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Haemorrhagic transformation in ischaemic stroke is more frequent than clinically suspected – A neuropathological study

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ABSTRACT

Objectives

The vast majority of literature on the frequency of the haemorrhagic transformation of ischaemic stroke is based on imaging studies. The purpose of the present study was to assess the added value of autopsy and neuropathological analysis in a neurology centre with emphasis on acute stroke care.

Methods

We retrospectively analysed the findings of 100 consecutive brain autopsies followed by detailed clinical correlation.

Results

The clinical diagnosis was confirmed by neuropathology in every patient with intracerebral haemorrhage and with non-cerebrovascular neurological disorders (e.g. primary tumours, metastases, infections). At admission 64 patients (age 62 years, SD 6.5) were diagnosed with acute ischaemic stroke. In 10 of these patients (16%) haemorrhagic transformation was diagnosed clinically by a second CT. In 24 cases (38%) haemorrhagic transformation was detected only at autopsy. The distribution of haemorrhagic transformation in our material was the following: small petechiae in 26.5%, more confluent petechiae in 29.4%, ≤ 30% of the infarcted area with some mild space-occupying effect in 29.4% and > 30% of the infarcted area with significant space-occupying effect or clot remote from infarcted area in 14.7%. Most of the PH1–2 transformations developed in thrombolysed patients and all of the PH2 type transformations were diagnosed already clinically.

Conclusions

We demonstrated that haemorrhagic transformation is frequent and often undiscovered in vivo. Our findings underline the importance of post-mortem neuropathological examination also in the era of advanced imaging techniques and prove that autopsy is the ultimate yardstick of our diagnostic and therapeutic efforts. The high number of haemorrhagic transformations diagnosed only after death is an important novel finding with clinical implications.

1. Introduction

Although the rate of clinical autopsies has been declining drastically for decades, it remains an important tool of quality control in clinical practice. It serves to determine the exact cause of death, reveals unexpected complications of disease processes including adverse or any other effects of treatment as well as validates the cause of death for epidemiological statistics [1–3]. Autopsies make important contribution to the under- and postgraduate training in medicine. Clinico-pathological studies are of major importance, because (agreeing with the Agency for Healthcare Research and Quality U.S. Department of Health and Human Services) 'clinical diagnoses, whether obtained from death certificates or hospital discharge data, contain major inaccuracies compared with autopsy diagnoses' [4].

Our university hospital has a catchment area of 500,000 inhabitants, and about 800 acute stroke patients are treated annually in our stroke centre. The ratio of thrombolysed patients is 19%, higher than the average of Western-European countries [5]. In the everyday clinical practice at admission and during the course of the disease the various imaging modalities (CT, MRI) provide the main sources of information on structural/morphological changes in the brain. Although all of our acute stroke patients were immediately investigated by CT or MRI at admission (and repeated if required by the patient's deteriorating condition), neither ethical nor financial limitations allow performing daily CT/MRI during the agony phase for estimating the 'final' pathological findings of patients with poor outcome. Because the autopsy rate of patients who died at our neurology department is > 90%, we have access to the results of brain autopsies which is a unique opportunity in the era of declining brain autopsy rates [3].

Haemorrhagic infarction is a frequent complication of ischaemic stroke [6–8], although it is not always accompanied by clinical deterioration [7–10]. The effect on clinical outcome is also unclear and most of the literature data regained from studies on thrombolysis for

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ischaemic stroke [7,11,12], mainly due to the fact that haemorrhagic transformation is a frequent complication of thrombolysis or anticoagulant therapy. Previous studies have focused on the possible aetiological role of the following parameters: age [8,10,11,13,14], systolic and diastolic arterial blood pressure [14,15], congestive heart failure [11], body temperature [15], serum glucose level [8,14], treatment with anticoagulants [10,15], pre-treatment with aspirin [10,11], early ischaemic signs on CT [11,13,15], mean infarct volume [10,11,15], plasma matrix metalloproteinase-9 [15]. The adequate time window for detection of haemorrhagic transformation is also disputed [16] and autopsy is the method which provides the most accurate diagnosis in stroke. Our goals were to i) analyse the correlation between clinical and neuropathological diagnosis; ii) to assess the clinically undisclosed findings revealed with the neuropathological analysis in a series of consecutive cases reflecting the routine practice of a stroke centre, iii) to emphasize the importance of the neuropathological evaluation in establishing the real frequency of haemorrhagic transformation which may warrant modifications of stroke protocols and diagnosing clinically undetected brain diseases.

