Intisari

Latar belakang. Attention Deficit/Hyperactivity Disorder (ADHD) adalah gangguan neurobehaviour pada anak yang disebabkan oleh berbagai faktor, diantaranya faktor genetik dan yang paling sering diakitkan adalah gen dopamine receptor D4 (*DRD4)* dan gen dopamine transporter 1 (*DAT1)*. Hubungan pola genetik terhadap gambaran klinis dan neuropsikologi masih belum diketahui. Penelitian ini bertujuan untuk mengetahui hubungan polimorfisme gen *DRD4* dan gen *DAT1* terhadap gambaran neurologis dan neuropsikologi pada anak ADHD di Yogyakarta.

Metode. Enam puluh lima anak ADHD dan 70 kontrol dilakukan pemeriksaan pola genetik, klinis neurologis dan neuropsikologi dengan menggunakan instrument kuesioner penelitian, SPPAHI, ACTRS, ACPRS, DSM IV, WISC II, MMMSEC, *Stroop Test*, yang sebelumnya dilakukan uji reliabilitasnya. Penilaian dilakukan dengan skor kuantitatif. Alel gen *DAT1* dan *DRD4* dianalisis dengan metode PCR. Batas signifikan p<0,05

Hasil. Pola alel gen *DRD4VNTR 7Repeat* tidak didapatkan pada penelitian ini karena pola alel yang didapatkan *VNTR 2R*(ADHD 66,2%; kontrol 63,4%) dan pola alel gen *DAT1 VNTR 10Repeat* (ADHD 90,3%; kontrol 85,2%), tidak didapatkan bukti sebagai faktor risiko ADHD (gen *DRD4* p 0,926; gen *DAT1* p 0,830), tidak terbukti berhubungan dengan sub tipe ADHD (gen *DRD4* p 0,102; gen *DAT1* p 0,916), gen DAT1 9/10R signifikan berbeda bermakna dengan score VIQ sedangkan DRD4 2R tidak berhubungan gambaran klinis dan neuropsikologisnya. Analisis bivariat mendapatkan pola asuh p <0.001, penghasilan orang tua p <0.001(2,013–79,739), riwayat BBLR p <0.001(3,075–24,426), riwayat gizi BGMp 0.004 (1,548–15,830), riwayat hiperaktif p 0,011 (1,176–7,572) dan riwayat antisosial p 0,003 (1,484 –7,572), signifikan sebagai faktor risiko ADHD. Pada gambaran klinis dan neuropsikologi berbeda signifikan antara anak ADHD dan kontrol, didapatkan nilai MMMSEC orientasi p <0.001(9,98±1,192:11,10±1,079), registrasi p 0.004(2,69±0,498:2,90±0,302), recal/memory p 0.002 (2,63 ± 0,651: 2,91 ± 0,371), bahasa p <0.001(10,91±1,389 : 11,69±0,713), total MMMSEC p <0.001(32,98±2,414 : 35,39±1,875), VIQ p <0.001(103,18 ± 15,155 : 114,27±12,748), FIQ p <0.001(101,06±13,087 : 108,63±10,685), SPPAHI p <0.001(97,91±11,468 : 39,23±20.3314), ACPRS p <0.001(14,98±3,435 : 6,14±2,994), ACTRS p <0.001(15,5±3,749 : 5,39±3,719), NST p <0.001(25,28±3,79 : 18,41±3,25), IST p 0.02(34,90±8,13 : 28,87±4,17), NST error p <0.001(1,79±1,23 : 1,23±0,42), IST error p 0.02(2,3±1,86 : 1,86±0,75), Persentase NST *error* p 0.05(60.42% : 42.94%), Persentase IST error p 0.05(68.53% : 50,71%), NST correct p 0.02(22,54 ± 1,68 : 16,27 ± 1,772), IST correct p <0.001 (27,18 ± 2,44 : 24,47 ± 2,76), dan adanya *restless leg syndrome* p 0.006. Hasil analisis bivariat subtype ADHD terhadap gambaran neurologis klinis dan neuropsikologi didapatkan perbedaan signifikan untuk nilai MMMSEC orientasi p 0.016; bahasa p 0.029;dan TOTAL p 0.027,nilai FIQ p <0.001, skor SPPAHI p 0.048.Pola asuh p <0,001(7,574 – 428,293), penghasilan orang tua p <0.001(10,359 –390,772), dan riwayat gizi dibawah garis merah p 0,029 (1,325–203,234), independent sebagai faktor risiko ADHD**.**

Simpulan. Frekuensi polimorfisme VNTR *DAT1 10R* tertiggi di Yogyakarta dibandingkan negara-negara lain, tidak didapatkan VNTR *DRD4 7R* tetapi pola alel tertinggi adalah *DRD4 2R,* polimorfisme VNTR *DAT1 9/10R* signifikan berhubungan dengan score VIQ, sedangkan polimorfisme gen *DRD4 2R* dan gen *DAT1* 10R tidak berhubungan dengan kejadian ADHD dan tidak pula berhubungan dengan gambaran neurologis dan neuropsikologi tertentu, tidak terdapat hubungan antara *DAT1 10R* dan alel *DRD4 2R* diantara subtipe ADHD dan terdapat perbedaan gambaran klinis dan neuropsikologi yang berbeda diantara subtipe ADHD.

