Is Type 2 Diabetes a Risk Factor for Silent Ischemic Brain Lesion?

Key words: MRI, periventricular hyperintensity, white matter hyperintensity, cohort study

Type 2 diabetes (DM) has been known to be a significant risk factor for symptomatic brain infarction not only in the western countries but also in the Hisayama study in Japan (1, 2). In the Hisayama population, lacunar infarction was the most common subtype of cerebral infarction and had a greater variety of risk factors, including not only hypertension but also ECG abnormalities, diabetes, obesity, and smoking, than did atherothrombotic infarction or cardioembolic infarction (2). The mechanism is considered to be acceleration of atheromatous plaque formation in the major intra / extra cranial arteries and microatheroma in branch atheromatous disease. Moreover, it is known that blood coagulability and platelet aggregation are increased in DM patients. In the report based on 1,237 ischemic stroke cases of NINCDS databank including 184 cases with lacunar infarction, DM was a significant risk factor for multiple lacunar infarction (Odds Ratio [OR]: 2.3, Confidential Interval: 1.1-4.5) as well as hypertension (OR: 2.5) (1). Wannamethee (3) emphasized the importance of established type 2 diabetes as an independent risk factor for stroke from a 16.8-year follow-up observation study. There were 347 stroke cases in the 7,649 men. Men who developed diabetes during follow-up (n=320) and men with established type 2 diabetes at screening (n=98) both showed a significantly increased risk of stroke (adjusted relative risk, 2.27). In addition, a J-shaped relationship was seen between nonfasting insulin and risk of stroke in the 5,567 men without diagnosis of diabetes at screening. DeFronzo (4) suggested that insulin resistance is a multifaceted syndrome for DM, obesity, hypertension, dyslipidemia and atherosclerosis.

Concerning the prognosis of brain infarction, Kameyama (5) reported that elderly brain infarction patients with DM showed a significantly poor prognosis 30 years ago. We recently examined the prognosis of the ischemic stroke patients with or without DM using the databank made by our Japanese Standard Stroke Registry Study (JSSRS). The change in Japan Stroke Scale (JSS) of DM group was significantly worsened during admission, and modified Rankin Scale at discharge was also significantly poor in the DM group compared with the non-DM group (6). Tuomilehto et al (7) also reported that diabetic subjects have a very high risk of death from stroke, particularly women.

On the other hand, the role of DM as a risk factor for silent brain infarction or white matter lesion in non-stroke subjects is controversial. Lechner et al (8) reported an increased number of risk factors including hypertension, diabetes, smoking, hyperlipidemia and cardiac disease correlated to the grade of silent white matter lesions.

Our study showed that hypertension (OR: 4.07), diabetes (OR: 2.41), alcohol intake 58 g/day (OR: 2.58), retinal artery sclerosis (OR: 2.14), and age (OR: 1.77) were significant and independent risk factors for subcortical silent brain infarction (cystic lacuna). For white matter lesion except lacuna, and periventricular hyperintensity (PVH) only hypertension and age were independent risk factors (9).

In this issue of the journal, Saitoh et al (10) describe that DM is not a significant risk factor for silent ischemic brain lesion in the Funagata study.

They studied brain MRI in 187 normal subjects who examined DM using 75 g OGTT. Ischemic rating score and PVH grade were not related to impaired glucose tolerance or DM. Ischemic rating score involved etat crible, lacuna and white matter hyperintensity without T1 low intensity. It would be of interest if they analyze the groups divided into cystic lacuna and T2 hyperintensity without T1 low intensity. Because our previous study which investigated silent brain lesion involving etat crible, cystic lacuna, T2 hyperintensity and PVH showed that the most significant risk factors were age and hypertension, but DM also was mildly related to cystic lacuna (11).

Kertesz et al (12) also demonstrated that the most important risk factors for PVH and “MRI unidentified bright objects” (UBO) were age and hypertension in stroke patients. Liao et al (13) studied the severity of white matter lesions (mainly PVH) associated with hypertension, and found that treated uncontrolled hypertensive subjects have greater odds of white matter lesions than those with treated controlled hypertension in the ARIC study. A postmortem pathological study of incidental subcortical lesions identified on MRI in elderly showed that these histological changes are characteristic of etat crible which, like subcortical MRI lesions, is associated with age and hypertension (14).

Furthermore, a large intervention study for 3,867 DM patients (United Kingdom Prospective Diabetes Study: UKPDS) demonstrated that strict control of DM was significantly reduced the complication rate of microangiopathy but did not
reduce complications of macroangiopathy such as ischemic stroke (15). However, strict control of hypertension with drugs demonstrated a significant risk reduction for stroke (−44%) in DM patients (16).

In conclusion, DM may not be the primary risk factor for silent ischemic brain lesion, especially for white matter lesions including PVH. But silent brain lesion is considered to be a significant risk for symptomatic subcortical infarction. Therefore, it is necessary to elucidate the mechanism causing ischemic stroke in DM.

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Reference