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AUTONOMIC DYSREGULATION IN CHILDREN: CONTEMPORARY APPROACH TO DIAGNOSIS AND TREATMENT

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The present article provides an overview of autonomic dysregulation (AD) processes in children. AD refers to a disruption in the normal functioning of the autonomic nervous system (ANS), leading to violations of various physiological processes.

The goal of the article was to provide an overview of AD processes in children and discuss contemporary approaches to its assessment and management.

Materials and methods. The systematic review was prepared in accordance with international recommendations; the work strategy involved searching several global databases without language restrictions on documents. Study selection criteria for inclusion were diagnostic criteria for any psychopathological or neurodevelopmental condition reflecting at least one index of ANS functioning, use of any AD assessment scale, reporting, outcome, and correlation between AD and ANS values.

Discussion. Autonomic dysregulation is a complex phenomenon with a wide range of manifestations and associated with several medical conditions that can have a significant impact on children's health, quality of life, and wellbeing. Autonomic dysregulation is a complex disorder that can have a significant impact on health, development of the affected children and their families. Autonomic dysregulation is often manifested by recurrent stereotypic symptoms that affect multiple systems including cardiovascular, neuroendocrine, respiratory, genitourinary, sexual, gastrointestinal, and skin reactions. Recent studies have shed light on the mechanisms of AD, including the role of genetic factors and environmental influences, as well as the importance of a good ANS balance.

Conclusion. A better understanding of the ANS role in health and disease may lead to new approaches to health maintenance, prevention, and treatment of diseases in which AD is an important pathogenic component.

Key words: autonomic nervous system, autonomic balance, autonomic dysregulation, heart rate variability, children.

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ВЕГЕТАТИВНА ДИСРЕГУЛЯЦІЯ У ДІТЕЙ: СУЧАСНИЙ ПІДХІД ДО ДІАГНОСТИКИ ТА ЛІКУВАННЯ

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У статті подано огляд процесів вегетативної дисрегуляції (ВД) у дітей. ВД означає порушення функціонування вегетативної нервової системи (ВНС), що призводить до дисбалансу різних фізіологічних процесів.

Метою цієї роботи було надання огляду сучасних підходів до процесів ВД у дітей, їх оцінки та лікування. Цей огляд був підготовлений відповідно до міжнародних вказівок у кількох глобальних базах даних.

Вегетативна дисрегуляція – це складне явище з широким спектром проявів, пов'язане з багатьма захворюваннями, які можуть мати значний вплив на здоров'я, якість життя та благополуччя дітей. ВД впливає на серцево-судинну, нейроендокринну, респіраторну та інші системи. Останні дослідження пролили світло на механізми ВД, включаючи роль генетичних та екологічних факторів.

Висновок. Розуміння ВД може призвести до покращання здоров'я, профілактики та лікування низки захворювань.

Ключові слова: вегетативна нервова система, вегетативна дисрегуляція, варіабельність серцевого ритму, діти.

Introduction. The autonomic nervous system (ANS) plays an important role in maintaining homeostasis and responding to changes in the internal and external environment. Studies of sympathovagal balance examine differences in physiological responses under the control of the sympathetic and parasympathetic part of the nervous system [1]. Autonomic dysregulation (AD) (or dysautonomia) refers to a disruption in the normal functioning of the ANS, leading to dysregulation of various physiological processes [2; 3]. It is a complex phenomenon with a wide range of manifestations and associated with several medical conditions that can have a significant impact on the health and wellbeing of children. Children are particularly vulnerable to AD and its effect on their health and development can be profound [4].

In recent years, the interest in AD study in children deepens [5]. Advances in technology have made it possible to measure ANS activity in a non-invasive and accurate manner, leading to a better understanding of the mechanisms underlying AD and its clinical implications [6]. AD is often identified by recurring, stereotypical symptoms that impact various systems including cardiovascular, neuroendocrine, respiratory, genitourinary, sexual, gastrointestinal, as well as skin and pupillary reactions. In the present article, we examined the contemporary approach to AD in children, with a focus on its assessment, etiology and management [7–11].

