

NeuroPharmacology

Original Article

Creatine kinase and C-reactive protein-additional diagnostic markers for attention deficit hyperactivity disorder (ADHD)?

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Abstract

Aim: CK and CRP are unspecific markers, elevated in a variety of diseases including various psychiatric disorders. To date, there is no systematic research about CK and CRP levels and ADHD, also related to ADHD specific medications. **Methods:** We checked in a placebo controlled manner serum CK and CRP levels of unmedicated ADHD patients and compared them to those of ADHD patients medicated with Methylphenidate and Atomoxetine. **Results:** Our results suggest that the CK level is elevated (1,9umol/sl, $p=0.017$) and that the CRP level is lower (1.0umol/sl, $p=0.018$) in ADHD patients, compared to healthy, i.e. non-ADHD contrasts and that this elevation is modified by Atomoxetine (CK: 1.7umol/sl; CRP: 2.1umol/sl) and Methylphenidate (CK: 2.8umol/sl; CRP: 0.7umol/sl). **Conclusions:** We conclude that CK and CRP levels should be checked in ADHD patients especially if they are medicated with methylphenidate or atomoxetine.

Keywords: ADHD, C-reactive protein, creatine kinase.

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Introduction

Attention Deficit/Hyperactivity Disorder [ADHD] is a neurological disorder that is thought to be related to the chemistry of the brain and its anatomy [1]. It is characterized by a persistent pattern of inattention, hyperactivity and impulsivity. While some of these are normal in children and adolescents, in children with ADHD, these characteristics are more frequent and severe. The National Institute of Mental Health (NIMH) estimates that 3 to 5 percent of all school age children suffer from ADHD.

ADHD usually begins in early childhood and can last well until adulthood. Some children do outgrow Attention-deficit/Hyperactivity Disorder but it is estimated that 60 percent of all children with ADHD will have symptoms until adulthood. While all children show the characteristics of inattention, hyperactivity and impulsivity, children with Attention-deficit/Hyperactivity Disorder will present these characteristics more intensely than healthy children of the same age. The Diagnostic & Statistical Manual for Mental Disorders (DSM-IV-TR) provides the current definition criteria for diagnosing a person with

ADHD. This diagnosis should be made by a qualified medical professional with critical input from the child's parents or caregiver. A diagnosis of ADHD is made when at least two of the criteria are met, inattention, hyperactivity or impulsivity. The symptoms, according to the DSM-IV-TR, need to have duration of at least 6 months to a point where it is disruptive and inappropriate for the person's developmental level.

The hyperactivity, i.e. the raised restlessness and the reduced pain perception may also increase the probability of inflammation and accidents.

The use of Methylphenidate (MPH) and Atomoxetine (ATX) to treat ADHD is increasing. Although MPH's and ATX's mechanism of action is largely unknown, inhibition of the dopamine transporter in presynaptic neurons with a lesser effect on norepinephrine and serotonin reuptake has been proposed. As with other amphetamine like drugs, both direct and indirect sympathomimetic effects are noted, and minor inhibition of monoamine oxidase has been described. MPH and ATX have also been demonstrated to affect blood flow and glucose metabolism in the cerebrum, basal ganglia, and cerebellum. Beneficial therapeutic behavioral effects include decreased motor activity and decreased impulsivity. Whereas the short-term benefits of stimulant medications like MPH and ATX are well documented in the treatment of ADHD, long-term benefits are controversial.

The most common adverse effects of therapeutic MPH and ATX use include headaches, insomnia, decreased appetite, abdominal pain, tachycardia, hypertension, hypomania, toxic psychosis, increased crying, feelings of restlessness or "being high", tic exacerbation, movement disorders, stereotypies, and perseverative behavior.

Given that toxic effects following MPH and ATX exposure previously have not been well studied, existing management recommendations are largely based on case reports of intentional

overdoses and chronic abuse. Reported complications in such instances have included cardiac dysrhythmia, psychosis, vasculitis, hepatic dysfunction, as well as rhabdomyolysis. As with other abused drugs, some reported complications, such as endocarditis, skin lesions, and panlobar emphysema, are specific to the route of abuse.

C-reactive protein (CRP) is one of the plasma proteins known as acute-phase proteins: proteins whose plasma concentrations increase by 25% or more during inflammatory disorders [2]. CRP can rise as high as 1000-fold during inflammation. Conditions that commonly lead to changes in CRP include infection, trauma, surgery, burns, inflammatory conditions, and advanced cancer [3]. Moderate changes occur after strenuous exercise, heatstroke, and childbirth. Small changes occur after psychological stress and in several psychiatric illnesses [4].

