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Pupillary light reflex in children with ADHD

Hamrakova A[1,2], Ondrejka I[2], Sekaninova N[1,3], Peregrim L[2], Tonhajzerova I[1,3].

[1]Department of Physiology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic
[2]Clinic of Psychiatry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin and University Hospital in Martin, Slovak Republic
[3]Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

Abstract

Attention deficit/hyperactivity disorder (ADHD) is one of the most frequently seen mental disorders in children with an increasing risk for other mental disorders. ADHD represents a primary biological dysfunction of the central nervous system, such as dysregulation of frontal-subcortical-cerebellar catecholaminergic circuits and imbalances in the dopaminergic system. However, autonomic nervous system, comprised of two primary branches - sympathetic and parasympathetic nervous systems that are normally in dynamic balance, plays an essential role in the regulation of body functions. Although it is generally assumed that the autonomic regulation is impaired during ADHD the information related to this dysregulation is limited. One of the options to observe changes of autonomic balance in ADHD is pupillary light reflex (PLR). Pupillometric evaluation can be used for the assessment of functioning of both autonomic nervous system branches and certain parameters of pupil responsivity can be helpful as a tool for medical diagnostic and treatment. In conclusion, these findings suggest the pupillometry as a non-invasive method that can indicate abnormalities in the complex central autonomic network regulating PLR.

Key words: ADHD, pupillary light reflex, autonomic dysfunction

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed mental disorder in children and one of the most investigated diagnoses in medicine. ADHD was incorporated into the official medical nomenclature as Hyperkinetic Reaction of Childhood 50 years ago, in 1968 (1). ADHD has an increased risk of developing an entire spectrum of comorbid psychiatric disorders like behavioral, anxiety and mood disorders, specific developmental disorders including learning disorders and also sleep disorders (2). It is defined as a persistant neurodevelopmental disorder characterized by three main symptoms – inattention, hyperactivity, impulsivity (3, 4, 5). In children suffering from ADHD the innattention is typically expressed as daydreaming and inability to focus on a single task for a long period and the attention of mind is easily distracted by small and irrelevant stimuli. The hyperactivity is manifested as excessive talking, fidgeting, and also restlessness (6). Impulsivity, another symptom of ADHD, includes actions that are extremely rash, inconsiderate, inappropriate to the situation and that often result in undesirable consequences (7). It is generally assumed that ADHD is associated with autonomic nervous system dysfunction (8), which could be noninvasively studied using pupillometry. However, the studies in children and adolescent patients are rare. This review focuses on potential central

Corresponding author:
A. Hamrakova, Department of Physiology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovak Republic, Clinic of Psychiatry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Kollárova 2, 036 59 Martin, Slovak Republic, E-mail: andrea.hamrakova@gmail.com

autonomic dysregulation indexed by PLR providing novel important information about dynamic balance between sympathetic and parasympathetic nervous systems in patients suffering from ADHD.

Epidemiology of ADHD

Worldwide prevalence of ADHD is estimated to be around 5% in children and 2.5% in adults (5). According to epidemiological studies male sex, low socioeconomic status, and young age are associated with a higher risk of development of ADHD (9). Despite the fact that majority of children suffering from ADHD will not continue to meet all criteria for ADHD as adults, studies show that ADHD is a chronic disease with symptoms experienced over the lifetime (5, 10). The predictors of persistence of ADHD symptoms to adulthood include family history of the hyperkinetic disorder, psychiatric comorbidity, and psychosocial adversity (11).

Diagnosis of ADHD

Complex history with detailed information focused on symptoms specific to the diagnosis remains a „gold standard“ and should be used for determining reliable diagnosis of ADHD. Diagnosis should be based on a detailed clinical interview including the age of onset, each ADHD symptom, and functional impairments. The disorder diagnostic criteria have been developed and specified through decades (5). According to International Classification of Diseases, 10th Edition (ICD-10) hyperkinetic disorder defines the presence of inattention, impulsivity, and hyperactivity with the beginning before the 7th year of life that lasts for at least 6 months, occurs in different situations and disrupts social functioning of the child. It is indispensable the presence of all three symptom circuits (12). The criteria of the US classification system Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) are more mild, not all three symptoms must be present to diagnose ADHD (13). ADHD in DSM-IV defines three different types of ADHD according to prevalent symptoms: combined inattentive, hyperactive, and impulsive (about 80%), predominantly inattentive (about 10 to 15%), predominantly hyperactive and impulsive (about 5%) (13). The World Health Organization (WHO) uses stricter criteria for the diagnostics of hyperkinetic disorder (equivalent to the combined ADHD subtype); therefore, epidemiological data on the prevalence of hyperkinetic symptom in school population is lower than results based on the DSM-IV criteria (14). According to the new classification Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (2013), six or more of the symptoms have to persist for at least 6 months to a stage that negatively impacts directly on social and academic/occupational activities. For adolescents and adults five or more symptoms are required. The age of onset criterion for ADHD is different in older classification (DSM-IV) compared to novel classification (DSM-5); specifically, it has been raised from 7 (DSM-IV) to 12 years (DSM-5). Evidence of the symptoms can be obtained directly from the child or from the parents, often the teachers (15). Reports on behavioral symptoms of the patient can be helpful for evaluation of treatment respond and managment strategy (3). The ADHD diagnosis can be valid only when it is assessed with standard criteria for psychiatric disorders (9).

