

**Evaluation of Some Blood Components as
Inflammatory Markers in Children with
Attention Deficit Hyperactivity Disorder**

Thesis

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By

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List of Abbreviations

Abb.	Full term
<i>5-HT</i>	<i>Serotonin</i>
<i>ACTH</i>	<i>Adrenocorticotrophic hormone</i>
<i>ADHD</i>	<i>Attention deficit hyperactivity disorder</i>
<i>ADHD-H</i>	<i>Attention deficit hyperactivity disorder / hyperactive-impulsive type</i>
<i>ADHD-I</i>	<i>Attention deficit hyperactivity disorder / inattentive type</i>
<i>APA</i>	<i>American Psychiatric Association</i>
<i>ASD</i>	<i>Autism spectrum disorder</i>
<i>BD</i>	<i>Bipolar disorder</i>
<i>b-LPH</i>	<i>b-lipotropin</i>
<i>C.S</i>	<i>Cesarean section</i>
<i>C4B complement</i>	<i>Component 4B complement</i>
<i>CBC</i>	<i>Complete blood count</i>
<i>CD</i>	<i>Conduct disorder</i>
<i>CGI-S</i>	<i>Clinical Global Impression Scale</i>
<i>CNS</i>	<i>Central nervous system</i>
<i>COX-2</i>	<i>Cyclooxygenase 2</i>
<i>CPRS-L</i>	<i>Conners' Parent rating scale-long version</i>
<i>CRF</i>	<i>Corticotropin-releasing factor</i>
<i>CRH</i>	<i>Corticotropin-Releasing Hormone</i>
<i>CRP</i>	<i>C- reactive protein</i>
<i>CRS-R</i>	<i>Connres' Rating Scales Revised (CRS-R)</i>
<i>D4 receptor</i>	<i>Dopamine receptor D4</i>
<i>DAT1</i>	<i>Dopamine active transporter</i>
<i>DRD4</i>	<i>Dopamine receptor D4</i>
<i>DRD5</i>	<i>Dopamine receptor D5</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>DSM-5</i>	<i>Diagnostic and statistical manual of mental disorders</i>
<i>EDTA</i>	<i>Ethylenediaminetetraacetic acid</i>
<i>EEG</i>	<i>Electroencephalogram</i>
<i>F MRI</i>	<i>Functional magnetic resonance imaging</i>
<i>FEP</i>	<i>First episodes psychotic</i>
<i>GABA</i>	<i>G-aminobutyric acid</i>
<i>HDRS</i>	<i>Hamilton Depression Rating Scale</i>
<i>HPA</i>	<i>Hypothalamus–pituitary adrenal</i>
<i>HTR1B</i>	<i>5-hydroxytryptamine receptor 1B</i>
<i>ICD-10</i>	<i>10th revision of the international statistical classification of diseases and related health problems</i>
<i>IFN</i>	<i>Interferon</i>
<i>Ig</i>	<i>Immunoglobulin</i>
<i>IL</i>	<i>Interleukin</i>
<i>IL-1B</i>	<i>Interleukin 1 beta</i>
<i>IQ</i>	<i>Intelligent quotient</i>
<i>IR</i>	<i>Immediate release</i>
<i>MCH</i>	<i>Mean corpuscular hemoglobin</i>
<i>MCHC</i>	<i>Mean corpuscular hemoglobin concentration</i>
<i>MCV</i>	<i>Mean corpuscular volume</i>
<i>MDD</i>	<i>Major depressive disorder</i>
<i>MHC</i>	<i>Major histocompatibility complex</i>
<i>MINI KIDS</i>	<i>Mini-International Neuropsychiatric Interview for children and adolescents</i>
<i>MLR</i>	<i>Monocyte to lymphocyte ratio</i>
<i>MPV</i>	<i>Mean platelet volume</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>MRI</i>	<i>Magnetic Resonance image</i>
<i>MRS</i>	<i>Magnetic resonance spectroscopy</i>
<i>NE</i>	<i>norepinephrine</i>
<i>NICU</i>	<i>Neonatal intensive care unit</i>
<i>NLR</i>	<i>Neutrophil to Lymphocyte ratio</i>
<i>NSAIDs</i>	<i>non-steroidal anti-inflammatory drugs</i>
<i>OCD</i>	<i>Obsessive compulsive disorder</i>
<i>ODD</i>	<i>Oppositional defiant disorder</i>
<i>PCT</i>	<i>plateletcrit</i>
<i>PDD</i>	<i>Pervasive developmental disorder</i>
<i>PET</i>	<i>Positron emission tomography</i>
<i>PET-CT</i>	<i>Positron emission tomography-computed tomography</i>
<i>PFC</i>	<i>Pre- frontal cortex</i>
<i>PIQ</i>	<i>Performance Intelligent quotient</i>
<i>PLR</i>	<i>platelet to lymphocyte ratio</i>
<i>POMC</i>	<i>proopiomelano cortin</i>
<i>POPs</i>	<i>persistent organic pollutants</i>
<i>RDW</i>	<i>Red cell distribution width</i>
<i>SCID 1</i>	<i>Structured Clinical Interview for DSM IV Axis I Disorders</i>
<i>SLC6A3</i>	<i>Solute carrier family 6 (neurotransmitter transporter), member 3</i>
<i>SNAP-25</i>	<i>Synaptosomal nerve-associated protein 25</i>
<i>SSRI</i>	<i>Selective Serotonin Reuptake Inhibitors</i>
<i>SUD</i>	<i>Substance use disorder</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>T-DSM- IV-S</i>	<i>Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale</i>
<i>Th1</i>	<i>Type 1 T-helper cell</i>
<i>Th2</i>	<i>Type 2 T-helper cell</i>
<i>TIQ</i>	<i>Total Intelligent quotient</i>
<i>TLRs</i>	<i>Toll-like receptors</i>
<i>TNF</i>	<i>Tumor necrosis factor</i>
<i>VIQ</i>	<i>Verbal Intelligent quotient</i>
<i>WISC</i>	<i>Wechsler Intelligence Scale for children</i>

