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Saidkhodjaeva Saida

PhD, Associate Professor, Department of Neurology
Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan
e-mail: dr.saida25@gmail.com

INNOVATIVE NEURO REHABILITATION OF AGGRESSIVE BEHAVIOR AND COGNITIVE ABILITIES OF CHILDREN WITH HIV-ENCEPHALOPATHY

The chronic medical conditions in the pediatric population pose a range of potential cognitive and emotional - behavioral challenges not only to the child, but also to the family members and health care providers. Neurological sequels and neurocognitive disorders in infected children are due to static or progressive encephalopathy that influences different domains such as speech and language, memory, learning, information processing and motor functioning. This paper comprehensively reviews the issues of personal observations and carried out modern psycho-neurological investigations of 170 children infected with HIV . The necessity of using the innovative NIRVANA neurorehabilitation system based on immersing the patient into virtual reality and game motivation, which contributed to a significant improvement in motor and emotional disorders, was shown. Virtual reality (VR) shows perspectives for healthcare applications because it provides patients with an exciting, often interesting, approach to achieving the goal of increasing productivity. Also, a persistent tendency to improve the intellectual level and quality of life of physical and emotional activity.

Key words: HIV infection , neurorehabilitation, HIV encephalopathy, children, NIRVANA, memantine.

Introduction

Worldwide, thirty five million people are infected with HIV, with approximately 3.2 million (9%) of them being under the age of 15 [1]. HIV (human immunodeficiency virus) infected children are at risk of growth failure and developmental disorders [2,3]. Severe neurodevelopmental, cognitive and motor dysfunctions have also been shown since the first reports of pediatric AIDS in the 1980s [3,4,5]. Growth failure is common in HIV-infected children; they are shorter and thinner than healthy counterparts [6]. HIV associated neurologic disease was demonstrated in 30% - 60% of infected children and adolescents [7]. Neurological sequels and neurocognitive disorders in infected children are due to static or progressive encephalopathy that influences different domains such as speech and language, memory, learning, information processing and motor functioning. Time of infection, viral load, CD4 count, antiretroviral medication, co-morbid diseases and environmental conditions are effective factors [8-10]. The prevalence of delay in cognition, motor function, speech and language was reported in 8% - 60% of HIV-infected children by Ruel et al. also showed significant motor and cognitive disorders in 93 HIV-infected children with CD4 cell counts of 350 cells/μL and percentages of more than 15% [7]. Boyede et al. also demonstrated that RPM cognitive scores (nonverbal test of general intelligence) were lower for HIV-positive compared with HIV-negative children [10]. On the other hand, medical treatment including combination of antiretroviral therapy (ART) and supportive medications prolong survival and also promote rowth and developmental status [11]. Also, children with chronic illness, in general, are found to be at greater risk for psychiatric problems, including depression, anxiety, and feelings of isolation. Children with HIV/AIDS have additional factors in complexity of their illness and treatment as well as in the adverse psychological circumstances and poverty in which many live. Prevalence rates for psychiatric disorders in perinatally-infected children vary from 55% to 61%. The most common disorders found are anxiety disorders, followed by attention-deficit hyperactivity disorders, conduct disorders, oppositional defiant disorders, and mood disorders. [12].

Antiretroviral therapy alone is not enough to alter the neurocognitive effects of HIV infection. The stimulation techniques provided by caring people at home can lead to significant improvements in the neurocognitive status of HIV-infected children undergoing antiretroviral therapy [10]. Moreover, a wide range of potentially effective

