Institutionen för kvinnors och barns hälsa
Enheten för barn- och ungdomspsykiatri

Attention-Deficit/Hyperactivity Disorder and Disruptive Behavior Disorders in adolescence related to levels of platelet MAO-B and polymorphisms in two candidate genes

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Skandiasalen, Astrid Lindgrens barnsjukhus

Fredagen den 7 oktober 2011, kl 09.00

Kerstin Malmberg

Huvudhandledare:
Docent Jan-Olov Larsson
Karolinska Institutet
Institutionen för för Kvinnors och barns hälsa

Bihandledare:
Professor emeritus Lars Oreland
Uppsala universitet
Institutionen för neurovetenskap
Enheten för farmakologi

Professor Paul Lichtenstein
Karolinska Institutet
Institutionen för Medicinsk epidemiologi och biostatistik

Fakultetsopponent:
Professor Bruno Hägglöf
Umeå universitet
Institutionen för klinisk vetenskap
Barn- och ungdomspsykiatri

Betygsnämnd:
Professor Niklas Dahl
Uppsala universitet
Institutionen för immunologi, genetik och patologi; Medicinsk genetik

Professor Carl Göran Svedin
Linköpings universitet
Institutionen för klinisk och experimentell medicin

Docent Elisabeth Fernell
Göteborgs universitet
Sektionen för psykiatri och neurokemi

Stockholm 2011

ABSTRACT

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) and Disruptive Behavior Disorders (DBD) (including Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD)), are common developmental and behaviour diagnoses among adolescents. Several of their symptoms, have been linked to genotypes (e.g. monoamine oxidase A Variable Number of Tandem Repeats (MAO-A VNTR) and the 5–HydroxyTryptamine Transporter gene-Linked Polymorphic Region (5-HTT LPR)) as well as to platelet Monoamine oxidase B (MAO-B) activity.

Aim: 1) To study the symptoms of ADHD and DBD phenotypes in adolescents and their association with MAO-B activity in platelets, MAO-A VNTR and 5-HTT LPR genotypes separately and in combination. 2) To describe the complexity of the phenotypes in relation to various psychiatric problems and risk behaviours. 3) To investigate psychiatric and behavioural symptoms separately, rather than the complete diagnosis and their association with individual and combinations of candidate genes.

Methods: A population-based sample of twins including 177 girls and 135 boys was interviewed using the Swedish version of Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL). Diagnoses of ADHD and DBD were compiled based on the Diagnostic and Statistical Manual of Mental Disorders Text Revision (DSM-IV-TR) diagnostic criteria. Blood was drawn from the subjects and analysed for platelet MAO-B activity and polymorphisms in the MAO-A VNTR and 5-HTT LPR genotypes.

Results: 1) For both boys and girls the heterozygote 5-HTT LPR genotype was found to be related to symptoms of CD. Girls exhibited an association between low platelet MAO-B activity and symptoms of ODD and DBD. An association was found in boys between the short MAO-A VNTR allele and symptoms of DBD, as well as between ADHD-like problems and the presence of a short 5-HTT LPR or short MAO-A VNTR allele, in combination with high levels of platelet MAO-B enzyme activity. 2) In girls, subthreshold diagnoses of ADHD and DBD coexisted with symptoms of depression, mania, panic attacks, phobias, anorexia nervosa, motor tics and post-traumatic stress disorder (PTSD) while in boys with symptoms of depression and PTSD. In both boys and girls, smoking and high alcohol consumption contributed to a high risk of having these phenotypes. 3) The combination of low MAO-B activity in platelets and polymorphism in the 5-HTT LPR genotype was associated with several psychiatric symptoms.

Conclusions: Polymorphisms in the 5-HTT LPR and MAO-A VNTR as well as MAO-B activity platelet separately and in combination are related to both ADHD and DBD. The complexity of the ADHD and DBD phenotypes was shown by the association with several psychiatric and behavioural problems. A broad clinical assessment is needed for adolescents with such preliminary diagnoses and the serotonergic system should be further investigated when studying genetic influences on the complex ADHD and DBD phenotypes.

Keywords: MAO-A, MAO-B, 5-HTT, ADHD, ODD, CD, subthreshold diagnosis

ISBN 978-91-7457-460-9