2. Subjects and methods

2.1. Patient population and data collection

We retrospectively analysed the clinical records of patients who died in the Department of Neurology, University of Debrecen, and had general autopsy in the Department of Pathology and brain autopsy in the Neuropathology Laboratory during the previous two calendar years. All stroke patients were treated on specialized stroke units with multiparametric monitoring. All patients were older than 18 years of age, mean age was 62.66 years (SD 6.51). The following data were collected retrospectively from the patients' clinical notes: sex, age, survival time after stroke, suspected clinical diagnoses, administration of antiplatelets and anticoagulants over the hospitalisation, NIHSS (National Institutes of Health Stroke Scale) at admission, results of the performed CT, CTA (computed tomography angiography) or MRI examinations and the general autopsy findings.

Patients with ischaemic cerebral infarction had acute onset focal neurological deficit and brain imaging with or without ischaemic lesion. Haemorrhagic stroke cases had focal neurological deficit and brain imaging evidence of intraparenchymal haemorrhage. Cases with primary intracerebral tumours had histologically verified tumour, brain imaging evidence of the neoplasm; they were admitted due to disease progression (deteriorating hemiparesis, dysphagia or epileptic seizures). Patients with brain metastasis had clinically diagnosed or histologically verified extracerebral primary tumour, brain imaging evidence of the metastasis; they were admitted due to disease progression (increased intracranial pressure or epileptic seizures) or acute ischaemic stroke. Patients with central nervous system infection had evidence of neurological symptoms or meningeal signs indicative of meningitis or meningo-encephalitis and cerebrospinal fluid analysis had evidence of elevated cell count and protein content with or without decreased sugar level depending on the infectious agent.

2.2. Neuropathological analysis

Brains were immersed in 10% buffered formalin for 3 weeks according to standard procedures [17] to allow good fixation. We measured the formalin-fixed whole brain and brainstem & cerebellum weight, respectively, to have the weight ratio of the supra- and infratentorial part as an index of atrophy or weight gain (e.g. due to oedema). After detailed description of the general appearance coronal slices of 0.75 cm sickness were cut. This method is adequate to diagnose gross pathologies including haemorrhage, infarct, haemorrhagic transformation and other pathologies such as herniation, secondary brain stem haemorrhage, arachnoideal cyst, tumours. In cases of haemorrhagic transformation of cerebral ischaemia we identified the subtypes according to that Fiorelli et al.: HI1: small petechiae, HI2: more confluent petechiae, PH1: $\leq$ 30% of the infarcted area with some mild space-occupying effect, PH2: > 30% of the infarcted area with significant space-occupying effect, or clot remote from infarcted area [7].

After the macroscopic evaluation approximately $2 \times 2 \times 0.5$ cm tissue blocks were sampled (which fit into standard size cassettes used for histotechnical processing) from areas recommended by BrainNet Europe (frontal cortex, temporal cortex, cingulate gyrus, parietal cortex, pre-postcentral gyrus, occipital cortex, hippocampus anterior, hippocampus posterior, basal forebrain, striatum, thalamus, midbrain, pons, medulla, vermis, cerebellum) [18]. After histotechnical processing and embedding to paraffin wax, sections of 7 μm thickness were cut and stained with haematoxylin and eosin (H&E), and luxol fast blue and Nissl (LFB/Nissl) to assess basic pathological changes. Immunohistochemistry has also been performed to assess age-related, neurodegenerative or other pathologies according to standard procedures [18]; because our study is a clinicopathological analysis of stroke cases immunohistochemical data were not included in the assessment. Evaluation was performed by a neuropathologist aware of the sample localization and patient history. The clinical findings were compared with the neuropathological results.

3. Results

All patients (n = 100) had brain CT at admission. In possible thrombolysis candidates, computed tomography angiography (CTA) was also performed at arrival and all thrombolysed patients had a second control CT within 24 h after thrombolysis. Repeat CT were done if the patient's condition deteriorated (loss of consciousness, paresis, new clinical symptoms, etc.) to exclude any treatable cause of deterioration (e.g. haemorrhage, haemorrhagic transformation, secondary brainstem haemorrhage, oedema, etc.).

Clinically 64 patients (62.74%, female n = 40, male n = 24, mean age 62.6 years, SD 6.51) were diagnosed with acute ischaemic stroke during hospitalisation, regardless of CT signs of ischaemic infarct or absence of it at admission. In 10 of these patients haemorrhagic transformation of the infarct was diagnosed already by the clinicians (Fig. 1).

