

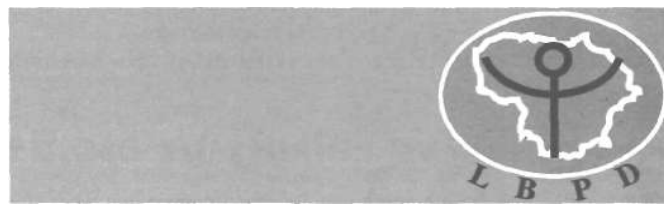
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VIRŠELYJE – Giedriaus (g. 1976 m.) grafikos darbas „Informacinis perdavimas“ 2013 m. (iš gydytojos psichiatrės Danguolės Survilaitės pacientų kūrybos „aukso fondo“). Giedrius – labai talentingas menininkas, jo darbai spalvingi, mistiški, pasižymi tik jam būdinga simbolika, paveiksluose dažnai piešiamos žmonių galvos, veidai, akys, žuvys. Tai pirmasis Giedriaus darbas mūsų žurnale. Trys Giedriaus darbai jau puošė „Psichiatrijos žinių“ viršelius

PUSLAPIS INTERNETE <http://biological-psychiatry.eu>

We are pleased to present the latest issue of the Journal of Biological Psychiatry and Psychopharmacology, featuring groundbreaking research and insightful reviews that advance our understanding of complex neuropsychiatric disorders and their treatment. This issue includes comprehensive literature reviews, detailed case reports, and an innovative diagnostic tool, all of which contribute to the ongoing dialogue in the fields of biological psychiatry and psychopharmacology.

Biomarkers for Suicidal Behavior

The first publication in this issue, authored by Karolina Laurinaitiene and Vesta Steibliene, titled “Biomarkers for Suicidal Behavior: A Narrative Literature Review,” addresses the urgent public health issue of suicidal behavior. This review meticulously analyzes 54 articles, shedding light on the intricate interplay of genetic, neurobiological, neuroendocrine, neurotrophic, inflammatory, metabolic, and neuroimaging markers that influence suicide risk. The authors emphasize the potential of biomarkers to enhance our understanding of the biological underpinnings of suicidal behavior, ultimately informing more effective prevention and intervention strategies. Their findings underscore the multifactorial nature of suicide and the need for integrated approaches to its study and treatment.

Transcranial Magnetic Stimulation in Parkinson’s Disease

Rokas Janciauskas and Edgaras Dirzius contribute a literature review on “Transcranial Magnetic Stimulation in the Treatment of Motor and Neuropsychiatric Symptoms of Parkinson’s Disease.” Parkinson’s disease, while primarily a motor disorder, frequently presents with neuropsychiatric symptoms such as mood disorders, cognitive impairment, and psychosis. This review assesses 56 publications from 2014 to 2024, highlighting the efficacy of transcranial magnetic stimulation (TMS) as a non-invasive treatment option. The authors present compelling evidence for the benefits of TMS on both motor and mood symptoms, with particular attention to protocols targeting the primary motor cortex and dorsolateral prefrontal cortex. This review advocates for TMS as a promising adjunctive treatment, offering new hope for improving patient outcomes.

Case Reports on Complex Psychiatric Conditions

This issue also features three intriguing case reports. The first, by Inga Ruzelyte and Vigintas Vilkas, explores the “Association Between Malignant Neoplastic Process and Atypical Psychotic Disorder.” This report presents a 53-year-old man with an atypical psychotic disorder, ultimately linked to a paraneoplastic neurological syndrome associated with renal carcinoma. This case underscores the importance of considering organic origins in atypical psychiatric presentations.

The second case report by Milda Dubininkiene, Darius Leskauskas, and Rasa Pakanaviciute discusses “The Psychiatric Consequences of Long-COVID in Adolescents.” This report highlights the prolonged mental health challenges faced by a 16-year-old girl post-SARS-CoV-2 infection, emphasizing the need for long-term follow-up and comprehensive care in pediatric long-COVID cases.

The third case report, authored by Milda Sakalauskiene and Darius Leskauskas, examines “Attentional Problems as the Makeup of Obsessive-Compulsive Disorder and Its Differential Diagnosis from ADHD.” This report details the diagnostic challenges and treatment considerations in distinguishing OCD from ADHD in an 18-year-old female patient, demonstrating the complexities of managing overlapping psychiatric conditions.

Innovative Diagnostic Tool: SDS-3 Scale

We are also excited to introduce a new diagnostic tool, the Short Version of the Sexual Distress Scale (SDS-3), translated and validated in Lithuanian language by Erikas Ankudavičius, Aurelija Podlipskytė, Vesta Steibliene, and Julius Burkauskas. The SDS-3 is a concise, reliable, and valid instrument for assessing sexual distress over the past 30 days, validated through a large international study involving 82,243 participants. This tool promises to enhance the quality of sexual health assessments in both research and clinical settings.

PhD Thesis: Advances in Idiopathic Normal Pressure Hydrocephalus

Finally, we present the PhD thesis of Mindaugas Urbonas, titled “Significance of Transorbital Ultrasound and Thyroid Hormones in Idiopathic Normal Pressure Hydrocephalus.” This study introduces transorbital ultrasound as a novel diagnostic method and explores the endocrine factors influencing postoperative outcomes. Urbonas’s research offers valuable insights into the prognostic value of thyroid hormones and the impact of ventricular volume changes on the quality of life in iNPH patients.

We hope that the articles in this issue will inspire further research and clinical advancements in the field of biological psychiatry and psychopharmacology. We are committed to providing a platform for innovative research and dialogue, and we look forward to your contributions and feedback.

Sincerely,

prof. Vesta Steibliene
Editor-in-Chief in the field of General Hospital Psychiatry
Journal of Biological Psychiatry and Psychopharmacology

Biomarkers for suicidal behavior: the narrative literature review

Savižudiško elgesio biožymenys: naratyvinė literatūros apžvalga

Karolina LAURINAITIENE, Vesta STEIBLIENE

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SUMMARY

Introduction. Suicidal behavior remains a complex and pressing public health concern worldwide, necessitating a deeper understanding of its underlying mechanisms to enhance prevention and intervention strategies. Biomarkers, measurable indicators of biological processes or states, offer promising avenues for elucidating the biological underpinnings of suicide risk.

Aim. To review the experience of clinical trials and the most relevant study data regarding the relationship between suicidal behavior and various biomarkers, aiming to emphasize the neurobiological basis of mental health conditions and monitor changes in biomarkers over the course of treatment to enhance patient treatment response.

Methods. Literature search was performed using research published in the PubMed, PsycINFO, and Google Scholar databases, that reviewed the suicidal behavior and relationship between genetic, neuroendocrine, neurobiological, neuroimaging, metabolic and inflammatory biomarkers.

Results. This literature review analyzed 54 articles which investigated the relationship between biomarkers and suicidal behavior. The results suggest that suicidal behavior is influenced by a complex interplay of genetic, neurobiological, neuroendocrine, neurotrophic, inflammatory, metabolic, and neuroimaging markers. Genetic predispositions, particularly involving serotonin-related genes, combined with dysregulations in neurotransmitter systems, hormone levels, and inflammatory processes, contribute to increased suicide risk. Structural brain changes associated with emotional regulation and decision-making further underscore the multifactorial nature of suicide.

Conclusion. The interplay between genetic, neurobiological, neuroendocrine, inflammatory, metabolic, and neuroimaging markers contributes to the understanding of suicidal behavior. Integrating these biomarkers enhances to understanding of suicide etiology and informs the development of more effective prevention and intervention strategies.

Keywords: Suicidal behavior, biomarkers, inflammation, neuroimaging, genes

SANTRAUKA

Įvadas. Savižudiškas elgesys visame pasaulyje išlieka sudėtinga ir opi visuomenės sveikatos problema, kuri reikalauja gilesnio supratimo apie savižudiško elgesio pagrindinius mechanizmus, siekiant gerinti prevencijos ir intervencijos strategijas. Biožymenys yra perspektyvūs rodikliai padedantys geriau suprasti savižudybės rizikos biologinius mechanizmus.

Tikslas. Apžvelgti klinikinių tyrimų patirtį ir aktualiausius tyrimų duomenis tarp savižudiško elgesio ir įvairių biožymenų, siekiant pabrėžti psichikos sutrikimų neurobiologinį pagrindą ir stebėti biožymenų pokyčius gydymo eigoje, siekiant pagerinti paciento atsaką į gydymą.

Metodai. Literatūros paieška buvo atlikta naudojant PubMed, PsycINFO ir Google Scholar duomenų bazėse paskelbtus tyrimus, kurie apžvelgė savižudišką elgesį ir ryšį tarp genetinių, neuroendokrinių, neurobiologinių, neurovaizdinių, metabolinių ir uždegiminių biožymenų.

Rezultatai. Šioje literatūros apžvalgoje buvo analizuojami 54 straipsniai, kuriuose buvo tiriama ryšys tarp biožymenų ir savižudiško elgesio. Rezultatai rodo, kad savižudišką elgesį įtakoja sudėtinga genetinių, neurobiologinių, neuroendokrinių, neurotrofinių, uždegiminių, metabolinių ir neurovaizdinių žymenų sąveika. Genetinis polinkis, ypač susijęs su serotoninu susijusiais genais, kartu su neurotransmiterių sistemų, hormonų lygio ir uždegiminių procesų reguliavimo sutrikimais, padidina savižudybių riziką. Struktūriniai smegenų pokyčiai, susiję su emocijų reguliavimu ir sprendimų priėmimu, dar labiau pabrėžia daugiafaktorinį savižudybės pobūdį.

Išvada. Genetinių, neurobiologinių, neuroendokrinių, uždegiminių, metabolinių ir neurovaizdinių žymenų sąveika prisideda prie supratimo apie savižudišką elgesį. Šių biologinių žymenų integravimas pagerina supratimą apie savižudybių etiologiją ir padeda kurti veiksmingesnes prevencijos ir intervencijos strategijas.

Raktiniai žodžiai: Savižudiškas elgesys, biožymenys, uždegimas, neurovaizdiniai tyrimai, genai

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INTRODUCTION

Suicide affects people of all ages, genders, and backgrounds. According to World Health Organization (WHO), more than 700 000 people die by suicide every year globally [1]. According to the data of the Lithuanian Institute of Hygiene, 562 suicides were registered in Lithuania in 2023 [2]. Suicide is a complex phenomenon influenced by a combination of genetic, environmental, and psychological factors. While there is evidence suggesting that biological factors may play a role in suicide risk, it's crucial to emphasize that suicide is a multifaceted issue with no single cause. Biological factors often interact with other dimensions to contribute to an individual's vulnerability. These factors undoubtedly contribute to the complex interplay of variables influencing suicide risk. Understanding the specific molecular, genetic, or neurobiological factors associated with suicidal thoughts and behaviors contributes to a more comprehensive understanding of the phenomenon. Understanding how suicide depends on biomarkers is instrumental in advancing suicide prevention strategies, providing more accurate risk assessments, and fostering the development of targeted interventions.

Research on suicide biomarkers involves exploring various biological, genetic, neurobiological, and psychosocial factors. Numerous biomarkers have been investigated, but it's important to note that the field is complex, and no single biomarker can definitively predict suicide risk. Instead, a combination of factors is typically considered for a more comprehensive assessment. The most important categories of biomarkers that have been examined in the context of suicide.

Methods

This literature review was performed using search criteria on keywords in research published at PubMed, PsycINFO, and Google Scholar. The keywords were "suicidal behavior", "biomarkers", "inflammation", "neuroimaging" and "genes". The search was carried out in December 2023 and included studies published up to 2023 to ensure the inclusion of the most recent research findings. Studies were included if they investigated the association between biomarkers (genetic, neurobiological, neuroendocrine, inflammatory, metabolic, or neuroimaging) and suicidal behavior. Only peer-reviewed articles written in English were considered for inclusion. Studies focusing on animal models, non-human subjects, or non-suicidal outcomes were excluded. In the end 54 articles were used for this review.

RESULTS

Genetic biomarkers

Numerous studies have suggested a genetic component in suicidal behavior, indicating that individuals with a family history of suicide or mental health disorders may be at a higher risk [3, 4]. The heritability of suicidal behavior is estimated to be around 30–50%, as reported by various twin, family, and adoption studies [5–7]. One of the key genetic factors associated with suicide risk is a family history of mental health disorders, particularly mood disorders like depression and bipolar disorder [8]. Mann, Brent and others researchers has identified specific genetic markers and variations associated

with an increased susceptibility to these disorders, which in turn may contribute to a higher risk of suicidal behavior [9, 10].

Genes also play a role in regulating the levels and functioning of neurotransmitters, which are chemicals that transmit signals in the brain. Serotonin, in particular, is a neurotransmitter associated with mood regulation, and variations in genes related to serotonin function may contribute to suicide risk. The serotonin transporter gene (5-HTT) and the tryptophan hydroxylase gene (TPH) are two key genetic components that have been studied in the context of suicide risk and mental health disorders. Understanding the genetic basis of suicide risk, including the role of genes like 5-HTT and TPH, is an ongoing area of research. Both genes are involved in the regulation of serotonin, a neurotransmitter that plays a crucial role in mood regulation, emotion, and behavior [11, 12].

The serotonin transporter gene, also known as SLC6A4, codes for the serotonin transporter protein responsible for reabsorbing serotonin from the synaptic cleft, terminating its action in the synaptic cleft and recycling it for future use. The 5-HTT gene has a common polymorphism known as the serotonin transporter-linked polymorphic region (5-HTTLPR), which has two main variants: the long (L) allele and the short (S) allele. Individuals with the short allele may have reduced serotonin reuptake efficiency. Caspi et al., has associated the short allele of 5-HTTLPR with an increased risk of developing mood disorders, including depression, and a higher susceptibility to suicidal behaviors [13, 14]. The interplay between the 5-HTT gene and environmental factors, such as stress and trauma, is crucial in understanding how genetic predispositions contribute to suicide risk. The interaction between the short allele and environmental stressors has been implicated in an elevated risk of suicidal ideation and attempts [13, 15].

Tryptophan hydroxylase (TPH) is an enzyme involved in the synthesis of serotonin. The TPH gene, particularly the TPH1 and TPH2 isoforms, codes for this enzyme. Variations in the TPH gene have been associated with altered serotonin levels and have been investigated in the context of mood disorders and suicidal behavior. Studies have explored the role of TPH polymorphisms in suicide risk, with some findings suggesting an association between certain genetic variants and an increased susceptibility to suicidal thoughts and behaviors [16, 17].

Neurobiological markers

Research on the link between suicide and neurobiological markers has been a growing area of interest, and several studies have explored various aspects of the neurobiology of suicide. The serotonin system is a key component of the neurobiological mechanisms implicated in suicide behavior. Serotonin, also known as 5-hydroxytryptamine (5-HT), is a neurotransmitter that plays a crucial role in regulating mood, emotion, impulsivity, and aggression. Dysregulation of the serotonin system has been consistently associated with an increased risk of suicidal behavior. Serotonin is involved in the modulation of mood, and alterations in serotonin levels have been linked to mood disorders such as depression.