CRP is therefore a test of value in medicine, reflecting the presence and intensity of inflammation, although an elevation of C-reactive protein is not a specific diagnostic sign of any one condition.

Regarding CRP, to date there are no data about changes of CRP levels in ADHD patients with and without MPH and ATX treatment available. For that reason we investigated CRP levels of children suffering from ADHD, receiving no medication, MPH or ATX and compared them with healthy contrasts.

We assumed that ADHD itself as well as ADHD-specific medications, e.g. ATX, which increases nor-adrenaline, may lead to an increase of this unspecific marker. MPH, which increases dopamine, may have the same effect. This hypothesis could confirm that the CRP could be a further component of ADHD diagnosis, as well as structured clinical-psychiatric, neurological and psychological examinations and also serve to detect adverse side effects of ADHD-specific medications.

Creatine kinase (CK), also known as creatine phosphokinase (CPK) is an enzyme that transfers a N-Phosphoryl-group of the phospho-Creatin on ADP and transfers ADP to ATP. The Attention Deficit Hyperactivity Disorder (ADHD) is characterized by reduced concentration, and increased impulsiveness as well as restlessness. It is based on a lack of dopamine, especially in the frontal lobe and prefrontal region. The raised restlessness and the reduced pain perception increase also the probability of accidents [1].

We also saw that various psychiatric disorders and conditions lead to permanent muscle damages and therefore also to an increase of e.g. GGT [5] and CK [6] and also, that medications, especially Methylphenidate, which increases dopamine, may lead to an increase of this unspecific enzyme [7, 8], whereas Atomoxetine seems to lower serum CK levels [8].

Methods

With respect to CK, 60 in- and outpatients, 45 of which were diagnosed as ADHD in accordance with the ICD-10 criteria (15 of which had no medication, 15 received 20-30mg methylphenidate as monotherapy and 15 Atomoxetine 40mg as monotherapy) were examined [8]. The 15 contrasts were patients with adaptation and attachment disorders and patients without any psychiatric diagnosis respectively.

60 Subjects suffering from ADHD, were included in our study. They were 8-17 years of age, 54 of them were boys.

We examined 60 patients with average intelligence (IQ 77-112), diagnosed according to the DSM-IV criteria without comorbidities and after exclusion of neurological disorders, and thyroid dysfunction in our clinic and compared

them with contrasts, diagnosed with adaptation and attachment disorders. 15 of the ADHD patients had no medication, 15 received methylphenidate as monotherapy in various dosages and 15 Atomoxetine as monotherapy. Blood samples were taken in the morning.

Statistical analysis was performed by t-tests, using SPSS v12.0.

Results

The results of the CK data [8] show, that the CK (reference value: < 2,80 umol/sl), was significantly higher in ADHD patients (1,9 umol/sl), than in patients without individual pathology (1,8 umol/sl) ($p=0.017$). Those with Atomoxetine therapy (1,7 umol/sl) didn't show any significant contrasts to the non-ADHD group. The methylphenidate group showed significantly higher CK values (2,8 umol/sl) than the ADHD group without medical therapy ($p=0.014$), than the group with atomoxetine ($p=0.012$) and the ADHD group without psychopharmacological treatment ($p=0.017$) [8].

The CRP data of this study show, that CRP is not generally elevated in ADHD subjects, but that the elevation is associated with medication.

In particular, the results show that the CRP (reference value: < 2,80 umol/sl), was significantly lower in ADHD patients (1,0 umol/sl), than in patients without individual pathology (1,8 umol/sl) ($p=0.018$). Those with Atomoxetine therapy (2,1 umol/sl) didn't show any significant contrasts to the non-ADHS group. The methylphenidate group showed significantly lower CRP values (0,7 umol/sl) than the non ADHD group ($p=0.014$), than the group with atomoxetine ($p=0.012$) and the ADHD group without psychopharmacological treatment ($p=0.016$) (figure 1).

