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Reverse asymmetry and changes in brain structural volume of the basal ganglia in ADHD, developmental changes and the impact of stimulant medications

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Abstract

We discussed the cross section studies and the meta-analysis of published data in children and adolescents with ADHD (both drug naive and receiving stimulant medications), in comparison with healthy children and adolescents of the same age. In children and adolescents with ADHD the deceleration of the maturation dynamics of discrete CNS structures is found, volume reduction and decreased grey matter in prefrontal and occipital regions, which is accompanied by reverse asymmetry of the basal ganglia volume (putamen, nucleus caudate). The above mentioned developmental characteristics are valid only for the ADHD children, who have not been treated by stimulant medications. The stimulant treatment eliminates the mentioned changes into various extend. These developmental changes of CNS structures volume are missing in girls.

INTRODUCTION

ADHD is a heterogenic developmentally determined disorder. Its etiology is genetic or/and perinatal, the symptoms can be modified by exogenous factors (upbringing, parental behavior, depriving conditions in a family or institution). The leading factors, parallel with frequent co-morbid disorders, are inattention, hyperactivity impulsivity and problems in school, social and family life (surroundings/environment). The occurrence in child population in the age from 6 to 17 years fluctuates according to Barbosa *et al.* 2002 between 6.5–7.5%. In summary it can be stated that during the years of school attendance, between 6–15 years, according to Polnaczyk *et al.* 2007 the occurrence is 5.29% of child population. The boys to girls ratio is being stated between 3–4:1. In 60–80% of patients are the diagnostic criteria for DSM IV or ICD 10 met, so that the diagnosis can be considered doubtless. In 50–80% children with ADHD persist some of the symptoms still adulthood (Frodl *et al.* 2012). What is the interdependence between the behavioral characteristics and the neuropsychological

ORIGINAL ARTICLE

development of the ADHD children? How do the CNS structures develop in these children and do the stimulant medications influence the development?

GENETICS

However, although twin studies demonstrate that ADHD is highly heritable with genetic factors explaining on average 76% of the phenotypic variance in the population (Faraone *et al.* 2005), these findings must not be confused with neurobiological determinism (Taylor *et al.* 2004). Replicated association has been reported for several candidate genes, including DAT1, DRD4, SNAP-25, DRD5, 5HTT, HTR1B, and DBH (Faraone *et al.* 2005). A recent report by Brookes *et al.* 2006 confirmed the association of ADHD with especially for the DRD4 and DAT genes. Fuke *et al.* 2005 suggested that the 10-repeat allele of DAT 1 is related to a greater gene expression. The 10/10 genotype has been associated with increased dopamine concentration in the CSF, lower IQ, several neuropsychological and neurophysiological functions (Koutsilieri E *et al.* 2014).

MAGNETIC RESONANCE

Many of the imaging studies verify a reduction of the brain volume, cerebellum and nucleus caudate in children with ADHD (Valera *et al.* 2007, Castellanos *et al.* 1994, 1996, Hynd *et al.* 1993, Uhlíková *et al.* 2007). Imaging studies indicate anomalies or loss of normal asymmetries in the lateral ventricles, striatum, globus pallidus, and anterior frontal regions (Castellanos *et al.* 1996), with reduced metabolic activity in left frontal and parietal regions and anomalous electrical activity on the left (Tannock, 1998). Valera *et al.* 2007 carried out a meta-analysis and qualitative analysis of neuroanatomical abnormalities in ADHD, which were published in MEDLINE and PsycINFO before 2005. This meta-analysis confirmed the presence of abnormalities found by MRI in comparison with healthy subjects. Anatomic brain MRIs for 57 boys with ADHD and 55 healthy matched controls, aged 5 to 18 years, were obtained using a 1.5-T scanner with contiguous 2-mm sections. Volumetric measures of the cerebrum, caudate nucleus, putamen, globus pallidus, amygdala, hippocampus, temporal lobe, cerebellum; a measure of prefrontal cortex; and related right-left asymmetries were examined along with mid sagittal area measures of the cerebellum and corpus callosum. Subjects with ADHD had a 4.7% smaller total cerebral volume (p=0.02). Analysis of covariance for total cerebral volume demonstrated a significant loss of normal right > left asymmetry in the caudate (p=0.006), smaller right globus pallidus (p=0.005), smaller right anterior frontal region (p=0.02), smaller cerebellum (p=0.05), and reversal of normal lateral ventricular asymmetry (p=0.03) in the ADHD group. The normal age-related decrease in caudate volume was not seen, and increases in lateral ventricular volumes were significantly diminished in ADHD (Castellanos *et al.* 1996). In normal children the caudate and the putamen volume is elevated in the right in 85% of 104 children (age 4–18 years old) (Giedd 1996).

DEVELOPMENTAL VOLUMEMETRY OF ADHD CHILDREN CHANGES DURING STIMULANT THERAPY

The basal ganglia consist of the caudate, putamnen, globus pallidus, subthalamic nucleus, and substantia nigra. Caudate volumes decrease during the teen years and are relatively larger in females. This sexual dimorphism is interesting in light of smaller caudate nucleus volumes reported for male predominant disorders, such as ADHD (Giedd *et al.* 1994).

Methylphenidate has been shown to at least partially normalize abnormal volume most frequently in the basal ganglia and related areas (Czerniak *et al.* 2013).

