

## EDITORIAL

# What causes lacunar stroke?

J M Wardlaw

A quarter of all ischaemic strokes (a fifth of all strokes) are lacunar type.<sup>1</sup> Lacunar infarcts are small infarcts (2–20 mm in diameter) in the deep cerebral white matter, basal ganglia, or pons, presumed to result from the occlusion of a single small perforating artery supplying the subcortical areas of the brain.<sup>2</sup> Although a recognised stroke subtype for over 50 years, the cause of lacunar ischaemic stroke,<sup>2</sup> and whether it is different to cortical ischaemic stroke, remains under debate.<sup>3,4</sup> Furthermore, lacunar stroke is not benign; 30% of patients are left dependent,<sup>5</sup> and scant long term data suggest that up to 25% of patients have a second stroke within 5 years.<sup>6</sup> Therefore, the prevention and treatment of this common stroke subtype may be less than ideal.

## PROBLEMS IN THE STUDY OF LACUNAR STROKE

Several factors have hampered the study of lacunar stroke. Firstly, few patients die from lacunar stroke; if they do, death may occur long after the stroke, making autopsy material scant and difficult to interpret, and the small cerebral vessels require meticulous dissection. Studies of risk factors and causation have predominantly used a clinical diagnosis of stroke type, probably resulting in some misclassification. Although lacunar infarcts are associated with specific neurological syndromes, and most patients with a clinical lacunar syndrome have a small deep subcortical infarct on brain imaging (if visible), 10–20% actually have a recent small cortical infarct in a location that explains their stroke presentation.<sup>7</sup> Similarly, 10–20% of patients with a clinical mild cortical stroke actually have a recent relevant lacunar infarct on imaging.<sup>7</sup> Epidemiologically, these patients behave more like the lesion type on imaging than the clinical syndrome of the lesion they actually have.<sup>7</sup> Many studies have used an inappropriate control group; age matched normal controls can only indicate whether or not a particular risk factor is associated with stroke, whereas identification of associations specific to lacunar stroke requires a control group with a different

type of ischaemic stroke. Finally, some classifications, such as the Trial of Org 10172 in Acute Stroke Treatment (TOAST) method<sup>8</sup> actually use risk factors (such as embolic sources or hypertension) to determine the stroke type, thus potentially biasing studies of differences in risk factors. Hence, inadvertent misdiagnosis of lacunar as cortical stroke, and vice versa, the paucity of pathological material, and bias in some clinical classification systems may have confounded previous pathology, prognosis, and risk factor studies.

## IS THE CAUSE OF LACUNAR DIFFERENT FROM CORTICAL ISCHAEMIC STROKE?

The lacunar hypothesis supports the concept that lacunar ischaemic stroke is due to an intrinsic cerebral small arteriolar abnormality,<sup>2</sup> in contrast to cortical ischaemic stroke, which is commonly due to embolism from the heart or large arteries. Although some studies suggest that many lacunar strokes are caused by emboli, and while it is perfectly possible for a small embolus to enter and occlude a lenticulostriate artery,<sup>9</sup> a systematic review of risk factors including only studies using subtype definitions for ischaemic stroke free of risk factors found that atrial fibrillation and carotid stenosis were associated more with non-lacunar than lacunar infarction (relative risk (RR) of lacunar versus non-lacunar infarction: atrial fibrillation 0.51, 95% confidence interval (CI) 0.42 to 0.62; ipsilateral carotid stenosis 0.35, 95% CI 0.28 to 0.44).<sup>10</sup> Indeed, common causes of large artery (cortical) infarction, such as emboli from the large arteries or heart,<sup>11–13</sup> or intracranial large artery atheromatous stenoses,<sup>12</sup> appear unlikely to cause more than 10–15% of lacunar strokes.<sup>14–17</sup> Perhaps lacunar infarcts due to emboli or middle cerebral artery stenoses are recognisable by being larger than non-embolic/stenotic lacunes,<sup>12,18</sup> possibly because the embolus/stenosis occluded the origin of several lenticulostriate arterioles simultaneously. There is a suggestion that lacunar stroke secondary to middle cerebral artery stenosis may be more common in south Asian populations

than in western white populations, but this remains to be clarified. Only 6% of all particles (even the smallest) injected into the carotid arteries in an experimental model ended up in the lenticulostriate arteries, the rest going to the cortical arteries or their cortical branches.<sup>9</sup> Studies that suggested stronger associations between lacunar stroke and emboli cited carotid stenoses as mild as 25%<sup>16</sup> or cardiac abnormalities not clearly associated with embolism (for example, left ventricular hypertrophy),<sup>13</sup> or they had no, or an inappropriate control group. It would certainly be useful to be able to infer the likely underlying mechanism of lacunar ischaemic stroke (that is, to identify the 10–15% of embolic/stenotic versus other intrinsic small vessel strokes) from the appearance of the brain lesion, as that might help target effective secondary prevention regimens, but much more work is required to see whether different patterns actually exist, before determining how closely these relate to the underlying mechanism.

