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COMBINATION OF FOLINIC ACID AND PSYCHOTHERAPY AS A MODERN METHOD OF TREATMENT OF AUTISM SPECTRUM DISORDER – A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Autism spectrum disorder (ASD) is a complex disorder of the development and functioning of the central nervous system. The onset of the disorder is usually in early childhood. It is characterized by difficulty in reading and communicating feelings, disturbances in the ability to build interpersonal relationships, as well as impoverishment and stereotypical behavior.
Materials and methods: This article, based on a PubMed review of available research, examines the impact of folinic acid and Picture Exchange Communication System therapy on improving communication in children with ASD.
Results: In the first of the reported studies, a double-blind study was conducted - 48 children with an autism spectrum disorder and language impairment were randomized to receive 12 weeks of high dose folinic acid or placebo. The improvement in verbal communication, as measured by a standardized ability-appropriate tool, was significantly greater in participants receiving folinic acid compared to those receiving placebo.
In the second test, 20 children were qualified for the study. The program consisted of 24 sessions of individual speech therapy and followed the six phases proposed in the PECS training manual. All children were clinically assessed by a team of child psychiatrists, neuropsychologists and speech therapists. After the study was completed, there was a clear increase in children's understanding of all instructions compared to the initial phase of the program.
Conclusions: The therapies described above improve the communication skills of patients on the autism spectrum. Not only does it provide an augmentative or alternative communication tool for children to express their needs, it also significantly improves understanding of contextual information.

KEYWORDS

Autism Spectrum Disorder, Folinic Acid, Psychotherapy, Communication

CITATION

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Introduction.

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition that manifests primarily through pronounced challenges in social interaction and communication. Individuals with ASD often experience significant difficulty in forming and maintaining interpersonal relationships, as well as in interpreting social cues. In addition, they typically display rigid, repetitive behaviors or routines, along with intensely focused interests that may seem unusual in their scope or intensity. These symptoms usually become noticeable in early childhood, although the presentation can vary widely between individuals in terms of severity and specific characteristics. ASD affects multiple areas of daily functioning, often leading to impairments in personal life, academic performance, and social development. Many individuals with autism also exhibit challenges in language acquisition, intellectual development, or adaptive functioning, depending on where they fall on the spectrum. The disorder's impact is multidimensional, influencing not just cognitive and communicative abilities, but also emotional and behavioral regulation. According to the ICD-10 (International Statistical Classification of Diseases and Related Health Problems), the autism spectrum encompasses several distinct diagnostic categories. These include childhood autism, atypical autism, and Asperger’s syndrome. While each subtype presents with unique traits, they all share a core set of difficulties related to social functioning, restricted interests, and repetitive behaviors. Understanding these categories helps in tailoring support and interventions to meet the diverse needs of individuals on the spectrum [1,2].

Pathophysiology

Recent neuroanatomical studies suggest that autism spectrum disorder (ASD) is associated with atypical patterns of brain development, involving both regional overgrowth and underdevelopment. Specifically, certain brain areas appear to be enlarged, while others may be reduced in size or show signs of disrupted connectivity [3]. These irregularities are thought to result from abnormal proliferation, migration, and organization of neurons during critical periods of prenatal and early postnatal brain development. Key regions implicated in ASD include the frontal lobe, which is responsible for executive functions and decision-making; the mirror neuron system, believed to play a role in imitation and social understanding; and the limbic system, which regulates emotion and memory. Additional abnormalities are often observed in the temporal lobe, crucial for language processing and social cognition, and in the corpus callosum, the major structure facilitating communication between the two hemispheres of the brain. These structural and functional differences support the theory that ASD stems from disrupted neural connectivity, leading to the wide range of cognitive, social, and behavioral symptoms seen in affected individuals [4,5].

Causes of ASD

The underlying cause of autism spectrum disorders is widely believed to involve neurological abnormalities, although the exact etiology remains largely unknown. Current research points to a multifactorial origin, where both genetic and environmental components likely interact during early development to contribute to the onset of the disorder. Among the most frequently proposed contributing factors is a genetic predisposition, particularly involving mutations or irregularities in genes such as EN2, located on chromosome 7, which has been associated with brain development and neural patterning.

In addition to genetic influences, a number of environmental and physiological risk factors have been suggested. These include advanced paternal age, especially in men over 40, which has been linked to an increased likelihood of de novo genetic mutations. Certain metabolic disorders, such as gluten or casein intolerance, have also been proposed to affect neurodevelopment, although the evidence in this area remains controversial. Moreover, disruptions in the gut micro biota - sometimes referred to as "intestinal dysbiosis" - are gaining attention for their potential role in altering brain-gut communication, possibly influencing behavior and cognition.