Reduced serotonin availability in the synaptic cleft has been associated with dysregulated mood states and an increased vulnerability to suicidal ideation. [18]. Post-mortem studies of the brains of individuals who died by suicide have shown alterations in serotonin receptor density and distribution [19]. Changes in serotonin receptor subtypes, such as the 5-HT1A and 5-HT2A receptors, have been reported in specific brain regions associated with mood regulation and impulsivity [20, 21, 22].

Neuroendocrine biomarkers

The relationship between the neuroendocrine system and suicide is complex, involving intricate interactions between hormones, stress response pathways, and neurotransmitter systems. The neuroendocrine system, which includes the hypothalamus, pituitary gland, and adrenal glands (HPA axis), plays a crucial role in regulating various physiological processes and responding to stressors. It regulates the secretion of cortisol, the primary stress hormone. Chronic activation of the HPA axis, leading to elevated cortisol levels, has been observed in individuals with mood disorders and those at risk for suicide [23, 24]. Corticotropin-Releasing Hormone (CRH) and vasopressin, released by the hypothalamus, are also involved in the regulation of the stress response. Alterations in the release of these hormones have been implicated in mood disorders and suicidal behavior [25, 26]. Thyroid hormones, including triiodothyronine (T3) and thyroxine (T4), play a role in regulating metabolism and energy balance. Alterations in thyroid function have been associated with mood disorders and may contribute to suicidal ideation [27]. Oxytocin is a neuropeptide that plays a crucial role in social bonding, emotional regulation, and stress modulation. It is released during positive social interactions, such as hugging or bonding between individuals. While oxytocin is often associated with positive social behaviors, recent research has explored its potential involvement in the neurobiology of suicide [28]. Oxytocin has been shown to modulate the stress response and may have anxiolytic (anxiety-reducing) effects. Dysregulation of the stress response is implicated in mood disorders and suicidal behavior [29]. Variations in the oxytocin receptor gene (OXTR) have been studied in relation to psychiatric conditions, including mood disorders and suicidal behavior. Polymorphisms in OXTR may influence individual differences in oxytocin receptor sensitivity, potentially impacting social behavior and emotional regulation [30]. Oxytocin administration has been explored as a potential treatment for improving maternal mental health during the perinatal period [31].

It's very important to mention sex hormones, including testosterone and estrogen, which can influence mood and behavior. Testosterone is the primary male sex hormone, and its role in aggression and mood regulation has been studied in the context of suicide. Some studies have suggested a potential association between low testosterone levels and an increased risk of suicide in men [32]. Estrogen, the primary female sex hormone, has neuroprotective and mood-stabilizing effects. Some studies have suggested a potential protective role of estrogen against suicidal behavior, particularly in women. Estrogen has been implicated in regulating serotonin and other

neurotransmitter systems, which may contribute to its impact on mood and suicidal behavior [33]. Transitions involving hormonal fluctuations, such as puberty, postpartum, and menopause, may be associated with changes in mood and an increased vulnerability to mental health disorders, including suicidal behavior [34].

Neurotrophic Factor Biomarkers

Neurotrophic factors are proteins that play a crucial role in the development, survival, and function of neurons. Altered levels of neurotrophic factors have been implicated to suicidal behavior. Brain-derived neurotrophic factor (BDNF), a protein that supports the survival and growth of neurons, has been studied in relation to suicide. Reduced BDNF levels have been reported in post-mortem studies of the brains of individuals who died by suicide [35]. Nerve Growth Factor (NGF) is another important neurotrophic factor involved in the growth, differentiation, and survival of neurons. It is involved in various processes, including synaptic plasticity and neuronal maintenance. Changes in NGF levels have been implicated in mood disorders, and some studies suggest a potential link to suicidal behavior [36, 37]. Insulin-Like Growth Factor (IGF), which shares structural similarities with insulin, is involved in cell growth and differentiation, including in the central nervous system. IGF is involved in neuroplasticity, which refers to the brain's ability to reorganize itself and form new connections. Dysregulation in neuroplasticity is often observed in mood disorders and conditions linked to suicidal behavior [38, 39]. Transforming Growth Factor-Beta (TGF- β) is involved in various cellular processes, including cell growth and differentiation. Changes in TGF- β signaling have been implicated in mood disorders, and its role in suicidal behavior is an area of ongoing investigation [40]. It's essential to note that the relationship between neurotrophic factors and suicide is complex, and alterations in their levels may be influenced by various factors, including genetics, environmental stressors, and comorbid psychiatric conditions.

Inflammatory biomarkers

There was identified alterations in inflammatory markers in individuals who have attempted or died by suicide. Some studies suggest that elevated levels of certain cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), may be associated with an increased risk of suicidal behavior. Additionally, alterations in the levels of other immune system-related molecules, including C-reactive protein (CRP) and certain inflammatory signaling pathways, have been observed in individuals with suicidal tendencies. Elevated levels of inflammatory markers, such as CRP, have been observed in individuals at risk for suicide [41]. Interleukin-6 (IL-6), a key pro-inflammatory cytokine, has been associated with suicidal behavior [42]. Elevated levels of Tumor Necrosis Factor-Alpha (TNF- α) are often associated with inflammatory dysregulation, which has been observed in individuals with psychiatric conditions linked to suicide risk [43]. TNF- α is implicated in the activation of microglia, the immune cells in the brain, contributing to neuroinflammatory processes that may impact mood and behavior [44]. Dysregulation of TNF- α is associated with alterations in the

stress response, including the hypothalamic-pituitary-adrenal (HPA) axis, which is relevant to mood disorders and suicide risk [45]. Dysregulation of Interferon-Gamma (IFN- γ), an immune regulatory cytokine, has been associated with suicidal ideation [46].

Metabolic biomarkers

The association between dysregulation of lipid metabolism and suicide is an area of research that explores how disruptions in lipid balance may contribute to the risk of suicidal behavior. Lipid metabolism involves the synthesis, storage, and breakdown of lipids, which play crucial roles in various physiological processes, including the structure of cell membranes and signaling pathways. Lipid peroxidation can result in the production of reactive aldehydes, such as malondialdehyde (MDA), which serve as biomarkers of oxidative stress. Increased lipid peroxidation has been associated with suicidal behavior [47, 48].

Neuroimaging markers

Neuroimaging studies have provided valuable insights into the neural mechanisms underlying suicidal behavior. Various brain regions and functional connectivity patterns have been implicated in individuals with a history of suicidal thoughts or attempts. Some data suggests that structural alterations in specific brain regions, particularly those involved in emotion regulation, decision-making, and impulse control, may contribute to the neurobiological basis of suicide. Alterations in the prefrontal cortex, amygdala, and hippocampus have been reported in suicide-related neuroimaging studies [49, 50]. The prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC), is implicated in decision-making, impulse control, and emotional regulation. Structural abnormalities in the prefrontal cortex (PFC) have been associated with suicide risk [51]. A key region for emotional processing is amygdala. Changes in amygdala structure, such as alterations in volume or connectivity, have been linked to suicidal behaviors and emotional dysregulation [52]. The hippocampus, involved in memory and emotion regulation, may show structural changes in individuals with suicidal thoughts or behaviors. Reduced hippocampal volume has been reported in some studies [53]. The Anterior Cingulate Cortex (ACC) plays a role in emotional regulation and decision-making. Alterations in ACC structure have been associated with suicidal ideation and impulsive behavior [54]. The Orbitofrontal Cortex (OFC) is involved in reward processing and decision-making. Structural changes in the OFC have been linked to impaired decision-making and increased suicide risk [55].

DISCUSSION

Suicide risk involves intricate interactions among genetic, neurobiological, hormonal and environmental factors. Family history of suicide or mental health disorders indicates a higher risk of suicidal behavior. Also, specific genetic markers and variations, particularly those related to serotonin regulation, contribute to suicide risk. Polymorphisms in genes like 5-HTT and TPH are associated with altered serotonin function and increased susceptibility to mood disorders and suicidal behaviors. Dysregulation of the serotonin system, including altered serotonin levels and receptor distribution, is consistently linked to an increased risk of suicidal behavior. Post-mortem studies reveal alterations in serotonin receptor density in individuals who died by suicide. Neuroimaging studies show structural changes in brain regions involved in emotion regulation, decision-making, and impulse control in individuals with suicidal thoughts or attempts. These findings highlight the complex interplay between genetic predispositions, neurotransmitter dysregulation, and neurobiological abnormalities in the manifestation of suicidal behavior. Understanding these biomarkers is crucial for developing effective strategies for suicide risk assessment, prevention, and intervention.

CONCLUSION

Biomarkers may serve as early indicators of suicidal tendencies before overt symptoms manifest. Early identification through biomarkers allows for timely intervention, potentially preventing the escalation of suicidal thoughts into attempts. Biomarkers can aid in the development of personalized treatment approaches. Understanding an individual's unique biological profile may lead to targeted therapeutic interventions, enhancing the effectiveness of treatments for individuals at risk of suicide. Also biomarkers provide objective measures that complement traditional subjective assessments for mental health professionals. Monitoring changes in biomarkers over the course of treatment can provide insights into treatment response. Biological markers help emphasize the neurobiological basis of mental health conditions, potentially reducing the stigma associated with mental health issues. This shift in perception can contribute to more empathetic and informed societal attitudes toward suicide. Suicide prevention and understanding require a comprehensive approach that addresses the multifaceted nature of this public health concern.

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Transcranial magnetic stimulation in the treatment of motor and neuropsychiatric symptoms of Parkinson's disease: a literature review

Transkranijinės magnetinės stimuliacijos panaudojimas gydant motorinius ir neuropsichiatrinčius Parkinsono ligos simptomus: literatūros apžvalga

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SUMMARY

Introduction. Parkinson's disease is primarily a motor disorder, but oftentimes causes neuropsychiatric symptoms to emerge. Patients have an increased risk of mood disorders, cognitive impairment and dementia, as well as impaired sleep and psychosis. Because the effectiveness of treatment with medications is reduced with prolonged use, supplemental treatment options are required. As a result, transcranial magnetic stimulation has emerged as a potential non-invasive treatment option due to its facilitatory or depressive effects on cortical and subcortical activity.

Aim. To assess the newest scientific literature on the efficacy of transcranial magnetic stimulation in treating motor and neuropsychiatric symptoms of Parkinson's disease.

Methodology. Literature search was performed using the "Pubmed" database. The following keywords and their combinations were used: "Parkinson's disease", "motor symptoms", "non-motor symptoms", "depression", "anxiety", "cognitive impairment", "dementia", "TMS", "treatment". 56 full-text publications written in the English language were reviewed. The time period selected was 2014-2024. Descriptive analysis was performed for the literature review.

Results. Transcranial magnetic stimulation has been shown to improve both motor and neuropsychiatric symptoms in Parkinson's disease patients. The most robust evidence is for treating motor symptoms by targeting either the primary motor cortex, or in conjunction with the prefrontal cortex using a high frequency protocol, the latter protocol also contributing to improvements in mood. Additionally, improvements in mood and less so cognitive impairment were observed after targeting the dorsolateral prefrontal cortex. The therapeutic effect is transient and dependent on the amount and frequency of sessions, and needs to be maintained with supplemental use.

Conclusions. Parkinson's disease is a complex disorder which may cause both motor and neuropsychiatric symptoms, requiring a multimodal approach for its treatment. One treatment modality of emerging interest is transcranial magnetic stimulation, which is promising for improvement of motor, mood and cognitive symptoms.

Keywords: Transcranial magnetic stimulation, Parkinson's disease treatment

SANTRAUKA

Įvadas. Parkinsono liga - motorinis sutrikimas, tačiau dažnai sukelia ir neuropsichiatrinčius simptomus. Pacientai turi didesnę nuotaikos, kognityvinių, miego sutrikimų, demencijos bei psichozės riziką. Kadangi vaistų veiksmingumas gydant šią ligą mažėja po ilgalaikio jų vartojimo, svarbus papildomas gydymas. To pasekoje daug dėmesio skirta neinvazinei transkranijinei magnetinei stimuliacijai dėl jos efekto slopinant arba skatinant smegenų žievės ir požieivio jaudrumą.

Tikslas. Apžvelgti naujausią literatūrą, aprašančią transkranijinės magnetinės stimuliacijos veiksmingumą gydant motorinius ir neuropsichiatrinčius simptomus sergant Parkinsono liga.

Metodai. Literatūros apžvalga atlikta naudojant duomenų bazę „PubMed“. Buvo naudoti šie raktažodžiai ir jų kombinacijos: „Parkinson's disease“, „motor symptoms“, „non-motor symptoms“, „depression“, „anxiety“, „cognitive impairment“, „dementia“, „TMS“, „treatment“. Apžvelgtos 56 visatekstės publikacijos anglų kalba, spausdintos 2014-2024 metais. Literatūros apžvalgai naudota aprašomoji analizė.

Rezultatai. Transkranijinė magnetinė stimuliacija buvo veiksminga palengvinant tiek motorinius, tiek neuropsichiatrinčius Parkinsono ligos simptomus. Stipriausi įrodymai gydant motorinius simptomus buvo stimuliuojant arba pirminę motorinę žievę, arba kartu stimuliuojant priešaktinę žievę naudojant aukšto dažnio protokolą, kuris stimuliuojant abi smegenų sritis taip pat prisidėjo prie nuotaikos pagerėjimo. Tuo tarpu užpakalinės šoninės priešaktinės žievės stimuliacija prisidėjo prie nuotaikos ir kiek mažiau kognityvinių sutrikimų gerinimo. Vis dėlto terapinis efektas praeinantis ir priklausomas nuo sesijų kiekio bei dažnio, o papildomos sesijos reikalingos efektui išlaikyti.

Išvados. Parkinsono liga – kompleksinis sutrikimas, sukeliantis tiek motorinius, tiek neuropsichiatrinčius simptomus, kurių palengvinimui reikalingas daugiaveiksnis gydymas. Vienas iš pasirinkimų – transkranijinė magnetinė stimuliacija, kurios potencialiam efektui tirti gydant motorinius, nuotaikos bei kognityvinius simptomus sergant Parkinsono liga skiriama vis daugiau dėmesio.

Raktažodžiai: Transkranijinė magnetinė stimuliacija, Parkinsono ligos gydymas

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INTRODUCTION

Transcranial magnetic stimulation (TMS) is a method of safe and non-invasive brain stimulation via electromagnetic induction, which works in modulating cortical and subcortical activity and their resulting effects by discharging an electrical current into a TMS coil, producing a brief perpendicular magnetic pulse to a certain depth from the surface of the scalp, which leads to axonal depolarization [1–3].

