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Review article

Neurorehabilitation in Children with Cerebrovascular Insult: Why Are We Late?

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SUMMARY

Introduction. Pediatric stroke (PS) is a rare disease with the global incidence of 1.2 – 13/100,000, but nevertheless, is an important cause of disability in children. What makes it a challenging research topic is its alarming upsurge in the prevalence of 35%. The most prevalent motor deficit in that regard is hemiparesis in 50% to 80% of children with PS.

Literature review. The following databases were used for the purpose of this study: PubMed, Medline, Scopus, Google Scholar. Asymptomatic clinical picture and a very rare use of indicated hyperacute recanalization therapy make rehabilitation the primary therapeutic approach in children affected with PS. The present studies suggest that the greater capacity of brain neuroplasticity in children can be relevant in recovery, but also indicate some specific consequences of injury made to a developing brain. Robotic neurorehabilitation (RNR) activates brain neuroplasticity, i.e. stimulates new motor learning which contributes to motor function recovery after brain damage. RNR, in combination with virtual reality, is able to expand the effects of conventional rehabilitation, the children find it interesting, and it motivates them to be actively involved in time-consuming, specific, high-intensity exercises. Motor recovery is intensified by learning and repetition of tasks, with a robot providing additional strength in the performance of movements, with continual measurements of objective parameters.

Conclusion. The recommendations for use of RNR in children affected with PS are based on expert consensus and weak evidence, since there is lack of randomized, controlled studies.

Keywords: **cerebrovascular insult, child, neuroplasticity, robot neurorehabilitation**

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INTRODUCTION

Pediatric stroke (PS) is defined as an injury to a child's nervous system caused by an occlusion or rupture of a blood vessel in the brain or spinal column before or after birth (1). PS is a rare pediatric disease, with a global incidence of 2-13/100,000, and 3-25/100,000 children in developed countries (2). The reason for this contradiction lies probably in inconsistent diagnostic criteria, i.e. in the failure to recognize PS early in its course, and in unevenly developed health care systems. In well developed countries, the quality of perinatal care is at a higher level, and therapeutic approaches implemented in pediatric population produce better survival rates, as has been evidenced in children with cerebral palsy, the cause of which can be PS as well (3). It is an alarming information that the prevalence of childhood stroke in 2013 was by 35% higher than that in 1990 (4), with a dire prospect of further rise of global brain stroke prevalence in the following 30 years (5).

There are several PS classifications in the literature, but the following two are the most common. According to the time of appearance, PS is defined as perinatal stroke (occurring from 20 weeks of gestation to the first 28 days after delivery) and childhood stroke (occurring from 29 days to 18 years of age) (2). According to the underlying mechanism by which it occurs, PS is classified as arterial ischemic stroke, cerebral sinus venous thrombosis, and hemorrhagic stroke (6). Although these same types of stroke occur in adult population as well, their etiologies are essentially different. In adult brain stroke patients, the usual risk factors are associated with their lifestyle, including hypertension, diabetes and atherosclerosis, while in children the risk factors for brain stroke are more diverse in nature (7). The most common risk factors for perinatal cerebrovascular insult are heart diseases, infections, blood clotting disorders, and perinatal accidents. For childhood stroke, the risk factors can be divided into three most common categories: arteriopathy, heart disease, and prothrombotic conditions. Other risk factors involve infection, sickle cell disease, trauma, genetic or metabolic disorders (7, 8). From the point of view of rehabilitation, it is important to stress that these two groups of children (perinatal stroke and childhood stroke) are heterogenous by etiology, risk factors, clinical picture, and outcome. Robot neurorehabilitation significantly expands the boundaries of conventional rehabilitation, activating childhood brain neuroplasticity, which is essential in motor and functional recovery.

LITERATURE REVIEW

Clinical picture of a motor defect after pediatric stroke

It is important to stress that PS represents a huge rehabilitation challenge as the cause of physical, cognitive, speech, and psychosocial disability. PS is a significant cause of disability in children due to its lifelong motor and cognitive consequences (9). The clinical picture of PS varies depending on the child's age, with younger children usually presenting with motor deficits, while older children often demonstrate a combination of speech and motor deficits. PS may present as weakness of one arm and/or leg (hemiplegia) or weakness of both arms and/or legs (quadriplegia or triplegia). Impairments may involve muscle weakness and loss of dexterity, disorders of muscle tone and of quality and coordination of movement, and the distribution of these impairments often varies (10). The most common motor deficit is hemiparesis in 50% to 80% (11), while a long-term impairment of cognitive functions is present in 50% of PS survivors (12). An important specific aspect of pediatric PS in contrast to adult PS is a delayed onset of motor deficits. In fact, the acute phase perinatal stroke in fetal period is asymptomatic; in premature children, it can be asymptomatic or associated with apnea, bradycardia, seizures and encephalopathy, while in full-term newborns, the clinical picture involves seizures and encephalopathy. From the above reasons, perinatal stroke is often unrecognized in its acute phase, but its presentation is delayed till early childhood or beyond, and it is then termed presumed perinatal stroke. Perinatal stroke is the leading cause of hemiparetic cerebral palsy in childhood, and the clinical picture of cerebral palsy from the abovementioned reason may precede the diagnosis of perinatal brain stroke (2, 13).