At autopsy we found territorial ischaemia in 59 patients (91%) and lacunar infarct(s) in 5 patients (8%). Brain autopsy revealed haemorrhagic transformation in additional 24, altogether in 34 cases (53%) (16 thrombolysed and 18 non-thrombolysed patients). Data of individual patients with haemorrhagic transformation of ischaemic stroke are listed in Table 1. Among ischaemic stroke cases with haemorrhagic transformation there were 21 female and 13 male patients. The mean age was 75.61 years (SD 9.68). Survival time was 12.03 days (SD 12.18), which was 15.18 days (SD 15.13) in thrombolysed and 9.22 days (SD 8.27) in non-thrombolysed patients.

All of the acute stroke patients were immediately investigated by CT at admission (not shown in Table 1). Repeat CT were done in all thrombolysed patients within 24 h after thrombolysis and in 6 cases due to clinical worsening. One patient had brain MRI at admission, due to that hypodensity on his first brain CT was atypical for ischaemia. MRI verified acute ischaemia in the territory of middle cerebral artery (Table 1).

The distribution of haemorrhagic transformation in our material was the following: HI1 26.5%, HI2 29.4%, PH1 29.4% and PH2

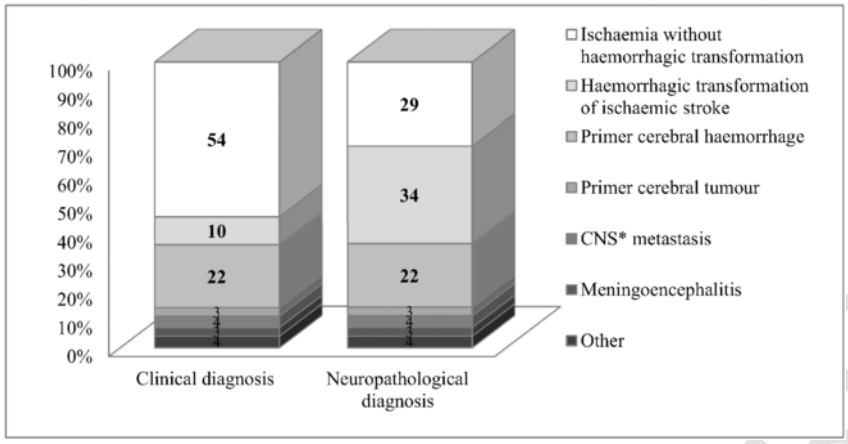

Fig. 1. Distribution of cases by major clinical and neuropathological diagnosis (see colour code). The clinical diagnosis was confirmed by neuropathology in every patient with intracerebral haemorrhage and with non-cerebrovascular neurological disorders (primary tumours, metastases, infections). In 10 of these patients haemorrhagic transformation of the infarct was diagnosed already by the clinicians. Brain autopsy revealed haemorrhagic transformation in 24 additional, all together in 34 cases. *CNS = central nervous system. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

14.7% (Tables 1–2). Fig. 2 shows examples for each subtypes of haemorrhagic transformation.

None of the patients with haemorrhagic transformation received oral anticoagulant over their hospitalisation, although 4 of them were on coumarin or warfarin therapy at admission with ineffective INR (< 1.7) level. Thirty-one patients received prophylactic low molecular weight heparin (LMWH) therapy and 17 patients received antiplatelet therapy (Table 1). Cases with haemorrhagic transformation (diagnosed either clinically or by autopsy) consisted of 16 thrombolysed and 18 non-thrombolysed patients (Table 1, Fig. 3). Most of the PH1 and all of the PH2 type transformations developed in thrombolysed patients. All of PH2 transformations were diagnosed already clinically (Tables 1–2).

According to CT, brain haemorrhage was the clinical diagnosis in 22 patients (21.56%, female n = 6, male n = 16, mean age 75 years, SD 19.7). The neuropathological findings were confirmatory in all clinically diagnosed haemorrhagic cases (Fig. 1). According to the clinical records in one case trauma, in another case anticoagulant side effect was the aetiological factor. Underlying neuropathology in the background of cerebral bleeding was revealed in two cases (cerebral amyloid angiopathy and arteriovenous malformation, respectively). Brain autopsy revealed one clinically unknown cerebral haemorrhage; the male patient admitted with symptoms of mild vertebrobasilar insufficiency died unexpectedly, neuropathological evaluation described severe subarachnoideal haemorrhage as a consequence of ruptured basilar arterial aneurysm.

