

Malondialdehyde levels in adult attention-deficit hyperactivity disorder

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Objective: To evaluate the biochemical basis of adult attention-deficit hyperactivity disorder (A-ADHD), we compared lipid peroxidation status in the plasma of A-ADHD patients, and that of control subjects without A-ADHD by quantifying the levels of malondialdehyde (MDA), an end product of fatty acid oxidation. We aimed to examine the association between MDA and A-ADHD. **Method:** The study comprised 20 A-ADHD patients from Gaziantep University Sahinbey Research Hospital Psychiatry Clinic, diagnosed by 2 psychiatrists (H.A.S. and S.S.) according to the Turkish version of the adult ADD/ADHD DSM-IV-Based Diagnostic Screening and Rating Scale, and 21 healthy volunteers. Malondialdehyde levels were measured in plasma samples of both study groups. **Results:** The mean (standard deviation [SD]) MDA levels in patients (2.44 [0.84] nmol/mL) were significantly higher than those of control subjects (0.36 [0.20] nmol/mL) ($t = 11.013$, $df = 39$, $p < 0.01$). MDA levels were correlated with overall number of criteria met ($n = 20$, $p = 0.01$, $Ro = 0.56$) and total hyperactivity/impulsivity score ($n = 20$, $p = 0.02$, $Ro = 0.51$). **Conclusion:** The fact that MDA levels were increased in A-ADHD could be an indication of increased oxidative stress in this disease. We suggest that such changes may have a pathological role in A-ADHD. This is the first study evaluating the MDA levels in A-ADHD, and our findings may provide a scientific guide for the further clinical enzymologic and biochemical studies on this disorder.

Objectif : Pour évaluer le fondement biochimique du trouble d'hyperactivité avec déficit de l'attention chez l'adulte (THADA-A), nous avons comparé, pendant la présente étude, l'état de peroxydation des lipides dans le plasma des patients atteints de THADA-A et dans celui de sujets témoins sans THADA-A, en quantifiant les concentrations de malondialdéhyde (MDA), produit final de l'oxydation des acides gras. Nous voulions étudier le lien entre le MDA et le THADA-A. **Méthode :** L'étude a porté sur 20 patients atteints de THADA-A de la Clinique de psychiatrie de l'Hôpital de recherche Sahinbey de l'Université Gaziantep, dont le diagnostic a été posé par deux psychiatres (H.A.S. et S.S.) conformément à la version turque de l'échelle de diagnostic, de dépistage et d'évaluation du TDA-THADA fondée sur la classification DSM IV, et sur 21 volontaires en bonne santé. On a mesuré les concentrations de malondialdéhyde dans des échantillons de plasma prélevés chez les deux groupes d'étude. **Résultats :** Les concentrations moyennes (et l'écart-type [ET]) de MDA étaient beaucoup plus élevées chez les patients (2,44 [0,84] nmol/mL) que chez les sujets témoins (0,36 [0,20] nmol/mL) ($t = 11,013$, $df = 39$, $p < 0,01$). On a établi un lien entre les concentrations de MDA et le nombre total de critères satisfaits ($n = 20$, $p = 0,01$, $Ro = 0,56$) et le score total au niveau du sous-titre hyperactivité-impulsivité ($n = 20$, $p = 0,02$, $Ro = 0,51$). **Conclusion :** Le fait que les concentrations de MDA étaient élevées dans les cas de THADA-A pourrait indiquer une augmentation du stress oxydatif causé par cette maladie. Nous sommes d'avis que de tels changements peuvent jouer un rôle pathologique dans les cas de THADA-A. Il s'agit de la première étude au cours de laquelle on a évalué les concentrations de MDA chez des atteints de THADA-A, et nos constatations pourront guider scientifiquement les études enzymologiques et biochimiques cliniques plus poussées au sujet de ce trouble.

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Medical subject headings: adult; attention-deficit disorder with hyperactivity; malondialdehyde; oxidative stress.

J Psychiatry Neurosci 2007;32(6):435-8.

Submitted Dec. 18, 2006; Revised Feb. 26, 2007; Apr. 11, 2007; Accepted Apr. 11, 2007

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a complex neuropsychiatric syndrome that is one of the commonest childhood disorders,¹ estimated to affect 7% of children.² Current data indicate that childhood ADHD persists into young adulthood in 58%–70% of cases.³ Recent evidence supports a 4% prevalence rate of adult ADHD (A-ADHD).³

A-ADHD is principally a genetic disorder, but environmental and biochemical factors also play a role in its etiopathogenesis. The number of biological studies on A-ADHD has escalated in recent years. Neuroimaging, genetics and biochemistry are the hot points for new research.³

There are few studies evaluating the biochemical basis of A-ADHD. From a syndromic aspect, A-ADHD may be involved with some other systems, such as oxidative metabolism. Rare research studies have evaluated the oxidative metabolism of ADHD in animals and children but not in adults.^{4,5}

