Cognition in CADASIL

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Abstract—CADASIL is an early onset small vessel disease and genetic variant of pure subcortical ischemic vascular dementia (SIVD). The condition has been invaluable in defining the profile and neuroimaging correlates of cognitive deficits in pure SIVD. The recent completion of a randomized trial in cognitively impaired CADASIL patients has illustrated the feasibility of targeted therapeutic trials in narrowly defined subtypes of vascular cognitive impairment. This article highlights some of the advances on cognition in CADASIL. (Stroke. 2009;40[suppl 1]:S45-S47.)

Key Words: CADASIL syndrome ■ genetics ■ lacunar infarcts ■ vascular cognitive impairment ■ vascular dementia ■ white matter disease ■ stroke

Investigating the mechanisms and therapeutic approaches to vascular dementia (VaD) remains a challenge, for several reasons: First, VaD represents a heterogeneous condition encompassing various vascular pathologies and dementia mechanisms, which may coexist. Second, many elderly subjects have comorbid neurodegenerative disease, which is difficult to assess particularly during early stages but may nevertheless impact on cognition. Finally, many of the assessment tools, such as cognitive test batteries used in clinical trials, have been developed for patients with Alzheimer disease.

CADASIL is a genetically defined variant of small vessel disease (SVD) and subcortical ischemic vascular dementia (SIVD) which can be diagnosed by mutational screening of the NOTCH3 gene. Because of an earlier age of onset comorbid conditions from age-related pathologies are rare. This has enabled targeted studies on pure SIVD as the most prevalent subtype of VaD.

Cognitive Profile

The profile of cognitive deficits in CADASIL has been investigated by four major studies encompassing a total of 175 subjects.1–4 Two of them provided Z-scores based on reference to an own control group.2,4 Thus, these studies enabled direct comparisons between different cognitive domains. The two other studies focused on the influence of age and disease stage on the cognitive profile.1,3

Despite some differences in the choice of psychometric tests a common and distinctive pattern of neuropsychological abnormalities emerges. The most prominent deficits are seen on processing speed as assessed, for example, by the timed measures of the Trail Making Test (TMT) and the symbol digit test. In fact, abnormalities on the TMT B, a measure of processing speed and set shifting are remarkably consistent across all published studies and are seen both in early and advanced disease stages.2,3

Another frequent observation is deficits in verbal fluency.2–4 In the study by Buffon et al category (=semantic) fluency was more severely impaired than letter fluency,3 which is in line with observations in sporadic VaD. Both fluency tasks have a strong executive component. The prominent role of executive dysfunction and attentional deficits is further emphasized by deficits in error monitoring.1,2

In contrast, memory is relatively preserved.2–4 CADASIL patients may show some impairment on both immediate and delayed free recall. However, cued recall and recognition are often intact even in elderly and demented subjects suggesting that the encoding process is largely preserved in this condition.3 This pattern clearly differs from the memory deficits seen in patients with Alzheimer disease. Visuospatial functions and reasoning are less well investigated, although current data suggest they are relatively preserved particularly during early disease stages.1,3

Of interest, comparisons between prestroke and poststroke cases revealed more severe impairments on both speed and set shifting aspects of the TMT B in the poststroke group.1,4 These findings may in part reflect the expected effect of age and disease progression on cognitive scores. Of note, however, differences between prestroke and poststroke cases were largely limited to executive function scores, again underlining the prominent role of executive control in CADASIL.

Taken together, the cognitive profile in CADASIL is remarkably similar to the pattern of deficits seen in patients with sporadic SIVD. This is confirmed by a recent prospective study comparing CADASIL subjects with sporadic patients with SVD who had a lacunar stroke and white matter lesions on MRI.4 Among other aspects these similarities emphasize the significance of CADASIL as a model.
Neuroimaging Correlates of Cognitive Decline

SIVD is associated with various pathological processes including lacunar infarcts, incomplete ischemic lesions, microhemorrhages, and atrophy. The sensitivity and specificity of MRI in detecting these changes is limited, yet defining the neuroimaging correlates of cognitive decline remains of great interest.

Lacunar Infarcts

Two recent studies in CADASIL have demonstrated an independent influence of lacunar infarcts (LI) on cognition. Liem et al found significant correlations between the number of LI and various cognitive scores including a global and executive score. However, when considering age and other MRI metrics (eg, LI and CM) in multivariate analyses there was no independent effect of LI on cognition. The second study found significant correlations between normalized lacunar volumes and both MMSE and Mattis dementia rating scale (MDRS) scores. Importantly, correlations remained significant when age, white matter hyperintensity (WMH) volume, and cerebral microhemorrhages (CM) were considered in multivariate models. These findings are in accord with the observed stepwise decline of cognitive abilities in some CADASIL patients. They further agree with other imaging studies showing that LI are independently associated with cognitive impairment in the general population.