Pathogenenesis and risk factors of ADHD

ADHD is a complex multifactorial disorder caused by the combination of many different types of risk factors such as genetic, biological, environmental, psychosocial (9) with a small individual effect that act together to create a spectrum of neurobiological lability (16). Twin studies of ADHD have supported a strong genetic contribution to the ADHD with heritability 70–80% in both children and adults. Genes contribute to the onset, persistence, and also remission of ADHD. It is assumed that development of ADHD may be caused by changes in the structure of genes encoding proteins which participate in sig-

nal transmission in the nervous system. Among the monoamine neurotransmitters the most significant evidence of ADHD association is for variants in the genes encoding the D4 and D1B dopamine receptors. Other genes that show associations with ADHD include SLC6A4 (which encodes the sodium-dependent serotonin transporter), HTR1B (which encodes 5-hydroxytryptamine receptor 1B (also known as serotonin receptor 1B)), and SNAP25 (which encodes synaptosomal-associated protein 25). However, it is difficult to implicate any specific gene in ADHD due to diversity and complexity of the condition (5). Enviromental risk factors associated with ADHD involve prenatal and perinatal factors, such as maternal smoking and alcohol use, low birth weight, premature birth, and exposure to enviromental toxins. The multifactorial causation of ADHD leads to various profile of psychopathology, neurocognitive deficits, and structural or functional brain abnormalities. It is generally assumed that the cortical regions and subcortical structures contribute to the pathophysiology of ADHD. Specifically, the dorsolateral prefrontal cortex is linked to working memory, the ventromedial prefrontal cortex to complex decision making and strategic planning, and the parietal cortex to orientation of attention. The ventral and dorsal anterior cingulate cortex subserve affective and cognitive components of executive control, together with basal ganglia they create the frontostriatal circuit. According to the neuroimaging studies all of these structures (extending into amygdala and cerebellum) are impaired in children suffering from ADHD. Neurotransmitter circuits in brain have also been implicated in ADHD. The dopamine system is important for planning and initiation of motor response, activation, switching, reaction to novelty, and processing of reward. The noradrenergic system plays a crucial role for arousal modulation, state-dependent cognitive process, and cognitive preparation of urgent stimuli. Taken together, dysregulation of the frontal-subcortical-cerebellar catecholaminergic circuits and imbalances in the dopaminergic system play a crucial role in pathophysiology of ADHD (5).

ADHD and autonomic nervous system

The autonomic nervous system (ANS) is a part of the peripheral nervous system that independently regulates body functions such as the heart rate, digestion, respiratory rate, pupillary response, urination, sweating and sexual arousal (17). ANS plays an important role in human body because it regulates internal environment and also chain of physiological events for the purpose of adaptation an organism to environmental changes (18). The ANS consists of visceral afferent pathways, central nervous system integrating complex, as well as sympathetic and parasympathetic efferent pathways (19). The sympathetic nervous system is often defined as "fight or flight" system, while the parasympathetic nervous system is considered the "rest and digest" system (20). The activities of both branches of the ANS are in dynamic balance and respond to various stimuli, which is important for organism flexibility and adaptability. It is generally assumed that the function of autonomic regulation is impaired in children suffering from ADHD (8). Recent neuroimaging studies suggest the presence of structural brain abnormalities in children with ADHD, including prefrontal cortex (21). The prefrontal cortex is responsible for inhibitory influence on subcortical structures (e.g. amygdala) associated with defensive behavior and, thus, allows the organism to regulate its behavior in response to changing environmental demands. Amygdala has outputs to autonomic as well as other regulatory systems and becomes active during threat. Thus, under conditions of a threat, the prefrontal cortex becomes hypoactive which is associated with sympathetic excitation resulting in impaired cardiac autonomic function in ADHD (8). Moreover, it is generally known that dopamine and noradrenaline are dysregulated in ADHD, which plays a crucial role in pharmacological approach. While noradrenaline is an important neurotransmitter in ANS, the dysregulation of noradrenaline seen in ADHD may increase the possibility of autonomic dysfunction (22). Taken together, complex neurobiological mechanisms leading to

prefrontal cortex hypofunction and noradrenaline dysregulation are included in autonomic imbalance associated with ADHD.