Three basic types of TMS exist: single pulse (sTMS), discharging a single pulse every few seconds; paired-pulse (ppTMS), discharging two paired pulses with either identical or different intensities every few milliseconds; and repetitive TMS (rTMS), delivering a combination of more than two pulses every interval of less or equal to two seconds [3].

An increasing amount of data has shown TMS to be promising in both the diagnosis and treatment of various adult neurological and psychiatric conditions, with rTMS being the predominant type used in their treatment, due to its effects on neuronal plasticity and potentiating synaptic transmission in treated patients, currently is approved for treatment of obsessive-compulsive disorder, smoking cessation and major depressive disorder, with a response rate of 40-60% in the latter [2, 4, 5].

The most common complications reported have included headaches (6.9%) and discomfort at the stimulation site (2.7%), the most common serious complication of this treatment method being seizures, with a risk of around 0.01% per session, however, the risk increases substantially in patients with epilepsy, increasing to about 3% per session [6, 7].

An important topic of emerging research is TMS use as an adjunctive treatment in Parkinson's disease (PD), a progressive neurodegenerative disorder mostly presenting later in life that is caused by the accumulation of alpha-synuclein (Lewy bodies) in the neuronal bodies of various parts of the brain, predominantly substantia nigra, causing its degeneration and leading to a loss of dopamine in the basal ganglia, which control muscle tone and movement [3, 8].

The disease affects 0.1–0.2% of the population, with prevalence increasing to 1% in people above 60 years of age [8]. A core feature of the disease is parkinsonism, a group of disorders characterized by movement problems, including bradykinesia, rigidity, and tremor [9]. However, non-motor manifestations are also characteristic of the disease, affecting up to 99.7% of patients and can be either somatic, such as pain, gastrointestinal and olfactory dysfunction, urinary incontinence and orthostatic hypotension, or neuropsychiatric, such as cognitive impairment, sleep, mood disorders, dementia and psychosis. [10–12].

Currently, no specific laboratory or imaging tests exist to confirm the diagnosis of PD, and the disease is diagnosed clinically, by looking for characteristic symptoms and excluding other causes of Parkinsonism, such as medications, essential tremor, progressive supranuclear palsy, Lewy body dementia, multisystem atrophy, hydrocephalus or subcortical stroke [8].

Treatment of motor symptoms usually consists of dopamine replacement therapy using either levodopa, combined with carbidopa or benserazide, which are most effective at

providing symptom relief, or dopamine agonists, which have lesser efficacy but also fewer side effects; other medications based on symptoms, such as apomorphine or anticholinergics, and physiotherapy playing an important supplemental role [8, 9, 12–14]. Treatment of non-motor symptoms mirrors their treatment in the general population, but may be affected by adverse reactions from both motor and non-motor symptom management – for example – dopaminergic, anticholinergic medications, amantadine may contribute to psychosis, dopamine agonists may cause impulse control disorders, benzodiazepines may worsen cognitive function. In addition, there is a lack of evidence in terms of treatment of certain neuropsychiatric symptoms, such as anxiety or mild cognitive impairment [9].

Given these challenges as well as the limited efficacy of standard treatment, which provides effective symptom relief for only 3–6 years on average while causing uncomfortable side effects, it's extremely important to look for supplemental treatment options where possible to improve the patient's quality of life and extend the symptom-free period [8, 12].

This article will assess the newest scientific literature on the efficacy of transcranial magnetic stimulation in the treatment of motor and neuropsychiatric symptoms of Parkinson's disease.

METHODS

Literature search was performed using the "Pubmed" database. The following keywords and their combinations were used: "Parkinson's disease", "motor symptoms", "non-motor symptoms", "depression", "anxiety", "cognitive impairment", "dementia", "TMS", "treatment". 56 publications written in the English language were reviewed. The time period selected was 2014-2024. Descriptive analysis was performed for the literature review.

PD TREATMENT AND TMS

As PD is primarily a movement disorder, motor manifestations are a fundamental part of its progression, with resting tremor often marking its onset, and the other cardinal symptoms being bradykinesia, rigidity and postural instability [8,12]. Current treatment modalities for motor symptoms include dopamine replacement therapy in the early stages of disease, usually using levodopa in combination with carbidopa or benserazide, the latter preventing conversion of levodopa to dopamine in peripheral tissues, with dopamine agonists also being frequently used to stabilize the on-off periods that are experienced after prolonged use of the aforementioned treatment [12, 14]. Additionally, monoamine oxidase B inhibitor, such as selegiline or a catechol-O-methyl transferase inhibitor may be added to increase the half-life of levodopa, thus increasing the time it may remain in the central nervous system [12]. For up to 40% of patients who suffer the levodopa-induced side effect of dyskinesia (LID), or have a pronounced tremor, amantadine has been shown to be a useful option, additionally providing relief for most motor symptoms [12, 15]. For late-stage patients who don't respond to medications, invasive deep brain stimulation is available to stabilize the balance of excitatory and inhibitory signals, usually to either the subthalamic nucleus (STN) or globus pallidus [8, 16].

However, in addition to being expensive and laborious, as well as requiring strict selection criteria, this treatment usually only helps with tremor and rigidity, generally doesn't improve and may even cause or worsen neuropsychiatric symptoms, such as thought, mood and anxiety disorders, apathy, hypomania, and the patients continue to suffer from speech and swallowing impairments [16–18]. That is why some studies have emerged using TMS to stimulate cortical regions, with rTMS being the most appropriate protocol due to its longer-lasting effects in changing the amplitude of motor evoked potentials (MEP, which are used as a measure of cortical excitability) - either potentiating or depressing it [19, 20]. As a rule of thumb, high-frequency (HF) rTMS should increase cortical excitability, while low-frequency (LF) rTMS should decrease it [20]. Similarly, theta burst stimulation (TBS) is another frequently used rTMS protocol, which uses a theta stimulation pattern in either a continuous (inhibitory cTBS) or intermittent (facilitatory iTBS) manner to influence cortical excitability [21]. Although the mechanisms through which TMS produces its therapeutic effects are not clear, several studies using TMS as a diagnostic tool have identified that there is increased inhibition in patients suffering from PD, suggesting a reduced cortical excitability, while other studies identify hyperexcitability along with reduced plasticity [16, 21]. Marked reduction of short-interval intracortical inhibition (SICI, which is used to assess inhibition in the motor cortex) and cortical silent period (CSP, which should be reduced by increased inhibition) as well as ipsilateral CSP duration have been reported, in contrast to reduced intracortical facilitation (ICF) in other studies – these results may suggest polymorphic neurophysiological changes in PD [22, 23]. Various corticomotor excitability changes may lead to differing symptoms in PD patients, such as reduced corticomotor inhibition in patients suffering from freezing of gait [24]. Meanwhile, patients with cognitive impairments are shown to have higher SICI, with greatest inhibition in Parkinson's disease dementia, and progressively reducing ICF the more cognitive impairment progressed [25]. Furthermore, higher SICI correlated with worse Unified Parkinson's Disease Rating Scale (UPDRS) scores, while stronger ICF correlates with needing less dopaminergic medication [26].

MOTOR SYMPTOMS

The majority of studies evaluating rTMS use in treating PD have used an 8-coil TMS coil, which is able to target a cortical area focally, to apply to either the primary motor cortex (M1), the prefrontal cortex (PFC), or the supplementary motor cortex (SMC), although the effect sizes were modest [27]. However, emerging research has increasingly focused on treatment using rTMS protocols, often with an H-Coil (which is able to target deeper brain regions at the expense of focality) to target both hemispheres of usually either the PFC, M1, both, or SMC, at the same time, as the motor manifestations of PD are typically bilateral [3, 27, 28]. A meta-analysis using Bayesian network has found that targeting both bilateral M1 and PFC using high-frequency (5-20 Hz) rTMS was the most effective intervention in improving Unified Parkinson's Disease Rating Scale part III scores, with a mean difference of 7.60 points [28]. The rationale behind targeting both M1 and PFC is to

simultaneously induce improvements in motor and cognitive function [21]. In addition, High-frequency stimulation of only M1 bilaterally using an 8-coil has long been established to show improvements in motor function in PD patients, such as UPDRS scores, walking speed and key tapping, with an effect being greater at 25 Hz than 10 Hz frequency [3]. Furthermore, HF rTMS (20 Hz) using an 8-coil over M1 bilaterally has been demonstrated to improve dysphagia, a swallowing dysfunction symptomatic in up to 54.5% of PD patients, which was measured by UPDRS, Activities of Daily Living (ADL) and Arabic-Dysphagia Handicap Index (A-DHI) as well as Video-fluoroscopy – there were significant improvements in all items over the sham group that lasted for 3 months after the sessions [29].

Meanwhile, in patients with dysarthria, the stimulation of the primary sensorimotor areas has been shown to lead to an increased speech rate and tongue movements as well as improvement in voice quality and intensity [30].

Gait disturbance, as characterized by slow speed, short steps and reduced walking ability, are one of the most debilitating symptoms of PD, and can lead to functional decline and falls: it has been shown that when paired with physical therapy, both 1Hz and 25Hz rTMS over M1 bilaterally is effective in enhancing improvements in walking speed and complex walking tasks, with the improvement correlating with increased CSP and SICI [31]. Similarly, a meta-analysis found that for freezing of gait, as measured by FOG-Q, walking time, TUG and UPDRS, frequencies of 1 Hz to 25 Hz all appear to show substantial efficacy, 25 Hz group having a statistically insignificant yet better effect size than the others, and stimulation of M1, SMC or M1 and DLPFC together all appearing to be similarly efficacious stimulation sites, with stimulation of DLPFC alone showing no positive effect for these scores [32]. In addition, the positive effects of stimulating M1 on bradykinesia and rigidity seem to be present even after a single rTMS session, with repeated daily sessions for 10 days showing improvements that last for a month, supplemental monthly sessions counteracting the decay of TMS benefits [21]. However, pairing low-frequency (1 Hz or less) stimulation over M1 or M1 and dorsal premotor cortex combined doesn't seem to show significant improvement, although studies exist showing LF rTMS benefits in treating motor symptoms by stimulating only M1 [28, 33, 34]. Additionally, The dorsal premotor cortex doesn't seem to show benefits even when higher-frequency (>1 Hz) rTMS is applied, possibly because this area is not as affected by neurodegeneration of substantia nigra due to having less vital input from the basal ganglia [21]. However, low-frequency stimulation has been shown to be effective in treating motor symptoms when stimulating SMC, though several physiological studies suggest that LF rTMS less than 0.9 Hz does not induce changes in cortical excitability [3, 35–37]. In general, abnormal SMC activity has been associated with bradykinesia and dyskinesia, basal ganglia to SMC motor pathways involved in voluntary movement control showing greatest deficits in individuals suffering from PD [21]. Evidence exists showing both the benefits of single-session applications to SMC without long-term effects, and lasting benefits of repeated sessions for 24 hours to 20 weeks after

application [21, 38].

The cerebellum has also been postulated to be an important target, although the results have been mixed: it has been demonstrated that cTBS applied over the lateral or bilateral cerebellum may decrease levodopa-induced dyskinesia (LID) without improving motor symptoms, while LF rTMS over the right lateral cerebellum improved gross motor movements while worsening fine motor movements [21]. As for comparative rTMS effectiveness in people using versus not using medication, cTBS and LF rTMS have been demonstrated to have the highest short-term and long-term effect on motor function when the patients are in the “off” state, while HF rTMS seems to be most effective in the “on” state [39]. On a physiological level, iTBS has been shown to restore plasticity of M1 and improve GABA-A-ergic neurotransmission, however, the clinical implications of this are unclear, although these neurophysiological effects correlate with disease severity [40]. Currently, a study evaluating iTBS effect while paired with physiotherapy is underway [41]. There is still, however, no consensus on which symptoms in PD patients are most likely to respond to TMS treatment, and the heterogeneity of protocols in studies of TMS as a treatment tool makes evaluation difficult [16].

MOOD DISORDERS

Depression and other mood disorders in Parkinson's Disease is one of the most important factors of patient's poorer quality of life, occurring in 2.7–90% of patients depending on the study, leading to poor cognitive performance, worse functional status and reduced medication adherence: depressive instead of motor symptoms being the most powerful predictor of beginning dopaminergic treatment [27, 42]. The root causes of depression in Parkinson's are still up for debate, with current theories attributing it to degeneration of monoaminergic neurotransmitter systems and fronto-cortical dysfunctions as well as neuroinflammation [42]. Current treatment consists mainly of selective serotonin reuptake inhibitors or tricyclic antidepressants, sometimes in combination with acetylcholinesterase inhibitors or MAO inhibitors [8, 42].

The earliest and most established use of rTMS has been in the treatment of medication-resistant depression using high frequency stimulation of the left dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex [1, 43]. DLPFC is also an important cortical target in treating PD-associated depression, and has been shown to improve its symptoms as well as general mood [21]. In a meta-analysis of 7 studies evaluating the efficacy of rTMS in treating PD-associated depression, four out of five qualitatively evaluated studies showed significant improvement in both clinician-administered Hedge's G and the self-administered Beck scores [43]. Another study found remission in 62% of depressed patients in terms of Beck and Hamilton Rating Scale for Depression (HDRS) scores using deep transcranial magnetic stimulation with an H-coil over M1 and PFC, and postulated that part of the antidepressive effect may be due to motor symptom improvement, as there were correlations between HDRS and ADL scores [34]. This is in contrast to a 2016 study that didn't find any improvement in mood symptoms of Parkinson disease over sham after 10 daily

sessions of treatment using an 8-coil over either M1 or DLPFC separately or both M1 and DLPFC, as measured by Hamilton Depression Rating Scale, but found a pronounced placebo effect in using TMS [44]. A 2020 meta-analysis found that only HF rTMS over left DLPFC had positive therapeutic effect – the effect persisted long-term, but was not more effective than oral fluoxetine, which was in contrast to some previous studies indicating that stimulation of DLPFC may be more powerful [45]. Furthermore, a 2022 study comparing the efficacy of HF rTMS, escitalopram, pramipexole and “routine treatment” (which consisted of levodopa and benserazide) showed better efficacy of both medications and TMS over “routine treatment” in treating PD-associated depression, but both medications had higher overall effect over TMS [46]. In terms of depression scores, the newest meta-analysis found that stimulating the dorsolateral prefrontal cortex had a statistically significant anti-depressive effect, with an effect size on depression scales of 0.42, however, only the self-administered Beck group score of 0.51 was significant, the effect size of Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale groups was not statistically significant, $p > 0.05$ [47]. As for anxiety, A study found HF rTMS with an 8-coil to be effective in treating both its and depression symptoms in Parkinson disease while using Visor 2 neuronavigation system to allow for precise targeting of DLPFC and the effect remained at 4 weeks follow-up [48].