Hypertension and diabetes are said to be strongly associated with lacunar ischaemic stroke. However, in studies using risk factor free ischaemic stroke subtype definitions, there was only a marginal excess of hypertension with lacunar versus non-lacunar infarction (RR 1.11; 95% CI 1.04 to 1.19) and no difference for diabetes (RR 0.95; 95% CI 0.83 to 1.09).<sup>10</sup> Nor was there clear evidence of any association between smoking, prior transient ischaemic attack, excess alcohol consumption, or raised cholesterol in lacunar compared with non-lacunar infarction.<sup>10</sup>

## IS THERE OTHER EVIDENCE OF A DIFFERENT MECHANISM IN LACUNAR ISCHAEMIC STROKE?

After lacunar ischaemic stroke, a recurrence is more likely to be lacunar than cortical; 47% of recurrences after a lacunar stroke were lacunar compared with 15% of recurrences after a non-lacunar stroke.<sup>19</sup> If lacunar and cortical ischaemic strokes were due to the same mechanisms, then recurrent strokes would be equally likely to be cortical after a lacunar stroke as lacunar, which appears not to be the case.

Lacunar ischaemic stroke also appears to be more closely associated with white matter lesions (WMLs) than does cortical ischaemic stroke. WMLs are abnormal areas of hypodensity (on computed tomography scans) or hyperintensity (on T2 weighted magnetic resonance imaging (MRI)) in the deep hemispheric and periventricular white matter and brain stem.<sup>20</sup> They are in turn associated with cognitive decline,<sup>21</sup> and

increased risk of future stroke, particularly lacunar type.<sup>22</sup> WMLs also progress rapidly after lacunar stroke.<sup>23</sup> After lacunar stroke, 15–20% develop dementia (more than might reasonably be attributed to the amount of brain damage caused by a lacunar infarct).<sup>6, 21, 24</sup> After lacunar ischaemic stroke, new “silent lacunar infarcts” occur on follow up imaging.<sup>25</sup> Asymptomatic small deep white matter infarcts, in addition to the symptomatic lesion, have been seen on MR diffusion imaging at presentation with lacunar ischaemic stroke.<sup>26</sup> The imaging appearance of these asymptomatic lacunar infarcts suggests that they are slightly older than the presenting lesion. Cerebral microhaemorrhages, which are tiny, apparently asymptomatic bleeds (or “leaks”) in the brain are also associated with lacunar stroke and WMLs.<sup>27</sup> These observations suggest that most lacunar strokes are the clinically focal manifestation of what is actually a diffuse abnormality of the small cerebral arterioles, which, if extensive enough, can also manifest clinically as cognitive decline and dementia.<sup>28</sup>

### WHAT IS THE CEREBRAL SMALL VESSEL ABNORMALITY?

Detailed pathology studies in the 1950s identified abnormal small deep perforating (lenticulostriate) arteries resulting in lacunar infarcts,<sup>29</sup> termed segmental arterial wall disorganisation (since called lipohyalinosis or fibrinoid necrosis). In lipohyalinosis, the vessel wall appears thickened, with focal dilation, and eventually leads to disintegration of the wall with an infarct around it. This arteriolar abnormality remains the most commonly described defect to date.<sup>30, 31</sup> However, there is debate about the pathology and its relationship to symptoms; many studies did not ascertain that the lesion seen at autopsy was symptomatic, some studied multiple small “holes” in the brain regardless of symptoms, and many lesions came from few patients.<sup>32</sup> Lipohyalinosis is found in areas of the brain corresponding with WMLs on imaging.<sup>33</sup>