Pupillary light reflex

Pupillary light reflex (PLR) describes the constriction and subsequent dilatation of the pupil in response to light as a result of the antagonistic actions of the iris sphincter and dilator muscles (Fig. 1) (23, 24). Generally, PLR regulates the intensity of light entering the eye (25). PLR not only serves as a major determination of retinal image quality but also provides an important metric of ANS function. The pupil constriction in response to light is mainly under the influence of the parasympathetic nervous system. The afferent limb of the PLR originates in the retina composed of the photoreceptors (rod and cone cells), bipolar cells, and RGC (retinal ganglion cells). The RGC axons that contribute to the optic nerve carry the neuronal signal from the photoreceptors. At the optic chiasm the nerves from the nasal retina cross to the contralateral side while the nerves from the temporal retina continue ipsilaterally. Further, the axons of RGCs exit the optic tract and carry the afferent pupillomotor signal *via* an extrageniculate pathway at the pretectal olivary nucleus located in the dorsal midbrain. The pretectal nuclei receive input from both optic nerves and, in turn, send efferents to both Edinger-Westphal nuclei also located in the midbrain. The Edinger-Westphal nuclei send efferent preganglionic parasympathetic fibers that travel with the nervous oculomotorius and synapse with postganglionic parasympathetic neurons at the ciliary ganglion. Short postganglionic nerve fibers leave the ciliary ganglion to innervate the ciliary sphincter that enables contraction of the iris sphincter muscle *via* the neurotransmitter acetylcholine leading to pupil constriction. Normally, the pupils of both eyes respond identically to a light stimulus, regardless of which eye is being stimulated. Light entering one eye produces a constriction of the pupil of that eye, the direct response, as well as a constriction of the pupil of the unstimulated eye, the consensual response. Both branches of ANS are required for pupil dilatation, i.e. recovery phase of the PLR (Fig.2) (26). The parasympathetic innervation of the iris sphincter muscle is inhibited by central supranuclear inhibition of Edinger–Westphal nuclei *via* α2-adrenergic receptor activation leading to relaxation of the sphincter muscle and pupil dilatation. Moreover, the iris dilator muscle contracts *via* excitation of the α1-adrenergic sympathetic pathway. The sympathetic pathway is composed of paired three-neuron arc on both the right and left sides of the central and peripheral nervous system (23). The central neuron originates in the hypothalamus and descends through brainstem and upper spinal cord to terminate in the ciliospinal centre of Budge at the level of C8-T1 (28). The pre-ganglionic neuron ascends from the ciliospinal centre of Budge to synapse with the post-ganglionic neuron at the superior cervical ganglion which is located at the periarterial plexus near the carotid artery bifurcation. Finally, post-ganglionic nerves travel to innervate the contraction of the iris dilator muscles, mediated by noradrenaline at the neuromuscular junction, resulting in pupil dilatation. Taken together, the constriction of pupil also called „miosis“ is regulated by sphincter muscle of the pupil and is under parasympathetic control. On the other hand, pupillary dilatation or „mydriasis“ is managed by dilatator iris muscle under symphatetic control. The pupil diameters varies from 7.5-8 mm diameter at full mydriasis to 1.5-2 mm at full miosis. Since both parts of pupil reflex are regulated by different components of the ANS different parameters of the PLR should be considered as indicators for either sympathetic or parasympathetic modulation (23). Pupillometry is a non-invasive technique simple to perform and offers valuable information on both branches of ANS. Examination of the pupil provides an important metric of ANS function and can be used as a diagnostic tool for indentifying parasympathetic or sympathetic deficits (23, 28).

