

### Methylene tetrahydrofolate reductase C677T polymorphism in Korean livedoid vasculopathy patients



*To the Editor:* Livedoid vasculopathy (LV) is a rare, chronic, ulcerative disease that significantly impairs the quality of life of patients.<sup>1</sup> Previous case series have described the association between LV and various hypercoagulable conditions, including methylenetetrahydrofolate reductase (MTHFR) polymorphism and hyperhomocysteinemia.<sup>1-3</sup>

This single-center, retrospective, case-control study included 43 patients with histologically confirmed LV between 2005 and 2019. Among them, hypercoagulable conditions were assessed in 28 patients who underwent 1 or more coagulation laboratory tests. A non-LV control group included 69 patients with psoriasis or eczema to compare MTHFR polymorphism and homocysteine level with patients with LV.

Of 28 patients with LV, 10 (35.7%) showed 1 or more coagulation laboratory abnormalities (Supplemental Table I, available via Mendeley at <https://doi.org/10.17632/ddghn6cdp6.2>), which is a little lower than the 41.4% to 52% reported in Caucasian studies.<sup>2,3</sup> In Caucasians, factor V Leiden mutation, prothrombin G20210A mutation, and antiphospholipid antibody presence were most common.<sup>1-3</sup> In contrast, none of these were detected in our patients. Instead, in our patients, MTHFR C677T TT homozygous polymorphism (29.2%) was the most frequent, followed by increased

concentration of lipoprotein(a) (27.3%) and homocysteine (12.5%).

C677T polymorphism, the most common polymorphism of MTHFR, which is an essential enzyme in homocysteine metabolism, would lead to the elevation of the plasma homocysteine level, and elevated homocysteine level is a well-known risk factor for atherosclerosis. LV has been reported to be associated with MTHFR C677T polymorphism or hyperhomocysteinemia, or both.<sup>1-3</sup>

The univariable and multivariable logistic regression both showed that female sex and MTHFR C677T TT genotype were significantly associated with LV (Table I). However, 87.5% of patients with LV showed a homocysteine level within normal reference ranges. This implicates that MTHFR C677T polymorphism could increase the risk of LV regardless of the homocysteine level. In line with our findings, several case reports demonstrated MTHFR C677T TT homozygous polymorphism with normal homocysteine level in LV.<sup>1</sup> In parallel, a study demonstrated that 47% of patients with vascular events had MTHFR polymorphism with a normal homocysteine level, and no other thrombophilia risk factors were identified.<sup>4</sup>

In fact, MTHFR C677T polymorphism is not the only factor that influences homocysteine level. Because the homocysteine metabolism by MTHFR requires folate and vitamin B<sub>12</sub> as cofactors, supplementation of them can lower the homocysteine level and compensate the decreased activity of MTHFR.<sup>5</sup>

**Table I.** Associations between livedoid vasculopathy and different factors

| Variable*                          | Livedoid vasculopathy<br>(n = 28) | No livedoid<br>vasculopathy (n = 69) | Odds ratio (95% CI)            |                                |
|------------------------------------|-----------------------------------|--------------------------------------|--------------------------------|--------------------------------|
|                                    |                                   |                                      | Crude                          | Adjusted                       |
| Age, y                             | 45.6 ± 15.1                       | 43.8 ± 17.0                          | 1.01 (0.98-1.03)               | ...                            |
| Female sex                         | 20 (71.4)                         | 25 (36.2)                            | 4.40 (1.69-11.44) <sup>†</sup> | 5.18 (1.77-15.11) <sup>†</sup> |
| MTHFR C677T genotype <sup>‡</sup>  |                                   |                                      |                                |                                |
| CC homozygote                      | 4 (16.6)                          | 25 (36.2)                            | Reference                      | Reference                      |
| CT heterozygote                    | 13 (54.2)                         | 36 (52.2)                            | 2.26 (0.66-7.73)               | 3.33 (0.90-12.40)              |
| TT homozygote                      | 7 (29.2)                          | 8 (11.6)                             | 5.47 (1.27-23.64) <sup>§</sup> | 6.87 (1.44-32.90) <sup>§</sup> |
| Homocysteine, μmol/L <sup>  </sup> | 9.3 ± 4.1                         | 8.9 ± 3.0                            | 1.04 (0.90-1.19)               | ...                            |

CI, Confidence interval; MTHFR, methylenetetrahydrofolate reductase.

\*Data are presented as number (%) or as mean ± SD.

<sup>†</sup>P < .01.

<sup>‡</sup>Data were available except for 4 patients with LV.

<sup>§</sup>P < .05.

<sup>||</sup>Data were available except for 4 patients with LV and 2 controls.

**Table II.** Comparison of patient characteristics of livedoid vasculopathy according to the methylenetetrahydrofolate reductase (*MTHFR*) C677T genotypes

| Variable*                          | MTHFR genotypes       |                          |                       | P value |
|------------------------------------|-----------------------|--------------------------|-----------------------|---------|
|                                    | CC homozygote (n = 4) | CT heterozygote (n = 13) | TT homozygote (n = 7) |         |
| Onset age, y                       | 27.0 ± 9.6            | 40.8 ± 15.7              | 33.7 ± 14.8           | .244    |
| Disease duration, y                | 9.8 ± 8.7             | 9.2 ± 8.0                | 7.0 ± 2.6             | .913    |
| Disease severity score (range 0-9) | 4.5 (3-6)             | 5.3 (3-9)                | 5 (3-8)               | .499    |
| Homocysteine, μmol/L               | 7.0 ± 2.8             | 8.6 ± 2.8                | 11.9 ± 5.5            | .105    |

*MTHFR*, Methylenetetrahydrofolate reductase.

\*The results are presented as mean ± SD or as median (range).

When patient characteristics of LV were compared against different *MTHFR* C677T genotypes, *MTHFR* polymorphism was not related with any patient characteristics (Table II). Theoretically, the *MTHFR* C677T polymorphism might be related only with the incidence of LV, not with further progression of the disease.

This study has some limitations, including its retrospective nature and the small number of patients due to the rarity of LV. However, the present study is the largest study, to our knowledge, to demonstrate the associated hypercoagulable conditions in Korean patients with LV, as well as the first study worldwide to find that the *MTHFR* C677T polymorphism increases the risk of LV by comparison with non-LV control.

In summary, more than one-third of Korean patients with LV had hypercoagulable abnormalities, of which *MTHFR* C677T polymorphism was the most frequent. Female sex and *MTHFR* C677T TT genotype were independent risk factors of LV. In contrast, the homocysteine level was normal in most patients.

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#### Clinical, histopathologic, and molecular profiles of *PRKARIA*-inactivated melanocytic neoplasms



To the Editor: Protein kinase A regulatory subunit-α (*PRKARIA*) is inactivated in a subset of melanocytic neoplasms, including pigmented epithelioid melanocytoma (PEM), melanotic schwannoma (MS), and the exceptionally rare pigmented epithelioid melanoma.<sup>1,2</sup> The genomic profiles of PEM and MS have been well described; PEM typically lacks genomic alterations (GAs) in the *TERT* promoter or *CDKN2A* gene or significant chromosomal copy number alterations, whereas MS shows monosomies of chromosomes 1, 2, and 17. Cohen et al<sup>2</sup> recently described histopathologic findings of a single case of