Recurrent hypertensive intracerebral haemorrhages: what should we do when a new hemispheric ischaemic event strikes?

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SUMMARY

Hypertensive intracerebral haemorrhage is usually a once in a lifetime event and recurrences are rare. Most recurrences usually develop within 2 years of the first event and the majority usually target the basal ganglia and thalami. Failure of blood pressure control is the most important, potentially preventable, culprit behind the development of primary intracerebral haemorrhages. However, the occurrence of a recurrent bleed in patients with optimally controlled hypertension should always prompt the physician to think of a new co-operating factor. We report on a 60-year-old hypertensive woman who developed right-sided thalamic haemorrhage 5 days after sustaining a lacunar infarct of the left thalamus for which she had been prescribed a dual antiplatelet therapy: aspirin and clopidogrel. She had a history of two bilateral sequential hypertensive deep cerebellar haemorrhages which were developed 2 years ago.

BACKGROUND

The treatment of new cerebral ischaemic events in patients with a history of recurrent hypertensive cerebral haemorrhages is challenging. Emergency room doctors, general practitioners and internists should always be aware of this problem and an expert opinion should always be sought before introducing any form of antiplatelet and/or anticoagulation therapy in such patients. The benefit/risk of the latter types of therapy should always be carefully assessed.

CASE PRESENTATION

A 60-year-old hypertensive right-handed woman was brought to our A&E by her family on 30 October 2012. The family stated that the patient developed sudden severe pancephalic headache and left-sided weakness and that the patient collapsed shortly thereafter, about 2 h ago. She had a 12-year history of systemic hypertension, which had been well controlled during the past 1 year by using oral enalapril and metoprolol. In addition, she took daily atorvastatin tablets. The family denied any history of trauma, fall or seizures.

Her past notes revealed that she had developed two sequential spontaneous hypertensive deep cerebellar haemorrhages. The first haemorrhage was on the right side and occurred in October 2010 whereas the second one hit the patient after 57 days and was on the left side. A review of her neurological examination showed that the patient had a scanning speech and an ataxia of stance and gait. The patient could walk but with minor

assistance, since then. She was able to dress herself and eat independently.

However, on October 25 2012, she developed sudden right-sided hemianaesthesia and weakness. She visited our A&E and underwent routine blood testing as well as a CT brain scan. The latter demonstrated a lacunar infarct at the left thalamus. The treating emergency physician prescribed oral aspirin and clopidogrel tablets and discharged the patient home on the second morning. That is to say, the latter cerebral ischaemic event occurred 5 days prior to the current presentation.

Examination showed a blood pressure of 164/103 mm Hg, a regular pulse rate of 92 beats/min, a respiratory rate of 18 cycles/min, and a temperature of 36.8°C. She was obtunded, quadriplegic and both plantar reflexes were extensors. The deep tendon reflexes were exaggerated on the right side and were hypoactive on the left one.

An emergency non-contrast CT brain scan revealed a new right-sided thalamic haemorrhage and a recent left-sided thalamic lacune (figures 1 and 2).

INVESTIGATIONS

A battery of routine blood (including platelets count, prothrombin time and activated partial thromboplastin time) and urine investigations was ordered; all of them turned out to be within their normal reference range, except that her total cholesterol was 251 mg/dl and low-density lipoprotein cholesterol was 136 mg/dl. The patient's new presentation and the location of the new haematoma did not necessitate performing conventional cerebral angiography; in addition, there was a lack of expertise in our radiology department with respect to this invasive investigation. Her 12-lead ECG showed left-axis deviation and voltage criteria of left ventricular hypertrophy, an observation that was confirmed using transthoracic echocardiography; her ejection fraction was 62% and no regional wall motion abnormalities were noted.