White Matter Hyperintensities

The impact of T2-/FLAIR WMH on cognition is less clear and probably more complex. Most larger studies found significant correlations between WMH volumes and cognitive scores in univariate analyses. However, when considering age and other MRI metrics (eg, LI and CM) in multivariate analyses there was no independent effect of WMH volumes on cognitive scores. These findings suggest that the volume of WMH is clinically less important. In support of this, a recent longitudinal study found no correlations between changes of WMH volumes and changes of cognitive scores over time. However, there are several limitations to the application of T2-/FLAIR in displaying white matter pathology (limited sensitivity and specificity, lack of quantitative information on a voxel level, secondary effect of brain atrophy on volumetric measures).

Brain Atrophy

Advances in image postprocessing have enabled increasingly accurate measurements of brain atrophy. The role of brain atrophy in CADASIL has been investigated by three recent studies. These studies have demonstrated an independent impact of whole brain atrophy (WBA) on global cognitive scores in cross-sectional analyses. Moreover, longitudinal measurements have shown that the percentage brain volume change (PBVC) correlates with changes in cognitive scores over time. These data agree with similar findings in sporadic SIVD and indicate that brain volume loss reflects a clinically meaningful aspect of the pathology. The observed correlation with cognitive scales over time justifies the explorative use of PBVC as an adjunct marker in intervention trials and in fact, sample size estimates suggest that measurements of PBVC might help reduce the number of patients needed to demonstrate a treatment effect in a randomized trial.

The role of hippocampal volume (HV) has been addressed by a recent large study including 144 patients. In multivariate analyses including age, LI and WMH volume, WBA, HV, and CM, HV was independently associated with global cognitive scores. These findings suggest that hippocampal atrophy is not merely part of a general atrophic process, but has added strategic importance.

Microstructural Tissue Damage

Another aspect that is increasingly recognized as being clinically important is microstructural tissue damage. MTD may extend into tissue appearing normal on T2-/FLAIR images but can be sensitively detected by other imaging techniques such as magnetization transfer (MT) and diffusion tensor imaging (DTI). These techniques provide quantitative information on a voxel level and are thus particularly informative.

A series of studies performed in CADASIL subjects have demonstrated correlations between cognitive scores and MT/DTI metrics in both white and subcortical gray matter. Similar correlations were also found for brain tissue appearing normal on T2-/FLAIR images. These findings reinforce the idea that the extent of MTD (which may be subtle and widespread) is clinically relevant. And in fact, whole brain histograms of both MT and DTI metrics have established correlations between cognitive scores and average values of both MT ratio and mean diffusivity. An impact of MTD on cognition is further suggested by a longitudinal DTI histogram study showing that changes of average mean diffusivity correlate with changes of cognitive scores over time.

Cerebral Microhemorrhages and Strategic Lesions

The impact of CM on cognition has been investigated by two recent studies. These studies found no independent influence of CM on cognition when age, LI, and WMH volumes were considered in multivariate models. CM are best detected on T2*-weighted or gradient echo MRI and are present in up to 69% of CADASIL patients. Only recently, investigators have started to look at the influence of lesion location on cognition. These studies have identified strategic locations for LI, microstructural tissue damage, and localized brain atrophy that seem to impact on cognition in CADASIL and probably also in sporadic SIVD.

Treatment

Disruption of cholinergic fibers by subcortical ischemic lesions has provided the rationale for testing cholinesterase inhibitors (ChEI) in VaD. There have been several trials on ChEI conducted in patients with possible or probable VaD. Yet, for reasons outlined in the Introduction and elsewhere, these trials have been difficult to interpret.

To determine the benefit of ChEI in patients with subcortical ischemic vascular cognitive impairment, we recently conducted a multinational randomized trial investigating the efficacy of donepezil in cognitively impaired CADASIL patients. Contrasting with trials in sporadic VaD this trial found no beneficial effect of donepezil on overall cognition.
as assessed by changes of the V-ADAS-cog score (primary end point), ADAS-cog, and the MMSE. Importantly, however, improvements were noted on several measures of executive function including the timed measures of the TMT A and B and the executive interview–25. The clinical relevance of these findings is not clear as there were no treatment effects on instrumental activities of daily living (IADL) and dementia severity. Nevertheless, it appears that some cognitive aspects in CADASIL and possible also in sporadic SIVD may benefit from cholinergic therapy. Apart from its relevance for CADASIL, this trial emphasizes the need to consider etiologic subgroups and to incorporate executive function test in future VaD trials. It further illustrates the feasibility of randomized trials in CADASIL as a model for pure SIVD.

Disclosures

None.

References

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