COGNITIVE IMPAIRMENT

Basal ganglia degeneration in PD can lead to cognitive decline, and may even result in Parkinson's Disease with Dementia (PDD), which mainly affects executive function while maintaining memory, learning and higher-level language abilities relatively intact, cognitive impairment occurring in up to 78% of PD patients [49, 50]. This is due to disruption of fronto-striatal dopamine networks as well as cholinergic deficiencies extending to frontal areas, which are associated with executive function [49,51]. However, dopaminergic therapy, especially dopamine agonists may also worsen cognitive symptoms such as executive dysfunction and attention deficits, and may even exacerbate hallucinations and delusions, which are also a relatively common finding in PDD [50]. Current treatment consists of acetylcholinesterase inhibitors, such as rivastigmine, which may worsen tremor and increase the incidence of adverse drug reactions, and removal of exacerbating agents, such as changing dopamine agonists for levodopa/carbidopa [8, 50].

TMS in PD cognitive impairment and dementia has not been extensively studied: one meta-analysis found no significant effect over sham on cognitive function when targeting either M1 or PFC [52]. However, a later pilot study using 20 Hz rTMS over M1 demonstrated it having a minor effect on cognition, specifically Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores, but not Clinical Dementia Rating Scale (CDR) and Memory and Executive Screening (MES), however, the study acknowledged that targeting other regions may be necessary [53]. For example, in a crossover study, Tower of London task improvements were observed after rTMS was used on the right

DLPFC instead of the usual left DLPFC [54]. Low-frequency rTMS over the scalp vertex of patients with PD two times per day for ten days has also been shown to significantly improve MMSE scores [51]. In contrast, iTBS in PD over two sessions failed to show an improvement in frontal executive function and memory when applied over left DLPFC [55]. However, a longer exposure of iTBS twice a day for three days with 1–2 days in between for patients with mild cognitive impairment has been shown to lead to cognitive improvements for up to one month after application, likely mediated by improvement on visuospatial abilities [56].

CONCLUSIONS

Parkinson's disease is a polymorphic neurodegenerative disease which causes both motor and non-motor symptoms in the vast majority of this patient population [11]. Non-motor symptoms can include neuropsychiatric manifestations such as mood disorders, impaired sleep, cognitive impairment, dementia and psychosis [12]. Although the neurophysiological basis of Parkinson disease symptoms is complex and yet to be fully elucidated, various rTMS protocols have shown promise in treating both motor and neuropsychiatric manifestations of this disease [21, 27]. It is well established that targeting M1 bilaterally using an 8-coil HF rTMS is one of the most effective

currently devised protocols in alleviating a wide array of motor symptoms, such as gait disturbances, dysphagia, bradykinesia and rigidity, though newer research suggests that targeting both M1 and PFC, which is often done with an H-coil, may be a similarly promising method [3, 27]. Meanwhile, the left DLPFC using HF rTMS seems to be the most appropriate target in treating PD-associated depression, although the effect is not superior to that of common medications used to treat it [45, 46]. In contrast, a singular best protocol for treating cognitive impairment and dementia in PD patients is yet to be found, though targeting DLPFC could be promising [54, 56]. In general, more sessions over a longer period of time as well as using higher frequencies of up to 25 Hz ostensibly increase the efficacy of rTMS when applied over M1 or PFC, and supplemental sessions are needed to maintain its benefits [3, 21]. Future research should focus on comparing the efficacy of HF rTMS using an 8-coil versus an H-coil (or other coils used for deep rTMS) in targeting different brain regions and their combinations, as well as whether the effect is additive to using pharmacotherapy. In addition, more research is needed to elucidate the wide array and dynamics of cortical excitability changes as well as their relationship to various symptoms during PD, and the mechanism through which rTMS achieves its therapeutic effect.

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The association between malignant neoplastic process and atypical psychotic disorder: a clinical case study

Piktybinio navikinio proceso ir atipinio psichozinio sutrikimo sąsajos: klinikinio atvejo analizė

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SUMMARY

Paraneoplastic neurological syndromes (PNS) are a complex of neurological symptoms caused by the body's autoimmune reaction against the tumour. The autoimmune process can affect different structures in both the peripheral and central nervous systems, thus the clinical manifestation of PNSs can be very diverse. This article presents a 53-year-old man who developed psychosis for the first time in his life. The disorder manifested with atypical clinical symptoms and a limited response to psychopharmacotherapy was observed, which raised the suspicion of an organic origin of the disorder. A detailed diagnostic workup revealed carcinoma of the right kidney. This pathology was assessed as unrelated to the mental disorder. A diagnosis of unspecified dementia was made, suspecting Lewy body dementia. After the patient had completed active oncological treatment, a significant positive dynamics in his mental status was observed during a follow-up consultation with a psychiatrist. The diagnosis of dementia was excluded. Retrospectively assessed, the psychiatric disorder was of secondary origin, i.e. a manifestation of paraneoplastic neurological syndrome.

Key words: psychotic disorders, neurocognitive disorders, paraneoplastic syndromes, autoimmune diseases of the nervous system.

SANTRAUKA

Paraneoplastiniai neurologiniai sindromai (PNS) – tai neurologinių simptomų visuma, sukeliama autoimuninės organizmo reakcijos prieš naviką. Autoimuninis procesas gali pažeisti skirtingas struktūras tiek periferinėje, tiek centrinėje nervų sistemose, todėl klinikinė PNS raiška gali būti įvairi. Straipsnyje pristatomas 53 m. vyras, kuriam pirmą kartą gyvenime pasireiškė psichozė. Sutrikimas debiutavo netipiniais klinikiniais simptomais, stebėtas ribotas atsakas į psichofarmakoterapiją, todėl įtarta organinė sutrikimo kilmė. Atlikus išsamią diagnostiką, nustatyta dešiniojo inksto karcinoma. Ši patologija vertinta kaip nesusijusi su psichikos sutrikimu. Nustatyta nepatikslintos demencijos diagnozė, įtariant Lewy kūnelių demenciją. Pacientui užbaigus aktyvų onkologinį gydymą, pakartotinės gydytojo psichiatro konsultacijos metu stebėta reikšminga teigiama psichikos būklės dinamika. Demencijos diagnozė atmesta. Retrospektyviai vertinta, jog psichikos sutrikimas buvo antrinės kilmės, t.y. paraneoplastinio neurologinio sindromo išraiška.

Raktiniai žodžiai: psichozės, neurokognityviniai sutrikimai, paraneoplastiniai sindromai, autoimuninės nervų sistemos ligos.

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INTRODUCTION

It is estimated that 13–23% of the population have experienced sporadic psychotic symptoms at some point in their lifetime and 1–4% will meet criteria for a psychotic disorder [1, 2]. The majority of first-episode psychosis are of primary origin: 51% of cases eventually lead to the development of schizophrenia and 32.5% to the development of another non-affective mental disorder [3]. A secondary origin of the first-episode psychosis is identified in 3–10% of cases [4, 5]. Although there are no specific pathognomonic features that allow easy differentiation of psychosis aetiology, an atypical clinical presentation should raise suspicion that the disorder may be of organic origin. These include: older age, no family history of mental illness, a course resistant to psychopharmacotherapy, and decline in somatic status. Catatonic symptoms, disturbances of consciousness (e.g. severe disorientation, confusional, “dreamlike” states) and visual hallucinations are more frequent in secondary psychosis. Complex hallucinations and certain delusions, usually associated with beliefs about the mistaken identity of others (e.g. Capgras syndrome), are also more common in secondary psychosis than in schizophrenia [6–8]. Organic mental disorders can be caused by a wide range of medical conditions: metabolic, infectious, neurological disorders, toxin poisoning, use of medication or psychoactive substances and so on.

Paraneoplastic neurological syndromes (PNS) are a complex of neurological symptoms caused by the body’s immunological reactions against the tumour, rather than by the direct effect of the tumour or its metastases on the nervous tissue. The tissue is cross-reactively affected because specific intracellular antigens can be expressed not only by cancer cells but also by neurons. Less than 1% of oncological patients develop PNS, with approximately 60% of patients developing neurological symptoms before the oncological disease is diagnosed [9]. Since the autoimmune process can affect different structures in both the peripheral and central nervous systems, the clinical presentations of PNS can be diverse. This article reviews a clinical case of autoimmune paraneoplastic encephalitis presenting with an atypical, rapidly progressive mental disorder.

CLINICAL CASE

We present a 53-year-old working male, who was urgently admitted to the Department of Cardiology after he developed a hypertensive crisis. During the admission, the patient complained of severe headache; on objective examination, the patient was observed to have disturbance in orientation and his behaviour was disorganised (episodic psychomotor agitation, aggressive behaviour). During the course of inpatient treatment, it was discovered that patient’s condition had started to deteriorate two months ago: he felt fatigue, lacked energy, became slower, had a decreased appetite and lost about 12 kg in weight. The patient’s medical history: he has had uncontrollable arterial hypertension with hypertensive encephalopathy, no history of surgery and no allergies. He denies any history of head injuries, loss of consciousness or seizures. Family health history: patient’s father died of renal

oncological disease.

During his inpatient treatment at the Cardiology Clinic, the patient had his first seizures of unknown origin (consciousness was reduced but not completely lost, limb movements were asynchronous, occasional shouting during the ictus, and the seizures would last from a few minutes to an hour), his eyesight started to deteriorate, and he experienced episodes during which objects appeared to be distorted. Blood tests (complete blood count (CBC), K⁺, Na⁺, glucose concentrations, renal and hepatic function tests) and a computed tomography (CAT) scan of the brain were carried out to determine the cause of patients’ mental status deterioration and the new-onset seizures, but no clinically significant abnormalities were found. In the absence of underlying somatic pathology that could have caused the worsening of patients’ condition, he was referred to the Department of Psychiatry for treatment.

During his admission to the Psychiatric Clinic, the patient complained of persistent fatigue, episodic body tremors and anxiety. He described episodes during which he could not control himself, saw strange visuals and was disoriented. The objective assessment of his mental state showed psychotic symptoms: visual hallucinations (seeing frightening creatures in front of him), derealisation (at times objects seemed distorted and unreal), restlessness, inner tension, slowed thinking, impaired concentration, depressed mood, insomnia and decreased appetite. During the inpatient treatment, despite administered psychopharmacotherapy, the patient’s condition continued to deteriorate: alternating states of psychomotor agitation and psychomotor inhibition (to the point of stupor, elements of mutism and passive-negativity) were observed, disturbances in the thought processes and volition intensified, and convulsive seizures recurred. Unusually, the patient’s mental state could change spontaneously within a few hours, e.g. the patient would be in a stupor for several days, then suddenly begin to communicate in a meaningful way, and talk about his state of being.

Over the course of his inpatient treatment, the patient was treated in three different psychiatry clinics, which may have led to a lack of consistency and direction with the psychopharmacotherapy. Throughout the hospitalization period, valproic acid 1000 mg per day (mg/d) was administered to prevent seizures. Tranquillizers were assigned to anxiety, insomnia and episodic psychomotor agitation: starting with Diazepam up to 50 mg/p (continued for 10 days), followed by a change to Lorazepam up to 10 mg/p (for 14 days). Gradually, tranquillisers were discontinued to avoid the development of dependence on benzodiazepines. In the first psychiatry clinic where the patient was treated, treatment of psychotic symptoms was started with combination of Haloperidol 10 mg/p (continued for 10 days) and Olanzapine up to 10 mg/p (continued for 20 days), which was discontinued after the patient refused to take the drug. Treatment with a neuroleptic was then changed to Quetiapine up to 100 mg/p (continued for 14 days). No symptom dynamics were observed with the above-mentioned typical and atypical neuroleptics and their combinations. Due to the treatment-resistant course of the disease, a consilium decided to transfer the patient to another psychiatry clinic for further treatment and more

detailed examination. There, Quetiapine was discontinued and neuroleptic treatment was changed to Tiapride 300 mg/p (continued for 14 days). After a week, with no improvement in symptoms, it was decided to add a second neuroleptic – Quetiapine was reintroduced at up to 75 mg/p (continued for 14 days). The patient was transferred to a third psychiatric clinic. As psychotic symptoms persisted and the treatment was considered ineffective, Quetiapine was discontinued. A combination of Tiapride and Olanzapine up to 20 mg/p (continued for 1 month) was tried. No significant clinical effect was obtained, so these drugs were gradually discontinued. Quetiapine was reinitiated and the dose was titrated to 300 mg/p. A partial clinical effect was achieved: psychotic symptoms and psychomotor agitation were reduced, emotional lability and insomnia were slightly alleviated, and the patient was somewhat more critical about his mental state. Other symptoms were unaffected by the drug: thinking remained of reduced productivity, lacked coherence, and the patient remained hypobulic.

As the psychosis debuted with atypical symptoms and a treatment-resistant course was observed, detailed diagnostic work-up was carried out to differentiate a possible organic origin of the disorder. A psychological examination of cognitive functions revealed impairment in fixation memory, maximum retrieval capacity and retention of information in long-term memory; the Mini Mental State Examination (MMSE) scored 11 point for moderate cognitive impairment. Urinary and blood tests (CBC, K⁺, Na⁺, Mg²⁺, Ca²⁺, glucose, cortisol, aldosterone concentrations, renal, hepatic and thyroid function tests, coagulation tests, C-reactive protein) were performed and no clinically significant changes were found. Diagnostic tests for HIV, syphilis, neuroborreliosis and tick-borne encephalitis were negative, and tests for heavy metals were clear of pathological abnormalities. Upper abdominal ultrasonography showed a left renal calculi, a cyst in the right kidney and a mass in the left adrenal gland. Magnetic resonance imaging (MRI) of the brain with contrast-enhanced imaging was performed: in T2-weighted mode imaging, focal areas of signal intensity (FA SI) were observed in the supratentorial brain region bilaterally, parietally and occipitally, as well as in the right temporal subcortically and in the white matter - the lesions were assessed as nonspecific, possibly microangiopathic. The scan also revealed atrophic lesions in the subarachnoid convexity and in the Sylvian fissure, which were considered to be insignificant. No evidence of pathologic contrast accumulation was detected. Considering the ultrasound findings in the right kidney and the left adrenal gland, as well as the complicated family history of oncological diseases, abdominal and pelvic CAT scans were performed: a tumour was found in the right kidney. A biopsy for final tumour verification confirmed cystic clear cell carcinoma of the right kidney. Due to the patient's difficult mental state, it was decided to postpone the surgery and to reschedule it once the patient's state improved.

The diagnosed oncological disease was considered to be unrelated to the psychiatric disorder, and further testing continued. Electroencephalogram (EEG) recorded: irregular, frequent, suppressed bioelectrical activity, with a tendency

towards generalised paroxysmal pathological activity, more pronounced in the left frontal region. The cerebrospinal fluid analysis showed no abnormalities (glucose 3,69 mmol/l, total protein 0,311 g/l, chloride 125 mmol/l). After assessment of the available data, an interdisciplinary consortium diagnosed dementia of unspecified origin, with suspicion of Lewy body dementia, and a concomitant disease – right renal cell carcinoma. The definitive confirmation of Lewy body dementia required a brain positron emission tomography (PET) scan. The patient was referred for outpatient oncological treatment and further investigations for suspected Lewy body dementia.