The nature of the intrinsic arteriolar abnormality remains unresolved. It may be microatheroma, poor cerebral blood flow, or vasospasm. It is difficult to see why atheroma would affect the small arterioles when there is a lack of association with the better understood large artery atheroma in lacunar infarction.<sup>10, 14</sup> Vasospasm, inducible in animal models with extreme hypertension, causes fibrinoid necrosis, but the association of lacunar infarction with any excess of hypertension (more than other types of ischaemic stroke) in patients is

weak (RR 1.11; 95% CI 1.04 to 1.19).<sup>10</sup> Thickened vessels may narrow or occlude the lumen, leading to ischaemia, but relatively few truly occluded vessels have been seen pathologically.<sup>29, 30</sup> Thickened vessel walls may be stiff and impair autoregulation, and indeed patients with WMLs may have impaired autoregulation.<sup>34</sup> Some studies found reduced cerebral blood flow (CBF) in patients with WMLs,<sup>35</sup> but others did not.<sup>36</sup> CBF is difficult to quantify: “reduced” CBF may be artefactual,<sup>37</sup> or simply the consequence of a reduction in normal tissue to supply. None of this explains what starts the vessel abnormality, only the features or behaviour of the vessels and the possible mechanisms for damaging the brain, once the abnormality is established.

### IF NOT OCCLUSION AND ISCHAEMIA, THEN WHAT?

The underlying abnormal lenticulostriate artery can be seen in about 10% of lacunar infarcts on detailed MRI scans.<sup>38</sup> Although this appearance could be an intra-luminal thrombus (a small arteriolar “hyperdense middle cerebral artery sign” equivalent), other features suggest that blood products had passed into the vessel wall and perivascular space. The infarcts appear to be around, rather than at the end of the abnormal segment. Lesions that resemble an “incomplete” lacunar infarct (perivascular oedema related lesions) at autopsy<sup>39</sup> suggest that the “infarct” was actually due to oedema fluid leaking from the arteriole and damaging adjacent tissue.

Increased “leakage” of intravenously injected MR contrast agent across the blood–brain barrier have been found on detailed MR imaging in patients with WMLs.<sup>40</sup> There are numerous other examples in a rather scattered literature pointing to “leaky” small arterioles predisposing to WMLs and lacunar ischaemic stroke, of which the following are but a few. Extravasated plasma proteins have been found at autopsy in WMLs in patients with ischaemic cerebrovascular disease in life.<sup>41</sup> Discrete areas of extravasated plasma proteins have been seen around small cerebral arterioles in hypertensive primates.<sup>42</sup>

These combined observations suggest that the initiating step for most lacunar ischaemic stroke and WMLs may be failure of the arteriolar endothelium (that is, the blood–brain barrier) allowing extravasation of blood components into the vessel wall, and consequently vessel wall, perivascular neuronal, and glial cell damage.<sup>28, 39, 41, 42</sup> This would explain the features described histologically,<sup>29, 31, 32</sup> and the association

with microhaemorrhages (small blood leaks).<sup>27</sup>

Is there other evidence of endothelial failure? Patients with isolated lacunar infarction, or lacunar infarction plus WMLs, have elevated systemic plasma markers of endothelial activation (plasma intercellular adhesion molecule 1, thrombomodulin, and tissue factor pathway inhibitor) compared with age matched normal controls.<sup>43</sup> However, in the absence of non-lacunar controls, it is unclear if these patterns are specific to lacunar stroke. Several studies have identified retinal microvascular abnormalities that were associated with increased risk of stroke, cognitive impairment, and white matter lesions. Those most closely related to these cerebral abnormalities (microaneurysms, retinal haemorrhages, and soft exudates) were most commonly seen when there was breakdown of the blood–retinal barrier.<sup>45</sup> Unfortunately most of these studies did not examine stroke subtypes, so more work is required.

### SUMMARY

The mechanism underlying, and the long term consequences of, lacunar ischaemic stroke, the cause of a quarter of all ischaemic strokes, are poorly understood, but are not benign. Evidence supports the hypothesis that, in most lacunar strokes, the vascular abnormality is pathologically diffuse, even if the clinical manifestations are focal, and result from small vessel endothelial damage, subtle increase in blood–brain barrier permeability, and leakage of substances toxic to the brain into the perivascular tissue. As originally proposed in the lacunar hypothesis, only a small proportion of lacunar stroke appears to result from artery to artery or cardiogenic emboli or intracranial large artery stenoses. These latter embolic/stenotic lesions may be recognisable by their size (being larger).

It might be questioned how this presumably gradual process could produce a sudden lacunar infarct. In fact, lacunar stroke symptoms (more than other stroke subtypes) not uncommonly progress after onset.<sup>44</sup> Perhaps the interstitial fluid composition eventually reaches a critically abnormal point where the axons cease to transmit signals, or the vessel wall thickening narrows the lumen and reduces blood flow, or fails to allow nutrients out and waste products of metabolism back into the circulation. This diffuse endothelial failure might also account for additional asymptomatic lacunar infarcts observed at presentation with,<sup>26</sup> or during follow up after,<sup>25</sup> a symptomatic lacunar infarct with no underlying embolic source.