Kata kunci:ADHD, gen *DRD4*, gen *DAT1*, neurologi klinis, neuropsikologi, test fungsi kognitif

Abstract

Background. Attention Deficit/Hyperactivity Disorder (ADHD) is a pediatric neurobehaviour disorder caused by various factors, among them are genetic factors. Among these genetic factors, the most frequently associated genes were dopamine receptor D4 (DRD4) and dopamine transporter 1 (DAT1) genes. The effects of particular genetic patterns on the clinical and neuropsychological features are still largely unknown. The objective of this study is to find the association between polymorphism gen DRD4 and DAT1 with ADHD, and their influences on the clinical and neuropsychological features in children with ADHD in Yogyakarta area.

Methods. Sixty-five ADHD children and 70 controls went through genetic, clinical, neurological and neuropsychological studies by using these questionnaires, SPPAHI, ACTRS, ACPRS, DSM IV, WISC II, MMMSEC, Stroop Test, preceded by a reliability test. These results were scored quantitatively. DAT1 and DRD4 genetic profiles were analyzed by PCR. Results were significant if $p<0.05$

Results. DRD4 VNTR 7 Repeat allelic pattern was not found in the current study, while 2R allelle (ADHD group 66.2%; control group 63.4%) and DAT1 VNTR 10Repeat allele (ADHD 90.3%; controls 85.2%)were the most common patterns, these genes were not associated with ADHD (DRD4 gene $p = 0.926$; DAT1 gene $p = 0.830$), nor its subtypes (DRD4 gene $p = 0.102$; DAT1 gene $p = 0.916$), DAT1 9/10R allele were significantly associated with VIQ scores while DRD4 2R did not affect the clinical and neuropsychological profiles. Bivariate analyses suggested parenting style $p<0.001$, family income $p<0.001$ (2.013 -79.739), a history of LBW $p < 0.001$ (3.075-24.426), nutritional history of BGM $p = 0.004$ (1.548-15.830), a history of hyperactivity $p=0.011$ (1,176-7.572) and a history of antisocial $p=0.003$ (1.484-7.572), were significant risk factors for ADHD. There were clinical and neuropsychological profile differences between ADHD and controls groups, MMMSEC orientation sub-score $p<0.001$ (9.98 ± 1.192: 11.10 ± 1.079), registration sub-score $p = 0.004$ (2.69 ± 0.498: 2.90 ± 0.302) , recall / memory $p = 0.002$ (2.63 ± 0.651: 2.91 ± 0.371), language sub-score $p<0.001$ (± 1.389 10.91: 11.69 ± 0.713), total MMMSEC score $p<0.001$ (32.98 ± 2.414: 35.39 ± 1.875), VIQ $p<0.001$ (103.18 ± 15.155: 114.27 ± 12.748), FIQ $p<0.001$ (101.06 ± 13.087: 108.63 ± 10.685), SPPAHI $p<0.001$ (97, 91 ± 11,468: 39.23 ± 20.3314), ACPRS $p<0.001$ (14.98 ± 3.435: 6.14 ± 2.994), ACTRS $p<0.001$ (15.5 ± 3.749: 5.39 ± 3.719), NST p< 0001 (25.28 ± 3.79: 18.41 ± 3.25), IST $p = 0.02$ (34.90 ± 8.13: 28.87 ± 4.17), NST error $p<0.001$ (1.79 ± 1.23: 1.23 ± 0.42), IST error $p = 0.02$ (2.3 ± 1.86: 1.86 ± 0.75), percentage NST error $p = 0.05$ (60.42%: 42.94%), percentage IST error $p = 0.05$ (68.53%: 50.71%), NST correct $p = 0.02$ (22.54 ± 1.68: 16.27 ± 1.772), IST correct $p<0.001$ (27.18 ± 2.44: 24.47 ± 2.76), and restless leg syndrome p = 0006. Results of analysis in ADHD subtypes on the clinical and neuropsychological found significant differences in MMMSEC orientation sub-score $p=0.016$; language sub-score $p = 0.029$; and total score $p = 0.027$, FIQ $p<0.001$, SPPAHI score $p=0048$. Multivariate analysis found that parenting style $p<0.001$ (7.574 - 428.293), family income $p<0.001$ (10.359 -390.772), and nutritional history of BGM $p = 0.029$ (1.325 - 203.234), were independent risk factors for ADHD.

Conclusions. 10R DAT1 polymorphism frequency were higher in Yogyakarta area than other countries, 7R DRD4 alleleic pattern was not found while the most common were 2R DRD4, 9/10R DAT1 polymorphism were significantly associated with VIQ score, whereas polymorphism gen DRD4 2R and DAT1 10R were not associated with AHD and also with the particular clinical and neuropsychological features, there were no differences in the proportion of 10R DAT1 allele and 2R DRD4 allele between ADHD subtypes and there were differences in the clinical and neuropsychological profiles between ADHD subtypes.

Keywords: ADHD, DRD4 gene, DAT1 gene, clinical neurology, neuropsychology, cognitive function tests