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Modern concept of vascular cognitive impairment

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Background: Vascular cognitive impairment (VCI) has superseded vascular dementia and multi-infarct dementia as the concept to be used in cognitive decline due to cerebrovascular disease.

Method: The literature was reviewed with regard to the concept of VCI and its incidence, pathophysiological substrate, clinical features and management.

Results: A change in the diagnostic paradigm from the current Alzheimer-based definition of vascular dementia to VCI will allow the earlier identification of cases and will identify a different population from that recognized using the current criteria for vascular dementia.

Conclusions: Case identification at the earliest possible stage affords the greatest opportunity for treatment that may slow the rate of progression.

Keywords: vascular dementia/vascular cognitive impairment/dementia/leukoaraiosis/subcortical

Historical note

For most of the twentieth century dementia was routinely attributed to arteriosclerosis and consequent chronic cerebral ischaemia. This view changed with the increasing recognition of Alzheimer's disease and the demonstration that infarcts and not chronic ischaemia were the basis of what came to be termed multi-infarct dementia.[1,2] The term 'vascular dementia' subsequently replaced multi-infarct dementia as it was recognized that there were many aetiologies apart from multiple infarcts including single infarcts in eloquent areas, episodes of hypotension, leukoaraiosis, incomplete infarction and haemorrhage.

However, by the end of the twentieth century, the increasingly recognized Alzheimer's disease entirely eclipsed vascular dementia. Because Alzheimer's disease was thought to be the major cause of dementia, the criteria for Alzheimer's disease[3–5] formed the basis for those of all dementia. Alzheimer's disease was separated from vascular dementia

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Table 1 The ischaemic scale.

Feature	Value
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History/presence of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2
	Total score

Scores >7 suggest a vascular aetiology for dementia, whereas scores ≤ 4 do not support a vascular aetiology.

using clinical features thought to reflect vascular risk factors, vascular events and the manifestations of systemic and cerebral vascular disease. These elements are typically codified using the ischaemic score (Table 1).[6] This basis for the definition has resulted in published criteria for vascular dementia emphasizing memory loss and usually the progression and irreversibility of the cognitive decline, none of which are necessarily the case.

The old criteria for vascular dementia also define dementia as the level of cognitive impairment at which normal daily functions are impaired. They will therefore identify only late cases, so underestimating the prevalence of cognitive impairment due to vascular disease and denying early cases the benefit of timely preventative treatment.

Consequently, over the past decade there has been a paradigm shift towards a new concept, that of vascular cognitive impairment (VCI)[7] and this is now widely accepted as a more appropriate concept than the old concept of vascular dementia (Fig. 1).

Still there has been another major change with the increasing recognition of mixed dementia, where vascular dementia co-exists with other causes of dementia, particularly Alzheimer's disease. These are now known to be common. Eighty per cent of the elderly have evidence of cerebrovascular disease[8] and mixed vascular dementia and Alzheimer's disease may account for up to half of all dementia.[9–12] Furthermore, the interaction between the vascular component and other components doubles more than the rate of progression compared with pure Alzheimer's disease alone.[9,13]