A few months later, after completing his oncological treatment, the patient was admitted to the Psychiatric Department for further investigation of the aetiology of his dementia. During the consultation, a significant change in patient's mental status was observed: thinking was more coherent and his cognitive functions had partially recovered. The diagnosis of dementia was rejected. As the psychiatric symptoms were significantly reduced after the oncological treatment, it was retrospectively assessed that the psychiatric disorder was a manifestation of PNS. Suspecting paraneoplastic autoimmune encephalitis, additional tests were performed for the differential diagnosis, such as cytological examination of cerebrospinal fluid and testing for antibodies associated with paraneoplastic neurological syndromes. Both tests were without pathological abnormalities. Considering the clinical case retrospectively, the criteria for the diagnosis of PNS are still sufficient: a classic PNS syndrome, in this case limbic encephalitis, was observed (for a more detailed description, see the "Discussion" section), and an oncological process was diagnosed [10, 11]. The final psychiatric diagnosis of the patient was other specified psychiatric disorder due to brain damage, dysfunction and somatic disease.

DISCUSSION

This report presents a case of paraneoplastic encephalitis presenting with acute progressive neuropsychiatric disorder. Paraneoplastic neurological syndromes are usually classified according to the location of the nervous system affected. The classic clinical syndromes affecting the central nervous system, also known as "high-risk" syndromes, are encephalomyelitis, limbic encephalitis and subacute cerebellar degeneration. The case report describes paraneoplastic limbic encephalitis (PLE): the inflammatory processes is localised in the hippocampus, amygdala, hypothalamus, limbic cortex, and the gyrus cinguli. The syndrome is characterised by neuropsychiatric symptomatology: new-onset seizures, disturbances in mood, behaviour, cognitive functions, and psychotic symptomatology are possible [12]. Symptoms of hypothalamic involvement may also be present, such as endocrine disturbances, hyperthermia, hypersomnia to somnolence.

The diagnostics of PNS is divided into three stages. First stage involves identifying the area of brain involvement by performing brain MRI and EEG scans. In paraneoplastic limbic encephalitis, brain MRI shows atrophy in the limbic regions, and MRI in fluid-attenuated inversion recovery (FLAIR) shows hyperintensity in the temporal and limbic regions [13].

The EEG shows slowed local or widespread pathological activity and/or epileptiform activity, most prominent in the temporal lobes [14,15]. However, pathological abnormalities are not always detected on brain MRI and EEG. In the second stage, inflammatory aetiology of the disorder is identified and other possible causes are excluded. The most important factor in this stage is the detection of onconeural antibodies in serum or cerebrospinal fluid, but these are found in only 60–70% of patients. Also important is the examination of the spinal fluid, with 90% of cases showing at least one of the following pathological parameters: pleocytosis, oligoclonal bands, elevated protein level or immunoglobulin G index. The third stage aims to identify the localisation of the tumour causing PNS [10, 16, 17]. In the clinical case described, no significant changes were found in the cerebrospinal fluid, and the changes observed on brain MRI were not consistent with typical PLE. We note that the onconeural antibody test is not informative because it was performed late, after the oncological treatment. Cases in which laboratory and imaging tests do not reveal abnormalities characteristic to PNS are not rare. According to the updated diagnostic criteria, verification of PNS is possible without it: a “high-risk” clinical syndrome and an established oncological process are sufficient [10, 17]. Due to the challenging differential diagnosis, PNS remains underdiagnosed worldwide [11, 18].

The treatment of the disease consists of two main elements: removal of autoantibodies and symptomatic treatment. The most effective method of removing the antibodies is oncological treatment, which stops the immune

response and enables a full recovery. Severe psychiatric impairment should not be a contraindication for oncological treatment, as the removal of the tumour also leads to the regression of some neuropsychiatric symptoms. Autoantibody elimination includes suppression of the active immune system by immunotherapy in various combinations (glucocorticoids, intravenous immunoglobulin, plasmapheresis, cyclophosphamides) [16, 19]. Symptomatic treatment includes management of epileptic seizures, correction of psychiatric symptoms and stabilisation of vital functions. The efficacy of treatment and prognosis of paraneoplastic encephalitis depends mainly on the morphology of the primary tumour, the clinical stage of the cancerous process and the severity of the existing neuropsychiatric symptomatology. Some patients recover completely, while others experience residual neuropsychiatric symptoms of varying severity, lethal outcomes are possible as well. Late identification of the underlying condition and delayed oncological treatment are associated with worse prognosis and possible recurrence [20].

In summary, this clinical case demonstrates that the differential diagnosis of psychiatric disorders starts with the identification of the clinical presentation of the disorder (typical or atypical). For psychiatrists treating oncology patients, it is important to include paraneoplastic neurological syndromes in the differential diagnosis of atypical psychiatric disorders. Early diagnosis and treatment of PNS is associated with better outcome and, conversely, delayed treatment is associated with residual neuropsychiatric symptoms or lethal outcome.

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The psychiatric consequences of long-COVID in adolescents: a case report

Ilgojo COVID sindromo poveikis paauglių psichikos sveikatai: klinikinis atvejis

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SUMMARY

There are no diagnostic tests or consent international definition for long COVID in children [1]. Long-COVID is a typical condition of adults with a history of probable or confirmed SARS-CoV-2 infection in the previous 3 months and with symptoms lasting over 2 months not explained by an alternative diagnosis [2]. We present a case report of a 16 year old girl, who experienced mental health decline after SARS-CoV-2 infection that manifested with depressive symptoms. Patient's mental and somatic condition was evaluated 5 times in one year period and once again after 2 years. Patient attended psychotherapy and was treated with Fluoxetine up to 20 mg a day for reduction of depressive and anxiety symptoms. A reduction of symptoms was registered 2 weeks after beginning of treatment but 55 weeks after virus exposition symptoms reoccurred. Certain symptoms, such as anxiety, difficulties concentrating, and fatigue, persisted despite the reduction of other symptoms. This case report shows dynamics of long-COVID syndrome in 2 year period.

Key-words: long-COVID syndrome, children, adolescents, mental health

SANTRAUKA

Šiuo metu ilgajam COVID sindromui nėra sutarto tarptautinio apibrėžimo ir diagnostikos metodo pediatrijoje [1]. Remiantis PSO apibrėžimu, ilgojo COVID sindromas – dažnai suaugusiems asmenims pasireiškianti būklė, kuriai būdinga per paskutinius tris mėnesius galima ar patvirtinta SARS-CoV-2 infekcija, lydima dviejų ilgai besitęsiančių kitaip nepaaiškinamų simptomų [2]. Šis klinikinis atvejis aprašo 16 metų merginą, kuriai po SARS-CoV-2 infekcijos sutriko psichikos būklė ir manifestavo depresinė simptomatika. Vienerius metus nuo COVID-19 ligos pasireiškimo pacientės somatinė ir psichikos sveikata vertinta 5 kartus, taip pat mergaitės būklė įvertinta pakartotinai po dviejų metų. Nuotaikos ir nerimo korekcijai taikytas gydymas Fluoksetinu iki 20 mg/p bei psichoterapeuto konsultacijos. Taikant gydymą, po dviejų savaitių stebėta teigiama pacientės psichikos būklės dinamika, tačiau 55 savaitę po užsikrėtimo SARS-CoV-2 infekcija, stebėtas būklės regresas. Tam tikri simptomai – nerimas, sunkumai koncentruoti dėmesį bei nuovargis išliko pasiekus kitų simptomų redukciją. Šis klinikinis atvejis iliustruoja ilgojo COVID sindromo simptomų dinamiką dviejų metų laikotarpiu.

Raktiniai žodžiai: ilgojo COVID sindromas, vaikai, paaugliai, psichikos sveikata

INTRODUCTION

The Long COVID syndrome among children and adolescents has been minimally explored [3]. It has been identified that Long COVID syndrome, characterized by one or more symptoms persisting for 4 weeks post SARS-CoV-2 infection, was present in 25.24% of cases for children and adolescents and 29.19% of hospitalized cases [4]. Various somatic and mental health changes characterize Long COVID syndrome. Patients often report experiencing fatigue, headaches, muscle or joint pain, chest pressure or pain, changes in taste or smell, 'brain fog,' sleep disturbances, difficulties returning to active activities, leading to an increased susceptibility to other diseases [5, 6]. It has also been observed that hospitalized newborns due to SARS-CoV-2 exhibited eating disorders – they refused to eat. Older children displayed increased attachment, distraction, irritability, restlessness, and anger [7].

Three possible explanations for the pathophysiology of Long COVID syndrome have been distinguished: the first hypothesis states that during acute infections, organs that determine long-lasting symptoms are damaged. However, severe cases of COVID-19 are rarely diagnosed in children and adolescents, making this hypothesis unsuitable to explain the mechanism of Long COVID syndrome in this age group. The second hypothesis suggests that the SARS-CoV-2 virus persists in the body after infection, causing long-term symptoms. The third hypothesis is 'autoimmune' – it is believed that antibodies are formed in the patient's body, which 'attack' the body's tissues. None of these hypotheses may be accurate for this age group, as there is a lack of scientific studies evaluating the pediatric and adolescent populations [1]. Mental health changes may have been influenced not only by the virus's impact on health but also by changes related to the epidemiological situation – changes in the environment and lifestyle, quarantine restrictions, distance learning, social distancing.

In Lithuania, the consequences of Long COVID syndrome for children's health have not been assessed, hence presenting a clinical case of Long COVID syndrome to draw the attention of medical practitioners and Lithuanian scientists to the problem of Long COVID, describing the clinical case of a 16-year-old girl.

CLINICAL CASE

The patient (16 years old) sought medical attention due to mood fluctuations, low self-esteem, narrowing of interests, social withdrawal, disrupted sleep, fatigue, and decreased energy following a COVID-19 infection. The patient's father complained that the patient became tearful and expressed anxiety. Concurrently with COVID-19 illness, neurological symptoms (headaches and cognitive impairment – brain fog, memory loss, difficulty concentrating) and rheumatological symptoms (joint pain, tingling in the toes) emerged, leading to referrals for pediatric neurology and pediatric rheumatology consultations. The patient had not been vaccinated against COVID-19. The patient contracted COVID-19 on January 1, 2022. SARS-CoV-2 was not confirmed by PCR testing, but a confirmed COVID case in the close environment was reported in December 2021 and January 2022. The patient received outpatient care for 7 days, experiencing subfebrile temperatures for 4 days. Before contracting COVID-19, the girl had not sought psychiatric

consultations with child and adolescent psychiatrists. About 6 years ago, the girl had attended psychotherapeutic consultations several times due to difficulties in communicating with peers and feelings of loneliness. According to the father, the girl appeared somewhat melancholic before contracting SARS-CoV-2 infection, but a significant deterioration in mental health was observed after the illness. The patient's mental and somatic condition was assessed 5 times per year and once every 2 years using a questionnaire developed by the authors. Additionally, the girl received outpatient psychiatric consultations and treatment.

The evaluation involved a standardized questionnaire with questions about the expression of various psychiatric symptoms, assessing the frequency of symptom manifestation over a 1-month period. The survey took place remotely via video camera, with separate interviews for the girl and her father. Mood, anxiety, phobias, suicidal thoughts, fatigue, loneliness, anger, irritability, distractibility, appetite, and restlessness were assessed using a scoring system (0 points – symptoms never occurred; 1 point – symptoms occurred occasionally; 2 points – frequently; 3 points – very frequently; 4 points – always).

The first assessment of the patient's condition was conducted 10 weeks after COVID-19 infection. The father noted that the patient appeared more sad than happy. The girl constantly seemed fatigued, anxious without reason, and concerned about her health. Loneliness and anhedonia were persistent. The patient often quickly became irritated and angry. Suicidal thoughts and irrational worries occasionally occurred, and she slept slightly less than usual.

At the 12th week post-infection, the patient sought outpatient care from a child and adolescent psychiatrist. The patient was prescribed Fluoxetine capsules, gradually titrated up to 20 mg/day, and this medication regimen was continued throughout the treatment period along with psychotherapy. The girl was re-evaluated 2 weeks after the initiation of medication. Positive dynamics were observed on medication and psychological support: according to the patient and her father, mood improved. However, according to the father, the girl often felt fatigued, occasionally worried without reason or about her health, and appeared lonely. According to the father, episodic suicidal thoughts and anhedonia occasionally occurred, and the girl experienced distractibility. The patient herself reported feeling an improvement in her condition: she expressed experiencing pleasure more often in daily activities but still occasionally worried without reason, mentioned occasional intrusive thoughts, and had difficulty concentrating.

At 27 weeks post-COVID-19 infection (13 weeks from the start of treatment), the patient and her father were contacted again. Significant improvement in the patient's condition was observed. According to the patient and her father, mood improved, suicidal thoughts reduced, and the patient often felt pleasure in daily activities. However, according to the father, the girl often appeared fatigued, occasionally worried without reason or about her health, and seemed lonely. The patient reported feeling often fatigued and started to sleep slightly more than usual, occasionally worrying about her health (Table 1).

At 41 weeks post-COVID-19 infection (27 weeks from the start of treatment), the patient and her father were contacted

Case reports

Table 1. Dynamics of Long COVID Syndrome Symptoms Over a 2-Year Period According to the Patient's Subjective Assessment and the Father's Objective Assessment

Symptoms Manifesting Within a 1-Month Period	Time elapsed post SARS-CoV-2 infection, (weeks)											
	10		14		27		41		55		96	
	Evaluator		Evaluator		Evaluator		Evaluator		Evaluator		Evaluator	
	Patient	Father	Patient	Father	Patient	Father	Patient	Father	Patient	Father	Patient	Father
Fatigue	++++	++++	+	+++	+++	++	++	+	+	++	+	++
Unexplained Anxiety	++	++++	++	++	0	+	0	+	+	+	++	++
Hypochondriasis	0	++++	0	++	+	+	+	+	+	++	0	+
Feeling of Loneliness	0	++++	0	++	0	+	+	++	++	+++	0	+++
Anhedonia	+	0	++	+	++	++	++	+	+	+	+	+
Irritation and Anger	+++	++	+	+	0	+	+	+	+	+	+	++
Suicidal Thoughts	0	+	0	+	0	0	0	0	0	+	0	0
Intrusive Thoughts	0	+	0	+	0	0	0	0	0	0	0	0
Paranoid Thoughts	+	+	0	0	0	0	0	0	0	0	0	0
Difficulty concentrating	+++	++++	+	+	0	0	+	+	0	+	+	+
Fear of Separation from a Close Person	0	0	0	0	0	0	+	0	+	0	0	0
Social Anxiety	0	0	+	0	0	0	0	0	++	0	+	+
Concerns about Appearance and Desire to Lose Weight	0	0	0	0	0	0	0	0	+	0	0	0
Restlessness	0	0	+++	++	+++	++	+++	++	+++	+++	++	++
Specific Phobia	0	0	0	0	0	0	0	0	0	0	+	0

*0 - symptoms never manifested; + symptoms manifested occasionally; ++ - symptoms manifested frequently; +++ - symptoms manifested very frequently; ++++ - symptoms manifested always.

again. According to the father, the patient's mood remained stable, but the girl often appeared lonely. According to the father, the girl only occasionally felt pleasure in regular activities, seemed fatigued, occasionally worried without reason or about her health, and slept slightly more than usual. The patient herself reported often feeling fatigued, occasionally worrying about her health, feeling irritable and lonely, and sleeping slightly more than usual.