methods have been identified to reduce the severity of inflammatory reactions connected HIV-associated neurocognitive disorder in adults. Many of these methods pass the second phase of testing. Nowadays, there are no unified recommendations for the use of these techniques in adults and no studies of efficacy in children have been conducted [12]. However, recent studies in this area demonstrate that the addition of special rehabilitation methods, such as virtual reality technologies, to safely correct cognitive and motor impairment in children with HIV encephalopathy is necessary to standard multidisciplinary rehabilitation. Virtual reality (VR) shows perspectives for healthcare applications because it provides patients with an exciting, often interesting, approach to achieving the goal of increasing productivity [13]. Virtual reality technology (VR) is quickly becoming a popular application for research in the field of physical rehabilitation and motor control [14]. Indeed, according to Dahdah et al., for the first time data show that semi-immersive virtual reality can be effective in improving performing functions and the processing speed of information in patients with brain injuries. In addition, VR increases motivation and pleasure in patients (important factors for successful rehabilitation), which also contributes to the restoration of behavioral and cognitive nature, which is also noted by Dvorkin et al. Other researchers point out that routine rehabilitation exercises may seem tedious because of their repetitive nature. Moreover, patient motivation is an important factor in the success of rehabilitation [15]. Computerized programs and the VE rehabilitation system during rehabilitation sessions increase patient motivation, provide flexibility and shorten the treatment period
[16]. In addition, being a more high-tech intellectual method of treatment, it can be more maneuverable and easier to promote in rehabilitation and brings pleasure in the recovery of patients.

The most popular technologies are those with full immersion and without additional motion recognition devices, since the latter limit the range of movements and give negative influence due to the weight of the input device, causing the patient to prematurely fatigue during exercise.

Objective: to evaluate the effectiveness of neurorehabilitation in children with HIV encephalopathy using the interactive virtual reality NIRVANA system

Material and Methods

The study included 170 children (92 boys – 59,74% and 78 girls – 40,6%) who were registered for HIV infection and receiving antiretroviral therapy (HAART). The average age of the patients was 14.53 ± 1.58 years (12-18 years), the time from the moment of HIV diagnosis was 7.05 ± 3.36 years (1-13 years), the duration of antiviral therapy was 6.41 ± 3.47 years (1-13 years old). In 43 patients (25.29%), the vertical route of infection was diagnosed, and in no case the mother took HAART during pregnancy. In other children, the infection pathway is identified as parenteral. The average virus concentration was 345.85 ± 181.45 copies / ml, while in 23 patients (14.94%) HIV RNA in the blood was not determined. The average number of CD4 + cells was 461.91 ± 230.32 in 1 mm3 of blood.

A neurological study included a standard neurological examination, including an assessment of consciousness and certain mental functions, speech, praxis, gnosis, functions of the cranial nerves, the state of the motor and sensory spheres, the autonomic nervous system, as well as functional and visualization methods (electroencephalography and magnetic resonance tomography).

Also, in the process of neurological research, the degree of neurological dysfunction was assessed using the screening scale for pyramidal extrapyramidal disorders for children older than 7 years, proposed by V.V. Glushchenko and P.B. Shabanov in 2013, according to which dysfunction was assessed according to a 6-point system (0 points - no violations - 5 points - severe violations) depending on the volume and strength and passive and active movements, the characteristics of tendon and periosteal reflexes, coordination and posture .

Neuropsychological screening included the identification of disorders of praxis, for which we used the assessment of kinesthetic (afferent), spatial, dynamic (kinetic) praxis by visual and tactile pattern. This patient, was asked to connect 1 and 2 fingers of the hand into a ring, squeeze fingers into a fist, leaving 2 and 3 fingers extended, raise a hand up, bending at the elbow (“voting”), touch the ear and eye with your hand. The assessment included the determination of the functional ability of the afferent basis of movement, the visual-spatial organization of movement, the perception of the body diagram, the arbitrary regulation of movements and the dynamic organization of movements. The result was presented in points, where 0 points corresponded to the absence of violations and 5 points to random movements and the inability to accept outside help.

All patients included in the study underwent testing aimed at studying the psychological and cognitive status of patients, including test methods: “Raven’s progressive matrix scale” (state of intelligence) and pediatric quality of life

questionnaire (PedsQL) for adolescents of 13-18 years old.

