Prognosis of cerebral cavernomas: on to treatment decisions

Published Online
December 1, 2015
http://dx.doi.org/10.1016/S1474-4422(15)00340-3

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In patients with non-traumatic intracerebral haemorrhage (ICH) establishment of whether the cause is a macrovascular lesion is important, because this might be treatable. In a study of 298 patients with ICH who were younger than 70 years,[1] a standardised diagnostic work-up of CT angiography within 48 h of onset, followed by MRI, magnetic resonance angiography, or digital subtraction angiography within 4–8 weeks identified 69 macrovascular lesions, ten of which were cerebral cavernous malformations (CCMs). The advent of MRI has enabled easy detection of CCMs, and nowadays a quarter of detected vascular malformations are CCMs.[2] However, whether risks of treatment of CCMs are counterbalanced by elimination of the risk of new or recurrent ICH depends on the risk of ICH and its clinical consequences. In a meta-analysis of individual patient data in *The Lancet Neurology*, Margaret Horne and colleagues[3] calculated the risks of symptomatic ICH for patients with an untreated CCM.

In their comprehensive literature search, the investigators identified 22 publications that included 2957 patients. Data from 1337 patients (45%) could not be obtained, showing the challenges of undertaking individual patient data analyses. Therefore, the analysis was based on data from 1620 patients. During a median follow-up of 3·5 years, 204 patients had a symptomatic ICH, yielding a 5-year risk of 15·8% (95% CI 13·7–17·9). Location of CCM (brainstem *vs* other) and mode of presentation (ICH or focal neurological deficit [FND] *vs* other) were independently associated with ICH risk during follow-up (table). In 640 (40%) of 1620 patients, data were also available on the combined outcome of ICH or FND; findings were similar, but were less precise. Age, sex, and CCM multiplicity did not add independent prognostic information.

We commend the investigators for their ability to assemble data from seven cohorts, including two from Asia, without any missing data. 1159 (72%) of the patients presented clinically (ICH, FND, or seizure); in the other 461 (28%) patients the CCM was an incidental finding. Risk of bias of individual studies was low—one of the items checked when the investigators applied the PRISMA individual participant data statement.[4] The size of the dataset with 204 primary outcomes allowed robust estimation of the joint prognostic information of five preselected characteristics.

Horne and colleagues[3] chose the five potential predictors well on the basis of previous publications and practicability, which is in accordance with recommendations for modern prognostic research.[5] This careful selection of predictors enhances applicability in clinical practice, in part because sophisticated laboratory tests are therefore not obligatory to allow prediction of risk. External validation of the model was not possible because all worldwide available data were already used for derivation—a common problem with prognostic modelling for rare diseases.

The absolute risks of symptomatic ICH or focal deficits can now be compared with the risks of death, non-fatal ICH, or new or worse persistent FND after treatment of CCMs. These risks have been reviewed, and seem favourable compared with risks of new or recurrent ICH.[6] The next challenge is to build a decision analytical model that compares risks of death, ICH, and FND with and without treatment to guide clinicians treating a patient with a CCM. Such a model would start with a risk prediction model similar to that developed for patients with unruptured intracranial aneurysms.[7] That analysis identified uncertainties that needed further study and triggered the development of the PHASES score,[8] which was also based on a meta-analysis of individual patient data. A next step could be to combine the risk prediction of ICH with a new meta-analysis of individual patient data and prediction model to assess risks of treatment according to type of treatment, size and site of the CCM, and method of presentation of the patient. The decision model should also take into account the time dependency of the risks of ICH and FND if the CCM is left untreated, since Horne and colleagues[3] found a 3·5-times

	Brainstem location	Other location	All locations
ICH (1620 patients at risk)			
ICH or FND presentation	30·8%	18·4%	26·4%
Other presentation	8·0%	3·8%	4·3%
All presentations	27·7%	8·2%	15·8%
ICH or FND (640 patients at risk)			
ICH or FND presentation	51%	22%	35%
Other presentation	23%	4%	5%
All presentations	45%	9%	17%

FND=focal neurological deficit. ICH=intracerebral haemorrhage.

Table: **Kaplan-Meier estimates of 5-year risks**

decreased risk of ICH from the first to the fifth year of follow-up in patients presenting with ICH or FND. Finally, for the decision to treat, the utility of awareness of an untreated incidental CCM should be assessed as another element. A modelling approach for patients with CCMs is important because randomised trials are not likely to be feasible in view of the low prevalence of CCM and the potentially strong a-priori beliefs on treatments, which might hinder the enrolment of sufficiently large numbers of patients, even in an international collaboration. This issue, allegedly, was one of the problems with the ARUBA trial,[9,10] which assessed medical management with or without interventional treatment for unruptured brain arteriovenous malformations—a disorder with some similarities with CCMs. Hence, meta-analysis of individual patient data from properly designed cohort studies of the risks of neurosurgery and stereotactic radiosurgery are warranted to provide elements for an appropriate decision model.

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We declare no competing interests.

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Human genetics shines a light on ischaemic stroke

Published Online December 18, 2015 http://dx.doi.org/10.1016/S1474-4422(15)00400-7

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Application of unbiased genome-wide approaches has contributed to the understanding of complex disease. For example, genome-wide association (GWA) studies have been used to identify more than 50 discrete loci associated with coronary artery disease.[1] Biological investigation of the causal genes at these loci has provided new insights into the pathogenesis of coronary artery disease, as in the case of *ADAMTS7*.[2] Although ischaemic stroke shares some common causes with coronary artery disease, efforts to dissect the genetics of stroke have been arduous because of the heterogeneous causes and clinical presentations. Ischaemic stroke can be classified into clinically distinctive subtypes based on pathophysiological differences; precise phenotyping of these subtypes in patients is crucial to investigate the underlying genetic causes. An Article[3] in *The Lancet Neurology* by the National Institute of Neurological Disorders Stroke Genetics Network presents the largest and most comprehensive GWA study of stroke and its subtypes so far. The results of this study lend support to previous genetic associations with ischaemic stroke and identify a new locus on chromosome 1p13. Equally important, the study pinpoints the specific stroke subtypes relevant for the reported genetic associations.

Of the replicated loci, it is notable that this report confirms the association between the *HDAC9* locus and ischaemic stroke, specifically in large artery atherosclerosis. This same locus—and indeed specific variant—is also reproducibly associated with coronary artery disease, suggesting a shared underlying causal gene and mechanism. However, as with all GWA study loci, it is now essential to identify the causal gene and the mechanisms related to risk of both stroke and coronary artery disease associated with this gene; the