Other factors that may increase the risk of ASD include perinatal complications such as oxygen deprivation during birth, early brain injuries, congenital infections like toxoplasmosis, and the presence of cerebral palsy. Furthermore, the use of intense or prolonged antibiotic therapy in infancy has been speculated to alter the gut-brain axis, possibly affecting neurological outcomes. While none of these factors can be considered definitive causes on their own, they highlight the complexity of ASD and underscore the need for further interdisciplinary research to better understand its origins [6].

Communication disorders in children with autistic disorders

In addition to difficulties in establishing proper social interactions, people with ASD have problems verbally and non-verbally communicating with other people. This disorder occurs in various forms and degrees of severity, and mainly concerns the transmission of one's needs, desires and thoughts through words, tone of voice, facial expressions and gestures, and the understanding of the content conveyed to them. In addition, there are difficulties with the appropriate reception of information from the environment (relationships between the actions of other people, the consequences of these actions) and relations between phenomena (difficulties in recognizing the context, clues), having only the literal meaning of individual words at their disposal [7]. Speech and social communication disorders include:

- echolalia - a thinking disorder manifested as unnecessary repetition of words or phrases spoken by other people; it is present at an early stage of a child's development, serves to enrich vocabulary and as a method of maintaining dialogue. People on the autism spectrum have been around for a long time. It can take the form of direct echolalia (immediate repetition of words, phrases, immediately after hearing them), delayed echolalia (when the heard content is repeated only some time after hearing) or functional echolalia (repeating the statement in the appropriate situational context);
- lack of motivation to establish contacts with the environment;
- difficulties in understanding non-verbal communication;
- compulsive asking questions while ignoring answers - these questions are asked in a stereotypical way, many times a day, regardless of how often the answer is given. It happens that the person suddenly stops talking and walks away, ignoring the needs of the interlocutor;

- visual thinking - oral information is often incomprehensible due to the short time of emission, therefore communication is more efficient when verbal statements are accompanied by visualization;
- focusing on a selected topic and continuing the thread regardless of the reaction of the environment - most often results from unawareness and misunderstanding of non-verbal signals sent by the interlocutor, it can lead to rejection and isolation;
- disorder of speech prosody (accent, intonation, rhythm) - speech is interrupted, disfluent, chanted;
- limited ability to understand the meanings associated with different tones of voice;
- literal interpretation of statements, problems with reading communication overtones (semantic-pragmatic disorders) [1.8].

Communication rules

Talking to children with ASD is a challenge. That is why it is important to be patient and follow the rules defined by psychologists. During the conversation, short, simple verbal messages should be given, and there should be pauses between sentences to give the child time to process them. Remember to avoid sarcasm, irony, ambiguous statements, idioms or proverbs. Also important is the mirroring technique, which involves naming the child's feelings (e.g. "you felt jealous"). In this way, it learns to identify its own emotions. When we want to issue a command or instruction, we should divide it into parts. It may be helpful to prepare a detailed flowchart, preferably in writing. You should also make sure you understand what your child has said and give feedback on how you feel about what he or she has said. In addition, we should pay attention to the compatibility of our verbal and non-verbal messages, look into the eyes of the interlocutor and direct the silhouette towards him [7-9].

Speech therapy

Unfortunately, autism and other diseases on its spectrum are incurable. However, the effects of these disorders can be mitigated [10]. Speech therapy is often used for this purpose. It consists of a set of specific interventions aimed at removing any disturbances in the communication process (from simple speech impediments to complete inability to speak). In the course of therapy, three fixed stages are distinguished: initial, proper and final. The initial stage includes all exercises that precede the proper therapeutic procedure. It includes breathing exercises, phonation exercises, articulation organs exercises, auditory exercises or exercises of individual mental functions (such as attention, memory). These exercises can be an integral part of the main stage, but then you need to expand or narrow their specific parts. The proper and final stages are specific to different types of therapy used for specific speech disorders. Speech therapy is tailored to the individual needs of the child and consists in building basic language, communication and cultural competences. In children suffering from ASD, speech therapists focus mainly on enriching active and passive vocabulary, learning the correct intonation, eliminating echolalia and stereotypical slogans, and also trying to teach the child to initiate and maintain a conversation. The therapy uses behavioral intervention, which is based on the system of reward and punishment. Currently, the positive approach dominates - the work of the pedagogue focuses on reinforcing correct behaviors and extinguishing incorrect (socially unacceptable) behaviors, with extinguishing not by negative reinforcement, but by the lack of positive reinforcement [8,11].