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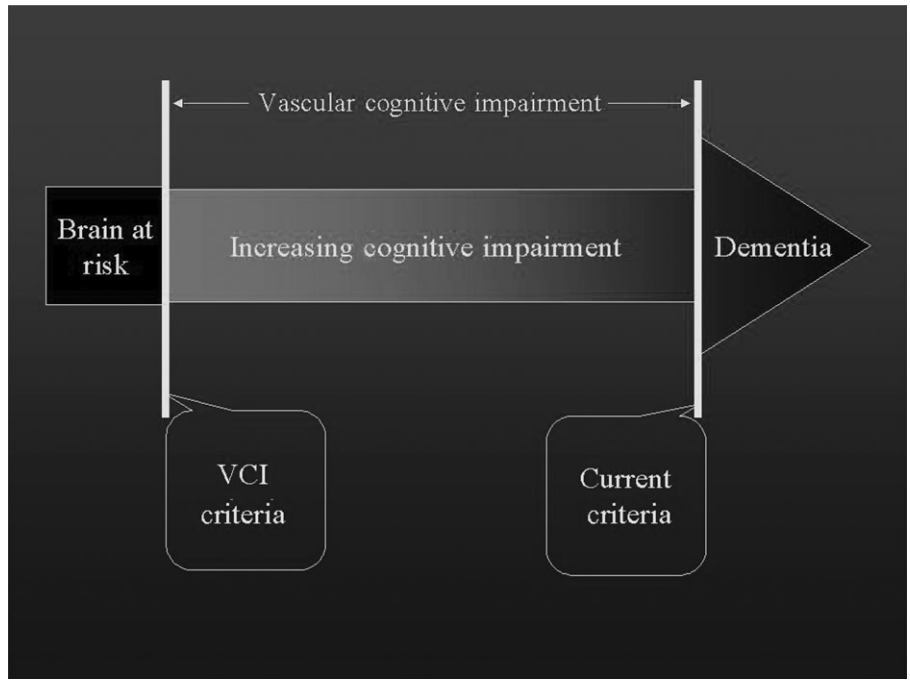

Fig. 1 Illustration of the stage of 'brain-at-risk' and the difference between VCI and the older concept of vascular dementia.

Epidemiology

The incidence of vascular dementia is about 3.8 per 1000 per annum although figures vary considerably depending on the study methodology and criteria used. The incidence in women rises from 0.3–1.36 in those aged between 65 and 69 years to 9.3 in those aged $\geq$85 years. For men, the corresponding figures are between 1.3 and 2.2 rising to 9.3 and 15.9 in those aged $>$90 years. Dementia from all causes has a prevalence of about 8% of the population over the age of 65. Between 9 and 39% (but typically 13–19%) of these cases are vascular. An additional 11–43% may be mixed dementia. The proportion of cases due to vascular dementia falls with increasing age but even so, the prevalence of all dementia rises so rapidly with age that the prevalence of vascular dementia also rises, from 0 to 2% in the 60–69 age group to up to 16% for males aged 80–89 years. Men are more commonly affected than women.

Data are now becoming available concerning the epidemiology of VCI. In patients under 74 years of age, VCI may be common. In those aged 75–84 years, cases of pure VCI, vascular dementia and those

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with a vascular component in the context of mixed disease outnumber those with pure Alzheimer's disease.

Risk factors

The classical risk factors predominate here and will not be outlined further. It is, however, common to patients with extensive vascular risk factors whose MRI scans show little cerebrovascular disease. The converse is also true, suggesting that host factors are important. A number of single-gene diseases of cerebral blood vessels are now well recognized. CADASIL is well recognized but there are others which have been clearly characterized[14,15] and others where knowledge is evolving. The Framingham Heart Study,[16] for example, has presented the first genome-wide linkage analysis for leukoaraiosis and identified one peak logarithm of the odds score of 3.69, indicating significant evidence of linkage, on chromosome 4p. This region is not the one where any of the known genes predisposing to stroke are situated and there is no clear candidate gene here although there are a number of aging and mitochondria-related genes. There is also evidence of a more polygenetic hereditary component to blood vessel susceptibility. The NHLBI Twin Study revealed 71% heritability for leukoaraiosis[17] and the Framingham and GENOA studies in 2004[18,19] confirmed significant heritability. This adds to the list of single-gene inheritable conditions associated with leukoaraiosis and raises the possibility that other genes encoding structurally important proteins might contribute to small-vessel cerebrovascular disease. Some of this may be mediated through angiotensin receptor and endothelial nitric oxide synthase gene polymorphisms.[20]

Other physiological factors are less well characterized. Orthostatic hypotension and blood pressure variability may play a role.[21] Nocturnal hypotension superimposed upon limited perfusion reserve and impaired vasoreactivity producing partial ischaemia leading to incomplete infarction has been a proposed mechanism, but evidence from Japan suggests that this is not the case and that nocturnal dipping of blood pressure reduces the risk of ischaemic damage.[22]

Pathogenesis and pathophysiology

Subcortical VCI is the most common single VCI variant, accounting for 40% of cases. Multiple smaller infarcts and small-vessel diseases are more often a substrate of vascular dementia than single major

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infarcts.[23] However, the processes that lead to VCI begin with leukoaraiosis.