Neuropathological evaluation confirmed all primary brain tumours (n = 3) and metastases (n = 4) cases (Fig. 1). The primary brain tumours were anaplastic astrocytoma in 2 patients and gliosarcoma in 1 patient. The metastases originated from pulmonary adenocarcinoma (n = 1), invasive ductal breast cancer (n = 1), sigillocellular gastric cancer (n = 1) and carcinoma of the uvula in the oral cavity (n = 1), respectively. Infections of the central nervous system (CNS) were diagnosed clinically in 2 patients. The brain autopsy confirmed the meningitis in both patients. In four cases with not life-threatening neurological conditions (e.g. neuronal heterotopy and microgyrification; arachnoideal cyst; silent aneurysm; opalescent meninges with mild mononuclear infiltration as a late consequence of a previous meningitis) the neuropathological evaluation confirmed the clinical diagnoses.

4. Discussion

The Department of Neurology, University of Debrecen is a regional stroke centre explaining the predominance of stroke patients in our autopsy series.

Brain autopsy confirmed the clinical diagnoses in all cases of cerebral haemorrhages, primer and metastatic tumours and central nervous system infections (Fig. 1). Neuropathological evaluation revealed the aetiology in two cases with parenchymal bleeding; it described cerebral amyloid angiopathy in one and arteriovenous malformation in another case. Only brain autopsy could reveal a clinically unknown cerebral haemorrhage; the male patient was admitted with symptoms of mild vertebrobasilar insufficiency, while neuropathological evaluation described severe subarachnoideal haemorrhage in the background of unexpected death as a consequence of ruptured basilar arterial aneurysm.

Autopsy provided the most additional information in ischaemic stroke. There are not many clinico-pathological reports on consecutive autopsy series with predominantly stroke cases and only few with special emphasis on haemorrhagic transformation in ischaemic infarcts. The reported frequency of HT in previous studies depended on several factors, e.g. whether the study was based on imaging methods or on autopsy results, whether the patients had received anticoagulant, antiplatelet or fibrinolytic treatment, or on the post-stroke time of control imaging. Additionally, the results of the clinical and neuropathological diagnostic tools are heterogenous, difficult to compare them, and the population examined can make it even more heterogenous due to the fact that autopsy results can be gained from fatal cases exclusively. Kerényi et al. analysed an autopsy series of 245 patients with ischaemic stroke with haemorrhagic transformation in 29% [8]. Lodder et al. reported an autopsy series with 48 patients dying within 15 days following a supratentorial cerebral infarct. In their analysis 16 patients (33%) had haemorrhagic transformation [19]. Toni et al. examined 150 consecutive patients with cerebral infarct in the anterior circulation. They performed CT or autopsy one week after the stroke and observed haemorrhagic transformations in 43%, mostly (89%) petechial haemorrhagic transformations and in 11% larger haematomas [6]. Celik et al. evaluated a series of 86 middle cerebral artery territorial infarction cases, who had received before neither antiplatelet nor anticoagulant therapy. By the follow up CT

Table 1
Data of patients with haemorrhagic infarction of ischaemic stroke.

