ABSTRAK

Polineuropati adalah komplikasi mikrovaskular diabetes melitus yang paling sering dijumpai. Penelitian ini adalah penelitian *cross sectional* yang dilaksanakan di RS Atma Jaya Jakarta pada September 2017-Maret 2018 yang bertujuan untuk mengetahui peran polimorfisme gen VEGF +936 C/T dan kadar VEGF-A plasma dengan polineuropati diabetik. Diagnosis ditegakkan berdasarkan gambaran klinis dengan menggunakan skoring *Diabetic Neuropathy Symptom* (DNS) dan *Diabetic Neuropathy Examination* (DNS) dan/atau berdasarkan gambaran pemeriksaan elektrofisiologis. Keseluruhan subjek menjalani pemeriksaan Indeks massa tubuh, polimorfisme gen VEGF 936 C/T dengan teknik PCR-RFLP, kadar VEGF-A plasma dengan teknik ELISA, HbA1C, kadar kolesterol total, HDL, LDL, dan trigliserida. Analisis data penelitian diuji menggunakan Uji *Chi Square*, *T test*, Mann Whitney, uji stratifikasi Mantel Haenszel dan regresi logistik. Didapatkan 152 total subjek penelitian, 69 0rang (45,4%) dengan polineuropati DM. Distribusi frekuensi polimorfisme gen VEGF 936 C/T berada dalam keseimbangan Hardy-Weinberg. Terdapat hubungan bermakna pola genotip dengan polineuropati DM (CT + TT vs CC) dengan POR 0,35; 95%CI 0,16-0,79 p=0,01. Kadar VEGF-A pada subjek polineuropati menunjukkan trend yang lebih tinggi dibanding tanpa neuropati, dan kadar VEGF-A plasma pada genotip CT+TT juga menunjukkan trend yang lebih tinggi dibanding CC meski tidak bermakna secara statistik. Analisis stratifikasi mantel haenszel menunjukkan bahwa variabel lama diagnosis DM, HbA1C, Indeks Massa Tubuh, kolesterol total, HDL, LDL, dan Trigliserida berperan sebagai *modifying factor* terhadap hubungan antara pola genotip dengan polineuropati DM. Uji regresi logistik multivariat menunjukkan kadar VEGF-A plasma (POR 1,004; 95%CI 1,001-1,007, p=0,02) lama diagnosis DM (POR 1,106; 95%CI 1,042-1,173 p=0,001) dan genotip CT+TT (POR 0,329; 95%CI 0,137-0,792 p-0,013) berkontribusi terhadap kejadian polineuropati DM. Uji regresi logistik pada subjek dengan HbA1C $\geq$ 7 didapatkan selain kadar VEGF-A (POR 1,009 95%CI 1,004-1,015 p=0,001) lama diagnosis DM (POR 1,187 95%CI 1,082-1,302 p=0,000), dan genotip CT+TT (POR 0,244 95%CI 0,073-0,813 p=0,022), LDL (POR 1,019 95% CI 1,002-1,035 p=0,027) juga berkontribusi terhadap kejadian polineuropati DM dan pola genotip CT+TT tetap berperan sebagai faktor protektif. Tidak didapatkan adanya hubungan bermakna antara pola genotip dengan gambaran fisiologis saraf antara kelompok polineuropati DM dan tanpa polineuropati DM. Temuan ini menunjukkan bahwa pola genotip CT+TT pada polineuropati diabetik berpotensi berperan sebagai faktor protektif terhadap kejadian polineuropati DM.

Kata kunci: polimorfisme gen VEGF +936 C/T, polineuropati diabetik, VEGF-A.

ABSTRACT

Diabetic polyneuropathy (DPN) is the most common microvascular complication of type 2 diabetes mellitus. This is a cross sectional study performed in Atma Jaya Hospital Jakarta on September 2017-March 2018 evaluating the role of vascular endothelial growth factor (VEGF) +936 C/T gene polymorphism and VEGF-A level in DPN. Clinical symptoms and signs were examined using DNE and DNS scoring followed by nerve conduction study. Diagnosis of DPN was established if the subject fulfill at least one positive findings of the examinations. All subjects underwent anthropometric examination to determine body mass index and laboratory procedures measuring HbA1C level, total cholesterol, LDL, HDL, and triglyceride, Polymorphism of +936 C/T VEGF gene (PCR-RFLP technique), and VEGF-A plasma level (using ELISA). Statistical analysis using t test or mann-whitney was performed to evaluate relationship between continuous data and chi square for categorical data. Mantel Haenszel analysis also performed to evaluate the interaction between genotype and diabetes duration, HbA1C, and lipid profile in its relationship with DPN. Multivariate logistic regression also performed to determine relationship between independent variables and DPN. Sixty nine (45,4%) of total 152 subjects fulfilled diagnostic criteria of DPN. Distribution of VEGF +936 C/T polymorphism is consistent with HWE. There was a significant relation between CT+TT of VEGF +936 genotype and diabetic neuropathy (OR 0,35 95%CI 0,16-0,79 p=0,01). Trend towards higher level of plasma VEGF-A level in DPN group compared with non DPN group was observed as well as between CT+TT vs CC genotype but not statistically significant. Mantel Haenszel stratification analysis showed that diabetes duration, HbA1C, Obesity, and lipid profiles acted as modifying factors. Multivariate logistic regression showed that plasma VEGF-A level (POR1,004 95% CI 1,001-1,007 p=0,02), diabetes duration (POR 1,106 95%CI 1,042-1,173 p=0,001), and CT+TT genotype (POR 0,329; 95%CI 0,137-0,792 p-0,013) related with DPN. Sub group analysis on subjects with HbA1C level ≥7 showed similar relationship showing that VEGF-A (POR 1,009 95%CI 1,004-1,015 p=0,001) diabetes duration (POR 1,187 95%CI 1,082-1,302 p=0,000), and CT+TT genotype (POR 0,244 95%CI 0,073-0,813 p=0,022), and LDL (POR 1,019 95% CI 1,002-1,035 p=0,027). Significant relationship between genotype and NCS findings were not observed. The results showed that CT+TT genotype of VEGF +936 gene may act as a protecting factor for DPN while VEGF-A, diabetes duration, and LDL acted as risk factors especially on subjects with HbA1C level ≥7.

Key Words: VEGF +936 C/T polymorphism, VEGF-A level, diabetic polyneuropathy