These asymptomatic lesions, gradually multiplying, could be the source of the WMLs. Neurons can switch off suddenly, even when the underlying process is gradual; for example, neurons switch off electrical activity (manifest as a stroke) as cerebral blood flow falls below about 25 ml/100 g brain/min, thus the fall in blood flow may have been gradual but the symptoms are sudden.

An important target for new therapeutic approaches to prevent or treat a common form of ischaemic stroke and cognitive decline may have been overlooked. It is important to understand this process better, not simply in order to reduce the burden of lacunar stroke, but because the same mechanism may also underlie WMLs and consequent cognitive decline to dementia. Lacunar ischaemic stroke has for too long been simply lumped together with other stroke subtypes; while it is likely that many older stroke patients will share common vascular risk factors, this tendency has hindered understanding of what appears to be an importantly different stroke subtype that may require different acute treatment and prevention. For example, the association with microhaemorrhages, a possible risk factor for intracerebral haemorrhage, is worrying, and may increase the risk of haemorrhage complicating anti-thrombotic drug treatment compared with their use in cortical ischaemic stroke. Further studies, using detailed, accurate, and unbiased patient classification, are needed to examine risk factors for lacunar stroke including blood-brain barrier function (now possible with detailed MRI),<sup>40</sup> how to identify those lacunar strokes that are due to embolism, and clarify long term outcomes. Study of small arteriolar abnormalities in other vascular beds (for example the retina, where the arterioles can be directly observed) and systemic endothelial abnormalities will help both in understanding the mechanisms of lacunar ischaemic stroke and in identifying diagnostic and prognostic markers.

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Huntington's disease

## Imaging Huntington's disease (HD) brains – imagine HD trials!

H P H Kremer

### Tensor based morphometry

The true and ultimate aim of research in Huntington's disease (HD) is to arrest the progressive neurodegeneration and thus the debilitating clinical and functional deterioration—or so it seems to those involved in the clinical care of the unfortunate individuals affected by it. Two major clinical challenges confront us: to retard, or better, to abolish disease progression in symptomatic individuals; and to prevent phenoconversion in presymptomatic individuals.

Huntington's disease is considered to be rare, but extrapolation of its estimated prevalence—in western countries 5 to 10 per 100 000—yields for the current 25 countries of the European Union (with 455 million people in 2004) a total number of between 22 500 and 45 000 clinically affected patients in various stages of the disease. The number of presymptomatic mutation carriers is much higher. Recent advances in our understanding of the molecular pathobiology have raised hopes that rational treatments may be near. Huntington's disease is caused by an expanded CAG triplet repeat in exon 1 of the *huntingtin* gene, and this mutation is expressed and translated into an expanded polyglutamine sequence in about half of all huntingtin protein molecules that are produced in the body cells. The physiological functions of the protein are still unknown. But many details of huntingtin interactions, cleavage, conformational changes, aggregation, and proteasomal breakdown have been clarified in the past decade.<sup>1</sup> Based upon these mechanistic models, various potential drugs have been proposed. In fact, efficacy of such proposals has been demonstrated in simple cellular or more complex animal models, such as transgenic flies or mice.<sup>2</sup> Another approach has been the large scale screening of promising compounds in simple systems<sup>3</sup>; and even older hypotheses regarding the causes of neurodegeneration, such as excitotoxicity, have yielded proposals for neuroprotective treatments. In fact, most of

the past and ongoing neuroprotection trials in HD have studied compounds derived from this hypothetical excitotoxicity.

But these trials have faced one major problem. All of them have used serial clinical or functional assessments of symptomatic patients as the primary outcome measure. Despite their demonstrated robustness, linearity, and relevance, the intrinsic variability of clinical outcome measures in treated cohorts has been large. As a result, phase II and III neuroprotection trials have typically included relatively large numbers of symptomatic patients who were followed for several years. Thus a North American trial which studied the effects of remacemide and coenzyme Q (CoQ) against placebo in a 2×2 factorial design enrolled 347 patients and followed them for 30 months. The study failed to show any benefits of the treatment, although a trend towards an effect of CoQ has been suggested.<sup>4</sup> Based upon this study, calculations predicted that a sufficiently powered CoQ trial would require more than 1000 patients to be followed for at least two years. The European EHDI trial that studies the effects of riluzole on disease progression in a 1:2 randomisation design enrolled 560 patients who were followed for 37 months. Results of this trial are pending. Previous interventions which studied baclofen, idebenone, vitamin E, and lamotrigine included 100 patients or fewer, but all of them turned out to be clearly underpowered. The lesson: Huntington trials need large numbers of participating patients, to be followed for years.