Initial work suggested that only CT-demonstrated leukoaraiosis had clinical correlations, the interpretation being that MR, a more sensitive tool, was detecting numerous asymptomatic lesions. That >90% of elderly individuals have some form of leukoaraiosis without necessarily being demented supports this.[24] More recent work using detailed neuropsychological assessment has shown that subtle, predominantly subcortical, deficits are associated with leukoaraiosis in the absence of dementia and in apparently normal aged subjects.[25–30]

The consequences of leukoaraiosis extend beyond its visible boundaries. Functional imaging (diffusion tensor MRI) shows abnormalities of diffusivity in normal appearing white matter in patients with leukoaraiosis and diffusivity correlates better with cognition than simple lesion load.[31]

The term leukoaraiosis encompasses a range of pathologies. The term originally referred to CT white matter changes,[32] but is also used to refer to white matter changes on MRI. However, a wide range of structural changes encompassing increased water content without functional loss through axon or myelin loss appear similar or identical on MRI. Deep white matter changes seen on MR correspond to myelin pallor on naked eye examination of slides when the MR changes are over 10 mm. The subcortical U-fibres are spared. Axons, myelinated fibres and oligodendrocytes are decreased in the affected areas, and spongiosis is also seen in the same areas. These changes blend gradually into surrounding tissue. Frank infarction is rare in lesions corresponding to leukoaraiosis, but is otherwise a common part of the pathology of the deep white matter. Small punctate lesions seen on MRI correspond to dilated perivascular (Virchow–Robin) spaces. When seen in the periventricular regions, leukoaraiosis is often due to breakdown of the ependyma, with increased fluid content of the local white matter with some loss of myelin and dilated perivascular spaces and is therefore less closely linked to hypertension. There is also evidence of breakdown of the blood–brain barrier in regions of leukoaraiosis and plasma proteins can be found in glial cells in close relation to demonstrable white matter lesions. Whether these changes are causal or merely consequences of ischaemia remains to be established, although extravasated plasma proteins are known to be neurotoxic.

There is continuing debate over whether there is a difference in the aetiology and cognitive consequences of periventricular as opposed to deep white matter leukoaraiosis. One MRI-based study has shown that they closely correlate with each other,[33] implying a shared aetiology but cognition was not studied. However, data from the Rotterdam scan study suggest a difference in prognosis, pattern of cognitive deficit and

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Table 2 The progression of leukoaraiosis and the associated patterns of cognitive impairment.

	Subjects	Age	Follow-up interval (years)	Leukoaraiosis progression		Cognitive domains affected
				Mean (ml/year)	Max (ml/year)	
Cardiovascular Health Study[36]	1919	74	5	N/A	N/A	3MS, digit symbol substitution and gait speed
Rotterdam Scan Study[30]	832	60-90	5.2	N/A	N/A	Stroop naming, letter-digit substitution; not memory or verbal fluency
Austrian Stroke Prevention Study[37]	329	60	3.6	0.23	5.23	Memory, conceptualization and visuopractical functions
PROSPER[38]	554	75	3	0.68	N/A	Stroop for periventricular but not deep white matter changes
Denmark[39]	26	81	5	0.68	5.4	WAIS verbal IQ, information and digit span subtests; not WAIS performance or MMSE

the presence of hypoxic markers according to lesion site.[34,35] There may also be differences in the genetic associations of periventricular and deep white matter leukoaraiosis.[20]

Several studies have reported on the progression of leukoaraiosis and its cognitive correlates in over 3500 subjects (Table 2).[30,36–39] Cognitive correlates of leukoaraiosis were universally found and cognitive decline was four times faster in those with the greatest progression of leukoaraiosis. The changes were modest but may underestimate rates of change in those at greatest risk as there was a pronounced tendency for those with greater cognitive impairment to decline assessment. In those studies where factors predicting the rate of decline were measured, greater disease (leukoaraiosis or cognitive) at entry predicted more rapid increases in leukoaraiosis and cognitive decline.