The assessment of AD in children can be challenging as it requires the measurement of multiple physiological

variables that are influenced by the ANS. The most commonly used methods for assessing ANS activity in children are heart rate variability (HRV) and skin conduction measurements [12–15]. AD can have multiple etiology, including genetic, environmental, and behavioral factors [16–19]. Environmental factors, such as exposure to stress, trauma, pollutant or toxins, can also affect ANS activity and lead to AD. Behavioral factors, such as poor sleep habits, lack of physical activity and unhealthy diet, could affect ANS activity too. The management of AD in children depends on the main cause and the severity of the symptoms. It must be focused on symptom relief and improving the quality of life of the child. This can include pharmacological interventions, non-pharmacological methods, such as biofeedback, relaxation techniques, and physical activity [20–22]. Physical activity has been shown to have a positive effect on ANS function, particularly in children with anxiety disorders. Regular exercises can improve ANS balance and reduce symptoms [23].

The purpose of the article is to provide an overview of AD processes in children and discuss contemporary approaches to its assessment and management. It aims to raise awareness of the relevant complex phenomenon and highlight the importance of a multidisciplinary significance for evaluation and treatment of AD in children.

Materials and methods. The systematic review was prepared in accordance with international guidelines [24]. The strategy of the work includes the search in several databases: PubMed, Wiley online library, Web of Knowledge/ Science, Medline, Cochrane Reviews, Oxford Medical, and others until 2024, without language limits of document. The total search included keywords and terms associated with measures of ANS functioning, autonomic balance and AD. Selection criteria for the study included the following data: empirical studies of children and youth, diagnostic criteria for any psychopathological or neurologic conditions reporting at least one index of ANS functioning (including heart rate, respiratory rate etc.), using any scale AD assessing, reporting, as outcome and correlation between AD and ANS parameters.

Discussion. AD is a complex phenomenon that can have a significant impact on the health and wellbeing of children. The assessment of ANS activity in children can be difficult: during a clinical study attention is mostly paid to the regulation of vascular tone, cardiovascular reflexes, skin autonomic reflexes, thermoregulation, autonomic innervation of the eyes, salivary and tear secretion etc. [3; 15; 25]. The oculocardiac reflex and celiac plexus reflex normally slow down the pulse by 8–10 beats but in children emotional reaction could hide the result. Along with this, instrumental measurements such as HRV and skin conductance indices can provide valuable information on changes in ANS function [2].

Most of the studies have shown that AD can have multiple etiology, including genetic, environmental and behavioral factors etc. The ANS can control immune cell activation via both sympathetic adrenergic and parasympathetic cholinergic nerve release of norepinephrine and acetylcholine. The hypothesis suggests that AD leads to dysregulation of immune tolerance mechanisms in immune cells leading to excessive production of pro-inflammatory cytokines and inactivation of processes, which takes place in macrophages and microglia. This switches the macrophage from producing pro-inflammatory cytokines to anti-inflammatory cytokines. Acetylcholine activation on the surface of immune cells leads to changes in immune cell polarization [7; 14]. In acute and chronic respiratory pathology in children, suppression of the immune response may be observed with a negative impact on the course of the disease [9; 26].

AD could appear even in the fetus and the prenatal autonomic nervous system could lead to impaired fetal immune tolerance mechanisms and a greater vulnerability resulting in neurodevelopmental abnormalities. For example, a study of S.S. Shetty et al. (2023) found that prenatal exposure to environmental toxins, such as lead and mercury, was associated with reduced autonomic balance in children [27]. Another data of L.A. Vitulano et al. (2022) show that children with prenatal pathology could have attention-deficit/hyperactivity disorder (ADHD) and reduced HRV compared to typically developing children, suggesting that ANS dysfunction may play a role in the pathophysiology of ADHD [28].

Very interesting data were presented by R. Cordani et al. (2022) analyzing a peculiar complex of neurodevelopmental disorder – Rett syndrome (RS), with multi-system involvement of breathing problems and AD [29]. They show that AD increases the risk of cardiorespiratory vulnerability in this group of patients. Assessment of HRV indexes provides an overview of autonomic health in RS and offers insight into how the sympathetic and parasympathetic components of the nervous system function. However, no study has evaluated HRV in RS patients to assess how the dynamics of autonomic function vary with age and changes during the day or night. The authors were using a monitoring ECG for measurement HRV in 45 patients with RS and examined the time and frequency domain sympathetic and parasympathetic indices.