Among the most frequent abnormalities in children with ADHD ranks (belong) hypo perfusion, reduced dopamin transmission and on it depending hypofunction of prefrontal and striatal regions (Pontius *et al.* 1973; Shaywitz *et al.* 1983; Castellanos *et al.* 1996; Filipek *et al.* 1997).

Filipek *et al.* examined 15 children with the ADHD diagnosis without comorbid disorders aged 13 and 15 matched healthy controls and determined reversible asymmetry of the nucleus caudate p<0.03. In healthy children is the right nucleus caudate larger than the left one, so called right to left asymmetry. Males had larger cerebral (9%) and cerebellar (8%) volumes (p<0.0001 and p=0.008. respectively), which remained significant even after correction for height and weight. In males only, caudate and putamen decreased with age (p=0.007 and 0.05, respectively). The left lateral ventricles and putamen were significantly greater than the right (p=0.01 and 0.0001, respectively). In contrast, the cerebral hemispheres and caudate showed a highly consistent right greater than left asymmetry (p<0.0001 for both).

In children with ADHD is often the opposite left to right asymmetry exerted, left nucleus caudate is bigger than the right one. Values of 0.05 (5%) or greater were found only for the pallidum and putamen in many ADHD children. Significant volumetric asymmetry favoring the left side was observed for the pallidum for the full series of 30 brains (left 6% greater than right), but a statistically significant asymmetry of pallidum was not observed in the brains of either the female or some male children considered separately (Caviness *et al.* 1996).

The above described abnormalities of prefrontal regions reflect the deficit of executive functions. These dysfunctions can be further divided into working memory deficits, the speech internalization deficits, reconstitution (behavioral analysis and synthesis) deficits (Barkley *et al.* 1997). The changes of basal ganglia

asymmetry in ADHD can explain the malfunction of adaptive and regulating functions (Bradshaw *et al.* 2000). In patients treated with methylphenidate, is the left to right asymmetry exceptional (Hyndt *et al.* 1993, Paclt *et al.* 2015).

Very important is the finding that detection of the left to right asymmetry in nucleus caudate and/or putamen in ADHD children is more frequent in subjects with co-morbidities of ADHD, especially Tourette syndrome and dyslexia, in children never treated with stimulants or atomoxetin (Aylward *et al.* 1996). The authors compared 16 boys with diagnosis of Tourette syndrome and co-morbid ADHD with 11 healthy controls, the groups were matched in accordance to age and the findings were that the volume of nucleus caudate and putamen exhibit a distinct difference (reduction) against healthy subjects. The question remains whether the ascertained asymmetry presents a risk for further development of ADHD symptoms and co-morbid disorders.

Basal ganglia are involved in motor control, influence the personality structure, affective states (emotional processing) and cognitive activity. The association circuit originates in (is based on) occipital structures and associative and parietal regions, therefore the regions close to sensitive and visual cortical regions. They can be related mainly to learning disorders for example dyslexia, but also to others like Tourette syndrome. The connection between optional pharmacotherapy with the rehabilitation of learning disorders, is yet unknown. Doubtlessly a closer clarification of positive influence of medication on improvement of the learning disabilities other disorders will be feasible.

Frodl *et al.* 2012 found increased volume of the putamen and globus palidus left p=0.0003. The stimulant treatment diminishes the stated left to right difference. The same side differences were detected in a meta analyses of the imaging studies results of adult subjects with ADHD (115 subject). In manual VMB the left to right difference (asymmetry) of the nucleus caudate was found as well.

Concentrations [mM] with standard deviations of selected metabolites in basal ganglia in patient and control groups are not different (Dezortova *et al.* 2015).

In the meta-analyses Nakao *et al.* 2011 states the following summary of 10 studies. 202 children were comprised into the meta-analyses. The meta-analytic differentiation of the total grey matter volume and the result were calculated using the standard random – effects models with the Globals procedure in the Signed Differences Mapping (SDM) software package.

The ADHD children group had global reductions in gray matter volumes, which were robustly localized in the right lentiform nucleus and extended to the caudate nucleus. Both increasing age and percentage of patients taking stimulant medication were found to be independently associated with more normal values in this region (Nakao *et al.* 2011).

We have detected significantly different DAT1/SLC6A3 genotype frequencies distribution between ADHD children and controls (Paclt *et al.* 2015). Allele 10 has not been shown to be a "risk" allele for ADHD, as previously indicated by meta-analysis. Additionally, a meta-analytical survey of human single photon emission computed tomography studies yielded no evidence of any significant association between polymorphisms of the VNTR in DAT1/SLC6A3 gene and individual variations in DAT1 availability in the human striatum. We have, however, identified rare genotypes 8/10, 7/10 and 10/11 as "risk" – (p<0.01) while the 9/9 genotype turned out to be protective (Šerý *et al.* 2015). The 10/10 genotype has been associated with increased dopamine concentration in the CSF, lower IQ, several neuropsychological and neurophysiological functions (Koutsilieri *et al.* 2014).

DISCUSSION

Abnormalities of caudate nucleus volume or asymmetry have been reported, although the studies differ in whether the normal caudate is asymmetric, and whether this asymmetry normally favors the right or the left caudate. These inconsistencies may reflect differences in methodology and comorbidity (Castelanos *et al.* 2002). The pharmacotherapy by stimulants changes the findings of stated methods. The left to right asymmetry of the nucleus caudate disappears, increases the thickness of the grey matter in prefrontal and occipital regions.

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