The Raven's test, proposed for the assessment of the level of intelligence, is based on the use of the ability to learn mainly on the generalization of one's own experience and the creation of schemes to handle complex events, logical thinking. This test is convenient in application and simplicity in interpretation, repeatedly confirms high indicators of validity and reliability. The test is not associated with linguistic abilities and skills and does not depend on the level of education. The Raven's matrix consists of 60 images combined into 5 matrices, in each it is necessary to select the missing fragment, using the identified patterns. In each matrix tasks are progressively complicated. Test tasks are performed without time limit, but it is noted how many tasks are completed correctly in the first 20 minutes. Thus, the Standard Progressive Raven Matrices test can be used both as a speed test (with time limits) and a performance test (without time limits). The choice of the test application regimen should be made depending on the purpose and conditions of the diagnosis (first of all, the possibility of the patient in long-term, continuous work with the test). Assessment is the percentage of correct answers, expressed in percent. Interpretation of the test allows us to distinguish 5 degrees of intellectual development: 1st degree - more than 95% - high intelligence; 2nd degree - 75-94% - intelligence is above average; 3rd degree - 25-74% - average intelligence; 4th degree - 5-24% - intelligence is below average; 5th degree is a defect.

Bass-Darki test, modified by G.V. Rezapkina, proposed in 2006, allows to diagnose various types of aggressive behavior. The test includes 35 statement questions. The test is suggested to the patient to apply the statement to himself. If he reacts in a similar way, the answer is given 1 point. During the interpretation, all issues are divided into 7 forms of aggression. The form that received more than 3 points is recognized as dominant in the patient. According to the test results, the following forms of aggressive behavior are distinguished: physical aggression (statements 1,8,15,22,29), indirect aggression (2,9,16,23,30), irritation (3,10,17,24,31) , negativism (4,11,18,25,32), resentment (5,12,19,26,33), suspiciousness (6,13,20,27,34), verbal aggression (7,14,21,28 , 35). The test is based on self-esteem. Its accuracy depends on the frankness of the patient. According to the results of the testing (increased level of aggression, inability to control emotions, etc.), it is not recommended to choose professions related to communication, maintenance, upbringing, training - that is, all professions related to people. Low values for this test testify to your delicacy, pliability and non-conflict. However, these indicators may prove a lack of perseverance in achieving their goals and defending their position.

The study of the quality of life of children is a new topical area of interdisciplinary research in domestic health care. The development of a methodology for studying the quality of life in pediatrics opens up the possibility of a comprehensive analysis of the physical, psychological and social functioning of children. For this, our study used the pediatric quality of life questionnaire PedsQL, version 4 (for children aged 13-18), published in 1998 and translated into Russian, includes 23 situations that describe physical, emotional, social activity and school life. The questionnaire is recommended for studying the quality of life of healthy and sick children, using these tools normative indicators of quality of life for the child population can be obtained. The use of the created tools in children with various diseases allows to expand knowledge about the attitude of children of a given age to their own health problems, treatment, degree of satisfaction with treatment; opens up new possibilities for assessing the impact of various diseases on the physical, psychological and social functioning of sick children. The test subject is asked to rate how each of these situations created difficulties over the past month. In this case, 0 points are assigned to a situation that has never created difficulties, 5 points - in the case of constant difficulties with the described action. Thus, the maximum score for each situation is 5 points (almost impossible activity), the minimum score is 0 (no difficulty. The maximum score in terms of physical activity is 32 points, emotional social and complex activity is 20 points, the total maximum score is 92 point.

All patients were randomly divided into two therapeutic groups: in the comparison group (85 patients), in addition to HAART, memantine hydrochloride was included in the treatment. The drug is a non-competitive antagonist of glutamate N-meth-yl-D-aspartate (NMDA) receptors, inhibits gluta-matergic neurotransmission and the progression of neurodegenerative processes, has a neuromodulat-ing effect. The mechanism of action is associated with the modulation of glutamatergic transmission, which mediates cortical-cortical and cortical-sub-cortical relationships in the brain. A series of con-trolled studies proved the ability of memantine to improve and stabilize cognitive functions, daily ac-tivity, and reduce behavioral disorders. It contributes to the normalization of mental activity (improves