Recent research indicates the other potential etiologies of AD in children. One possible cause is chronic stress, stressful experience, such as exposure to violence or abuse, bullying, aggressive behavior among school aged children which can lead to ANS dysregulation, resulting in a range of physical and emotional symptoms (L. Cavanagh et al., 2022) [16]. Chronic stress exposure is increasingly prevalent in modern society especially in school-age and could be a significant risk factor for negative health outcomes [8]. The imbalance of ANS control leads to dysregulation of physiological responses to stress and contributes to the cardiometabolic disorders pathogenesis including the global leading cause of death – cardiovascular diseases. A.M. Wafi (2023) considers that heart problem and hypertension are associated with central oxidative stress, mediated by the antioxidant enzymes in the central autonomic neurons that regulate sympathetic outflow and decrease activity [30]. The chronic stress also positively correlates with the development of metabolic syndrome in both children and adolescents.

Cardiovascular sensory dysfunction has been shown to contribute to sympathetic excitation. Central changes in the membrane sensitivity of pre-sympathetic neurons at several medullary and hypothalamic sites also contribute to

elevated sympathetic nerves activity. The enhanced sympathetic outflow has several effects on innervated visceral organs. Cardiac sympathetic nerves increase myocardial oxygen demands by releasing norepinephrine, which acts on myocardial adrenergic receptors [7].

Dysfunction of brain areas of ANS could provoke clinical manifestations of both epilepsy and migraine (D. D'Agnano et al., 2024) [19]. Despite their prevalence, autonomic signs are often misdiagnosed and their treatment is undervalued. The authors describe that autonomic manifestations are reported during seizures and migraine attacks according to their manifestation, focusing on the ANS role and on the parasympathetic outflow that often induces cranial autonomic symptoms. The ANS assimilates information from the internal body and the external environment, subsequently changing bodily functions to provide homeostasis maintenance. The ANS comprises cortical structures such as the orbitofrontal cortex, the anterior cingulate cortex, the insular cortex, along with hypothalamus, the amygdala, and various brainstem nuclei some of which modulate sympathetic output while others oversee parasympathetic output. Epileptic seizures are characterized as a temporary manifestation of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain and often accompanied by autonomic symptoms of AD. These AD symptoms may either supplement other seizure manifestations or serve as the primary sign of the seizure. Clinically significant autonomic disorders may accompany all seizure types (generalized, focal, and/or with unknown onset) across all phases (early ictal, ictal, and post-ictal). The most prevalent forms of epilepsy include temporal lobe epilepsy and self-limited epilepsy with autonomic reactions. However, complex AD is also a defining characteristic of some developmental and epileptic encephalopathies and even unexpected death.

T.D. Yeater et al. (2022) indicate that ANS is an important regulator of stress responses and exhibits functional changes in chronic pain states [18]. For example, recent reviews provide a framework for AD and shifts in neuroimmune communication to contribute to the pathophysiologic progression of osteoarthritis. Chronic joint pain may modulate autonomic functions and need non-pharmacologic pain interventions including physical exercise and psychological interventions.

B. Mueller et al. (2022) analyzing structural and functional relations between the ANS and immunity indicate that the immune system is connected anatomically and functionally [31]. These systems coordinate the central and peripheral response to perceived and systemic stress signals. Both the parasympathetic and sympathetic components rapidly respond to stress signals, while the hypothalamic-pituitary-adrenal axis and immune system have delayed but prolonged actions. The human studies (S. Giunta et al., 2024) have demonstrated consistent anti-inflammatory effects of parasympathetic activity [32]. In contrast, sympathetic activity has been associated with both increased and decreased inflammation.

Another possible cause of AD are acute or chronic inflammatory processes in the body which can affect ANS function, leading to such symptoms as tachycardia, hypotension and orthostatic intolerance (L. Monnens, 2022) [33]. M. Madrid et al. (2020) found that children with autoinflammatory disorders had significantly lower HRV compared to healthy controls, indicating dysregulation of the ANS [34].

Genetic factors may also play a role in the development of AD. L.P. Richer et al. (2023) found that children with a history of early-childhood onset obesity, febrile seizures had reduced HRV and increased sympathetic activity compared to healthy controls, suggesting a possible genetic predisposition to AD [27].