If we were to conduct 10 such European protection trials simultaneously, about a quarter of all the patients in the 25 EU countries would have to be enrolled and followed for many years. If we were to conduct an intervention in presymptomatic patients, the difficulties would be compounded because of the very long follow up times required to demonstrate phenoconversion. The logistics issue then becomes: how can we persuade

sufficient participants and generate resources for such trials? Shorter trials that require fewer patients would clearly be preferable. The statistical answer would be: let us reduce end point variability.

Enter the paper by Kipps *et al*<sup>5</sup> (*this issue, pp 650–5*), about imaging the structural disease progression in preclinical disease. Using a novel approach to statistical imaging, called tensor based morphometry, they were able to demonstrate over a period of two years a progressive regional grey matter loss in 17 presymptomatic Huntington mutation carriers compared with 13 mutation negative controls. In contrast, clinical measurements failed to pick up any deterioration. If this result can be confirmed by others, imaging would become a powerful tool in neuroprotection trials. Imagine an intervention trial in which 40 patients are randomised and followed for two years, with, as the major measurements, an MRI scan at baseline and at the end of the trial. Although such measurements would have to be considered surrogate end points, they would nevertheless assume a crucial role in the selection of compounds to undergo the final test of clinical efficacy: a randomised controlled clinical trial with 1000 patients enrolled and followed for 30 months, with clinical outcome as the primary end point. We could certainly start planning a “primary prevention” trial aimed at postponing (or abolishing?) the onset of the disease.

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Weight bearing asymmetry

# Weight bearing asymmetry in standing hemiparetic patients

D Pérennou

## MCA stroke may disrupt corticobulbar projection to brainstem output pathways involved in the vestibular control of balance

Postural disorders are a primary disability after stroke.<sup>1</sup> They lead to loss of autonomy and expose patients to a high risk of falling. We must bear in mind that following a total anterior circulation infarct, the median time to recover the ability to stand for 10 s is 44 days (25th–75th percentile: 38–57 days)<sup>2</sup>. Retraining the patient to stand is therefore a primary goal in post stroke rehabilitation, especially following hemisphere strokes.

Three main patterns characterise the standing posture of hemiparetic patients<sup>1</sup>: i) an increase in centre of gravity displacement, which reflects postural instability and results from orthopaedic, sensorimotor, and cognitive impairments; ii) the presence of a small area of stability beyond which the centre of gravity cannot move without exposing the patient to a loss of balance (this results either from an inability to control a stressed equilibrium system or from impaired co-ordination between posture and movement); and iii) weight bearing asymmetry, with more weight on the non-paretic leg. Unstable standing posture, although a major target in stroke rehabilitation, is still poorly understood. Weakness certainly plays a role, as do cognitive disorders observed in patients with lesions of the right hemisphere.<sup>3</sup> These cognitive disorders result in distortion of the coordinates used to distribute loading over the two legs while standing. Since some patients align their erect posture to a biological vertical contralesionally tilted, it has also been suggested that the shift in the center of gravity towards the ipsilesional leg might be a compensatory

strategy to prevent contralesional falling.<sup>1</sup>

In a very elegant experimental study published in this issue (pp 670–8), Marsden *et al* propose a new approach to the problem of postural instability in standing hemiparetic patients. Using the measurement of forces and movements elicited by galvanic and transcranial electrical stimulation, they have explored the possibility of asymmetric vestibulo-spinal excitability in chronic middle cerebral artery (MCA) stroke patients, in patients with isolated corticospinal tract lesions, and in normal subjects. Patients and subjects were required to stand barefoot on two separate force plates with equal weight on both legs and with eyes closed. One advantageous feature of galvanic vestibular stimulation is that it is possible to evoke a bilateral response by stimulating vestibular afferents on one side only,<sup>4,5</sup> which means any asymmetries that may exist in the response pattern can be identified. It also offers an opportunity to decide whether asymmetry arises from an abnormality in the processing of sensory information (altered response in both legs for a lateralised deficit of sensory information) or an abnormality in the motor control of one side of the body (altered response in one leg and not the other irrespective of which ear is stimulated). The main finding of the Marsden *et al* study was abnormal interleg response asymmetry to galvanic vestibular stimulation in stroke patients only, the amplitude of the response being higher on the non-paretic side than on the paretic side, and higher on the