After one year (55 weeks) post-COVID-19 infection (41 weeks from the start of treatment), a repeated assessment of symptom dynamics was conducted. A significant deterioration in the condition was observed. The father noted that the girl appeared more cheerful than sad, but very often seemed lonely, frequently appeared fatigued and distracted, and worried about her health. According to the father, episodic suicidal thoughts occurred, and the girl expressed anxiety without reason or fear of being ridiculed by someone close to her. The father mentioned that the patient occasionally became irritated and rarely felt pleasure in daily activities, sleeping slightly more than usual. The patient herself reported often feeling cheerful but often lonely and experiencing social anxiety. The girl occasionally became irritable, felt fatigued, and worried without reason or about her health. The patient only occasionally felt pleasure in daily activities and occasionally had thoughts about losing

weight, mentioning that she slept slightly more than usual.

Almost two years later (96 weeks) post-COVID-19 infection, a repeated meeting was held with the patient and her father. The girl stated that about a year ago, she discontinued Fluoxetine treatment due to a reduction in symptoms. According to the father, the girl felt well during the summer vacation (significant improvement observed in August 2023 (81–85 weeks)). With the start of the school year, the girl's mental state episodically worsened, particularly due to concerns about final exams. At 96 weeks, the father assessed that the girl appeared more sad than happy and very often seemed lonely. The patient often seemed restless, fatigued without reason, easily irritated, and occasionally worried about her health. Occasionally, the girl appeared as if anxious about her health, afraid that someone close to her might ridicule her. The father noted that the patient rarely felt pleasure, engaged in daily activities, provoked anger reactions, and had difficulty concentrating.

In conclusion, this case underscores the complexity and long-term dynamics of mental health symptoms in a pediatric patient post-COVID-19 infection. The presented clinical trajectory provides valuable insights into the potential prolonged impact of Long COVID Syndrome on mental health, emphasizing the need for comprehensive assessments and tailored interventions in children and adolescents.

DISCUSSION

In this clinical case, we present the dynamics of Long COVID Syndrome over a two-year period, manifested by changes in mental health. According to the literature, the most common mental health symptoms of Long COVID Syndrome in adults include fatigue, anxiety, depressive symptoms, difficulty concentrating, disturbed sleep, and memory impairment. While there is limited research assessing the impact of Long COVID Syndrome on children and adolescents, it has been found that fatigue, disturbed sleep, memory and attention issues, depressive symptoms, anxiety, and restlessness occur more frequently in this population [8, 9]. The symptoms observed in the presented patient align with those typically associated with Long COVID Syndrome. Jolanta B Zawilska and colleagues identified fatigue as the most pronounced psychiatric symptom of Long COVID Syndrome in children, adolescents, and adults [10]. In our clinical case, fatigue was the most persistent and prominently reported complaint.

Children and adolescents after COVID-19 infection often report anxiety and depressive symptoms [7]. Currently, the lack of appropriate instruments for assessing the impact of Long COVID Syndrome on the health of children and adolescents makes it challenging to differentiate between Long COVID Syndrome and depressive or anxiety disorders. The clinical case demonstrates that specific symptoms, such as anxiety, fatigue, and attention disturbances, persisted even after the reduction of other depression symptoms. This may suggest a specific association with Long COVID Syndrome and could aid in distinguishing it from depression caused by other factors. The precise differentiation would require a thorough history, assessing whether neuropsychiatric symptoms typical of Long COVID Syndrome manifested or worsened after COVID-19 illness. Additionally, an evaluation of the current epidemiological situation and, if necessary, COVID PCR or antibody testing could contribute to the differential diagnosis. Cozzi et al. found a direct link between Long COVID Syndrome

in adolescents and a general predisposition to psychiatric disorders [8]. Other studies have indicated that dysfunction and duration of symptom manifestation in children and adolescents with Long COVID Syndrome are directly related to their gender and age – symptoms are more pronounced and last longer in girls and adolescents [1]. Therefore, our presented patient falls into a high-risk group.

In a systematic literature review by Yong Bo Zeng and colleagues, it is emphasized that mental health symptoms are most pronounced 6–12 months after SARS-CoV-2 infection ($p < 0.01$). [11] In our described clinical case, the patient's symptoms were most pronounced at the onset of the illness and reduced with the application of both pharmacological and non-pharmacological interventions. The patient's mental state deteriorated again at week 55 (after 12 months), despite continued medication and psychological support. This aligns with the findings of Yong Bo Zeng and colleagues' literature review. After achieving remission, the girl's Fluoxetine treatment was discontinued, resulting in a recurrence of mental health regression. This clinical case demonstrates that the treatment duration for Long COVID Syndrome in adolescents may require a longer period of pharmacological intervention.

In summary, during this post-COVID era, when treating depression and anxiety disorders, it is crucial to consider the possibility of Long COVID, especially when cognitive dysfunction or inadequate treatment response is present. A comprehensive evaluation, including the history of illness and assessment of other Long COVID symptoms, may be needed for longer-term treatment or additional therapeutic measures. Informed consent was obtained from the patient and her father for the case analysis and article publishing. Bioethics number: BE-2-27 (2022-02-22).

Conflict of Interest

No conflicts of interest were reported by the authors during the study.

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Attentional problems as the makeup of obsessive – compulsive disorder and its differential diagnosis form adhd: a case report

Dėmesingumo problemos, maskuojančios obsesinį-kompulsinį sutrikimą, bei jo diferencinė diagnostika nuo aktyvumo ir dėmesio sutrikimo: klinikinio atvejo analizė

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SUMMARY

Obsessive-compulsive disorder (OCD) is a prevalent neuropsychiatric condition characterized by intrusive thoughts (obsessions) and repetitive behaviours (compulsions), affecting 1–3% of the population. Despite its distinct diagnostic criteria, accurate diagnosis and treatment are often challenging due to its chronic nature, polymorphism, and overlap with other psychiatric disorders like attention-deficit/hyperactivity disorder (ADHD). The possible co-occurrence of ADHD in adult OCD patients further complicates diagnosis and management, with reported prevalence rates varying widely. Differential diagnosis between OCD and ADHD is essential, given their distinct treatment approaches. The case of an 18-year-old female patient illustrates these diagnostic complexities, as she initially presented with symptoms of attention deficit but subsequently revealed manifestations of OCD. Treatment adjustments targeting them led to a significant improvement in her condition, highlighting the importance of comprehensive assessments. The presentation of this case also addresses the limitations of current diagnostic classification systems, such as disparities between the DSM and ICD criteria for ADHD diagnosis.

Keywords: obsessive – compulsive disorder; attention-deficit/hyperactivity disorder; attentional problems

SANTRAUKA

Obsesinis – kompulsinis sutrikimas (OKS) – lėtinis psichikos sutrikimas, kuriuo serga apie 1–3% populiacijos, pasireiškiantis įkyriomis mintimis (obsesijomis) ir pasikartojančiu elgesiu (kompulsijomis). Nepaisant aiškių diagnostinių kriterijų OKS diagnozavimas ir gydymas dažnai kelia iššūkių. Tam įtakos turi lėtinė OKS eiga, simptomų polimorfizmas bei klinikoje dažnai pasitaikantys gretutiniai psichikos sutrikimai, tokie kaip aktyvumo ir dėmesio sutrikimas (ADS). Galimo ADS ir OKS komorbidiškumo dažnis literatūroje itin varijuoja; nepaisant to, tiksli diferencinė diagnostika tarp OKS ir ADS yra būtina dėl kardinaliai skirtingos minėtų sutrikimų gydymo taktikos. Šis klinikinis atvejis aprašo 18 metų pacientę, kurios klinikiniam vaizde iš pradžių vyravo dėmesio sutrikimai, tačiau palaipsniui išryškėjo OKS simptomatika. Ženklaus būklės pagerėjimas taikant tikslingą, į obsesijas bei kompulsijas orientuotą gydymą, atskleidė tikslios bei išsamios diagnostikos svarbą. Šiame klinikinio atvejo pristatyme taip pat aptariami dabartinių praktikoje naudojamų diagnostikos klasifikacijos sistemų (DSM ir TLK) trūkumai bei galimi netikslumai, susiję su ADS diagnostika.

Raktiniai žodžiai: obsesinis – kompulsinis sutrikimas, aktyvumo ir dėmesio sutrikimas, dėmesingumo problemos

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by unwanted obsessions and/or compulsions. It is a common psychiatric disorder, affecting 1-3% of the general population [1, 2]. Due to its chronic nature, it has become one of the most disabling illnesses which are highly debilitating and resulting in great suffering for patients worldwide [3, 4]. Despite its prevalence, OCD presents challenges in accurate diagnosis and effective treatment, often being misdiagnosed and inadequately addressed [3]. One of the reasons for this is that OCD comprises comorbid symptoms with many other psychiatric disorders, for example, attention-deficit/hyperactivity disorder (ADHD), raising controversies over accurate diagnosis and overlap of their neural underpinnings [5]. The co-occurrence of ADHD in adult OCD patients is reported to range from 5.5% to 52% [6]. However, it is claimed that obsessive anxiety can be causally associated with inattention and executive dysfunction, leading to an inadequate diagnosis of ADHD in OCD subjects [7, 8]. It could contribute to a delay between the mean age of onset and age at diagnosis of OCD which recently has been reported to be 7.1 years (with the mean age of onset of 13.6 years and age at diagnosis of 20.7 years old) [9]. The heterogeneity of OCD together with the findings that 39% of mental health professionals and 50.5% of primary care physicians misdiagnosed OCD when asked to give their diagnostic impressions of individuals presented in clinical vignettes emphasises the great need for a careful examination of the patient and the importance of understanding the complexity and possible diagnostic challenges of OCD [9].

According to The International Statistical Classification of Diseases and Related Health Problems (ICD), Eleventh Revision (ICD-11), and The Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition, Text Revision (DSM-5-TR), essential diagnostic requirements for obsessive-compulsive disorder are the presence of obsessions and/or compulsions [10, 11]. Obsessions are repetitive and persistent thoughts, images, or impulses/urges that are experienced as intrusive and unwanted and are commonly associated with anxiety [11]. The person typically attempts to ignore or suppress obsessions or to neutralize them by performing compulsions, which are repetitive behaviours or rituals that the individual feels driven to perform in response to an obsession (e.g. repetitive washing, checking, and ordering of objects, mentally repeating specific phrases to prevent negative outcomes, reviewing a memory to make sure that one has caused no harm, and mentally counting objects) [10]. Compulsions are either not connected in a realistic way to the feared event or are excessive. Both obsessions and compulsions are time-consuming or result in significant distress or impairment in personal, family, social, educational, occupational, or other important areas of functioning [10, 11]. In the cases when functioning is maintained, it is only due to the significant additional effort of the patient. [10] It is also important to notice that the symptoms or behaviours are not a manifestation of another medical condition and are not present because of the effects of a substance or medication on the central nervous system (e.g., amphetamine), including

withdrawal effects [10, 11].

In addition to ICD-11 and DSM-5-TR definitions, studies in symptomatic OCD also point out some neurocognitive deficits and suggest impairment in executive function, processing speed, sustained attention, and nonverbal memory [4, 12]. Subdomains of executive function that have shown deficits include response inhibition, planning, decision-making, and encoding of nonverbal memory [12]. Despite earlier reports which presumed that OCD patients have elevated intellectual capacity, several studies have shown that individuals diagnosed with OCD have lower full-scale IQ and performance IQ as compared to control groups [13, 14]. Some authors view executive function deficits in OCD as an epiphenomenon caused by the overflow of intrusive thoughts [4, 15]. According to their executive overload model, cognitive deficits in OCD patients result from the attempt to gain control over automatic processes to reduce impulsive behaviour and lapses of attention. This leads to increased consumption of cognitive resources and in return diminished effective control [15].

ADHD is a complex disorder which includes a constellation of clinical manifestations based on attentional difficulties, hyperactivity, and impulsivity [16]. It is a common childhood disorder with only 2–3% prevalence into adulthood [17]. ADHD in adults is characterized by inattentiveness, impulsivity, hyperactivity, restlessness, and difficulties in organizing and planning, as well as making impulsive decisions [17]. It is noted that as many as 80% of adults with ADHD have at least one coexisting psychiatric disorder, including mood and anxiety disorders, substance use disorders, and personality disorders [18]. Studies report that as much as one-third of individuals referred for ADHD diagnostics do not have ADHD but do meet the criteria for affective, anxiety, and personality disorders [19]. Yet it is commonly believed that ADHD may reflect the most extreme version of attentional problems [20].

The two major systems of psychiatric classification, the American Psychiatric Association's DSM and the World Health Organization's ICD, differ in their description of ADHD [21]. ICD, Tenth Revision, Australian Modification (ICD-10-AM), which is currently still used in Lithuania, does not formally acknowledge ADHD but instead includes diagnostic criteria for hyperkinetic disorder (HKD). Diagnosis of HKD requires the presence of symptoms indicating both impaired attention and overactivity including impulsivity; they must also be present before 6 years of age [22]. As with DSM-5-TR, the symptoms must be found in two settings and other conditions that could cause them first have to be ruled out. Three subtypes of ADHD, termed "presentations", are recognized: predominantly inattentive presentation (ADHD-I: symptoms of inattention, but not hyperactivity/impulsivity), predominantly hyperactive/impulsive presentation (ADHD-HI: symptoms of hyperactivity/impulsivity, but not inattention), combined presentation (ADHD-C: symptoms of both inattention and hyperactivity/impulsivity), which are substantially diverse pertaining to their symptom profiles [11, 23]. The symptom compositions for HKD in ICD-10-AR are comparable with the "combined presentation" of

ADHD in DSM-5, but not the “predominantly inattentive” or “predominantly hyperactive-impulsive” presentations [24].