It is important to note that AD can also occur as a comorbidity of other medical and psychiatric conditions, such as anxiety disorders, depression, and ADHD (S. Doering et al., 2018) [4]. Management of comorbidities is an important component of pediatric AD treatment.

The pathogenesis of AD in children involves dysregulation of the ANS, specifically the sympathetic and parasympathetic branches. Dysregulation of the ANS can lead to a variety of physical and emotional symptoms, including tachycardia, bradycardia, orthostatic intolerance, and anxiety [30].

Last time researches highlighted the role of neuroinflammation in the pathogenesis of AD. Neuroinflammation, which can result from a variety of factors including chronic stress and infection, can lead to dysregulation of the ANS through the activation of pro-inflammatory cytokines and the disruption of neural signaling pathways [31; 32]. In the development of AD a peculiar role is played by epigenetic modifications. Epigenetic modifications, such as DNA methylation and histone modification, can alter gene expression and contribute to the development of chronic diseases (X. Wang et al., 2022) [35]. This study found out that children with a history of early life stress had altered DNA methylation patterns in genes related to ANS function, providing evidence for a potential epigenetic mechanism underlying AD.

Overall, recent research suggests that the pathogenesis of AD in children involves a complex interplay between genetic, environmental, and epigenetic factors. Dysregulation of the ANS, neuroinflammation and epigenetic modifications may all contribute to the development of this disorder. Further studies are needed to better understand the underlying mechanisms of AD and to develop targeted interventions for this condition [35; 36].

Clinical manifestations of AD can vary widely and may include such symptoms as tachycardia, bradycardia, dizziness, syncope, gastrointestinal distress, anxiety, and panic attacks [32; 37; 38]. These symptoms may occur in response to physical or emotional stress and can have a significant impact on a child's quality of life and daily functioning.

There is currently no widely accepted classification system for AD in children. However, researchers have proposed various subtypes of AD based on clinical manifestations and physiological abnormalities. For example, some researchers have suggested that the subtype of AD known as postural orthostatic tachycardia syndrome may represent a form of AD in which symptoms occur primarily upon standing (A. Attard et al., 2023) [39].

Another proposed subtype of AD is the hyperadrenergic form, in which symptoms are related to excessive

sympathetic nervous system activity (M.C.S. de Oliveira et al., 2023) [40]. This subtype is often associated with such conditions as hypermobility spectrum disorder and Ehlers-Danlos syndrome.

It is worth noting that the clinical manifestations of AD may overlap with those of other medical and psychiatric conditions, including anxiety disorders, chronic fatigue syndrome, and fibromyalgia (H. Leach et al., 2024) [41]. Therefore, a thorough medical evaluation and diagnostic workup are essential to rule out other potential causes of symptoms.

The management of AD in children depends on the underlying cause and the severity of the symptoms and must improve health, self-esteem, quality of life, self-monitoring and health promotion. Treatment options include pharmacological interventions directed at ANS, non-pharmacological interventions such as cognitive-behavioral therapy (CBT) and lifestyle changes, and addressing underlying comorbidities [35; 42].

As for treatment, the recent studies (A. Naseri et al., 2023) has highlighted the potential of pharmacological interventions directed at ANS like the anticholinergic glycopyrrolate improved symptoms and HRV in children with AD [37]. The study also found that glycopyrrolate was safe and well-tolerated in children. Pharmacological interventions, such as beta-blockers or anticholinergics, can be used to modulate ANS activity. However, these medications can have side effects and should only be used under the guidance of a qualified healthcare provider. For example, S. Wang et al. (2020) found that treatment with beta-blockers improved HRV and reduced symptoms in children with postural orthostatic tachycardia syndrome [38].

Non-pharmacological interventions, such as biofeedback, relaxation techniques, and physical activity, can be effective in improving ANS function and reducing symptoms [39]. Psychological interventions, such as CBT, may also be effective in the management of AD. J. Apolinário-Hagen et al. (2020) demonstrated that CBT improved HRV and reduced symptoms in children with functional abdominal pain and coexisting anxiety [20]. The study concluded that CBT may be an effective non-pharmacological intervention for improving ANS function in children with AD. S. Nagamitsu et al. (2022) show good results after CBT included changes in scores for self-esteem, quality of life, self-monitoring, and an adolescent health promotion scale [38]. A.M. Firth et al. (2022) found that biofeedback training improved HRV and reduced symptoms in children with asthma [12]. Another investigation of V. Malhotra et al. (2015) found that yoga practice improved HRV and reduced anxiety in children with autism spectrum disorder [42].