memory and ability to concentrate, reduces fatigue, symptoms of depression, etc.) and the correction of motor disorders. According to the study, it was proved that memantine can improve the metabolism of neurons, which is an important step to stabilize or prevent damage to neurons. These results emphasize the need for longer studies to assess the full potential of neuroprotective agents [17]. The drug was pre-scribed once, regardless of food intake, in an ini-tial dose of 5 mg / day, followed by a dose increase of 5 mg per day every 7 days until the maximum daily dose of 20 mg / day was reached. In addition to HAART and memantine hydrochloride, patients of the main group (85 patients) underwent neurore-habilitation using the NIRVANA virtual reality sys-tem (https://www.btsbioengineering.com/nirvana/). NIRVANA - is an outstanding therapeutic method for the rehabilitation of neurological diseases and impaired motor skills of patients of all ages. A wide selection of tasks of varying complexity is offered to stimulate motor skills and cognitive abilities. Ex-ercises can be carried out both individually and in groups [18]. Interactive virtual reality system for pa-tients with neuromotor impairment NIRVANA is the first system in the world that provides full sensory immersion (acoustic and visual) in virtual reality. NIRVANA reproduces scenarios that can be project-ed on horizontal and vertical surfaces: the patient can interact with the virtual environment naturally, moving against the background of the projected im-ages. NIRVANA is applicable to any rehabilitation institution that provides therapeutic treatment for patients with cognitive and motor deficiencies of the lower and upper extremities. NIRVANA is a really effective remedy for rehabilitation after lesions of the central nervous system (for example, as a result of a stroke of a head injury, encephalopathy) or in chronic and progressive neurological diseases (for example, Parkinson's disease or multiple sclerosis). The system includes a predefined set of exercises for the upper and lower extremities and body to help physicians. Some exercises aimed at restoring mo-tor function control and rehabilitation can be used in combination with several disorders, such as Par-kinson's disease, multiple sclerosis and unilateral paralysis. In addition to several modes and increas-ing levels of difficulty, each task is determined by multiple feedback sensory connections: in com-parison with the traditional therapeutic approach, the patient receives powerful cognitive and motor stimuli, which increases his motivation to perform more complex exercises. The completely non-inva-sive system, immersed in a visual, acoustic and ol-factory interactive virtual environment, is incredibly impressive and leaves an unforgettable experience. The system, based on the optoelectronic infrared markerless technology of mo-tion recognition, cre-ates virtual images on horizontal and vertical sur-faces, with which the patient interacts absolutely naturally. Additionally, a sound environ-ment is cre-ated, smells are reproduced;

NIRVANA is an outstanding therapeutic met-hod for the rehabilitation of neurological diseases and impaired motor skills of patients of all ages. A wide selection of tasks of varying complexity is suggest-ed to stimulate motor skills and cognitive abilities. Exercises can be carried out both indivi-dually and in groups. Classes can be of various types: percep-tive, aimed at perceiving the environ-ment, aimed at achieving a goal (following an animal or walking along a line), motor (an event occurs when the pa-tient crosses an object) or game (football, balloons, etc.).

Figura 1. NIRVANA innovative neurorehabilitation system

Thus, with the help of the NIRVANA system it is possible to carry out training of locomotion, balance, arm movements and their coordination. At the same time, developing virtual reality technologies are becoming more accessible, and the use of game consoles as such systems allows the patient to continue training at home (Figura 1). The patient performs exercises in a virtual environment through move-ments performed on an interactive screen. Move-ments allow you to move or manipulate specific objects in different directions (for example, balls, colors and butterflies) or create specific associa-tions (for example, number of colors) with dy-namic interaction in a virtual environment. When a patient touches virtual objects, he / she determines the audio and video feedback (using the sprite action). In particular, the subject can perform ideomotor sequences under the guidance of a therapist, numerical processing, inhibition control and arithmetic operations; can evaluate the numerical quantity and classification; perform deductive logical reasoning using specific virtual tasks.

The patient selects / explores some elements (colors, music, geometric shapes, animals, etc.) observed in a virtual environment. These elements remain visible to the observer for various times determined by the interaction between the virtual system, the therapist, and the patient. The patient touches the virtual target at a specific time; this action causes a visual change with typical audio / video feedback (positive influence); otherwise, the element disappears (negative reinforcement) (Figura 2).