Sex[a]	Age [y]	Co-morbidity[b]	Cause of death[c]	Stroke[d]	HT[e]	Survival time[f]	Control CT[g]	NIHSS 0 h[h]	rtPA/TAG/anticoagulant[i]
F	71	HT, DM, PF, M[j]	BP	AB	HI-1cl.	60 days	24 h	18	ia./−/LMWH
M	74	HT, MI, S, COPD	AMI	ICA	HI-2 path.	26 days	5 days	12	−/+/LMWH
F	77	HT, DM, PF, MI, COPD	H	AB	PH-1cl.	2 days	24 h		ia./−/−
M	63	HT	EP	AB	PH-1cl.	25 days	24 h	11	iv./+/LMWH
M	63	HT, DM, PF, COPD, PAD	BP	MCA	PH-2cl.	6 days	1.5 h, 24 h, 48 h	14	iv./−/coumarin*
F	74	HT, MI, COPD	BP	MCA	HI-1 path.	35 days	24 h	13	iv./+/LMWH
M	78	HT, PF, MI, S	BP	MCA	PH-1 path.	11 days	24 h	21	iv./+/LMWH
M	70	HT, S, PAD	BP	MCA	HI-1 path.	14 days	MRI at admission	16	−/+/LMWH
F	63	HT, DM, PAD	BP	MCA	HI-1 path.	7 days		14	−/+/LMWH
F	86	HT, S	BP	MCA	HI-1 path.	20 days		14	−/+/LMWH
F	73	HT, COPD	BP	MCA	HI-1 path.	9 days	4 h	13	−/+/LMWH
F	77	HT, PF, MI, S	BP	ICA	HI-path.	5 days		13	−/−/coumarin*, LMWH
F	70	HT, DM, S	BP	MCA	HI-2 path.	29 days		16	−/+/LMWH
F	92	PF, MI, S	BP	ICA	HI-2 path.	3 days	6 h	21	−/+/−
M	73	HT	BP	MCA	PH-1 path.	8 days		14	−/+/LMWH
F	71	HT, DM, MI	BP	ICA	PH-1 path.	4 days		6	−/+/LMWH
M	67	HT, M	SH	MCA	HI-2cl.	11 days	24 h		iv./+/LMWH
M	76	HT, PF	SH	MCA	PH-2cl.	7 days	24 h, 2 days	8	iv./+/−
M	68	HT	SH	ICA	PH-1 path.	18 days	24 h, 4 days	23	iv./+/LMWH
F	79	HT, DM, PF, COPD	CF	AB, AV	PH-1cl.	8 days	24 h	13	iv./−/LMWH
F	69	HT, DM, PF, MI, S	CF	MCA	PH-2cl.	3 days	24 h	21	iv./−/warfarin*
F	84	HT, COPD	CF	MCA	PH-2cl.	6 days	24 h	24	iv./−/−
M	83	PF	CF	MCA	HI-1 path.	10 days	24 h	21	iv./+/LMWH
F	78	HT, DM	CF	MCA	HI-2 path.	26 days	24 h, 13 days	5	iv./+/LMWH
M	70	HT	CF	MCA	PH-1 path.	4 days	24 h	16	iv. + ia./+/−
F	89	HT, DM, PF	CF	MCA	HI-1 path.	5 days	3 days	19	−/+/coumarin*, LMWH
F	92	HT, S, COPD	CF	MCA	HI-2 path.	14 days			−/+/LMWH
M	89	HT, DM, PF	CF	MCA	HI-2 path.	33 h		11	−/+/LMWH
F	99	HT, S, COPD	CF	MCA	HI-2 path.	5 days		17	−/+/LMWH
F	83	HT, DM, PF, M	CF	MCA	HI-2 path.	6 days		24	−/+/LMWH
F	56	HT, PAD, S, COPD	CF	MCA	PH-1 path.	27 h		20	−/+/−
F	66	HT, DM, MB	CF	AV	PH-1 path.	2 days			−/+/−
M	69	HT, DM, MI	PE	MCA	PH-2cl.	11 days	24 h, 10 days	19	iv./+/LMWH
F	79	HT	PE	MCA	HI-2 path.	7 days		19	−/+/LMWH

[a] Sex: F = female, M = male.

[b] Co-morbidities: HT = hypertonia, DM = diabetes mellitus, PF = atrial fibrillation, S = stroke in patient's history, M = malignancy in patient's history, COPD = chronic obstructive pulmonary disease, PAD = peripheral arteriosclerosis, MI = myocardial infarct in patient's history, MB = artificial valv in the heart.

[c] Cause of death: BP = bronchopneumonia, H = herniation, PE = pulmonary embolia, CF = cardiac failure, SH = secundary haemorrhage in the brain stem, AMI = acute myocardial infarct.

[d] Localization of stroke: ICA = internal carotid artery, MCA = middle cerebral artery, AB = basilar artery, AV = vertebral artery.

[e] Type of haemorrhagic transformation (HT): HI1 = small petechiae, HI2 = more confluent petechiae, PH1 = ≤ 30% of the infarcted area with some mild space-occupying effect, PH2 ≥ 30% of the infarcted area with significant space-occupying effect or clot remote from infarcted area, cl = already clinically diagnosed haemorrhagic transformation (which was confirmed by neuropathological evaluation, too), path = haemorrhagic transformation diagnosed only by neuropathological examination.

[f] Survival time: time between stroke and death.

[g] Control CT: time of control CT calculated from the time of admission. Repeat CT were done in all thrombolysed patients within 24 h after thrombolysis and in all cases when clinicians detected deterioration of the patient's neurological status.

[h] NIHSS 0 h: NIHSS at admission.

[i] rt-PA/TAG/anticoagulant: rt-PA = recombinant tissue plasminogen activator (Alteplase), iv = intravenous thrombolysis, ia = intraarterial thrombolysis, iv + ia = combination of intravenous and intraarterial thrombolysis, TAG: antiplatelet medication (acetylsalicylic acid or clopidogrel), LMWH = low molecular weight heparin.