In contrast to perinatal stroke, childhood stroke most frequently manifests with acute focal neurological deficits – hemiparesis (8).

Long-term (median, 10.8 years) follow-up of the patients with childhood stroke has revealed the presence of motor deficits in 63% of the affected children. In the total sample, moderate to severe disability after childhood stroke has been present in 23% of the children (14).

Neurorehabilitation

In both types of PS, perinatal and childhood stroke, rehabilitation is the predominant and often primary treatment approach. The reason for that is its asymptomatic clinical picture or a failure to recognize its acute symptoms. An asymptomatic clinical picture is typical of perinatal stroke in the fetal period and in some cases in premature newborns, so that in a subacute or chronic phase of PS rehabilitation is the sole therapeutic approach undertaken to improve the outcome. Failure to recognize the symptoms of perinatal stroke in its acute phase in premature, full-term newborns and in pediatric stroke, as well as the lack of implementation of the guidelines and protocols of treatment with hyperacute recanalization therapies (thrombolysis or mechanical thrombectomy) in childhood stroke (15), positions rehabilitation rather high in the order of treatment modalities for PS.

The standard of rehabilitation after PS involves kinesitherapy and occupational therapy, which may be individually extended (hydro-, electro-, thermotherapy). The recommendations may range from no therapy, outpatient therapy, and intense hospital-based rehabilitation. A specific aspect of pediatric patients with PS is reflected in the following – motor deficits become apparent during growth. It has been demonstrated that this patient population during growth and adoption of motor functions additionally „acquires" impairments in several domains of ICF (International Classification of Functioning, Disability and Health) (16). The consequence is that the years of growth and development of children with PS are at the same time the years of rehabilitation treatments, which is strenuous, tedious, and frustrating especially for adolescent children.

An important implausibility is that the rehabilitation protocols for children with PS have been based for a long time on the extrapolation of adult brain stroke data. This approach is scientifically unsound, bearing in mind the considerable differences in incidence, etiology, clinical presentation, and specific aspects of the central nervous system in adults and children with stroke (17). These differences suggest the need for the development of evidence-based rehabilitation protocols to be implemented in children after PS. In the current professional literature, due to a scarcity of evidence, the rehabilitation of pediatric patients after PS has been based mainly on recommendations. The Clinical Guideline Royal College of Paediatrics and Child Health for Diagnosis, Management and Rehabilitation (10), known in the literature as the United Kingdom guidelines, are the most comprehensive and concrete when rehabilitation modalities are concerned, with a limitation, however, since they refer only to childhood stroke. The guidelines imply that the rehabilitation of children with motor/mobility impairments follow the recognized principles of motor learning. The evidence to support the traditional neurodevelopmental therapy (NDT) for pediatric rehabilitation in neurological conditions is weak. Motor interventions that may be applicable to child stroke rehabilitation include constraint-induced movement therapy (CIMT), bimanual therapy, electromyographic (EMG) triggered neuromuscular stimulation (NMS), functional electrical stimulation (FES), robotic interactive therapy, and virtual reality.

Neuroplasticity after pediatric stroke

Neuroplasticity is the ability of the nervous system to modify and regenerate in response to new information or damage. The guideline of the Royal College of Paediatrics and Child Health that rehabilitation of chidren with motor deficits and movement impairments should follow the principles of motor learning directly implies neuroplasticity of the brain. An increased capacity for brain plasticity in children can be relevant in motor and functional recovery, but any disruption of the neuronal network may have children-specific deleterious consequences, which may imply that a developing brain has unique characteristics when injury and recovery are concerned. The answer to the question if the child brain is able to recover better and more rapidly after an injury is still unknown (17).

Ever since 1936, a theory has been widely accepted that younger brains recover better than the older ones. The theory was termed the Kennard principle, after Margaret Kennard, who was the first to publish her research on monkeys of the effect of age on motor functions after a brain lesion (18). She concluded that sooner the brain lesion occured, the compensatory recovery mechanisms were able to better improve the recovery outcomes. After six years, a research on the human population was published with an opposite conclusion concerning the results of intelligence and speech tests, known as the Hebb's principle. It was based on the theory that neurons that „fire together" „wire together", i.e. that they formed neuronal networks. According to the Hebb's principle, the brain is very susceptible to insults in its early development (19).

