213
Smoking status					
Current smokers	9	2 (22.2%)	289	72 (24.9%)	1.000
Past smokers	9	4 (44.4%)	287	136 (47.4%)	1.000
Oral anticoagulants	9	0 (0%)	287	21 (7.3%)	1.000
Pre-stroke disability					
mRS 0–1 pt.	9	6 (66.7%)	290	222 (74.1%)	0.707
mRS 0–2 pts.	9	8 (88.9%)	290	238 (82.1%)	1.000
Ischaemic stroke	9	9 (100.0%)	290	269 (92.8%)	1.000
Stroke severity [median, IQR]	9	8 (4–20.5)	290	5 (2–9)	0.090
NIHSS ≤7 pts.	9	4 (44.4%)	290	201 (69.3%)	0.146
NIHSS 8–14 pts.	9	3 (33.3%)	290	49 (16.9%)	0.193
NIHSS >14 pts.	9	2 (22.2%)	290	40 (13.8%)	0.368
Decreased consciousness					
Not present	9	6 (66.7%)	290	250 (86.2%)	0.125
1 pt. in NIHSS	9	2 (22.2%)	290	28 (9.7%)	0.225
≥2 pts. in NIHSS	9	1 (11.1%)	290	12 (4.1%)	0.333
Inflammatory markers					
CRP >10 mg/dl	9	7 (77.8%)	276	90 (32.6%)	0.008
Fibrinogen >4 mg/dl	9	4 (44.4%)	276	203 (73.6%)	0.067
Fibrinogen [median, IQR]	9	3.8 (3.4–5.8)	276	4.7 (4.0–5.8)	0.230
Stroke outcome at 3 months					
Mortality	7	3 (42.9%)	275	27 (9.8%)	0.028
Death or dependency (mRS 3–6%)	7	4 (57.1%)	275	113 (41.1%)	0.454
Dependency in survivors (mRS 3–5%)	4	1 (25.0%)	248	86 (34.7%)	1.000

between the 3rd and 9th day after stroke. According to previous studies, the incidence of DVT within the first 14 days post-stroke ranges from 10 to 75% of patients, depending on the applied methodology [1–5].

In a recent large trial by Dennis et al. [10] a total of 2518 acute stroke patients randomized to thigh-length graduated compression stockings for DVT prevention ($n = 1256$) or routine care ($n = 1262$) were evaluated with a compression ultrasound test at 7–10 days after stroke and if possible at 25–30 days after enrollment. In the initial examination, the ratio of combined symptomatic and asymptomatic DVT was 10.0% in the study group and 10.5% in the control group, which is fully consistent with our results. In another USG-based study, De Silva et al. assessed the incidence of DVT in 105 acute ischaemic stroke Asian patients. At the first evaluation performed 7–10 days after stroke they

found DVT in 30% of patients. On follow-up evaluation, performed 25–30 days after stroke, DVT was detected in 45% of patients. Those results may suggest that Asian population is more prone to develop DVT, when compared to Caucasians [11]. The protocol used in our study differed from previous ones and included two USG examinations performed in the acute phase of stroke within a gap of a few days. This allowed us to differentiate patients in whom DVT was most likely a direct consequence of the acute stroke, and not chronic immobility or pre-stroke thrombosis.

In our study, newly developed early stroke-related DVT was predominantly distal (7 of 9 cases), which stays in concordance with other studies [5, 11–14]. We decided to search for distal DVT as it also poses an indirect but significant threat, as the thrombi propagates above the knee in