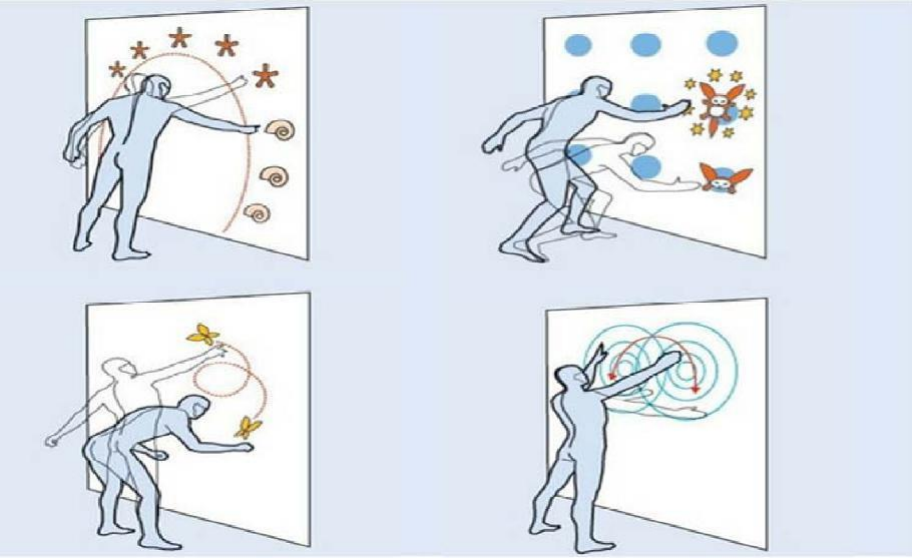

Figura 2. Exercise on a virtual environment by means of movement

Sessions were held every other day. The rehabilitation course was 20 sessions. Exercises were selected individually depending on the prevailing neurological symptoms.

The follow-up period was 6 weeks, at the end of which a re-study was carried out, including the Raven's scale, a questionnaire on the quality of life, a test for identifying praxis disorders and motor disorders.

All data was entered into Excell summary tables to calculate average values and their standard de-viations. Intergroup difference was evaluated using Student's t-test for 2 comparisons. Frequency com-parison was carried out using the chi- chi-square table criterion. The dynamics of the indicators was evaluated as a relative change in the initial indicator, expressed as a percentage.

Results and Discussion

In the course of the study, it was found that the applied treatment schemes contributed to a signifi-cant improvement in motor function in the aspect of pyramidal extra pyramidal disorders (the scoring decreased by 21.70%, $p < 0.001$ with the initial data, Table 1) and praxis (-10.79%, $p < 0.001$). The level of intellectual development also increased statisti-cally significantly, although clinically insignificantly (+ 2.53%, $p < 0.001$). As a result, the number of pa-tients with an average level of intelligence increased from 8 (5.19%) to 13 (8.44%, frequency difference

chi square = 1.33, nd). All aspects of the quality of life also showed a clinically insignificant, but statistically significant tendency to improve: thus, the difficulty score for physical activity decreased by 1.03% (p <0.01), emotional activity - by 2.20% (p <0.001), social activity by 1.34% (p <0.01), school activity by 0.44% (p <0.05). Such statistical reliabil-ity with minimal changes indicates a persistent unidirectional tendency to positive changes in a large number of patients, though by a small amount.