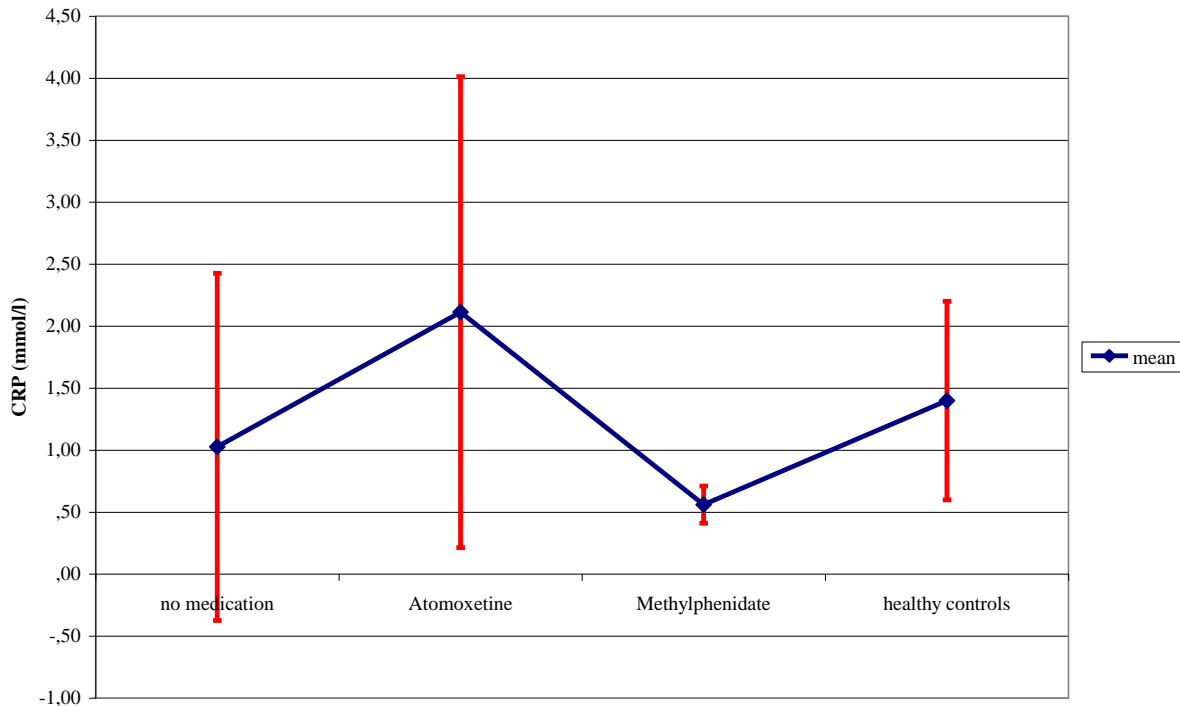


Fig. 1: CRP levels in ADHD patients medicated with no medication, with MPH and ATX contrasted to non-ADHD patients.

Discussion

Our data suggest that CK and CRP should be considered as an additional diagnostic marker for ADHD. Both parameters should be checked repetitively in case of psychopharmacological intervention, CK especially if a patient is medicated with MPH and CRP especially if a patient is medicated with ATX.

The relatively small sample sizes limit any generalization of the obtained results. Furthermore it must be considered, that differences were statistically significant, but all levels were within the reference values (range). We never saw really pathologically elevated CK or CRP values, neither in the healthy, nor in the ADHD/MPH/ATX group. Another limitation is the relatively short observation period. Although Methylphenidate starts to act within an hour, Atomoxetine needs several days until an effect

occurs. This fact implicates, that adverse side effects – such as a MPH/Atomoxetine elevation might need a longer period to be provoked. Altogether a longer observation period is warranted to confirm the results of this study.

Finally, Amphetamine is another effective option treating patients suffering from ADHD. To be able to compare these substances with respect to CRP/CK elevation, further research including also Amphetamine should be done. Amphetamine might also elevate serum CK levels, with respect to a possible CRP elevation there are no data available.

The other—although less effective – treatment options for ADHD, namely alpha receptor agonists and antidepressants, do not show any changes with respect to serum CK or CRP levels.

However, our results suggest, that CK and CRP levels could be elevated up to pathological levels in case of long-term treatment. If our results are confirmed, patients with elevated CK should be switched to ATX and patients with elevated CRP should be switched to MPH.

Key points:

-CK and CRP are unspecific diagnostic markers, which are elevated in a variety of somatic or psychiatric diseases.

-CK-CRP is also elevated in ADHD patients

-MPH raises CK additionally to the ADHD-specific elevation

-ATX raises CRP

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