MATTERS ARISING

Clinical overdiagnosis of vascular dementia versus necropsy confirmed series

Frisoni *et al*[1] have used their data from clinical diagnosis of vascular dementia to question the diagnostic usefulness of apolipoprotein E (apoE)-ε4 in the diagnosis of Alzheimer's disease. As previously pointed out, the criteria for vascular dementia do not exclude Alzheimer's disease and are meant as a "guideline" and "await testing and validation."[2 3] It is common to overdiagnose vascular dementia in many clinical series. Until and unless Frisoni *et al* have neuropathological confirmation of their diagnostic accuracy, their conclusions must be seriously questioned. In fact, as questionable as the diagnostic considerations for a clinical diagnosis of vascular dementia may be, other investigators have failed to replicate the increased ε4 allele frequency previously reported by Frisoni *et al* in clinical vascular dementia.[4-6]

Four series have independently measured the specificity, sensitivity, and positive predictive value of apoE genotyping in prospectively ascertained patients with neuropathologically confirmed dementia (table 1).[7-10] (Welsh-Bohmer *et al*, unpublished data). As often found in very large neuropathology series, vascular dementia was uncommon in each of these series. Moreover, the positive predictive value of having a single ε4 allele was greater than 95% in all series of symptomatic patients, despite differences in ascertainment protocols. For example, subjects in the CERAD series were enrolled early in their disease from more than 20 different centers. The positive predictive value in the interim report of this large series with 162 subjects was 97% (table 2) (Welsh-Bohmer *et al*, unpublished data).

Other authors besides Frisoni *et al* have implied that their clinical diagnoses are without error and should be accepted as the gold standard. Recently, Slooter *et al* reported that "apoE test characteristics for a diagnosis of Alzheimer's disease were calculated, with patients having another type of dementia as reference, and *our diagnostic work up as the gold standard.*"[11] The real question for the evaluation of these data is whether one accepts the clinical diagnosis of vascular dementia by Frisoni *et al* as the "gold standard" or whether one looks to necropsy confirmed series for formal measurement of the positive predictive value. The definitive diagnoses of Alzheimer's disease, vascular dementia, and other dementias are based on neuropathological criteria.[12] The missing data for Frisoni *et al*,[1] Slooter *et al*,[11] and others are the necropsy confirmed accuracy of their diagnoses. It is highly likely that many vascular dementia patients of Frisoni *et al* will meet the neuropathological criteria for Alzheimer's disease.

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Table 1 Specificity, positive predictive value, and sensitivity data from four necropsy confirmed series

Series	*Specificity (%)*	*Positive predictive value (%)*
CERAD (n = 162)	93	97 (115/119)
Duke (n = 67)[7]	100	100 (43/43)
Perth* (n = 66)[8]	100	100 (25/25)
OPTIMA† (n = 37)[9]	100	100 (55/61)

*No clinical information other than referring diagnoses.
†Includes only subjects diagnosed as probable Alzheimer's disease, not possible to combine ε4 allele and neuropathology in possible Alzheimer's group from the data in the publication.[9]

Table 2 CERAD neuropathology series of 162 patients with clinical Alzheimer's disease (AD)

apoE-ε4 test	*Primary diagnosis Probable AD*	*Primary diagnosis non-AD*	*Total*
ε4 + (4/4 or x/4)	115	4	119
ε4 – (x/x)	24	19	43
Total	139	23	162

The positive predictive value was 97% (115/119). The sensitivity and specificity of the test were 83% (115/139) and 83% (19/23) respectively.
Note: Two "non-AD, ε4 positive" cases carry secondary pathological diagnoses of "definite AD" along with the primary diagnoses of Pick's disease and hippocampal/entorhinal sclerosis, respectively. The other two "non-AD, ε4 positive" cases are the only two pathologically diagnosed with the more conservative CERAD category of "possible AD." Thus, by strict application of the CERAD criteria, these four cases were considered "non-AD." Reconsideration of the two definite AD cases raises the PPV to 98% (Welsh-Bohmer *et al*, unpublished data).

Frisoni et al reply:

We appreciate Roses and Saunders' attention to our work. They refer to a brief note[1] in which we discuss Roses' proposal[2] that the detection of an apolipoprotein (apoE) ε4/ε4 genotype in a demented patient might suggest a diagnosis of Alzheimer's disease with about 95% probability.

For these cross comments among authors to be useful contributions to the *Journal*'s audience, the proposed practical applications of apoE genotyping should be explicitly pointed out.

The Duke group has proposed apoE genotyping (*a*) in the demented patient to enhance the accuracy of the diagnosis of Alzheimer's disease,[2] and (*b*) in the patient with probable Alzheimer's disease to make the diagnosis of definite Alzheimer's disease.[3] Our letter[1] considered the first question and suggested that if the ε4 allele is increased also in vascular dementia, the likelihood that a *demented patient* has Alzheimer's disease does not increase from 66 to 94%[2] but only to 73% when he is found to have the ε4/ε4 genotype. Therefore, the diagnostic gain of apoE testing might be low. Far from claiming that our diagnosis of vascular dementia and therefore our estimate of the ε4 frequency are the gold standard of reference, we cautioned that both views "will need to be verified in clinicopathological studies considering the association of ε4 with non-Alzheimer's dementias".[1]

However, the data by Roses and Saunders in the above commentary consider the second issue, that of diagnosis of definite Alzheimer's disease in *patients with probable Alzheimer's disease*, further stressing what they recently argued in the *Lancet*.[3] What the authors convincingly propose is that the detection of an ε4 allele in patients with probable Alzheimer's disease brings the likelihood of them having definite Alzheimer's disease very close to 100%. Here, vascular dementia is no longer an issue. The central questions instead are: (*a*) what is the prior probability that a patient with probable Alzheimer's disease has definite Alzheimer's