Infarcts are of course important. Simple infarct volume is a determinant but because of the importance of location it is relatively weak and there has been debate over the minimum volume of infarction needed to produce dementia. Early work implicated volumes over 20 ml and in particular over 50 ml, but in more modern work, smaller volumes, usually in the range of 1–30 ml, are more typical. Low volumes (mean of 8 cm^3) correlate with cognitive status in VCI. Infarct location is crucial. For example, miniscule lesions of the thalamus can be devastating.

Atrophy on MRI has sometimes been taken to support degenerative or mixed dementia rather than vascular dementia, but there is now

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clear evidence to show that atrophy, particularly central atrophy, is a common feature in vascular dementia and also in association with vascular risk factors, transient ischaemic attacks and leukoaraiosis.

Clinical features

The old criteria for vascular dementia, being based on Alzheimer's disease, tended to select cases according to the presence of memory and cortical cognitive deficits, historically leading to an inaccurate view of the pattern of cognitive impairment. Data derived using such criteria were even sometimes used to validate them, a tautological process whereby analysis of case series meeting the old criteria for vascular dementia will reveal prominent memory loss in all cases. This has been taken as showing that memory loss is prominent in vascular dementia but this is so only because the cases were selected for memory loss. A better source of information is to look at the cognitive changes seen in cerebrovascular disease in general. Data derived this way reveal a predominant theme of a primarily subcortical dementia with early impairment of frontal lobe function. Memory impairment is usual, but is often not pre-eminent.

Consequently, the neuropsychological tests used in the assessment of Alzheimer's disease, in particular the mini-mental state examination (MMSE), are not appropriate tools in VCI. Instruments that include assessment of frontal, executive and subcortical function are required. Modifications of some of the tests originally developed for Alzheimer's disease may be helpful, but test batteries specifically developed for this purpose are most likely to be useful.[40,41]

Many of the commonly recognized features of the clinical history related to the previous concepts of multi-infarct and vascular dementia apply to much lesser degrees in VCI. In 90% of cases where multiple infarcts are responsible, there is also a history of stroke or transient ischaemic attacks. However, this is now known to be a rare pattern of disease in VCI and in the far more common subcortical form, a history of stroke may be absent in up to 40%. Focal signs are also less common. The presence of 'patchy' or unequal cognitive deficits is also a myth. It is only to be expected in true multi-infarct dementia where there are only very few (two or three) cortical infarcts. In vascular dementia, in general, the extent to which the cognitive deficit is patchy is not different from Alzheimer's disease, for example, although the domains affected are different.[42] Particularly, in subcortical disease, progression tends to be through repeated very minor changes such that neither a clear history of stroke or of temporal relationship between

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strokes, and cognitive decline is necessary for vascular dementia to be present.[43]

The description of dysarthria, mild haemiparesis, imbalance, pseudobulbar palsy, small stepping (magnetic) gait, emotional incontinence, some degree of dementia and incontinence (the 'lacunar state') dates back to the turn of the century and describes a minuscule proportion of all cases of vascular dementia.

Depression is common in vascular dementia, occurring in up to 20% of cases, and is disproportionately prominent in those cases with small amounts of infarction. It may be particularly related to frontal deep white matter lesions.

Diagnostic criteria

Two similar sets of criteria for the identification of vascular dementia have been proposed, but neither has met universal acceptance or been validated and both have been rendered obsolete. They remain of importance only in that many of the clinical trial and other study data pertinent to VCI have been derived using them.