Picture Exchange Communication System

PECS (Picture Exchange Communication System) is an alternative and augmentative communication system, developed in the United States in 1985 by Dr. Andy Bondy and MA Lori Frost. Its purpose is to support and initially develop the ability to communicate through pictures. Learning the system consists of 6 phases. In Phase I, the child is encouraged to use the cards to show their desire for a particular item. In phase II, the child must understand the importance of using cards and use them persistently in any communication situation. In phase III, it is encouraged to choose a target figure from several options. In phase IV, the child learns to make sentences from cards using action verbs and features of objects (such as color, size). In phase V, they are encouraged to answer the question "What do you want?" through simple flashcard phrases. In turn, in phase VI, the child answers the questions: "What do you see?", "What are you listening to?", "What is it?" and spontaneously asks and comments on situations using phrases created using cards [12-14].

Impact of PECS on communication

A study was conducted for which 20 children were qualified. Inclusion criteria included ASD diagnosis, age group 6-12 years, and no or minimal verbal communication. The program consisted of 24 weekly sessions of individual speech therapy. Eight visual and eight oral instructions were used to assess comprehension of commands: "go for...", "give me...", "hold...", "put in...", "go to...", "sit down", "eat...", "stop". All children were clinically assessed by a team of child psychiatrists, neuropsychologists and speech therapists. The assessment of the level of communication was carried out using the SON-R test. It is designed to measure the level of intellectual functions that underlie for learning speech and reading in people whose speech development is not normal, it was used individually by the team's neuropsychologists in children.

About 80% of the children progressed to Phase IV and started building phrases using action verb cards. About 60% of children reached stage V and only 20% reached stage VI. The decline in phase V and VI performance was most likely related to the complexity of the task and the time constraints of the study. The results of the study showed an increase in response to all verbal instructions when comparing data from phase II and phase IV of the PECS program; in six of the eight instructions, this improvement in children's outcomes was statistically significant. There was also a significant increase in response to visual instructions, as in the initial sessions, some children did not respond to certain commands at all. Statistical significance occurred in five out of eight statements [15].

Folate metabolism in the nervous system and the spectrum of autistic disorders

Folate plays a crucial role in neurodevelopment, particularly during prenatal and early postnatal periods. It is essential for DNA synthesis, repair, methylation, and overall cellular function in the developing brain. To exert its effects, folate must efficiently cross both the placental barrier during pregnancy and the blood-brain barrier in the infant's nervous system. This transport process relies on specialized mechanisms involving the high-affinity folate receptor alpha (FRα) and the reduced folate carrier (RFC).

In some individuals the presence of FRα autoantibodies - immune system antibodies directed against the folate receptors - can significantly impair folate transport. These autoantibodies block the binding and uptake of folate into cells, potentially leading to a functional folate deficiency in the brain, despite normal or even elevated blood folate levels. This disrupted folate metabolism has been increasingly studied in relation to neurodevelopmental conditions, particularly autism spectrum disorders.

Research indicates that children with ASD have a significantly higher prevalence of FRα autoantibodies compared to typically developing children. These findings suggest that altered folate transport to the brain - possibly due to an autoimmune response - may be a contributing factor in the development or severity of autism in some cases. The identification of this mechanism has opened new avenues for potential therapeutic interventions, such as high-dose folinic acid supplementation, which may help bypass the blocked receptor pathways and restore folate availability in the central nervous system [16,17].

Folinic acid therapy

To determine whether high doses of folinic acid could alleviate core and related symptoms of autism spectrum disorder, a randomized, double-blind trial was conducted. It has been hypothesized that high doses of folinic acid will alleviate communication-related ASD symptoms. In addition, we sought to determine whether the presence of FRα autoantibodies could be a predictor of response to folinic acid treatment.

In this study, 48 children with an autism spectrum disorder and language impairment were randomized to receive 2mg/kg folinic acid for 12 weeks or a placebo. Children were subtyped according to FRα autoantibody status. Verbal communication was assessed using the Clinical Evaluation of Language (CELF-5) scale. It contains structured tests of language skills (including observational and interactive measures) in order to obtain a complete picture of the language skills of the test subjects.

The improvement in verbal communication was significantly greater in participants taking folinic acid compared to participants receiving placebo for participants who tested positive for FRα autoantibodies. For participants without FRα activity, the improvement in verbal communication was not significantly different between the groups [18].

Conclusions

The therapies described above improve the communication abilities of patients on the autism spectrum. Thus, they increase the comfort of life for both children and their parents. They not only provide an augmentative or alternative communication tool necessary to express one's own needs, but also significantly improve the understanding of contextual information. However, these findings should be considered preliminary until treatment is evaluated in larger, multicenter trials of longer duration.

Disclosures

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During preparing this work the authors have used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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