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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].

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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 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: ≤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 × 2 × 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 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