Since then, and even to this day, the comparisons of children with adults after cerebral insults have been producing conflicting evidence as to the supposed better recovery outcomes in children. The studies tried to relate the factors of age, size, type, and location of lesions with outcomes. The dilemma has not been resolved so far, but it is important to stress that the patterns and pathways of recovery do differ between children and adults (20).

Prenatally, brain development consists mostly of neurogenesis and neuronal migration; postnatally, the proliferation of glial cells predominates, as well as integration and synaptic development in the formation of mature neuronal networks. An increased capacity for brain plasticity is an advantage when recovery is concerned, but a neuronal network disruption with a brain stroke can have harmful consequences, specific for an immature brain. The fact that, in contrast to adults, the whole brain undergoes restructuring after PS has been cited as evidence in that regard. The interrelationships of developmental plasticity, neuronal damage, and recovery have not been sufficiently studied (21). One approach implied that the recovery after a brain stroke recapitulated development programs, as indicated by numerous genes and cellular processes, which were reactivated after an insult and are typical of early phases of neurodevelopment. Other studies, however, reported significant differences in gene expression between an immature brain and periinfarction cortex in adult persons, after an insult. Knowing that the brain mass increases by a factor of four in pre-school age, it seems logical that in children natural growth and development can provide a longer period for recovery (22). Several studies of adult patients established that sensorimotor improvements occurred spontaneously in the first three post-stroke months, while cognitive and speech improvements continued to occur after that period of time. A theory of proportional recovery was proposed, with the remark that most adult brain insult patients recovered about 70% of their initial sensorimotor deficits of upper limbs in the period of three months after stroke. Basically, the period of time for recovery was temporally conditioned by the period of increased neuroplasticity (23).

It is reasonable to conclude that the possibility for recovery lasts longer in children. The studies of pre-school and school children with brain insult have shown the trend of improvement of gross motor functions (but not fine motor skills) in the first year after PS, while newborns in the same period of time (i.e. their first year of life) demonstrated deficits (24). The results of the studies suggested that PS was characterized by a complex interaction between developmental processes and neural injury, resulting in certain deficits, while others were improved, and that independent study of PS was essential, without any extrapolations of data valid for adult population (17).

There are three mechanisms which may describe post-insult neuroplasticity of the brain. The first mechanism involves increased functional activity in the somatosensory system on the opposite side of the brain from the infarction, as well as recruitment from distant cortical regions connected to the affected area. The second mechanism involves the improvement of the structural integrity of the corticospinal tract on the same side of the brain as the infarction. The third mechanism involves the restoration of interhemispheric functional connectivity and the network of the sensorimotor cortex on both sides of the brain. As a result, there is a reallocation of functions whose primary representation has been damaged (25).

Robotic neurorehabilitation

Robotic neurorehabilitation (RNR) activates brain neuroplasticity, instigating new motor learning, which contributes to motor and functional recovery after PS. RNR and virtual reality stimulate the recovery of traumatized neurons during time and reorganization of neuronal connections, presenting an interactive interface that simulates real-life situations with physical support to the lost motor functions (25). RNR devices are designed for specific high intensity exercises following the same algorithm, with a sensory feedback for self-correction, leading to long-term neuroplastic changes which produce improved functional outcomes in patients (Figure 1). Functional recovery is achieved through repetitive, high-intensity, diverse, and motivating motor exercises. RNR enables expert teams to create