According to some studies, OCD could be perceived as a disorder of attention, characterized by dysfunctional hyperfocus on typically ignored sensory and motor stimuli [25]. It was shown that patients with OCD experience the greatest impairments of sustained attention, followed by social phobia and eating disorders (bulimia nervosa and binge eating disorder); remarkably, all these disorders showed significantly greater difficulties with sustained attention than probable ADHD [20]. These findings indicate that impaired attention is non-specific for ADHD, and a markedly larger deficit may be associated with other disorders. It encourages clinicians to pay special attention to possible OCD when attentional complaints are expressed, as OCD symptoms may manifest in this unexpected manner [26]. Here we present the clinical case of such manifestation, illustrated by a young woman with a predominant complaint of long-lasting attentional problems.

CASE REPORT

An 18-year-old female patient was hospitalized at a psychiatric hospital due to complaints of difficulties in concentrating, attentional problems, and having too many thoughts in her mind which resulted in memory and sleep impairment as well as sadness and anxiety. Her initial diagnosis at the time of hospitalisation was a moderate depressive episode. The patient's medical history revealed that she was a second child from the first marriage; she had an older brother, who was deceased because of unnatural causes despite having no prior health issues (see below). There was no reported family history of psychiatric disorders or tic manifestations. Prenatal and perinatal periods were uncomplicated, and early psychomotor development went normally and timely. According to her parents, during the patient's preschool years she was a calm and shy child but, despite that, sought attention and was able to express affection decently. At the age of 4 years, she started to go to preschool in which she had a few friends and no significant difficulties in adapting. From the beginning of primary school (at the age of 6 years) the patient “faced difficulties in learning”: subjectively had problems with concentrating, a weaker memory, and a slower performance than her peers. According to her parents, she was still able to participate in all curricular activities successfully which was explained as a result of some extra support and care from an attentive teacher. From the 5th grade (when the patient was 11 years old) the complaints started to loom: she subjectively had a hard time sitting still during the lessons because of poor concentration and “many thoughts interfering to her mind”. Her academic performance started to decrease ever since (from an average of ~6-7 during the 5th grade to an average of 4 in the 11th grade). In the 7th grade (13 years old) she started to have trouble falling asleep because of many interfering thoughts and experienced an episodic, strong anxiety, led by an increased heart rate; at that time, she did not seek any medical treatment. While studying in the 8th grade (14 years old) the patient had experienced acute psychoemotional stress (homicide of her older brother) after which she started to commit actions of self-harm (cutting her forearms and

thighs with a razor); this behaviour lasted for approximately 6 months. During that period, she also felt increased anxiety while participating in social interactions with other peers, led by stuttering and vegetative reactions (e.g. increased palm sweating) and expressed a lack of motivation to study. Because of these complaints, she was administered to the Department of Adolescent Psychiatry. A psychological evaluation of her emotional status was performed (using the Hospital Anxiety and Depression Scale- HADS), which showed high levels of depression and medium levels of anxiety. A diagnosis of moderate depressive episode was established and the 10-day treatment in an in-patient setting was carried out due to her low mood, suicidal thoughts, and self-harm ideations. After her discharge from the hospital, she was advised to carry on taking Fluoxetine 20 mg/day. However, she refused to continue the treatment in an outpatient setting and stopped taking the medicine soon after the end of hospitalization. The patient recalled a notable improvement in her condition during the 9th grade (at 15 years old), characterized by improved sleep quality and increased motivation to participate in daily activities and studies. However, she was unable to identify any specific reasons for this positive change. In the 11th grade (17 years old) she experienced another deterioration of her mental status: strong, persistent anxiety, difficulties in concentrating due to “the feeling like more than 15 thoughts were jumping in her mind at the same time”, and sleep disturbances, including severe difficulty falling asleep and waking up in the morning. The patient claimed that due to her distorted sleep she missed many lessons and eventually was not motivated to go to school or participate in any activities at all. Her academic performance dropped significantly and, because of her poor attendance and attainment, she was strongly advised to leave her former school after completing the 11th grade. She decided to finish her secondary education (12th grade) at a school of vocational education and training; however, as the same symptoms persisted and her sleep remained distorted she was unable to attend classes again. It forced her to temporarily stop her studies. 4 months before her admission to the psychiatric ward, the patient was consulted by a neurologist regarding her sleep issues. Following a thorough neurological examination, no somatic pathology was identified, and the patient was referred to a psychologist for an evaluation of her emotional status. The psychological assessment revealed markedly high levels of anxiety (HADS anxiety score of 17, with a range of 0 to 7 considered normal and maximum score being 21 [27]) and signs indicative of depression (HADS depression score of 9, with a range of 0 to 7 considered normal and maximum score being 21 [27]). The neurologist recommended further evaluation by a psychiatrist to consider possible diagnoses of ADHD, depression, or anxiety disorder. After the following psychiatrist's consultation, the diagnosis of a moderate depressive episode was made and Bupropion 75 mg/day and Quetiapine 50 mg/day were prescribed. The patient used these medications for ~5 weeks but claimed that no clinically significant improvement was felt, which was the reason for her hospitalization.

Mental status during the first contact was as follows: tidy appearance, good hygiene; communicating with reluctance.

The patient was tensed and showed signs of anxiety, her mood and facial expressions were bland, she rarely engaged in eye contact. Her thinking was rather slow, concrete, with low productivity. No hallucinations, delusional ideas, signs of delirium or suicidal ideation were seen. The patient was correctly oriented in time and environment but talked quite inconsistently and could not give more details about many subjectively significant life events. Notable problems with concentration and sustained attention were evidenced by episodic distraction, lapses in dialogue, and difficulty retaining conversation topics. The patient also noted difficulties in falling asleep and fatigue during the daytime as well as strong anxiety accompanied by lowered mood and declined interest to participate in any activities. Neurological examination revealed no notable abnormalities at the time of assessment.

After a few days of hospitalisation, it was noticed that the patient had certain repeated behaviours (e.g. arranging her slippers in a specific manner beside her bed before sleeping). Upon reluctant confirmation, she revealed having numerous everyday rituals (e.g. compulsive need to adjust levers on household appliances before bedtime). Efforts to ignore or overcome those impulses resulted in difficulty falling asleep due to heightened distress and anxiety. The patient also reported that her frequent lapses in attention were caused by various perceived imperfections in her surroundings, particularly asymmetrical or uneven features on walls or furniture. She also described experiencing heightened perspiration in her palms, leading to obsessions about cleanliness and compulsive handwashing rituals exceeding 15 times a day. Difficulties in discarding her old possessions due to an intense fear of needing them afterwards (or “something bad would happen”) were also expressed.

A comprehensive psychological evaluation was planned to distinguish between potential mood or personality disorders, intellectual disability, ADHD, autism spectrum disorder (ASD), and OCD. Evaluation of intellectual abilities (WAIS-III) was as follows: verbal intelligence index was very low (VIQ 75), nonverbal intelligence index was lower than average (NIQ 81), and overall intelligence index was low (IQ 76). Her level of general knowledge was notably low compared to her age, and she displayed difficulties with orientation in social situations and memorization; her language expression was notably poor. According to WAIS-III, while engaging in constructive activities, the patient demonstrated a slow psychomotor pace; however, she exhibited significantly better performance in perceptiveness to details and establishing logical sequences of events, reaching normal values in these domains. Qualities of thinking were as follows: abilities for generalization were not higher than average and mostly based on nonessential features and accentuation of the function of the object. In the process of generalisation, some features of inert thinking were seen. In the adult ADHD Self-Report Scale (ASRS-v 1.1) likely signs of ADHD were noticed (the patient gathered 4 responses at specific severity levels in Part A and 8 responses at specific severity levels in Part B). In the obsessional compulsive inventory (OCI-R) the patient attributed herself significantly more obsessions/ compulsions than the general population (scored 47 points; recommended

cut-off for OCD is 21 (28)), especially obsessive thoughts (10/12 points), compulsive behaviour like excessive washing (9/12 points), ordering and checking (8/12 points) and hoarding (12/12 points). The patient’s personality assessment revealed immaturity, heightened sensitivity, low self-assurance, low self-esteem, and indications of particularity. These traits could contribute to difficulty in decision-making, fear of taking risks, and avoidance of unfamiliar situations. The patient exhibited a relatively high level of social discomfort, preferring solitude over social interaction. The Childhood Autism Rating Scale, Second Edition (CARS2-ST), completed based on information from both the patient and her mother, yielded a score of 22.5, indicating the absence of autism-specific features.

Initial treatment was started with a low dose of Paroxetine (20 mg/ day) together with Lorazepam (up to 3 mg/ day) to tackle the patient’s low mood and anxiety; augmentation with Quetiapine (75 mg/ day) was also selected. A quick and considerable improvement in anxiety and sleep quality occurred during the first 3 days of treatment and prompted a gradual reduction in Lorazepam to 2 mg/day and Quetiapine to 25 mg/day. A significant deficiency in attention and concentration persisted: though the patient’s ability to retain attention remarkably improved, she continued to complain of too many thoughts in her mind which complicated her daily activities. A tricyclic antidepressant Clomipramine (25 mg/ day) was introduced during the 5th day of her hospitalization; following the initiation of the treatment with Clomipramine, the patient reported a reduction in intrusive thoughts, leading to a notable improvement in sustaining attention as well as an improvement in some compulsive behaviours (e.g., reduced frequency of hand washing). On the 9th day of treatment, Clomipramine dosage was increased to 50 mg/day to reach the target dose while the dose of Paroxetine was also raised to 30 mg/day to manage anxiety symptoms and facilitate the tapering of Lorazepam until complete discontinuation. Further titration of Paroxetine and Clomipramine in an in-patient setting was not possible because of the manifestation of gastrointestinal complaints (strong nausea), and the patient’s refusal to continue higher doses and wait for the reduction of side effects.

After 17 days of hospitalization, the patient exhibited reduced anxiety levels, improved mood, sleep, attention, and depletion of intrusive thoughts and compulsive behaviours. Upon discharge, it was recommended to continue Paroxetine at 30 mg/day, Clomipramine at 50 mg/day, Quetiapine at 25 mg/day, and Lorazepam at 2 mg/day (gradually tapering until complete discontinuation). Treatment continuation for at least 12 months post-OCD remission, alongside cognitive-behavioural therapy (CBT), was recommended to prevent relapse and facilitate further improvement.

DISCUSSION

This clinical case is interesting due to many different aspects. The patient’s complaint of excessive thoughts and inability to concentrate is not typically associated with OCD, highlighting the diverse symptomatology of the disorder. Clinical manifestation of OCD symptoms could be suspected since the age of 11, which complies with the consideration that

obsessive-compulsive disorder has a bimodal age distribution with a first peak at age 11 and a second peak in early adulthood [15]. The patient's symptoms have been perceived as a part of moderate depressive episode both by in-patient and out-patient psychiatrists; a possible neurological deficit was also suspected and required the examination of a neurologist. We can only hypothesize whether the latest chosen outpatient treatment for the moderate depressive episode, which included Bupropion, was intended to address some of the potential ADHD symptoms as this dopamine and noradrenaline reuptake inhibitor is one of the second-line medications used for the treatment of ADHD [29]. The experienced difficulties and delays in diagnosing OCD could be attributed to the patient's below-average intellectual abilities, potentially worsening her introspection of OCD symptoms. For instance, it is noted that compulsions which occur in mentally disabled patients lack "ego-dystonic" qualities that normally lead to reporting their behaviours as excessive or absurd. It has also been documented that the assessment of observable behaviour has good reliability in diagnosing OCD in such patients [30]. In the presented clinical case, this aspect played a significant role in formulating the diagnosis as well.

During the process of differential diagnostics, the evaluation of whether the patient might have ADHD, OCD, or both posed a challenging task. It was known that even though ADHD and OCD appear to be considerably different in terms of their phenomenology, both can present with symptoms of inattention and distraction. Differentiating between primary attentional symptoms and attentional symptoms secondary to a core anxiety disorder was crucial as the attention/concentration difficulties, typical of these two pathologies, can represent symptomatic epiphenomena of different psychopathological nuclei [31, 32]. Completely different treatment strategies are needed: while stimulant medication is typically recommended as the first-line treatment for ADHD, some studies show that its use in OCD may exacerbate OCD symptoms; conversely, SSRIs, the first-line treatment for OCD, are not considered effective for ADHD [7, 33]. The possibility of both conditions co-occurring was also considered, given the reported prevalence rates of ADHD in adult OCD patients ranging from 3% to 52% [6]. However, the significant disparity in these statistics has led some authors to propose that genuine OCD-ADHD comorbidity might be uncommon, with one disorder potentially mimicking another [19, 31]. In certain studies it was suggested that OCD-ADHD comorbidity likely exists only in the presence of a primary or a history of tic disorder, which was absent in the patient's medical history [8, 19].

According to Abramovich, there are several differential features which can specify primary OCD from ADHD [19]. Firstly, most individuals with OCD often exhibit perfectionistic tendencies and are overly critical of their performance [19]. In the presented case the patient did not openly display perfectionism (possibly due to lower intellectual abilities) but her personality evaluation revealed traits of particularity and a focus on details. Secondly, in most cases OCD compulsive rituals are carefully planned, rigidly executed sequences of mental or behavioural acts that are

governed by specific rules; these characteristics are associated with overloading the executive system, particularly working memory, and would make OCD-compulsive rituals unlikely to be performed by individuals with primary ADHD [8, 19]. Given the individuals report intrusive thoughts instead, it is important to inquire whether these thoughts cause significant emotional distress, as seen in OCD, or not, as seen in ADHD. It is also necessary to assess whether the person is trying to cancel these thoughts by mental or behavioural rituals [19]. In this case, the patient described everyday rituals marked by specific rules and sequences of actions, accompanied by emotional distress due to her intrusive thoughts which were often followed by behaviour rituals to relieve them; in circumstances when she tried to resist these strong urges, intense anxiety emerged. Thirdly, ADHD is associated with behavioural impulsivity, sensation seeking, and risk-taking [32]. In contrast, studies show that OCD is characterized by reduced impulsivity compared to non-psychiatric controls and by significantly lower behavioural impulsivity and risk-taking compared to ADHD [19]. The patient's clinical presentation and psychological examination revealed a fear of taking risks and a tendency to avoid unknown situations. It aligned more closely with OCD as avoidance is a typical method to avert obsessions from triggering [34].