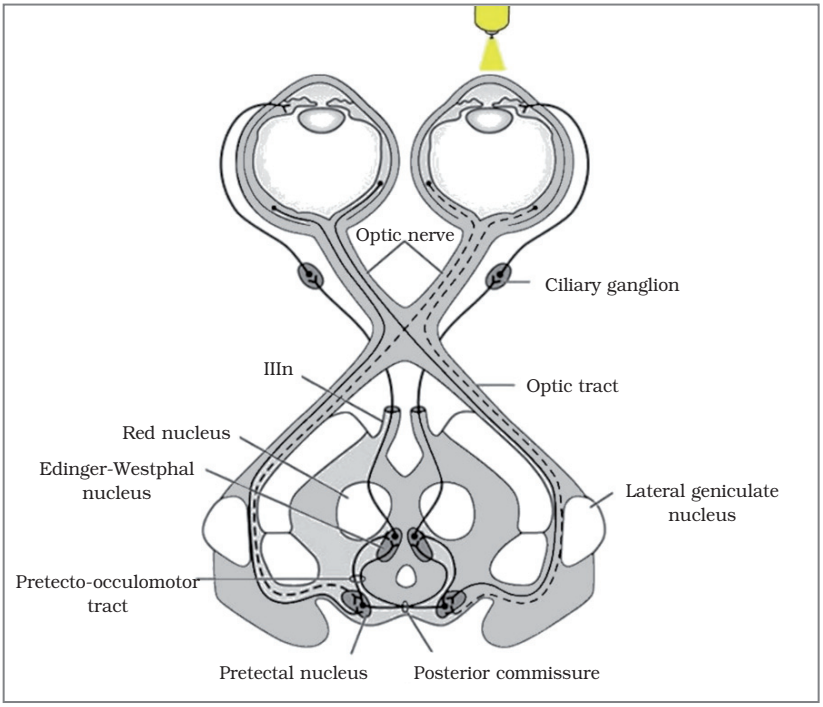

Fig. 1. Pathway of the pupillary light reflex (according to 24)

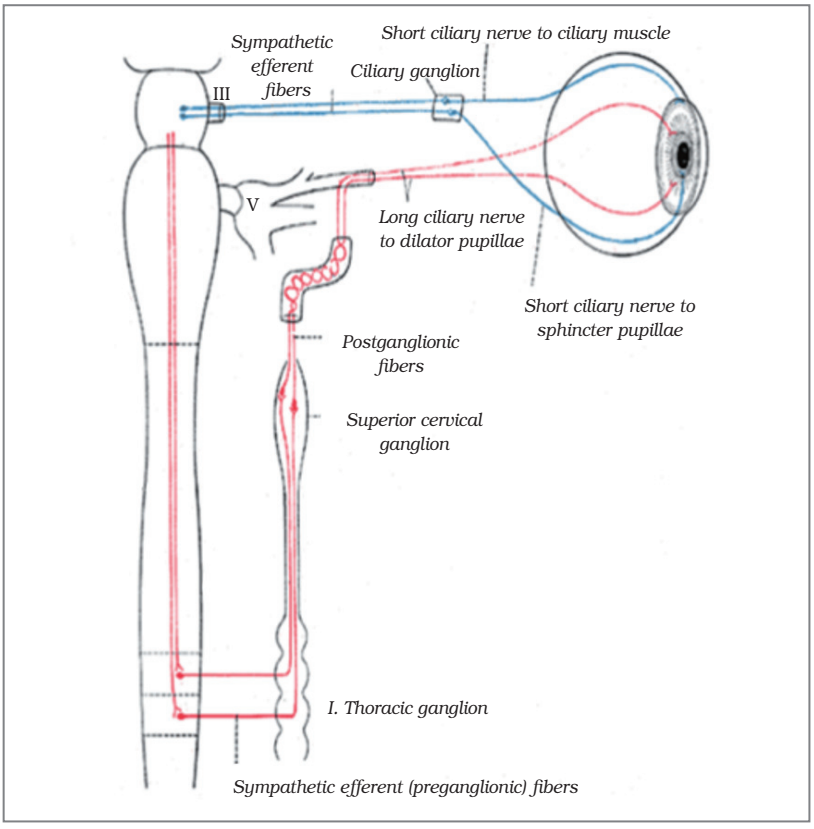

Fig. 2. Pupillary dilatation pathway (according to 26)