The NINDS-AIREN criteria define probable vascular dementia as cognitive decline from a previously higher level of functioning in memory and two or more cognitive domains, the decline being severe enough to interfere with activities of daily living. Evidence of cerebrovascular disease on both clinical examination and neuroimaging is required, as is evidence of a relationship between the stroke and cognitive decline, which can be provided by two of the following: (a) onset of dementia within 3 months after a recognized stroke, (b) abrupt deterioration in cognition and (c) stepwise deterioration. Abnormalities on neuroimaging are only considered to support the diagnosis of vascular dementia if they fulfil criteria regarding site and size, e.g. large vessel strokes in the following sites: bilateral anterior cerebral, posterior cerebral, association areas or carotid watershed (superior frontal, parietal); small vessel disease in the basal ganglia and frontal white matter; extensive periventricular white matter lesions; or bilateral thalamic lesions. The criteria for severity specify that leukoencephalopathy must involve at least 25% of the total white matter. These are purely arbitrary and no longer acceptable in modern work. A diagnosis of possible vascular dementia is made (a) if there are no neuroimaging data but there is clinical evidence of cerebrovascular disease or (b) in the absence of a clear temporal relationship between dementia and stroke or (c) in those with a subtle onset and variable course. Hemorrhagic lesions are permitted. Definite vascular dementia is diagnosed provided probable dementia exists, it is accompanied by histopathological evidence of

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cerebrovascular disease, and there is no histopathological evidence of other possible causes of the cognitive loss. Vascular dementia is excluded in cases with disturbed consciousness, psychosis, severe aphasia, major sensorimotor deficits or other brain diseases such as Alzheimer's disease that could themselves account for the deficit. Mixed dementia is not recognized, but the co-existence of Alzheimer's disease is termed Alzheimer's disease with cerebrovascular disease.[44]

The California criteria are not fundamentally different, but differ in details. Haemorrhagic and anoxic lesions are not included. The number and type of cognitive defects are deliberately not specified, but the loss should be sufficient to interfere with the conduct of the patient's customary affairs of life and should not be confined to a single narrow category. Two or more ischaemic strokes (at least 1 of which is outside the cerebellum) or 1 stroke with a clear temporal relationship to the onset of dementia are required. Risk factors and some clinical features are included as supportive features, but how these are to be operationalized is not stated.[45]

These criteria are now outdated and should not be used in clinical practice or new research work; they are included for reference as much of the published literature is based upon them. For time being, clinical diagnoses will have to be made without the benefit of clear criteria as none have yet been validated for early disease. However, guidelines outlining clinical, neuropsychological, imaging and genetic factors that may be relevant have recently been published.[46]

Differential diagnosis

The principal differential diagnoses are from mixed disease (VCI and Alzheimer's disease), Alzheimer's disease and depression supervening on stroke, as depression commonly follows stroke. The use of the ischaemic scale score (Table 1), scores of ≤ 4 suggesting Alzheimer's disease and those of 7 or supporting vascular dementia has 89% sensitivity and specificity. However, distinguishing mixed dementia and either vascular dementia or Alzheimer's disease remain difficult due to poor specificity. The use of CT to identify infarcts increases diagnostic accuracy.

Prevention

Many of the commonly recognized vascular risk factors have been identified as risk factors for vascular dementia. For most of these,

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evidence that risk factor modification protects against vascular dementia is lacking but it is reasonable to do so on first principles.

However, some data are now available that deal specifically with the cognitive benefits of risk factor modification. The Syst-Eur study showed that a reduction of 7 mmHg in systolic and 3.2 mmHg in diastolic blood pressure over 3.9 years halved incident dementia[47,48] although the absolute figures are a little less impressive at 3 cases per 100 patient-years. The PROGRESS study[49] demonstrated a reduction, over 3.9 years of follow-up, in risk of dementia from 7.1 to 6.3% (non-significant) and in cognitive decline from 11 to 9.1%, this benefit being attributable to the prevention of recurrent stroke.