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by persistent symptoms of inattention and/or hyperactivity- impulsivity. There are three subtypes of ADHD, one marked by predominantly inattentive symptoms (ADHD-I), the second by hyperactivity and impulsivity (ADHD-H) and the third display a combination of inattention and hyperactivity (*American Psychiatric Association (APA), 2013*).

The estimated prevalence of ADHD in childhood has been reported to be 5.3% (*Polanczyk et al., 2014*). Genetics and environmental factors have been postulated to be risk factors for ADHD, strong genetic influence has been reported for ADHD, with 5-9 times increased risk in the first degree relative of patients. Several authors have proposed an association between ADHD and inflammatory mechanism due to positive findings regarding inflammatory related genes (*Anand et al., 2017*).

Healthy animals injected with pro-inflammatory Interleukin-1B (IL-1B) and tumor necrosis factor alpha (TNF- α) cytokines demonstrate sickness behavior associated with social withdrawal (*Dantzer et al., 2008*). In humans, injection of low dose endotoxin deactivates the ventral striatum, a region critical for reward processing, producing anhedonia a debilitating depressive symptoms (*Eisenberger et al., 2010*).

The positive correlation between medical conditions associated with chronic inflammatory and immunological abnormalities including rheumatoid arthritis, malignancies, diabetes and multiple sclerosis and psychiatric illness suggests the presence of widespread underlying inflammatory process affecting the brain among other organs (*Najjar et al., 2013*).

Cytokines have also been reported to play a pivotal role in tryptophan metabolism and dopaminergic pathway in the brain, which are also implicated in ADHD. Accordingly, it is conceivable that alteration in pro-inflammatory and anti-inflammatory cytokines may be influential in the pathogenesis of ADHD (*Anand et al., 2017*). Immune competent white blood cells population: monocyte, lymphocyte and neutrophil play a crucial role in systemic inflammatory response to severe infection, injury and poly-trauma. Recently, a general immune response to endotoxaemia has been described by increase of circulating neutrophils and decrease number of lymphocytes (*Zahorec, 2001*).

Neutrophil to Lymphocyte ratio (NLR) is a new, simple and inexpensive marker of the systemic inflammatory response (*Semiz et al., 2014*). Few studies have examined NLR in population with mental disorders although it is inexpensive (*Cakir et al., 2015*). It is calculated as the ratio of neutrophil count to lymphocyte count (*Durmus et al., 2015*). It correlates with prognosis in distinct disease activity. Neutrophils one of most abundant and important mediators of innate immunity, are professional phagocytes which

mount the acute inflammatory response and act as the first line of defence against invading pathogens (*Gao et al., 2015*). An association between NLR and chronic stress was demonstrated in animal studies (*Erminio & Berton, 2009*). Increased level of NLR was reported to be indicative of enhanced cytokine production (*Turkmen et al., 2012*).

Platelets are involved in the secretions of pro-inflammatory as well as anti-inflammatory process. The platelet to lymphocyte ratio (PLR) is calculated as the ratio of platelet count to lymphocyte count and it is widely used simple marker that seems to be related with cardiovascular diseases, malignancies, chronic diseases and infection (*Topal et al., 2015*). PLR is a novel index reflecting a systemic inflammatory burden that combines prognostic values of an individual platelet and lymphocyte count (*Ommen et al., 2002*). PLR demonstrated as a prognostic factor in patients with systemic diseases and cancer. To date, few studies have examined the PLR in psychiatric disorders (*Yildis et al., 2016*). Platelets may reflect biochemical changes in the brain under different mental conditions (*Camacho & Dimsdale, 2000*).

Mean platelet volume (MPV) has been studied as inflammatory marker in relation to the disease activity. MPV may be increased in mild inflammation due to the emergence of large platelets in the peripheral circulation and conversely, may be decreased in the severe inflammation because of the consumption of large platelet in the inflammatory area (*Lee et*

al., 2015). MPV is an accurate measure of platelet size, is considered a marker and determinant of platelet function. MPV can be a potentially useful prognostic biomarker in patients with cardio-vascular diseases (*Yorbik et al., 2014*).

There are few studies that have examined the association between psychiatric symptomatology and inflammation in children and adolescent (*Mitchell & Goldstein, 2014*). Specifically very few studies have examined the association between inflammatory state and ADHD in children and adolescents, and these have yielded conflicting data (*Anand et al., 2017*).