Recent protocols for the management of AD in children emphasize the importance of a multidisciplinary approach that includes medical, psychological, and lifestyle interventions. Non-pharmacological interventions, such as exercise, relaxation techniques, and biofeedback, are often recommended as a first-line treatment, with pharmacological interventions reserved for more severe cases or when non-pharmacological interventions are ineffective [43–46].

A promising non-pharmacological intervention for AD is exercise. A systematic review of Xing et al. (2021) found that exercise training improved ANS function in children and adolescents with various medical conditions, including obesity, type 1 diabetes, and asthma [20]. The review concluded that exercise training should be considered as a safe and effective non-pharmacological intervention for improving ANS function in children. Studies of M. Daniela et al. (2022) show that the positive impact of physical exercise is well known and has been studied by many researchers, but its negative impact has been less studied [23]. Depending on the type, duration and individual characteristics of the person, doing the intensive exercise which could be considered a physiological stressor and the negative impact seems to be connected with the oxidative stress induced by effort.

One more non-pharmacological intervention for AD is biofeedback. Biofeedback is a technique that uses electronic sensors to measure physiological responses such as HRV and provides feedback to the patients to help them learn to control these responses [43]. A meta-analysis of P.M. Lehrer et al. (2020) found that biofeedback was effective in improving ANS function and reducing symptoms in children with various medical conditions, including asthma, anxiety, and chronic pain [13].

In addition to medical and non-pharmacological interventions, lifestyle interventions, such as dietary changes and stress management techniques can also be helpful in improving ANS function and reducing symptoms of AD. A study of R. Polito et al. (2021) found that a low-carbohydrate diet improved HRV and reduced symptoms in children with AD, suggesting that dietary interventions may be a promising approach for the management of AD [15].

In summary, the management of AD in children requires a multidisciplinary approach that includes medical, psychological, and lifestyle interventions. Non-pharmacological interventions, such as exercise and biofeedback should be considered as first-line treatment, with pharmacological interventions reserved for more severe cases. Recent research has highlighted the effectiveness of exercise, biofeedback, and pharmacological interventions such as beta-blockers for improving ANS function and reducing symptoms in children with AD.

Conclusion. AD is a complex disorder that can have a significant impact on the health and quality of life of affected children and their families. Recent research has shed light on the underlying mechanisms of AD, including the role of genetic and environmental factors, as well as the importance of the autonomic nervous system dysregulation.

While there is no widely accepted classification system for AD currently, researchers have proposed various subtypes based on clinical manifestations and physiological abnormalities. AD treatment is often individual and may involve a combination of pharmacological and non-pharmacological interventions.

There are several prospects for further research on AD in children. One important area of the study is the development of more targeted and effective treatment methods for this condition. Current treatment methods are often limited in their efficacy, and further research is needed

to identify more specific interventions that can overcome the basic mechanisms of AD.

Another area for future research is the identification of biomarkers that can aid in the diagnosis and classification of AD. Biomarkers may include genetic markers, neuroimaging techniques, or physiological measures, and their identification may facilitate earlier diagnosis and more accurate subtype classification.

Besides, further research is required to better understand the relationship between AD and other medical and psychiatric conditions, such as anxiety disorders, chronic fatigue syndrome, and fibromyalgia. This may lead to improved diagnostic criteria and more effective treatment approaches for children with overlapping symptoms.

Finally, longitudinal studies are crucial to better understand the natural history of AD in children and to identify factors that may contribute to the persistence or remission of symptoms over time. Such research can help in the development of early intervention strategies and prevention programs.

