# 알츠하이머병 인지장애와 피질하혈관성 인지장애: 바이오마커를 중심으로

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# Alzheimer disease and subcortical vascular cognitive impairment: biomarker perspective

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## Background

Cognitive impairment related to Alzheimer's disease (ADCI) comprises mild cognitive impairment (MCI) due to Alzheimer's disease (AD-MCI) and dementia due to AD (AD-dementia). On the other hand, cognitive impairment associated with subcortical small vessel changes (SVCI) consists of subcortical vascular MCI (svMCI) and subcortical vascular dementia (SVaD). One of our prerequisites for SVCI is "severe" WMH (cap or band ≥ 10 mm and deep white matter lesion ≥ 25 mm) on MRI.

### Amyloid positivity in ADCI and SVCI continuum

Although ADCI and SVCI can be two major contributors to cognitive decline in the elderly, there is a substantial overlap between the two conditions in terms of clinical and radiological findings. Lee et al (2011) showed that 31.1% of clinically diagnosed SVaD patients tested positive for amyloid scan. Recently a large sample from our group showed that amyloid positivity of AD-MCI, AD-dementia, svMCI and SVaD was 51.9%, 86.9%, 30.0% and 53.9%, respectively (paper in preparation).

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### Clinical implication of amyloid positivity in SVCI

Despite this overlap, differentiating amyloid negative (Aβ- ) SVCI from amyloid positive (Aβ+ ) SVCI (mixed ADCI and SVCI) is important because the treatment option and prognosis are different between the two groups. In fact, a study from our group (Ye et al, 2015) showed that the mean rate of MMSE decline was 1.63 per year for the Aβ+ SVaD while 0.48 per year for the Aβ - SVaD group. Amyloid burden also predicted faster decline in several neuropsychological tests and CDR-SOB scores. Kim et al (2016) also showed that higher amyloid burden increased risk of dementia conversion in svMCI group and was associated with faster decline in verbal and visual memory and CDR-SOB as well.

### How to predict amyloid positivity in SVCI without resorting to amyloid PET scan

Among many factors that differentiate Aβ- SVCI from A β+ SVCI patients, such factors as onset age, number of lacunes and medial temporal atrophy seem to be most reliable. A study from our group, for instance, showed that our criteria (Seoul criteria of SVaD) with age at onset ≤75, number of lacune ≥5, medial temporal atrophy ≤3 has high AUC (0.745) with a sensitivity of 49.0% and

specificity of 100% (Kim et al, 2014).

### Tau positivity of ADCI versus SVCI

We performed both amyloid (Florbetaben) and tau (Flortaucipir) PET in a total of 107 ADCI or SVCI patients that consisted of 61 SVCI (34 Aβ-, 27 Aβ+), 27 ADCI (8 Aβ+ AD-dementia, 7 Aβ- MCI, 12 Aβ+ MCI), and 19 Aβ- normal controls (NC). Expectedly, ADCI patients showed higher Flortaucipir uptake in the bilateral temporal, parietal, and frontal areas compared with NC or SVCI individuals. Contrary to our expectation, SVCI patients, both Aβ+ and Aβ-, showed higher Flortaucipir uptake only in the inferior temporal areas compared with Aβ- NC (Kim et al., 2018). We then tentatively defined "tau positivity" as *in-vivo* Braak stage being ≥ III/IV as suggested by a previous study (Schöll et al., 2016). As a result, while 95% and 32% of AD-dementia and AD-MCI patients showed tau positivity, only 12% of SVCI patients showed tau positivity. Particularly, compared with 70% tau positivity in Aβ+ ADCI patients (100% in Aβ+ ADD, 50% in Aβ+ AD-MCI), only 26% (7/26) of Aβ+ SVCI were tau positive. Finally, when we applied amyloid and tau biomarker framework (NIA-AA 2018) to our SVCI patients, Aβ+T+ SVCI patients showed a steepest cognitive decline, followed by Aβ+T- SVCI and Aβ-SVCI patients.

## Conclusion

About 30-40% of SVCI patients show positive amyloid scan. While Aβ+ SVCI patients generally show rapid cognitive decline, Aβ- SVCI patients can take relatively benign course. Although tau burden also plays a pivotal role in the cognitive deterioration in SVCI, tau positivity in SVCI was lower than expected (15%). Furthermore, when amyloid and tau information combined, Aβ+T+ SVCI, a malignant form of SVCI, only accounted for 12% of total SVCI patients. Therefore, identifying SVCI patients and managing them vigorously is important in clinical practice.