According to the Updated European Consensus Statement on diagnosis and treatment of adult ADHD, establishing all comorbidities before initiating treatment is crucial to determine the best treatment order, with priority given to the most severe disorder [33]. Pharmacological treatments should be introduced one at a time to monitor treatment response and side effects [31]. The initial psychopharmacological treatment has been oriented to the patient's visible anxiety and sleep disturbances, which caused significant distress and were considered to take its toll on her attentional deficiencies. A low dosage (20 mg/day) of Paroxetine, a selective-serotonin reuptake inhibitor (SSRI) which shows a marked anxiolytic effect and reduction in avoidance related to phobic symptoms, was initiated together with benzodiazepine Lorazepam (3 mg/day) and atypical antipsychotic Quetiapine (75 mg/day) for augmentation, anxiety reduction, and sleep induction. Subsequently, upon the disclosure of obsessive-compulsive symptoms, the treatment plan was adjusted. As SSRIs are the first-line pharmacological treatment of OCD and no superiority of one SSRI over the other could be seen in various meta-analyses, it was decided to continue Paroxetine [1, 2, 35, 36]. Quetiapine and Lorazepam were also kept: the addition of antipsychotics to standard serotonin enhancers is one of the most documented strategies for augmentation while benzodiazepines are common adjuvants to the reduction of anxiety [1, 35, 36]. It is generally recommended that OCD would be treated with a higher dose of SSRI than the one used in, e.g., depression as it is associated with better clinical response [1, 2, 34]. Nevertheless, the patient did not tolerate a higher than 30 mg dose of Paroxetine due to the complaints of gastrointestinal symptoms and her personal beliefs. Even though a significant reduction of anxiety was achieved, the disturbances in attention and concentration as well as obsessive thoughts and compulsive behaviours persisted so

a new psychopharmacological approach was needed. As the Cognitive Behavioural Therapy/ Exposure and Response Prevention (which is another first-line treatment option for OCD) [1, 36] was not available, a serotonergic tricyclic antidepressant Clomipramine was added, starting from 25 mg/ day. The efficacy of this medication in OCD treatment, according to some studies, appeared to be equivalent to or slightly better than that of SSRIs, although its side effect profile is less favourable [37, 38]. Some studies suggested that the combined treatment with Clomipramine and an SSRI is effective and well tolerated. [36, 39] The dosage was increased to 50 mg/day, with no significant side effects reported; the patient subjectively experienced fewer intrusive thoughts and improved concentration. OCD treatment guidelines indicate that 8–12 weeks is the optimal duration of an SSRI or Clomipramine trial to determine efficacy, but a few meta-analyses noted a significant improvement of OCD symptoms within the first 2 weeks and the greatest incremental gains occurring early in the course of treatment [34, 40, 41]. A similar pattern of improvement in the patient's condition was seen and a significant reduction of symptoms was reached during 17 days of hospitalization.

Likely signs of ADHD were seen in the adult ADHD Self-Report Scale (ASRS-v 1.1) but the positive response to treatment and clinical observation led to the conclusion that inattention symptoms might be a consequence of obsessional thinking rather than indicative of comorbid ADHD. This interpretation was supported by research indicating that the exhaustion of the executive system caused by obsessional thinking results in behaviours that are phenomenologically similar to symptoms of ADHD (e.g., distractibility, forgetfulness), but instead are

related to OCD. [8] The diagnostic decision may have been influenced by the limitations imposed by the current use of ICD-10-AM in Lithuania because under this classification system the patient may not meet the specific criteria for additional HKD but might suffice for the “predominantly inattentive” type of ADHD in DSM-5-TR. It emphasizes the misalignment between DSM-5-TR and ICD-10-AM regarding ADHD diagnosis, highlighting inconsistencies and challenges in diagnostic practices, particularly in regions where the ICD is the primary diagnostic manual [42]. This phenomenon could potentially explain the significant discrepancies observed in the reported prevalence rates of ADHD across various studies. As the ICD-11 revision of ADHD aligns more closely with DSM-5-TR, integrating subtypes of ADHD from DSM-5-TR and introducing additional subtypes, its future implementation might reduce discrepancies and promote uniformity in clinical practice.

In conclusion, this case report highlights the polymorphic nature of OCD and attentional problems which could disguise many of its typical symptoms. Additional research into OCD, its potential presentations, and its co-occurrence with ADHD is needed. Comprehensive studies that address the discrepancies between systems of psychiatric classification are required to gather reliable data on the prevalence of concurrent OCD and ADHD in adults. It would enable a precise assessment of their influence on clinical outcomes, prognosis, and the formulation of effective treatment approaches.

Patient consent for the case report was obtained.

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Trumpa seksualinio distreso skalės versija (*angl.* Short version of the Sexual Distress Scale, SDS-3)

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Vis didėjantis mokslininkų susidomėjimas seksualumo temomis patvirtina, kad seksualinė sveikata yra svarbus žmonių sveikatos ir gerovės aspektas [1]. Remiantis Pasaulio Sveikatos Organizacijos (PSO) apibrėžimu, seksualinė sveikata nėra tik seksualinio sutrikimo ar ligos nebuvimas, tai yra būseną, apimanti su lytiškumu susijusią, fizinę, emocinę, psichiką ir socialinę gerovę [2].

COVID-19 pandemijos metu atlikti tyrimai taip pat išryškino seksualinės sveikatos reikšmę psichikos sveikatai šiuo sudėtingu laikotarpiu [3]. Pavyzdžiui, remiantis tuo laikotarpiu internetu vykdytos apklausos, kurioje dalyvavo daugiau nei 6 tūkst. asmenų, duomenimis galime daryti prielaidą apie sąsajas tarp didesnio seksualinio aktyvumo lygio ir mažesnio dalyvių depresijos ir nerimo sutrikimų simptomų pasireiškimo [4].

Deja, nepaisant seksualinės sveikatos reikšmės žmonių psichikos sveikatai, sveikatos priežiūros specialistai ir pacientai vis dar nesijaučia pasiruošę komunikuoti seksualinės sveikatos klausimais ir laiko tai „tabu“ [5]. Todėl svarbu ieškoti stigmą mažinančių priemonių darbu su seksualine sveikata.

Seksualinė disfunkcija yra vienas iš veiksmingai veikiančių individų seksualinę sveikatą [6, 7], o seksualinės funkcijos sutrikimų paplitimas skirtingose grupėse yra didelis [8]. Pavyzdžiui, Vokietijos reprezentatyvioje imtyje su bent viena iš seksualinių disfunkcijų gyvenimo eigoje susidūrė 33,4 proc. vyrų ir 45,7 proc. moterų [6]. O kultūriškai į Lietuvą panašioje šalyje – Lenkijoje, 40 proc. moterų ir 36,5 proc. vyrų nurodė turėję bent vieną seksualinę disfunkciją [9].

Seksualines disfunkcijas apibūdina ne tik seksualinių funkcijų ar malonumo patyrimo sutrikimai, tačiau kartu patiriamas seksualinis distresas [10]. Seksualiniu distresu laikomos neigiamos emocinės reakcijos, tokios kaip, kaltė, nerimas, nusivylimas ir kt., susijusios su lytiniu gyvenimu [11]. Šios subjektyvios emocinės patirtys, susijusios su seksualiniais sunkumais, gali būti vertingas seksualinės sveikatos rodiklis [12]. Taip pat, Tarptautinės ligų klasifikacijos-11 (TLK-11) [13] ir Psichikos sutrikimų diagnostikos ir statistikos vadovo-Diagnostic and Statistical Manual of Mental Disorders, DSM-5) [14] sisteminiuose ligų sąrašuose seksualinio distreso patyrimas yra būtina sąlyga seksualinių disfunkcijų diagnostikai.

Seksualinio distreso matavimui vienas dažniausiai

naudojamų instrumentų – Moterų seksualinio distreso skalė (*angl.* Female Sexual Distress Scale, FSDDS) [15]. Tai yra 12 teiginių skalė, kuri pirmiausiai buvo sukurta moterų seksualinio distreso vertinimui, bet vėliau buvo validuota tiek vyrų, tiek moterų imtyse [16]. Siekiant sumažinti respondentų apkrovą pildant apklausas, FSDDS skalė buvo sutrumpinta ir iš jos teiginių sukurtos dar dvi skalės – 3 teiginių Seksualinio distreso skalė (SDS-3) [17] bei 5 teiginių Seksualinio distreso skalė (SDS-SF) [18]. Visgi, sklandesniam klinikiniam darbui bei didelių apklausų efektyvumui pagerinti, laiko taupymo sumetimais dažniau taikoma trumpesnė SDS-3 skalė [12].

SDS-3 skalė yra skirta seksualinio distreso įvertinimui per paskutiniąsias 30 dienų [12]. Skalę sudaro trys teiginiai, kiekvienas jų vertinamas penkiabalėje Likert'o skalėje nuo 0 (niekada) iki 4 (visada). Galutinį rezultatą sudaro visų teiginių balų suma. Susumuoti balai gali svyruoti nuo 0 iki 12. Didesnis suminis balas nurodo pastarųjų 30 dienų laikotarpiu patirtą aukštesnę seksualinę distresą.

SDS-3 instrumento validavimo tyrimas buvo Tarptautinio seksualinio elgesio tyrimo (*angl.* The International Sex Survey; ISS) dalis [19]. Tai yra 42 šalyse atliktas skersinio pjūvio internetinis tyrimas. SDS-3 skalė buvo vienas iš apklausos instrumentu padėjusių įvertinti seksualinę distresą. Anglų kalba sudaryta originali apklausa dvigubo vertimo principu buvo išversta į 25 kalbas, tarp jų ir į lietuvių kalbą [19]. Validavimo tyrime galutinę imtį sudarė 82 243 ISS tyrimo dalyviai, kurių vidutinis amžius buvo 32,39 (SD = 12,52) [10]. 57 proc. tiriamųjų buvo moterys, 39,6 proc. vyrai ir 3,4 proc. nurodė priskiriantys save kitai lytinei tapatybei. Tiriamieji surinkti iš 42 šalių, iš kurių 2094 (2,5%) buvo lietuviai [11].

Kadangi originaliame SDS-3 skalės tyrime [17] nebuvo pakankamai iširti psichometriniai rodikliai, skalės validumui ir patikimumui įvertinti buvo pasitelkti ISS tyrimo duomenys. Su jais atlikta vidinio suderintumo bei patvirtinančiosios faktorių analizės [12]. Patikimumo analizė indikavo aukštus patikimumo rodiklius (Cronbach $\alpha = 0,83$), o validumo analizė atskleidė 1 faktoriaus skalės struktūrą [12].

Apibendrinant, SDS-3 yra patikima ir validi skalė seksualinio distreso vertinimui, kuri gali prisidėti prie kokybiško įvertinimo moksliniuose tyrimuose bei klinikinėje praktikoje.

Toliau pateiktas sąrašas su seksualumu susijusių jausmų ir problemų, su kuriomis kartais susiduria žmonės.

Įdėmiai perskaitykite kiekvieną iš jų ir pasirinkite atsakymą, geriausiai apibūdinantį, kaip dažnai per pastarąsias 30 dienų su šia problema susidūrėte Jūs arba kaip dažnai ji kėlė Jums distresą.

	Niekada	Retai	Kartais	Dažnai	Visada
1. Susikrimtęs dėl savo seksualinio gyvenimo?	0	1	2	3	4
2. Menkavertis dėl savo seksualinių problemų?	0	1	2	3	4
3. Susirūpinęs dėl sekso?	0	1	2	3	4

Pastaba: skalę galima naudoti tik nekomerciniuose moksliniuose tyrimuose, rekomenduotina nurodyti šiuos informacijos šaltinius:

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Mindaugas Urbonas - Significance of transorbital ultrasound and thyroid hormones in idiopathic normal pressure hydrocephalus



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INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is underdiagnosed and undertreated disorder that causes deterioration of quality of life (QoL) among affected patients. One of the main factors that contribute to the progress of scientific research is the investigation of new methods and tools. In the course of this study, the application of transorbital ultrasound, which has not yet been described in the literature, was evaluated as a tool for the screening of the patients with suspected normal pressure hydrocephalus and also for the further follow-up after the surgery. As far as we know, there are no reports in the literature regarding low T3 syndrome in iNPH patients who had a ventriculoperitoneal shunt surgery. In this study, it was investigated that low T3 syndrome is not associated with a poorer quality of life after the ventriculoperitoneal shunt surgery in iNPH patients. There is limited data in the literature regarding the factors predicting quality of life patients with iNPH. This study was the first which reported that FT3/FT4 thyroid hormone ratio is related to the quality of life of patients with iNPH. During this study it was investigated that thyroid hormones tested before the surgery have a prognostic value in assessing the quality of life of patients with iNPH after the ventriculoperitoneal shunt surgery.

AIM

The aim of this study was to investigate the new diagnostic method and endocrine factors influencing the medium-term outcome after the surgery for idiopathic normal pressure hydrocephalus.

OBJECTIVES

1. To investigate the changes of the optic nerve sheath diameter (ONSD) between supine and upright positions preoperatively and postoperatively in iNPH patients.
2. To assess Evans index quantitatively using ultrasonographic ONSD measurements in supine and upright positions in iNPH patients.
3. To explore the changes in serum levels of thyroid-stimulating hormone, free thyroxine, free triiodothyronine preoperatively, the next day and 3 months after the operation in iNPH patients.
4. To investigate whether thyroid axis hormone levels on admission have an impact on the outcome with respect to the QoL, anxiety and depression symptoms in iNPH patients.
5. To investigate whether changes in ventricular volume have an impact on the outcome with respect to the QoL, anxiety and depression symptoms in iNPH patients.

CONCLUSIONS

1. The changes in ultrasonographic measurement of the optic nerve sheath diameter were investigated in patients with idiopathic normal pressure hydrocephalus when moving from the supine to the upright position (“gravitational challenge”) before and after the ventriculoperitoneal shunt surgery. The preoperative variation of optic nerve sheath diameter was 5.45 % and postoperative (4–5 day after the shunt surgery) 8.61 %, respectively.

2. Evans index can be assessed quantitatively by the ultrasonographic measurements of the optic nerve sheath diameter in patients with idiopathic normal pressure hydrocephalus when moving from the supine to the upright position.

3. Ventriculoperitoneal shunt surgery for patients with normal pressure hydrocephalus have beneficial effects on thyroid hormones. The changes in thyroid hormones resulted in a U-shaped curve throughout the follow-up period. The significant changes occurred the next day after the surgery, including a decrease in TSH, FT3, and an increase in FT4. Additionally, the decrease occurred in mean FT3 for patients with preoperative low T3 syndrome. At three months after the shunt surgery, thyroid hormones were restored to their baseline and/or normal values.

4. Overall, quality of life improved in 60 % of iNPH patients at 3 months after the ventriculoperitoneal shunt surgery. The change has been significantly linked with physical and social domains during the follow-up period of 3 months. Low T3 syndrome was not associated with poorer quality of life of patients with idiopathic normal pressure hydrocephalus treated with ventriculoperitoneal shunt surgery. The preoperative FT3/FT4 thyroid hormone ratio was associated with the quality of life and the symptoms of anxiety and depression in idiopathic normal pressure hydrocephalus patients after the surgery. Patients who had low-normal levels of FT4 and high levels of FT3 preoperatively were at increased risk for non-improvement in their quality of life after the ventriculoperitoneal shunt surgery as compared to patients with high normal levels of FT4.

5. The change in ventricular volume was associated with the quality of life of iNPH patients at 3 months after the ventriculoperitoneal shunt surgery. The change has been significantly linked with general health, vitality, and mental health domains. Also, the change was associated with the symptoms of anxiety and depression 3 months after the surgery.