Table 1 – Neuropsychological testing of children with HIV encephalopathy during 6 weeks therapy

scales	initial	6 weeks
Screening assessment of motor impairment	3,20±0,99	2,51±0,97***
Screening assessment of praxis disorders	2,58±0,88	2,22±0,83***
Raven scale	18,68±4,51	19,08±4,60***
PedsQL physical activity	18,30±4,91	18,09±4,78**
PedsQL emotional activity	15,50±2,23	15,17±2,56***
PedsQL social activity	14,10±2,93	13,89±2,87**
PedsQL school activity	19,29±1,23	19,21±1,34*

*Note: the significance of differences with the source data is *. One symbol- p <0.05, two symbol - p <0.01, three symbol - p <0.001.*

The distribution of patients by therapeutic groups revealed that in both groups there was a positive dynamics of all the studied parameters (table 2). At the same time, although the relative dynamics of the indicators was comparable in both therapeutic groups, in the main group of patients, all the studied parameters changed more pronounced (the dynamics of the score of motor disorders in the main group was -23.61% (p <0.001 with the initial data) versus -19, 78% in the comparison group (p <0.001 with initial data), ; praxis disorder score - 13.58% (p <0.001 with initial data) versus 7.99% (p <0.001 with initial data); score for Raven's scale + 3.49% (p <0.001 with the initial data) versus 1.56% (p <0.01 with the initial data), ; difficulty points for assessing the quality of life in terms of physical activity -1.24% (p <0.05 with the initial data) versus -0.82 (p <0.05 with the initial data), emotional activity -3.42% (p <0, 05 with initial data) versus -0.97% (p <0.05 with initial data), social activity -1.94% (p <0.05 with initial data) versus -0.75, school activity -0, 54% versus -0.33%, all aspects – i.d.). As a result, with initial comparable indicators in the groups, by the end of the observation period, the average score of praxis disorders in the main group was significantly lower than in the comparison group (p <0.05).

The NIRVANA virtual reality modulation system was created to increase the effectiveness of neurorehabilitation in patients with consequences of acute cerebrovascular accidents, paralysis, consequences of myocardial infarction, paresis (weakening of muscle strength), consequences of craniocerebral trauma, cerebral palsy, consequences of injuries to hands and feet [19]. We attempted to use this method in children with HIV encephalopathy - a progressive HIV-associated damage to the nervous system, the outcome of which is an irreversible damage to the nervous system and a deep neurological and cognitive deficit. The study showed the effectiveness of the method in preventing the progression of pathology and reducing the scoring of neurological deficiency.

In order to protect the nervous system in patients with progressive diseases, various medications are used, but so far there is no evidence base testifying to the effectiveness of medical measures. In this work, we investigated the effectiveness of memantine hydrochloride. A positive effect of the drug in the aspect of impaired movement and praxis was found, as well as a weak but persistent positive effect in terms of the level of intelligence and quality of life associated with difficulties in physical and emotionnal functioning.

Table 2 – Indicators of the neuropsychological status of children with HIV encephalopathy on the background of 6-week therapy, including memantine and the NIRVANA virtual reality method (in the numerator, the initial data, in the denominator, after 6 weeks of observation).

Scale	Main group (n = 77)	Comparison group (n = 77)
Screening assessment of motor impairment	3,18±0,98 2,44±1,01***	3,22±1,00 2,57±0,94***
Screening assessment of praxis disorders	2,58±0,88 2,08±0,75***	2,59±0,88 2,37±0,89^***
Raven scale	18,64±4,54 19,17±4,63***	18,71±4,52 19,00±4,60**
PedsQL physical activity	18,32±4,92 18,04±4,68*	18,29±4,93 18,14±4,91*
PedsQL emotional activity	15,49±2,23 14,99±2,76*	15,51±2,24 15,36±2,34*
PedsQL социальная активность	14,04±2,92 13,74±2,85*	14,16±2,95 14,04±2,91
PedsQLschool activity	19,25±1,26 19,14±1,36	19,33±1,20 19,28±1,32

Note: *the significance of the difference with the initial data is *, the significance of the difference between therapeutic groups ^. One symbol- p <0.05, two symbols - p <0.01, three symbols - p <0.001.*

Conclusion

This study revealed that in children with HIV encephalopathy, the use of memantine significantly improves motor impairment and praxis disorders, as well as a persistent tendency to improve the intellectual level and quality of life, physical and emotional activity. The additional use of the NIRVANA neurorehabilitation system, based on immersing the patient in virtual reality (visually and acoustically) and game motivation, is associated with an increase in the positive effect of therapy, mostly to praxis disorders.

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