Monogenic small vessel disease: rare but still important

David J Werring[1,2], David S Lynch[3]

[1] Stroke Research Centre
UCL Institute of Neurology
First Floor
Russell Square House
10-12 Russell Square
London WC1B 5EH

[2] Comprehensive stroke service
National Hospital for Neurology and Neurosurgery, Queen Square
University College Hospitals NHS Foundation Trust

[3]Inherited White Matter Disorders Group
National Hospital for Neurology and Neurosurgery, Queen Square
University College Hospitals NHS Foundation Trust

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Cerebral small vessel disease is the most common known brain disorder, causing about 25% of ischemic strokes, 80% of intracerebral haemorrhage, and contributing to most late-onset dementias. Although in most cases SVD is a sporadic disease (usually due to arteriolosclerosis or cerebral amyloid angiopathy), a small minority (1) are due to monogenic disorders.

The first monogenic SVD to be characterized was cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), in 1993(2). Initially considered rare, CADASIL is now recognized by all neurologists. With increasing access to genetic technology, the clinical spectrum of CADASIL has expanded to include less severe disease (for example only migraine, without stroke or dementia). CADASIL is caused by the accumulation of misfolded NOTCH-3 protein, with relevance for sporadic SVD mechanisms(3).

In this consensus statement (4) the authors consider CADASIL and seven other monogenic forms of SVD. It is likely that, as with CADASIL, these monogenic SVDs will also be increasingly recognized, their phenotypes will broaden, and they will provide mechanistic insights into sporadic SVDs.

This consensus statement is timely given the rapid recent identification of novel genes causing monogenic forms of SVD. Although CADASIL is a well-characterized, more recently described syndromes such as CARASAL (caused by mutations in *CTSA*), or the phenotype of single heterozygous mutations in *HTRA1* will be new to many.

A typical starting point for considering monogenic SVD is the finding of extensive (usually patchy or confluent) white matter signal change on MRI. Although this finding is non-specific, it is often possible to systematically define the phenotype in a way that progresses the diagnostic pathway(5, 6). Additional MRI findings supporting cerebral SVD include lacunes, cerebral microbleeds, enlarged perivascular spaces and ischaemic changes in the brainstem and deep grey nuclei.

After identifying that SVD is the underlying pathology, the question arises as to whether this is acquired (with a possible contribution from polygenic risks) or whether it is caused by a penetrant monogenic Mendelian disease.

The consensus statement lists several “red flags” for the identification of patients with monogenic disorders, including young age at onset, family history, consanguinity or extra-neurological features. These red flags make sense, and helpfully bring together the features that experienced clinicians use to decide when to seek a monogenic disorder in clinical practice. The authors then provide consensus guidelines for each of the included disorders. They have approached each disorder in a similar way, from consensus as to the underlying cause (which gene, which type of mutations), to the clinical and radiological presentations, to pregnancy management, and disease treatment.

The consensus statements regarding the genetic cause of CADASIL is useful, as *NOTCH3* is a large and polymorphic gene in which variants of uncertain significance are a frequent finding. The statement clearly summarizes what is known about pathogenic *NOTCH3* mutations, and guides when to employ skin biopsy to clarify the increasing clinical challenge of variants of uncertain pathogenicity.

One challenge facing the authors of this guideline is the lack of high-quality evidence to support many of the treatment recommendations. They have done a great service by systematically bringing together many expert opinions to reach consensus, but some of the recommendations will naturally stimulate discussion and debate.

The consensus statements regarding pregnancy management, of both CADASIL and *COL4A1/2* disease are particularly useful and clear, as these aspects are poorly studied and clinically challenging. For CADASIL, the most common disorder, no particular prophylactic treatment is recommended, although patients and clinicians should be aware of worsening migraine and potential for encephalopathy surrounding childbirth. However, for *COL4A1/2* disease, which is much rarer, pregnancies must be carefully managed, and delivery by caesarean section is advised, with care to avoid head injury, which can lead to fetal intracerebral haemorrhage.

The consensus group advises against thrombolysis for acute ischaemic stroke in CADASIL unless there is evidence of large artery occlusion. The rationale for this recommendation is not clear, but presumably relates to concerns about bleeding risk

associated with cerebral microbleeds, which are found in more than 60% of patients with CADASIL(7) and are often numerous, generating considerable anxiety regarding bleeding risk. In patients with “conventional” ischaemic stroke treated with rtPA, CMBs are associated with higher bleeding risk and poorer functional outcome(8). However, recent observational modelling data suggest that even many CMBs are unlikely to be associated with net harm in most patients with ischaemic stroke(9). Some clinicians might thus still recommend tissue plasminogen activator (tPA) as the only evidence-based pharmacological treatment for acute stroke (even if not due to large vessel occlusion) to people with CADASIL. It also remains unclear why statins are not recommended in patients with CADASIL who have had an ischaemic stroke, given their excellent safety profile and proven efficacy in cardiovascular prevention.

Nevertheless, this paper is a practical guide that will be useful to all clinicians involved in the diagnosis and treatment of monogenic SVD. Even if some of the recommendations are, inevitably, not based on high-level trial evidence, they serve as a useful starting point to help optimize the management of these patients, for whom there are no proven treatments. With improving genetic technology, new insights into disease mechanisms gained from studying monogenic SVDs raise the prospect of true disease modification (for example with gene therapy approaches) rather than simply managing conventional vascular risk factors.

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