Table 3 Unadjusted and adjusted odds ratio for early stroke-related DVT

	Univariate model			Multivariate model*		
	OR	95%CI	P	OR	95%CI	P
Age (for each additional 10 years)	0.91	(0.70–1.19)	0.507	0.64	(0.33–1.23)	0.176
Female sex	1.10	(0.29–4.22)	0.885	0.81	(0.20–3.37)	0.775
Hypertension	1.22	(0.25–6.04)	0.809	1.44	(0.27–7.61)	0.665
Congestive heart failure	2.51	(0.65–9.65)	0.180	1.71	(0.41–7.05)	0.458
Atrial fibrillation	1.08	(0.22–5.34)	0.929	0.65	(0.12–3.48)	0.609
Diabetes	2.32	(0.56–9.65)	0.244	4.16	(0.84–20.6)	0.079
Smoking status						
Current smoker	0.86	(0.17–4.37)	0.854	1.59	(0.28–8.89)	0.599
Previous smoker	0.89	(0.23–3.39)	0.862	0.97	(0.24–3.93)	0.969
Pre-stroke disability	1.05	(0.65–1.72)	0.834	0.97	(0.58–1.62)	0.923
mRS 0–1 pt.	0.74	(0.18–3.03)	0.670	0.95	(0.21–4.23)	0.947
mRS 0–2 pts.	1.75	(0.21–14.4)	0.602	0.44	(0.05–3.90)	0.460
Stroke severity						
Each additional 4 pts. NIHSS	1.30	(0.96–1.75)	0.083	1.21	(0.86–1.69)	0.271
NIHSS >7 pts.	2.82	(0.74–10.8)	0.129	2.11	(0.50–8.96)	0.307
NIHSS >14 pts.	1.79	(0.35–8.96)	0.479	1.34	(0.25–7.30)	0.732
Decreased consciousness						
≥1 pt. in NIHSS	3.13	(0.75–13.1)	0.117	2.09	(0.46–9.54)	0.337
≥2 pts. in NIHSS	2.90	(0.33–25.3)	0.334	1.90	(0.19–19.0)	0.583
Inflammatory markers						
CRP >10 mg/l	7.23	(1.46–35.8)	0.015	10.1	(1.93–52.9)	0.006
Fibrinogen >4 mg/dl	0.29	(0.07–1.11)	0.069	0.18	(0.04–0.74)	0.017

* Adjusted for elevated blood CRP level (>10 mg/dl) and fibrinogen level (>4 mg/dl)

Table 4 Adjusted odds ratio for 3-month mortality and unfavorable outcome (mRS 2–6)

	Death at 3 months*			Death or dependency ^a		
	OR	95%CI	P	OR	95%CI	P
Newly developed DVT	12.4	(1.72–89.4)	0.012	2.57	(0.39–17.0)	0.324
Age (for each additional 10 years)	2.05	(1.17–3.59)	0.011	1.55	(1.14–2.10)	0.005
Oral anticoagulants	5.58	(1.11–28.1)	0.036			
Pre-stroke nondisability (mRS 0–1)				0.25	(0.12–0.50)	<0.001
Stroke severity (for each 4 NIHSS)	1.78	(1.36–2.31)	<0.001	2.79	(2.08–3.74)	<0.001
CRP > 10 mg/l	2.94	(1.08–7.96)	0.034			

* Model adjusted for all presented variables; ^a Model adjusted for all presented excluding newly developed DVT

even up to 20% of cases [15, 16]. Therefore, the risk of proximal extension and possibility of developing PE as a sequel should not be neglected [17].

We assume that the cases of newly developed DVT may be significantly different from those diagnosed in other studies using only one USG examination during the first 2 weeks post stroke. In our study population, patients presenting with DVT at the first USG examination were less independent before stroke and did not show any increase in 3-month mortality [18]. Therefore, we cannot be certain when the clot formation was triggered. It is

possible, that in many cases DVT was already present before stroke onset.

The results of other studies provide evidence that the development of DVT is associated with elevation of systemic inflammatory markers [19, 20], which is partially consistent with our findings.

However, the issue of cause-and-results relationship of increased inflammatory markers and DVT is still a matter of debate. Besides, the number of published studies on acute stroke patients is very limited. In this aspect, our study provides a new perspective. It allows us to

distinguish patients developing stroke-related DVT in a very narrow time window after baseline evaluation, as the ultrasound examinations were performed with the median interval of 4 days. Such design gives information about the level of inflammatory markers directly preceding the clot formation, and has not been applied before. In other studies the gap between USG evaluation usually ranges from 2 to 4 weeks [10, 11].