non-paretic side than in controls. Since the changes in the reaction forces were observed early after vestibular stimulation (320–500 ms), the authors assumed that this initial response was likely to be purely vestibular in origin. Marsden *et al* also found that the degree of asymmetry induced by galvanic stimulation was correlated with the degree of corticospinal damage induced by transcranial magnetic stimulation. They concluded that MCA stroke may disrupt corticobulbar projection to brainstem output pathways which are involved in the vestibular control of balance. They suggested that stroke is associated with a lateralised deficit in the motor output stage of vestibular processing rather than in the sensory or spatial processing stages.

Postural rehabilitation must be guided by a better understanding of the postural disorders displayed by patients. There is no doubt that the paper by Marsden *et al* contributes to this knowledge. This new insight on the postural instability of standing stroke patients must now be confirmed and integrated with knowledge of the many other alterations and deficiencies which are involved in postural disorders caused by hemisphere strokes.

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Guillain-Barré syndrome

## Prognosis in the acute motor axonal form of Guillain-Barré syndrome

C M Gabriel

### Prognosis in axonal Guillain-Barré syndrome

**A** primary axonal form of Guillain-Barré syndrome was first described by Feasby and colleagues<sup>1</sup> in 1986. Initial indications were that this had a worse prognosis than demyelinating forms of the disease and it was suggested that recovery might require axonal regeneration along the entire length of the nerve fibre. In the intervening years it has become apparent that recovery from acute motor axonal neuropathy (AMAN) may actually be either rapid or slow. This is confirmed in a paper by Hiraga and colleagues (*this issue, pp 719–22*),<sup>2</sup> and in addition they observed that in patients with slow recovery, clinical improvement to independent ambulation may continue for more than four years.

In the early 1990s, AMAN was characterised in northern China as a rapidly ascending tetraparesis with Wallerian-like degeneration of motor fibres at necropsy.<sup>3</sup> This syndrome is most common in Japan and northern China, occurs uncommonly in Western countries, and is associated with *Campylobacter jejuni* (in 60–70%), *Haemophilus influenzae* (in 10–20%), and antiganglioside antibodies. Detailed ultrastructural study<sup>4</sup> showed that the earliest changes were of myelin disruption at nodes of Ranvier, followed by macrophage extrusion into the periaxonal space at the paranode, with separation of the axon from the adjacent

Schwann cell membrane, and subsequent degeneration of both Schwann cell cytoplasm and axon.

It has become clear in more recent years that although AMAN progresses more rapidly to nadir, recovery times for AMAN and acute inflammatory demyelinating polyradiculoneuropathy (AIDP) are similar, and that in fact some patients with AMAN recover more quickly,<sup>5</sup> especially if their illness is preceded by *Haemophilus influenzae*. Clinically, those who recover more rapidly are equally weak at the peak of their illness, though they are more likely to retain their tendon reflexes than those with AIDP.

Rapid recovery in AMAN in the current study was defined as an improvement of two or more Guillain-Barré syndrome disability scale grades in the first four weeks e.g. from bed-bound to independent ambulation, which occurred in 27% of the AMAN group. Such improvement would be incompatible with the primary pathology being Wallerian degeneration. Other explanations might be degeneration restricted to the distal motor nerve terminal where regeneration could occur quickly, immune mediated conduction block at the axonal membrane, or complement mediated damage to perisynaptic Schwann cells. This may imply additional pathological mechanisms distinct from those described

ultrastructurally by Griffin and colleagues. The authors also identified a small number of patients who were unable to walk six months after the illness but all of whom continued to improve until they could walk independently in subsequent years.

It is possible that several different pathophysiological processes exist in AMAN to explain the dichotomous recovery patterns: reversible distal nerve failure at motor terminals or conduction block at nodes of Ranvier in association with rapid recovery, and Wallerian degeneration requiring axonal regrowth which may continue over many months and years. In AIDP, conventionally considered a demyelinating condition, severe lesions may result in axonal degeneration as well as myelin destruction, and a similar distinction dependent on disease severity may occur in AMAN. Certainly there is no unifying hypothesis to date, but it is encouraging that all forms seem to be potentially reversible.

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## What causes lacunar stroke?

J M Wardlaw

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