Reactive oxygen species (ROS) can be evaluated indirectly by the measurement of some antioxidant enzyme levels such as superoxide dismutase, catalase or glutathione peroxidase, by products of lipid peroxidation such as malondialdehyde (MDA) or by some transition metal levels such as copper, zinc and iron.⁶

Malondialdehyde is the breakdown product of the major chain reactions leading to oxidation of polyunsaturated fatty acids (PUFAs) and thus serves as a reliable marker of oxidative stress.⁷ Recent studies have demonstrated that oxidative stress might have a role in the pathogenesis of various psychiatric disorders. Additionally, research groups have reported elevated MDA activity in various psychiatric diseases.^{8–11} These findings suggest that increased MDA, a destructive agent, could have an important role in the pathophysiology of psychiatric diseases.

When ROS are produced in excessive amounts or the enzymatic and nonenzymatic antioxidant defence systems are inefficient, some chain reactions causing cellular injury or even death of cells are activated.¹² ROS can also react with membrane-associated proteins, altering enzyme and neurotransmitter receptor function.¹⁰ We speculated that these effects may be associated with the cause of A-ADHD.

In the present study, we aimed to examine the association between MDA and A-ADHD, which, to the best of our knowledge, has never been evaluated in the literature.

Method

The study comprised 20 patients with A-ADHD from Gaziantep University Sahinbey Research Hospital, Psychiatry Clinic, Turkey, diagnosed by 2 psychiatrists (H.A.S. and S.S.) according to the Turkish version of the Adult ADD/ADHD DSM IV-Based Diagnostic Screening and Rating Scale as described by Gunay and associates,¹³ and 21 healthy volunteer control subjects.

Patients with a history of chronic systemic diseases such as diabetes mellitus and hypertension, and severe head injury

were excluded. After the patients and control subjects received a complete description of the study, all provided written informed consent. The ethics committee of the Gaziantep University Medicine School approved the trial. Also, a semi-structured form was used to detect several sociodemographic and clinical variables of the patients, and the medical records of the patients were reviewed.

Comorbid patients were included only when the other psychiatric conditions were in remission according to their Clinical Global Impression Scale scores (< 2 points for at least 2 mo), and the patients were allowed to take their medications. Case and control groups had a similar distribution in age, sex and smoking status.

Whole blood was collected by venipuncture into EDTA-lined vacutainer tubes. Plasma was obtained by centrifugation at 1000 g for 15 minutes at 4°C, separated and stored at –70°C.

The plasma MDA levels were determined by the method of Draper and Hadley¹⁴ based on the reaction of MDA with thiobarbituric acid (TBA) at 95°C. In the TBA test reaction, MDA and TBA react to form a pink pigment with an absorption maximum at 532 nm. The reaction was performed at pH 2–3 at 95°C for 15 minutes. The sample was mixed with 2.5 volumes of 10% (w/v) trichloroacetic acid to precipitate the protein. The precipitate was pelleted by centrifugation and an aliquot of the supernatant was allowed to react with an equal volume of 0.67% TBA in a boiling water bath for 15 minutes. After cooling, the absorbance was read at 532 nm. Arbitrary values obtained were compared with a series of standard solutions (1, 1, 3, 3 tetramethoxypropane). Results were expressed as nmol/mL.

Statistical analysis

In the case of homogeneity of the variables, the significance of differences between groups was estimated by 2-tailed *t* test. The homogeneity of the variables were evaluated by the Shapiro–Wilk test. Differences were accepted as significant when *p* < 0.05. Bivariate comparisons were examined with Spearman correlation coefficients, and values were corrected for ties.

Results

The mean (standard deviation [SD]) age of the patients was 27.95 (8.42) years; 6 of the 20 patients were women. Age, sex, weight, height, education level and marital status of the patients and control subjects were similar, and there were no significant differences between the groups (*p* > 0.05). Eleven patients had comorbid psychiatric disorders: 8 had anxiety disorders and the other 3 had psychiatric disorders such as mood disorders but not schizophrenia. Nine patients had only A-ADHD.

The mean (SD) plasma MDA level in patients with A-ADHD (2.44 [0.84] nmol/mL) was higher than those of the control subjects (0.36 [0.20] nmol/mL) (*t* = 11.01, *df* = 39, *p* < 0.05).

The median attention deficit subscores, hyperactivity/impulsivity subscores and total scores were 15, 17 and 29.5, respectively.

MDA levels were correlated with the number of hyperactivity criteria met ($n = 20$, $p = 0.01$, $R_o = 0.56$) and with the total score for hyperactivity/impulsivity ($n = 20$, $p = 0.02$, $R_o = 0.51$); sociodemographic features such as sex, age and weight were not correlated with MDA levels.