[j] Four of the patients with haemorrhagic transformation were on coumarin or warfarin therapy at admission with ineffective INR (< 1.7) level. After the diagnosis of stroke none of the patients received vitamin K antagonist.

performed 72 h after stroke they found HT in 8.5% of all examined patients, but in 40.6% of middle cerebral artery territorial infarction cases [14]. Okada et al. examined 160 acute ischaemic stroke patients. Their CT based results showed all together 40.6% HT, from which 15.4% could be seen in the first 1–4 days, 67.7% in the first 10 days and 100% within the first 30 days and they haven't detected any new HTs after the first month [20]. Hornig et al. evaluated 65 patients' data. They detected HT with brain CT in 28 cases, 40% in the first week, and the rest 60% in the second pos*t*-stroke week [16]. These earlier reports show how difficult it is to define the most appropriate time for the diagnosis of HT. Furthermore, diagnostic possibilities are often different in the routine practice as compared to well-defined and sponsored studies which last for a particular period of time. Moreover, ischaemic stroke patients usually have days or weeks [8,19] (in our sample 11.71 days, SD 13.16) before death with reduced level of consciousness and critical medical status. Therefore, the premortal diagnosis of haemorrhagic transformations could only be possible with daily repeat CT or MRI during the critically ill period, which is not possible either from the ethical or the financial point of view. Repeat CT are done in all thrombolysed patients within 24 h after thrombolysis [21], but not necessarily performed in non-thrombolysed patients, if the patient's condition doesn't requires or allows it. However it is well established that HT is not necessarily accompanied by deterioration of neurological status [7–10]. Fiorelli et al. reported that only parenchymal haematoma type 2 was associated with an increased risk of clinical worsening (at 24 h after stroke onset) and of death (at 3 months); all other types of haematomas did not independently increase the risk of late deterioration [7].

Table 2
Distribution of morphological types of haemorrhagic transformation in clinically or neuropathologically diagnosed patients.

	Non-thrombolysised		Thrombolysised	
	Clinically diagnosed	Neuropathologically diagnosed	Clinically diagnosed	Neuropathologically diagnosed
HI1	0	6	1	2
HI2	0	8	1	1
PH1	0	4	3	3
PH2	0	0	5	0
All	0	18	10	6

HI1: small petechiae, *HI2:* more confluent petechiae, *PH1:* ≤ 30% of the infarcted area with some mild space-occupying effect, *PH2:* > 30% of the infarcted area with significant space-occupying effect or clot remote from infarcted area.

The *clinically diagnosed* columns include those cases where the haemorrhagic transformation was detected by the control brain CT in vivo. The *neuropathologically diagnosed* columns include only those cases where clinically the haemorrhagic transformation was unknown and only the neuropathological evaluation detected it.

The reported frequency of the different types of HT in the literature depends on the treatment used in the acute phase of ischaemic stroke, but also on the HT subtypes' definitions used in that particular study. The distribution of haemorrhagic transformation in our material was the following: HI1 26.5%, HI2 29.4%, PH1 29.4% and PH2 14.7% (Table 2). Okada et al. defined four types of HT: spotty and scattered petechial haemorrhage, along the cortical margin of the ischaemic lesion (56.9%), diffuse haemorrhage (18.5%), small (< 3 cm in diameter) (13.8%) and massive (> 3 cm in diameter) (10.8%) haematoma [20]. Fiorelli et al. examined the subtypes and frequency of HT after iv. rtPA treatment in the ECASS I [7]. HT detection was based on control brain CT performed 36 h later. Due to the very different patient population from ours and the exclusively imaging-based HT diagnosis, the comparison between their and our results is meaningless. However, their results support those previous findings that the frequency and even the severity of HT are higher after rtPA treatment [10,11,22]. In our sample most of the PH1–2 transformations developed in thrombolysed patients (Table 2, Fig. 3). The high proportion of HT in our sample diagnosed only at brain autopsy can be explained partially by the fact that control CT is performed only 24 h after thrombolysis [21]. Although the half-life of t-PA is only few minutes, there is a prolonged effect on the coagulation cascade [23,24].