OUTCOME AND FOLLOW-UP

The patient's blood pressure was controlled by increasing her doses of enalapril and metoprolol tablets. Atorvastatin dose was increased to 40 mg/day, and a physiotherapy programme was ordered. Owing to obtundation, a nasogastric tube was placed. The patient was managed in the intensive care unit for 7 days. Her consciousness level gradually improved. She was then transferred to our general neurological ward where she stayed for a further period of 6 days. Her neurological examination, 13 days after admission, revealed asymmetrical spastic quadriparesis

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Figure 1 An emergency non-contrast axial CT brain scan at the time of A&E admission. There is a right-sided thalamic haemorrhage (red arrow) which extends laterally and involves the posterior limb of the right internal capsule (black line) and abuts on the lenticular nucleus (blue arrow). The absence of surrounding (cytotoxic) oedema indicates a very early presentation. Note the hypodense lesion at the left thalamic area, which represents the patient's recent lacunar ischaemic infarction (black arrow). A small hypodense slit-like area (yellow arrow) can still be seen at the left cerebellum; this is the site of the old haemorrhagic stroke. The site of the very first right deep cerebellar haemorrhage cannot be seen on these slices.

with bilateral exaggerated deep tendon reflexes and extensor plantars. There were spontaneous eye openings and movements, but the patient did not utter a sound. When we asked her to open and close and to move her eyes around, she did appropriately; she had thalamic type of dysphasia. She was dependent on a nasogastric tube for feeding; the family declined percutaneous endoscopic gastrostomy tube placement.

She was discharged home on day 13 in response to her next of kin. The family told us that the patient died after 2 days at night while sleeping.

Figure 2 An enlarged section of the patient's non-contrast axial CT brain scan. Note the right-sided thalamic haemorrhage and the left-sided thalamic lacunar ischaemic infarction.

DISCUSSION

Spontaneous non-traumatic hypertensive intracerebral haemorrhage (ICH) is one of the most lethal subtypes of strokes and accounts for 10–15% of all stroke types. Such a vascular accident is usually a once in a lifetime event, and recurrences are rare. Most of these recurrences usually target the basal ganglia and thalami. Recurrences commonly develop within 2 yrs of the first haemorrhagic event.^{1–3}

Longstanding systemic hypertension is responsible for at least 50% of primary ICH. Hypertension doubles the risk of developing haemorrhagic stroke, according to Thrift *et al.*⁴ Gradually, this hypertension exerts a necrotising effect on small penetrators (<300 µm in diameter) of the brain and results in the formation of Charcot-Bouchard microaneurysms. Rupture of the latter marks the development of ICH.²

Garcia and Ho⁵ found that these pathological changes preferably afflict the territory of penetrator arteries that branch off major intracerebral arteries often at 90° with the parent vessel; lenticulostriates (which supply the basal ganglia), thalamoperforators (which supply the thalami), superior cerebellar (which nourish deep cerebellar nuclei) and paramedian branches of the basilar artery are the usual targets.

Weisberg *et al.*⁶ noted that the commonest sites of hypertensive ICH (in order of decreasing frequency) are the putamen and adjacent internal capsule (which comprises half of all cases); the central white matter of the temporal, parietal or frontal lobes (so-called lobar haemorrhages); the thalamus; a cerebellar hemisphere (deep nuclei) and the pons.

Several researchers tried to uncover the incidence of recurrent hypertensive ICH, but they came up with diverse results. Richardson and Einhorn⁷ found that recurrent ICH affected 14% of their studied population whereas Douglas and Haerer⁸ found that none of their 34 surviving patients developed a recurrence. The pertinent medical literature mentions a range of 1.8–6%.^{9–12} Marquardsen¹³ commented on these wide and diverse incidences by stating that 'survivors from haemorrhage are too few to justify any statements concerning the risk of

recurrence in this type of stroke.' Our previous study¹ found an incidence of 7%.

Unlike the role of systemic hypertension in the development of primary ICH, the mechanism of recurrences in association with the poor control of blood pressure seems to be unclear. Passero *et al*¹⁴ found that 47% of their patients who developed recurrences demonstrated poorly controlled hypertension after the first event. On the other hand, Hirohata *et al*¹¹ found that the blood pressure of their patients was normal and well controlled with oral antihypertensive agents after developing their primary ICH.