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BIBLIOGRAPHY

1. Appenzeller O, Lamotte GJ, Coon EA. Introduction to Clinical Aspects of the Autonomic Nervous System. Volume 2. Sixth Edition. *Elsevier.* 2022. 548 p. https://doi.org/10.1016/C2021-0-02501-3.
2. Goldberger JJ, Arora R, Buckley U, Shivkumar K. Autonomic Nervous System Dysfunction: JACC Focus Seminar. *J Am Coll Cardiol.* 2019; 73(10): 1189– 1206. https://doi.org/10.1016/j.jacc.2018.12.064.
3. Hovaguimian A. Dysautonomia: Diagnosis and Management. *Neurol Clin.* 2023; 41(1): 193–213. https://doi.org/10.1016/j.ncl.2022.08.002.
4. Doering S, Halldner L, Larsson H et al. Childhood-onset versus adolescent-onset anxiety and depression: Epidemiological and neurodevelopmental aspects. *Psychiatry Res.* 2022; 312: 114556. https://doi.org/10.1016/j.psychres.2022.114556.
5. Pediatric Writing Group of the American Autonomic Society. Pediatric disorders of orthostatic intolerance. *Pediatrics.* 2018; 141(1): e20171673. https://doi.org/10.1542/peds.2017-1673.
6. Wagoner AL, Olson JD, Westwood BM, Fortunato JE, Diz DI, Shaltout HA. Children with orthostatic intolerance exhibit elevated markers of inflammation in the dorsal medulla. *Am J Physiol Heart Circ Physiol.* 2019; 317(2): H323–H329. https://doi.org/10.1152/ajpheart.00680.2018.
7. Carnac T. Schizophrenia hypothesis: Autonomic Nervous System Dysregulation of Fetal and Adult Immune Tolerance. *Front Syst Neurosci.* 2022; 16: 844383. https://doi.org/10.3389/fnsys.2022.844383.
8. Dearing C, Handa RJ, Myers B. Sex differences in autonomic responses to stress: implications for cardiometabolic physiology. *Am J Physiol Endocrinol Metab.* 2022; 323(3): E281–E289. https://doi.org/10.1152/ajpendo.00058.2022.
9. Fedorowski A, Olsén MF, Nikesjö F, Janson C, Bruchfeld J, Lerm M, Hedman K. Cardiorespiratory dysautonomia in post-COVID-19 condition: Manifestations, mechanisms and management. *J Intern Med.* 2023; 294(5): 548–562. https://doi.org/10.1111/joim.13652.
10. Kolacz J, Kovacic K, Dang L, Li Buk, Lewis GF, Porges SW. Cardiac Vagal Regulation Is Impeded in Children With Cyclic Vomiting Syndrome. *Am J Gastroenterol.* 2023; 118(7): 1268–1275. https://doi.org/10.14309/ajg.0000000000002207.
11. Alameda Cuesta A, Pazos Garciandía Á, Oter Quintana C, Losa Iglesias ME. Fibromyalgia, Chronic Fatigue Syndrome, and Multiple Chemical Sensitivity: Illness Experiences. *Clin Nurs Res.* 2021; 30(1): 32–41. https://doi.org/10.1177/1054773819838679.
12. Firth AM, Ask TF, Sütterlin S, Lugo RG. The Effect of Heart Rate Variability Biofeedback Training on Vagal Tone in Athletically Talented Secondary School Students. *Sports (Basel).* 2022; 10(10): 146. https://doi.org/10.3390/sports10100146.
13. Lehrer PM, Gevirtz R. Heart rate variability biofeedback: How and why does it work? *Front Psychol.* 2014; 5: 756. https://doi.org/10.3389/fpsyg.2014.00756.
14. Herring N. Autonomic control of the heart: going beyond the classical neurotransmitters. *Exp Physiol.* 2015; 100(4): 354–358. https://doi.org/10.1113/expphysiol.2014.080184.
15. Polito R, Valenzano A, Monda V, et al. Heart Rate Variability and Sympathetic Activity Is Modulated by Very Low-Calorie Ketogenic Diet. *Int J Environ Res Public Health.* 2022; 19(4): 2253. https://doi. org/10.3390/ijerph19042253.
16. Cavanagh L, Obasi EM. Chronic stress, autonomic dysregulation and prospective drug use among African American emerging adults. *Cultur Divers Ethnic Minor Psychol.* 2022; 28(1): 91–102. https://doi.org/10.1037/cdp0000364.
17. Wass SV, Smith CG, Daubney KR, et al. Influences of environmental stressors on autonomic function in 12-month-old infants: understanding early common pathways to atypical emotion regulation and cognitive performance. *J Child Psychol Psychiatry.* 2019; 60(12): 1323–1333. https://doi.org/10.1111/jcpp.13084.
18. Yeater TD, Cruz CJ, Cruz-Almeida Y, Allen KD. Autonomic Nervous System Dysregulation and Osteoarthritis Pain: Mechanisms, Measurement, and Future Outlook. *Curr Rheumatol Rep.* 2022; 24(6): 175–183. https://doi.org/10.1007/s11926-022-01071-9.
19. D'Agnano D, Cernigliaro F, Ferretti A et al. The Role of the Autonomic Nervous System in Epilepsy and Migraine: A Narrative Review. *J Integr Neurosci.* 2024; 23(7): 128. https://doi.org/10.31083/j.jin2307128.
20. Apolinário-Hagen J, Drüge M, Fritsche L. Cognitive Behavioral Therapy, Mindfulness-Based Cognitive Therapy and Acceptance Commitment Therapy for Anxiety Disorders: Integrating Traditional with Digital Treatment Approaches. *Adv Exp Med Biol.* 2020; 1191: 291–329. https://doi.org/10.1007/978-981-32-9705-0_17.
21. Biondi M, Valentini M. Relaxation treatments and biofeedback for anxiety and somatic stress-related disorders. *Riv Psichiatr.* 2014; 49(5): 217–26. (in Italian). https://doi.org/10.1708/1668.18262.
22. Chen B, Yang W, Luo Y, Tan EK, Wang Q. Non-pharmacological and drug treatment of autonomic dysfunction in multiple system atrophy: current status and future directions. *J Neurol.* 2023; 270(11): 5251–5273. https://doi.org/10.1007/s00415-023-11876-y.