There are now increasing data on drugs as preventive agents.[50] Interestingly, evidence that the statins protect against cognitive loss is relatively weak. The PROSPER study failed to demonstrate any benefit on stroke, leukoaraiosis, cognition or activities of daily living but did show a benefit on myocardial infarction and transient ischemic attack.[51,52] In a 4-year observational study of 1000 post-menopausal women, statin users had a trivially (1%) higher score on a modified MMSE.[53] The Cardiovascular Health study also showed no benefit.[54] Given the established benefits of the statins in preventing adverse vascular events, the discrepancy between these and antihypertensive therapy requires some explanation. This may lie in the fact that subcortical VCI is the commonest form of VCI and that hypertension is, by a very considerable margin, the most powerful treatable risk factor. Cholesterol has little association with small-vessel disease and the plaque stabilizing, antioxidant and other properties attributed to the statins may not be relevant to lipohyalinosis and so to small-vessel disease. Taking these observations together, it is readily possible to see why different treatments may have differing effects.

Non-steroidal analgesics do not protect against vascular dementia.[55] Ultimately, the goal is to prevent even VCI from developing by identifying and treating individuals at risk before the first appearance of disease; this very earliest stage is termed 'brain-at-risk'.[56]

Management

The treatment of vascular dementia is that of the underlying cause. Care must be taken to identify and treat depression, which is common both in association with dementia and after stroke. If there is any doubt, a course of treatment with antidepressant medication is usually justifiable. Treatment of hypertension should be started cautiously. Chronically hypertensive patients shift the autoregulatory range for cerebral blood flow to accommodate higher perfusion pressures. Even with

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treatment, this will not fully return to normal. They are thus susceptible to hypotension, a suspected mechanism for vascular dementia.

A few drug trials have been completed. There is some evidence for nimodipine in subcortical VCI[57] and it may be of limited help in other types of VCI.[58,59] Memantine offers some benefit in VCI.[60–62] Propentofylline may improve cognitive function on formal testing but does not seem to affect activities of daily living. Weak evidence exists for vincamine, vinpocetine, pentoxifylline and posatirelin, but there is no convincing evidence for any single drug and none of these can be recommended. The acetylcholinesterase inhibitors may be more helpful. Three trials encompassing a variety of probable and possible vascular dementia cases as well as mixed dementia have shown statistically significant but modest benefits for galantamine and donepezil over placebo in both cognition and activities of daily living although there remains a question as to how much of these benefits are due to the drugs effect on coexistent Alzheimer's disease.[63]

Prognosis and complications

The prognosis of vascular dementia varies considerably according to the criteria used to make the diagnosis. Multi-infarct dementia shortens life expectancy to about 50% of normal at 4 years from initial evaluation. In the very elderly, 3-year mortality may reach two-thirds, almost three times that of controls and 6-year survival may be as low as 12%, about a quarter of that expected in elderly and severely demented subjects. About one-third of the most severely affected elderly die from complications of the dementia itself, one-third from cerebrovascular disease, 8% from other cardiovascular disease and the rest from miscellaneous causes. Overall, the effect of vascular dementia on mortality is similar to, or mildly worse than that of Alzheimer's disease.

VCI increases the likelihood of subsequent dementia from 8 to 42% over 9 years and in the Canadian Study of Health and Aging, approximately half were dead and half institutionalized after 5 years. However, in 16% there was no cognitive decline, or even improvement, reflecting the diversity of potential outcomes in this condition.[64]

Conclusions

VCI represents a paradigm shift from vascular dementia towards a much earlier state, characterized most commonly by a subcortical frontal and executive pattern of cognitive impairment (as opposed to

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the previous concept of an Alzheimer-based amnestic syndrome). It may begin with very subtle deficits arising on the basis of leukoaraiosis and this proceeds through infarction etc. to a more advanced state. The rate of progression increases with increasing disease such that the prognosis for more advanced cases is at least as poor as it is for Alzheimer's disease. Conversely, early cases deteriorate only very slowly. The principal object of VCI as a concept is to facilitate case identification in this early stage, because progression may be preventable through modification of vascular risk factors etc. Data on VCI are still relatively limited, because much of the research done over the past two decades has been based now on the outdated criteria for vascular dementia. To help resolve this, the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network have recently published comprehensive guidelines for research studies in VCI and it is recommended that workers in this field follows these.[46]

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