Pupillary light reflex in ADHD

It is generally assumed that emotional changes influence pupil diameters. It should be noted that emotion dysregulation is common in individuals with ADHD, characterized by excessive and rapidly shifting emotions, often associated with irritable and aggressive behavior (29). Pupil reactivity is also influenced by ongoing cognitive processsing, fatigue, intelligence, and working memory (30). The studies related to PLR changes in children suffering from ADHD are rare. According to Wainstein *et al.* (31) pupil size represents a promising marker of cognitive states in humans, which reflects the activity of an *arousal* network related to the noradrenaline system. The study has analyzed pupil diameter in ADHD and control subjects during a visuo-spatial working memory task. ADHD patients performed a task in two different sessions, with and without methylphenidate, a noradrenaline–dopamine reuptake inhibitor. Off-medication patients showed a decreased pupil diameter during the task but the difference dissappeared when the patients were on-medication. Moreover, pupil size correlated with indicators of attention: the subjects'performance and reaction time variability (31). Thus, in studies using pupillometry these factors should be considered to obtain reliable parameters and results (30). Changes in pupil size and response to light can be also an indication of drug and medicine consumption.

Treatment of ADHD symptoms

Despite the fact there is no curable therapy for ADHD, current medicine focuses on reducing symptoms, child's school performance, interpersonal relationships, and transition to adulthood (5,10). Several therapy options including pharmacological and non-pharmacological interventions can help children with ADHD (5). The first-line treatment for ADHD is given by stimulants, mainly methylphenidate, and the usual second-line treatment is atomoxetine, a noradrenaline reuptake inhibitor. Both kinds of drugs increase the catecholamine availability at synapses (31). Methylphenidate, central dopamine reuptake inhibitor, has shown sympathomimetic effects in several studies related to ADHD (32). Hysek *et al.* (33) in the study regarding pharmacokinetic and pharmacodynamic effect of methylphenidate and MDMA (3,4-methylenedioxymethamphetamine or 'ecstasy') in healthy subjects showed significant changes in ANS like increasing blood pressure, heart rate, tympanic body temperature, and also pupil size (6.97 ± 0.18 after placebo and 7.10 ± 0.18 after methylphenidate administration). There was found no difference in pupil diameter after PLR (5.13 ± 0.19 after placebo and also after methylphenidate) (33). Another study has analyzed the effect of methylphenidate on pupil sizes in 6-11-year-old boys suffering from ADHD. Changes of pupil diameter were measured in photopic and mesopic conditions before administration of methylphenidate and after 1 hour of the stimulant intake. Despite the fact that methylphenidate may cause increasing of pupil diameter by sympathomimetic effects the findings showed that methylphenidate decreases the size of left pupil in photopic conditions, which may be associated with increased response to light (32). Doses of methylphenidate are independent from weight. According to the guidelines it is necessary to start with lower doses and titrate them weekly to an effective dose that does not lead to adverse effect (5,10). The most common side effects are appetite suppresion, initial insomnia, dysphoria, and irritability (5). Non stimulant drug atomoxetine as a noradrenergic reuptake inhibitor is used as an alternative treatment if stimulants are not tolerated well, in case of side effects, or when contraindications occur (3). While atomoxetine works by blocking of noradrenaline reuptake the increased neurotransmitter concentrations in the neuro-effector junction and in the periphery should lead to a pressor response. This idea is probably counteracted by a central sympatholytic action through activation of α-2 adrenoreceptors, which is similar to "clonidine-like" effect (34). A recent study suggests that children and adolescents treated with atomoxetine were characterized by a significant increase in heart rate and systolic blood pressure rather than subjects treated with methylphenidate (35). Atomoxetine should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, and serious heart rhythm abnormalities, or other serious cardiac problems (36). In case patients suffering from ADHD do not respond to monotherapy

a combined therapy with atomoxetine and methylphenidate might be effective altough cardiovascular safety of these combined therapies have not been studied enough (5). However, the knowledge related to PLR in pure ADHD without treatment is unclear. Thus, we suggest that the evaluation of PLR could provide a non invasive window into pathophysiological regulatory mechanisms in central regulatory network in children suffering from ADHD. Further research in this topic is important.

CONCLUSION

Pupillometry represents a noninvasive measurement of pupil diameter providing important information about a dynamic balance between sympathetic and parasympathetic nervous systems under central autonomic control. Therefore, the PLR could be proposed as a potential tool for early diagnostics of possible diseases related to the autonomic dysregulation. Moreover, it is assumed that PLR will be able to evaluate the efficacy of psychopharmacological treatment in addition to the assessment of clinical signs of ADHD. There is a possibility that pupillometry will be used in early identification of children with presyndromal psychopathology. Ongoing neurobiological and clinical researches support future advance in diagnostic and therapeutic approaches to ADHD.

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