Fiorelli et al. [7] and Berger et al. [22] evaluated the ECASS I and ECASS II data and established that only parenchymal haematoma type 2 was associated with an increased risk of clinical deterioration; all other types of haematomas did not independently increase the risk of late deterioration. In the NINDS rtPA study [25] 70% of the symptomatic HT corresponded to the parenchymal haematoma (PH1 and PH2) subtypes by ECASS classification [26–28]. The vast majority (73.5%) of symptomatic HT in the ECASS were in the PH1 and PH2 subgroups [11]. These data show that HTs accompanied by clinical worsening usually belong to parenchymal haemorrhages, appear as dens haematomas and they have pronounced space occupying effect. In our sample PH2 type transformations developed in thrombolysed patients and all of them were diagnosed already clinically. On the other hand, relatively large proportion of HT1–2 and PH1 haemorrhagic transformations were diagnosed only by brain autopsy even in a specialized stroke unit with multiparametric monitoring, despite the control CTs 24 h later in thrombolysed patients and other control CTs performed due to clinical worsening (in 6 cases).

Although some prior studies demonstrated the negative impact of the asymptomatic haemorrhagic transformations, even of the HI forms, on the outcome compared with those without HT of acute ischaemic stroke [29,30]. According to a previous study, based on both imaging and autopsy results, the pathogenesis of haemorrhagic infarctions and parenchymal haematomas are different; while haemorrhagic infarctions are the consequences of multifocal extravasation of red blood cells, usually in the grey matter, parenchymal haematomas probably represent haemorrhages from single damaged vessels, injured by ischaemia and following reperfusion [31]. Since the transformation occurs in the already necrotic tissue, often no clinical worsening, reflecting the development of HT, could be detected [32]. The general clinical condition of acute stroke patients with fatal outcome is very poor, there are several additional extracerebral factors (i.e. bronchopneumonia, acute myocardial infarction, pulmonary embolism) which may lead to the fatal outcome.

Instead of focusing on the reasons, clinical signs or treatment of haemorrhagic transformations, our aim was to emphasize the higher than expected frequency of its occurrence even without clinical signs and emphasize the need of clinical alertness even in asymptomatic cases. Since we evaluated only fatal cases, our results cannot be extrapolated to all ischaemic stroke cases. However keeping this in mind, in individual cases (e.g. in thrombolysed patients) clinicians may consider requesting brain CT short before discharging the ischaemic stroke patient.

Additionally we underline the importance of clinical autopsies which are still crucial in the correct diagnosis of haemorrhagic transformation of fatal stroke cases even in the era of advanced imaging techniques. Our study provided solid evidence that post-mortem neuropathological examination is important not only in confirming the clinical diagnosis but also reveals in a high proportion of patients undisclosed clinically relevant brain pathologies. Furthermore, post-mortem neuropathology is of educational value for trainees and specialists alike in clinical neurosciences, imaging and general pathology.

Conflict of interest

The authors have no competing interests.

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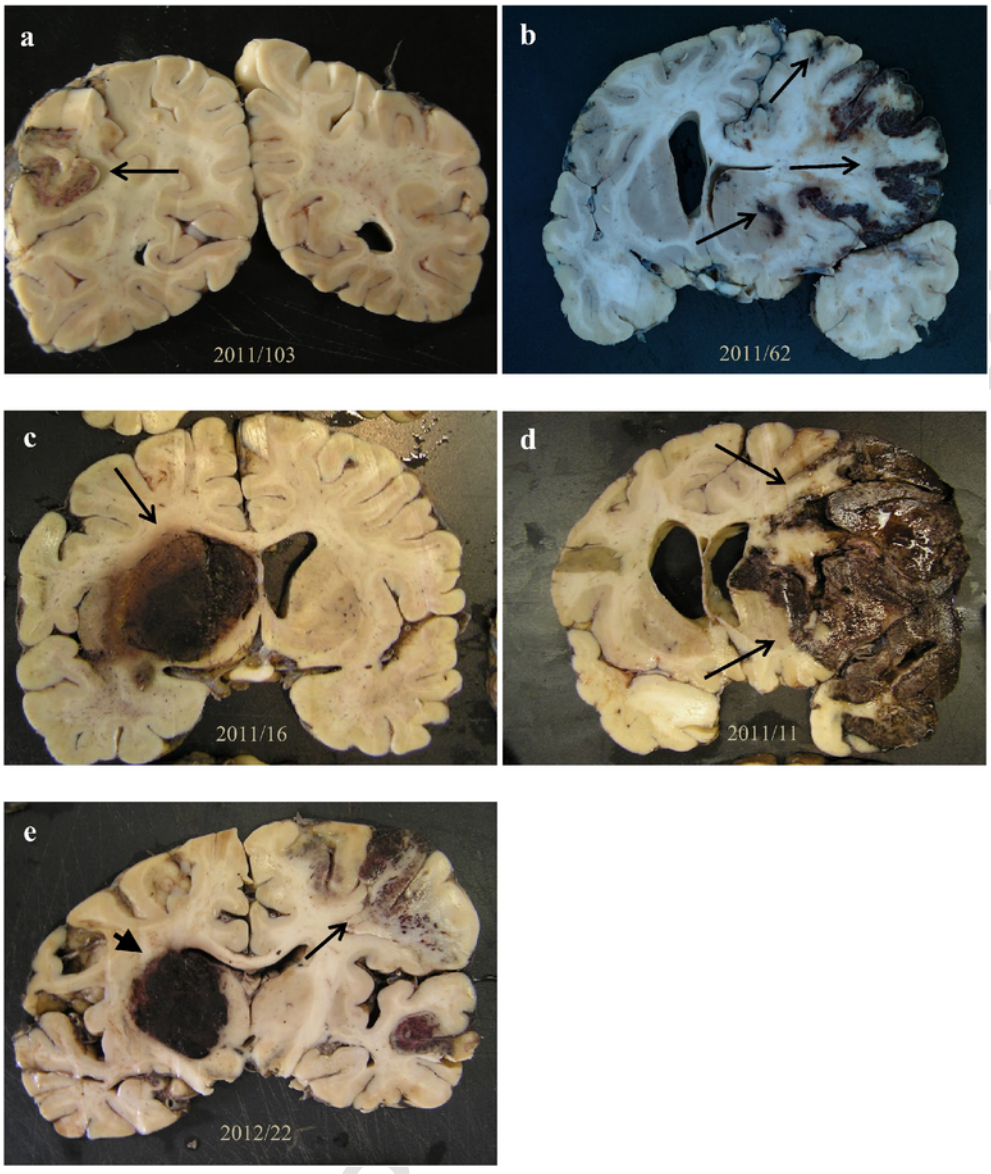