23. Daniela M, Catalina L, Ilie O, Paula M, Daniel-Andrei I, Ioana B. Effects of Exercise Training on the Autonomic Nervous System with a Focus on Anti-Inflammatory and Antioxidants Effects. *Antioxidants (Basel).* 2022; 11(2): 350. https://doi.org/10.3390/antiox11020350.
24. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ.* 2021; 372: n71. https://doi.org/10.1136/bmj.n71.
25. Matušková L, Javorka M. Adrenergic receptors gene polymorphisms and autonomic nervous control of heart and vascular tone. *Physiol Res.* 2021; 70(Suppl4): S495–S510. https://doi.org/10.33549/physiolres.934799.
26. Kox M, van Eijk LT, Zwaag J et al. Voluntary activation of the sympathetic nervous system and attenuation of the innate immune response in humans. *Proc Natl Acad Sci USA.* 2014; 111(20): 7379–84. https://doi.org/10.1073/pnas.1322174111.
27. Shetty SS, Deepthi D, Harshitha S et al. Environmental pollutants and their effects on human health. *Heliyon.* 2023; 9(9): e19496. https://doi.org/10.1016/j.heliyon.2023.e19496.
28. Vitulano LA, Mitchell JT, Vitulano ML, et al. Parental perspectives on attention-deficit/hyperactivity disorder treatments for children. *Clin Child Psychol Psychiatry.* 2022; 27(4): 1019–1032. https://doi.org/10.1177/13591045221108836.
29. Cordani R, Tobaldini E, Rodrigues GD et al. Cardiac autonomic control in Rett syndrome: Insights from heart rate variability analysis. *Front Neurosci.* 2023; 17: 1048278. https://doi.org/10.3389/fnins.2023.1048278.
30. Wafi AM. Nrf2 and autonomic dysregulation in chronic heart failure and hypertension. *Front Physiol.* 2023; 14: 1206527. https://doi.org/10.3389/fphys.2023.1206527.
31. Mueller B, Figueroa A, Robinson-Papp J. Structural and functional connections between the autonomic nervous system, hypothalamic-pituitary-adrenal axis, and the immune system: a context and time dependent stress response network. *Neurol Sci.* 2022; 43(2): 951–960. https://doi.org/10.1007/s10072-021-05810-1.
32. Giunta S, Xia S, Pelliccioni G, Olivieri F. Autonomic nervous system imbalance during aging contributes to impair endogenous anti-inflammaging strategies. *Geroscience.* 2024; 46(1): 113–127. https://doi.org/10.1007/s11357-023-00947-7.
33. Monnens L. The cause of eyelid ptosis, orthostatic hypotension and exercise intolerance. *Acta Paediatr.* 2022; 111(6): 1134–1136. https://doi.org/10.1111/apa.16312.
34. Madrid M, Bojalil R, Brianza-Padilla M, Zapoteco-Nava J, Márquez-Velasco R, Rivera-González R. The molecular profile of the inflammatory process differs among various neurodevelopmental disorders with or without cognitive component: A hypothesis of persistent systemic dysfunction and hyper-resolution. *Front Pediatr.* 2023; 11: 1132175. https://doi.org/10.3389/fped.2023.1132175.
35. Wang X, Guo Z, Yan F. RNA Epigenetics in Chronic Lung Diseases. *Genes (Basel).* 2022; 13(12): 2381. https://doi.org/10.3390/genes13122381.