Discussion

We found that the mean plasma MDA levels of patients having A-ADHD were significantly higher than those of the control group.

Numerous studies have indicated that free radical-mediated neuronal damage plays a role in the pathophysiology of depression and bipolar mood disorders.^{11,15} About 75% of adults with ADHD suffer from other psychiatric disorders such as depression and bipolar mood disorders.¹⁶ Similar neurotransmitters (dopamine, serotonin and norepinephrine) play a role in the etiopathogenesis of depression¹⁷ and ADHD.³ The oxidation of catecholamines such as dopamine and norepinephrine by monoamines may result in an increased radical burden.¹⁸ As in other psychiatric disorders, higher MDA levels may play a role in the pathophysiology of A-ADHD. A remarkable increase in MDA levels, other than in previously studied psychiatric disorders, suggests a strong association between A-ADHD and lipid oxidation.

Various studies have suggested that genetic factors, neurotransmitter imbalances, lead toxicity, food sensitivities or nutritional problems might affect behaviour in children with ADHD.^{19,20}

The etiology of ADHD is thought to include abnormal regulation of neurotransmitter systems, particularly dopamine.²¹ The precise fatty acid composition of the cell membrane can affect neurotransmitter functioning.^{22,23} Recent animal studies on dietary fatty acids have shown alterations in dopamine neurotransmission,^{23,24} which may reflect the potential role of fatty acid metabolism on the regulation of dopamine.²⁵ Other studies have suggested that both children^{26,27} and adults²⁸ with ADHD have altered fatty acid status. The metabolic pathways of omega-3 fatty acids are complex and low in efficiency. Both omega-3 and omega-6 compounds compete for the same enzymes.²⁹ Recent studies have demonstrated evidence of increased oxidative breakdown of fatty acids, which leads to low levels of omega-3 compounds in the cell membrane of subjects with ADHD.²⁵

Lipids have fundamental structural and functional roles in the central nervous system²² and are vulnerable to oxidation. The overproduction of ROS interferes with the structure of PUFAs³⁰ and causes loss of fluidity in the biological membranes. MDA, which may oxidize PUFAs, may be a hallmark of different levels of cell destruction.³¹ One study has also shown that fatty acid deficiency was significantly associated with the severity of reported behavioural problems.²⁷

An Indian study has shown that supplementation with flax oil-based omega-3 precursors in combination with antioxidants is effective in improving such symptoms of ADHD as impulsivity, restlessness, inattention and poor self-control. Pre- and postsupplementation hyperactivity scores showed statistically significant improvement.³² Our study has shown

an increase of lipid peroxidation in A-ADHD patients, and this might be the reason for fatty acid deficiency in subjects with ADHD. Our findings may explain the improvement of patients in the Indian study and may guide further psychopharmacological research.

In our study, MDA levels were correlated with the number of criteria met for hyperactivity and with total score for hyperactivity/impulsivity ($n = 20$, $p = 0.01$, $R_o = 0.56$ and $n = 20$, $p = 0.02$, $R_o = 0.51$, respectively) in our A-ADHD patients. Thus there may be an association between reliable measures of MDA levels and particular clinical symptoms and aspects of hyperactivity behaviour. Our results suggest that A-ADHD may be associated with fatty acid oxidation, a finding that may warrant further research. MDA may predict hyperactivity among subjects.

Limitations of this study include sample size, comorbid psychiatric disorders in remission and concomitant medications. Since comorbidity is high in A-ADHD and remission can be ensured only with treatment, the patients were allowed to take their medications.

Conclusion

This is the first study evaluating oxidative metabolism in A-ADHD. Our findings that the mean plasma MDA levels of patients having A-ADHD were significantly higher than those of the control group and that MDA levels were correlated with the number of criteria met for hyperactivity and with the total score for hyperactivity/impulsivity in the A-ADHD patients may provide a guide for further clinical enzymologic and biochemical studies on A-ADHD.

Competing interests: None declared.

Contributors: Dr. Bulut designed the study. Drs. Selek, Gergerlioglu, Yuce and Ekici aquired the data, which Drs. Savas and Yilmaz analyzed. Drs. Bulut, Selek and Yuce wrote the article, and Drs. Savas, Gergerlioglu, Yilmaz and Ekici revised it. All authors gave final approval for the article to be published.

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Correction

Auditory processing in schizophrenia during the middle latency period (10–50 ms): high-density electrical mapping and source analysis reveal subcortical antecedents to early cortical deficits

In the print version of the article by Victoria M. Leavitt, Sophie Molholm, Walter Ritter, Marina Shpaner, and John J. Foxe (*JPN* 2007;32[5]: 339-53), the callouts in the text for Figures 5 and 6 were reversed. Similarly, the captions for Figures 5 and 6 were reversed. [Please note: The online version has been corrected.]

We apologize to the authors and our readers for this error.