The increase of CRP level in patients with DVT, that we observed in our study, is fully consistent with published literature. However other studies, have not concentrated on stroke patients [19, 21, 22].

Surprisingly, our findings show that early stroke related DVT is inversely associated with elevated fibrinogen level. Unfortunately, available studies supporting the positive association between DVT and serum fibrinogen were conducted on small groups of patients, did not have such a narrow time window and did not address directly the acute stroke [23–27]. Therefore, it is difficult to make direct comparisons. We may speculate, that observed in our study inverse association between the elevated fibrinogen level and the development of DVT is a result of fibrinogen depletion due to active clot formation. However, this assumption is based on a small group of stroke patients, and gives a good rationale for further investigations.

In a study by Wang et al. the mean levels of plasma CRP and fibrinogen were significantly higher in 59 DVT patients compared to 26 healthy controls, i.e. 2.67 ± 0.91 versus 0.14 ± 0.08 mg/dl. Similar observation was made for fibrinogen (4.73 ± 1.36 vs. 2.79 ± 0.66 g/l, respectively). The authors suggest that interaction between inflammation and coagulation promote the development of DVT and may be involved in DVT pathogenesis [23]. Unfortunately, this was a small study and only the abstract is available in English. Therefore, its methodology stays unclear.

Ogata et al. [28] attempted to detect DVT in 56 acute haemorrhagic stroke patients within 72 h from the onset of symptoms and after 2 weeks using ultrasonography. They did not find any significant correlation between fibrinogen level and risk of DVT. However, trials not concentrating directly on stroke patients suggest that elevated fibrinogen level is associated with even a 4-fold increase in the risk of developing DVT [24–27].

According to our findings, pre-stroke disability level and stroke severity were independent predictors of achieving unfavorable outcome during the follow-up, which stays in concordance with other studies [29–32].

It is generally agreed that proper DVT prophylaxis improves stroke outcome, although there is no evidence supporting this thesis [33]. In our study early stroke-related DVT was an independent risk factor for death at 3 months with a slight trend for unfavorable outcome in survivors. De Silva et al. [11] reported that the presence of DVT

25–30 days after stroke was associated with higher ratio of poor outcome (defined as mRS 4–6) after 6 months (50 vs. 26%; $P = 0.024$). In patients diagnosed with DVT during 7–10 days after stroke this association was not statistically significant (52 vs. 32%; $P = 0.074$). Therefore, patients with acute stroke should be carefully screened for DVT risk factors at admission. Throughout the hospitalization they should also be at least clinically monitored for the development of DVT. It applies to all patients regardless of stroke severity, especially if serum CRP levels are elevated.

None of our patients was diagnosed with PE, however, the majority of deaths occurred after discharge from the hospital. We may speculate, that early stroke-related DVT is a clinical marker of other discrete conditions that increase the risk of death. It is also possible that those patients are more likely to have serious clinical course of thrombosis with higher risk of PE despite applied treatment.

Our study has certain limitations. Although ultrasound is highly sensitive and specific in detection of proximal DVT in symptomatic patients, it's sensitivity for distal DVT detection is much lower than proximal (62.1 vs. 93.9%) [34]. The sample size of early stroke-related DVT was too small (9 cases) to draw strong conclusions. Our cohort is skewed towards relatively stable patients with mild-to-severe strokes not requiring early transfer to other specialist units. Only two basic inflammation markers were tested in this study. We also did not perform routine autopsy in patients who died during the study period, therefore we cannot exclude that some deaths were due to PE.

In conclusion, our study shows that DVT which is definitely associated with acute stroke occurs in 3% of patients and significantly affects 3-month mortality. Elevated serum CRP level and not-increased fibrinogen serum level are independently associated with increased risk of DVT. Therefore, it may be reasonable to provide this group of patients with additional care and proper DVT prophylaxis in order to minimize the risk of thrombo-embolic complications.

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