36. Jammoul M, Naddour J, Madi A et al. Investigating the possible mechanisms of autonomic dysfunction post-COVID-19. *Auton Neurosci.* 2023; 245: 103071. https://doi.org/10.1016/j.autneu.2022.103071.
37. Naseri A, Sadigh-Eteghad S, Seyedi-Sahebari S, Hosseini MS, Hajebrahimi S, Salehi-Pourmehr H. Cognitive effects of individual anticholinergic drugs: asystematic review and meta-analysis. *Dement Neuropsychol.* 2023; 17: e20220053. https://doi.org/10.1590/1980-5764-dn-2022-0053.
38. Nagamitsu S, Kanie A, Sakashita K et al. Adolescent Health Promotion Interventions Using Well-Care Visits and a Smartphone Cognitive Behavioral Therapy App: Randomized Controlled Trial. *JMIR Mhealth Uhealth.* 2022; 10(5): e34154. https://doi.org/10.2196/34154.
39. Attard A, Attard S, Stanniland C, et al. Management of Psychiatric Conditions in Patients With Comorbid Postural Orthostatic Tachycardia Syndrome: A Literature Review and Case Vignette. *Prim Care Companion CNS Disord.* 2023; 25(1): 22nr03243. https://doi.org/10.4088/pcc.22nr03243.
40. de Oliveira MCS, Távora-Mehta MZP, Mehta N et al. Distinct Hemodynamic Responses That Culminate With Postural Orthostatic Tachycardia Syndrome. *Am J Cardiol.* 2023; 197: 3–12. https://doi.org/10.1016/j.amjcard.2023.03.027.
41. Leach H, Eccles A, Chew-Graham CA, Atherton H. Patient experiences of remote consulting with chronic fatigue syndrome/myalgic encephalomyelitis and fibromyalgia: a qualitative study. *BJGP Open.* 2024: BJGPO.2024.0079. https://doi.org/10.3399/bjgpo.2024.0079.
42. Malhotra V, Javed D, Wakode S, Bharshankar R, Soni N, Porter PK. Study of immediate neurological and autonomic changes during kapalbhati pranayama in yoga practitioners. *J Family Med Prim Care.* 2022; 11(2): 720–727. https://doi.org/10.4103%2Fjfmpc.jfmpc_1662_21.
43. Torres RD, Rashed H, Mathur P, Castillo C, Abell T, Terson de Paleville DGL/ Autogenic biofeedback training improves autonomic responses in a participant with cervical motor complete spinal cord injury – case report. *Spinal Cord Ser Cases.* 2023; 9(1): 31. https://doi.org/10.1038/s41394-023-00593-3.
44. Echemendia RJ, Burma JS, Bruce JM et al. Acute evaluation of sport-related concussion and implications for the Sport Concussion Assessment Tool for adults, adolescents and children: a systematic review. *Br J Sports Med.* 2023; 57(11): 722–735. https://doi.org/10.1136/bjsports-2022-106661.
45. Fan S, Cui Y, Liao Y, Jin H. Predicting therapeutic efficacy of pharmacological treatments in children with postural orthostatic tachycardia syndrome: A Mini-Review. *Children (Basel).* 2023; 10(7): 1093. https://doi.org/10.3390/children10071093.
46. Wang S, Zou R, Cai H et al. Heart Rate and Heart Rate Difference Predicted the Efficacy of Metoprolol on Postural Tachycardia Syndrome in Children. *J Pediatr.* 2020; 224: 110–114. https://doi.org/10.1016/j.jpeds.2020.05.017.

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