We reported on this patient previously² and we found that her blood pressure was well controlled after developing her very first primary ICH. Her examination notes stated that the patient's blood pressure was again well controlled with antihypertensive medications after developing the second cerebellar haemorrhage. This observation is consistent with that of Hirohata *et al*.¹¹

The development of lacunar strokes in patients with long-standing hypertension is not an unexpected finding. Occlusion of small penetrating arteries by hypertensive lipohyalinosis results in lacunar infarctions (of 3–20 mm in maximum diameter) deep in the brain parenchyma.¹⁵ The widespread and prolonged hypertensive degeneration of intracerebral small penetrators predisposes patients to the development of lacunar infarctions and intracerebral haemorrhages, and this is what had happened in our patient, who developed a left-sided thalamic lacunar ischaemic stroke 22 months after her second (recurrent) cerebellar haemorrhage.

The patient's cerebral ischaemic event highlights several challenging questions and leaves us in a dilemma: should this patient be prescribed an antiplatelet agent? Which one should we use? And, what is the optimal 'safe' daily dose?

Low-dose aspirin is an important therapeutic option in the secondary prevention of myocardial infarction and ischaemic stroke, especially in the light of its unique cost-effectiveness and widespread availability, and according to Gorelick and Weisman,¹⁶ absolute therapeutic cardiovascular benefits of aspirin must be balanced with the possible risks associated with its use, with the most serious being haemorrhagic stroke.

Bailey *et al*¹⁷ did a systematic review of studies reporting recurrent stroke in survivors of primary ICH. They concluded that recurrent stroke among survivors of primary ICH occurs at a rate of about 4% per patient-year, and most are recurrent ICH. Survivors of ICH have a higher risk of recurrent ICH than of ischaemic stroke, and this has implications for the use of antithrombotic agents in these patients.

On the other hand, Viswanathan *et al*¹⁸ found that antiplatelet agent use is relatively common following intracerebral haemorrhage but did not appear to be associated with a large increased risk of intracerebral haemorrhage recurrence. However, most of their patients received aspirin for secondary prevention of ischaemic heart disease, not ischaemic stroke.

He *et al*¹⁹ did a comprehensive meta-analysis of several trials. This meta-analysis, involving a wide variety of aspirin trials and cardiovascular indications (primary and secondary), integrated and assessed data from 55 462 participants in 16 trials that reported stroke subtypes. He *et al* concluded that aspirin therapy increases the risk of haemorrhagic stroke. However, the overall benefit of aspirin use on myocardial infarction and ischaemic stroke may outweigh its adverse effect on risk of haemorrhagic stroke in most populations.

Many studies^{20–22} have found that the combined use of aspirin and clopidogrel does not offer greater benefit for stroke

prevention than either agent alone but does substantially increase the risk of bleeding complications. In addition, a recent trial²³ concluded that among patients with recent lacunar strokes, the addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke and did significantly increase the risk of bleeding and death.

Our patient's current right-sided thalamic haemorrhage, therefore, can be explained by the recent introduction of a dual antiplatelet therapy; aspirin plus clopidogrel. Therefore, a low dose (75–100 mg/day) of aspirin alone would have been a reasonable option in this patient after developing her thalamic lacunar stroke. Her blood pressure elevation on admission was a reflex mechanism secondary to her new thalamic haemorrhage. The death of this patient could be due to deep venous thrombosis and pulmonary thromboembolism, a cardiac event (myocardial infarction or cardiac dysrhythmia) or another stroke.

Learning points

- ▶ Recurrent hypertensive intracerebral haemorrhage is a rare event but carries considerable morbidity and mortality.
- ▶ Some patients with such recurrences have a reasonably controlled systemic blood pressure and a search for other co-operative factors should always be carried out.
- ▶ An expert opinion should always be considered in patients who have a history of haemorrhagic stroke if they need an antiplatelet/anticoagulation therapy after developing thrombotic or vascular occlusive events.

Competing interests None.

Patient consent Obtained.

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