Fig. 2. Examples for different types of haemorrhagic transformation. *a*) *HI1*: small petechiae (*arrow*) *b*) *HI2*: more confluent petechiae (*arrow*) *c*) *PH1*: ≤ 30% of the infarcted area with some mild space-occupying effect (*arrow*) *d*) *PH2*: > 30% of the infarcted area with significant space-occupying effect (*arrow*) *e*) *PH2*: clot remote from infarcted area (*arrow-head*).

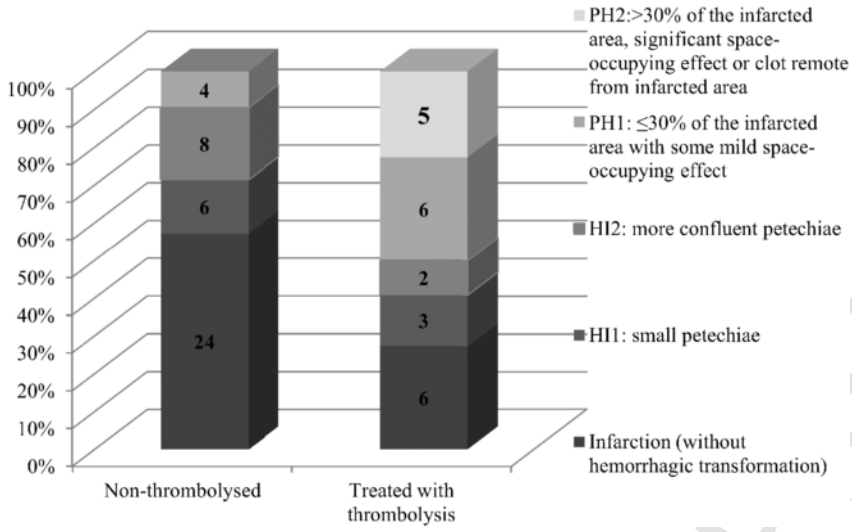

Fig. 3. Occurrence of haemorrhagic transformation evaluated by brain autopsy in thrombolysed and non-thrombolysed patients with ischaemic stroke (see colour code). All the cases in the figure are diagnosed by brain autopsy (including also those 10 cases diagnosed already clinically, too). Clinically 64 patients were diagnosed with acute ischaemic stroke during hospitalisation, in 34 of these patients haemorrhagic transformation of the infarct was diagnosed or confirmed by brain autopsy. Cases with haemorrhagic transformation consisted of 16 thrombolysed and 18 non-thrombolysed patients. Most of the PH1 and all of the PH2 type transformations developed in thrombolysed patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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