Figure 1. *LEXO® robotic gait rehabilitation*

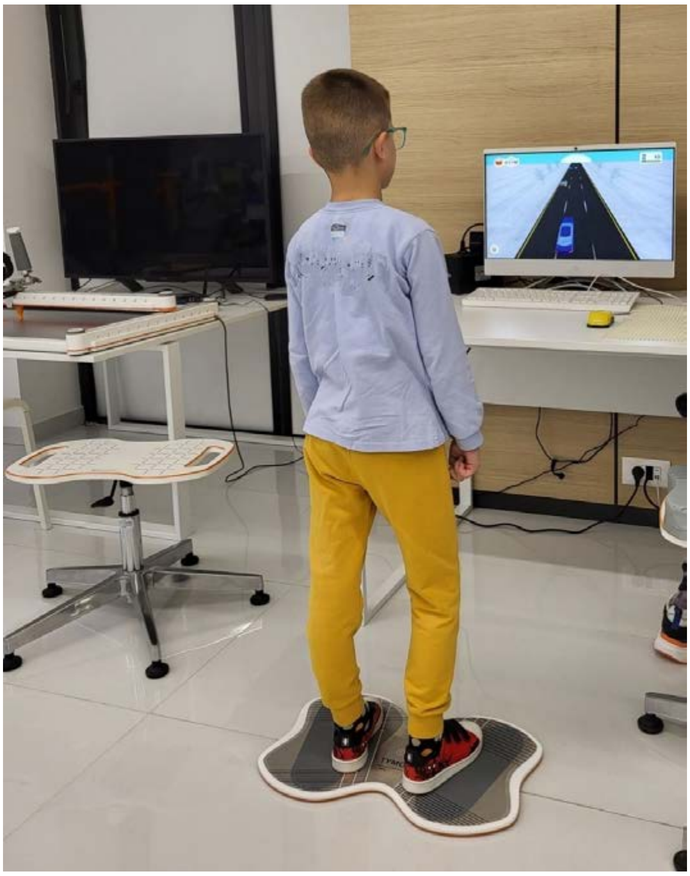

Figure 2. *TYMO® - Postural control and balanced therapy*

diverse rehabilitation programs, with a continual measurement of objective parameters and feedback information about the progress of rehabilitation treatment. These characteristics allow for individual tailoring and design of an optimal rehabilitation treatment. The combination of traditional individual kinesitherapy, RNR and virtual reality guarantees the best possible results. An absence of adverse effects is another positive characteristic (26). The most significant advantage of RNR and virtual reality in children is the provision of numerous therapeutic options in a motivating, interactive and funny way, through play. This therapy easily motivates children to take an active part in their own treatment, performing the movements that simulate everyday activities, with the important feedback that incorporates visual-perceptive and cognitive abilities. The interest incited in children with PS may extend treatment session duration and shorten the overall duration of rehabilitation (Figure 2). In addition to the above advantages of the therapy itself, there is a problem related to the examiner's assessment of RNR success, lack of consensus, and recommendations concerning evaluation indices for the assessment of rehabilitation success. In scientific papers, there has been a great diversity as to the use of tests and scales for the assessment of robotics-assisted rehabilitation (27).

The cortical areas associated with the control of human locomotor apparatus are supplementary motor area (SMA), prefrontal cortex (PFC), premotor cortex, primary motor cortex, primary somatosensory cortex, and sensorimotor cortex (28). A study that has examined the assessment of cortical activity change indirectly, by hemodynamic response monitoring aided by the functional near-infrared spectroscopy (fNIRS), has contributed significantly to the evidence-based affirmation of RNR use in children and adolescents. With the use of treatment with robot-assisted walking in patients below 18 years of age with neurological impairments, a huge cortical activation of SMA and PFC areas was reported, which could result in long-term neuroplastic changes with consequential improvements of functional outcomes (29).

It is a baffling fact that the use of RNR, despite its proven advantages, has been delayed in children compared to adult populations, which is reflected in the paper by Fasoli et al. (30), reporting a delay of 15 years for rehabilitation robotics in children versus adults. An important remark in the paper was that „the researchers have recently expanded their focus of interest to include children with neurological motility impairments as the consequence of cerebral palsy, acquired brain damage or brain stroke". It is the trend of research of heterogenous groups of children in recent past that has caused in current review papers and meta-analyses a low level of evidence about the success of robotics-aided neurorehabilitation in children with PS. The search of several scientific data bases (PubMed, Medline, Scopus, Google Scholar) revealed that such a conclusion was illustrated by only two review papers. The review paper by Mirkowski et al. (31), published first, assessed evidence-validated success of rehabilitation of motor and cognitive deficits after PS in the period 1980-2017 (31). In the period of almost forty years, only one paper by Fasoli et al. (32) dealing with the topic of robotic therapy of upper extremities in children after PS (32) fulfilled the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (33). Thanks to this study, level 4 evidence was established for the first time that RNR could improve upper extremity function in children with hemiplegia and spasticity after PS.

The second review paper by Hart et al. (34), as a continuation of the time frame from the previously mentioned paper (2018 - 2022), involved children from newborn age to 18 years of life, exclusively with the diagnosis of PS, in order to evaluate the success of motor deficit rehabilitation based on the ICF categories. The focus of the paper was neuromotor treatment of children with PS, singling out from the current professional literature evidence-based neuromotor treatment results. However, a still very low number of papers which would fulfill the criteria to be included into the assessment point to the chronic lack of homogenous, randomized studies dealing with the topic. In the category of Body Structures and Functions, robotic-assisted upper extremity motor practice, exoskeletons, or application of botulinum toxin to spastic muscles, gave results regarding an increased range of movement and muscle strength of the upper extremity. In the domain of Activity, recommended were robot-assisted bimanual training and Hand-Arm Bimanual Intensive Therapy in combination with other neuromotor therapies.

Muscle spasticity over grade 2 by modified Ashwort scale (MAS) is a limiting factor for the use of RNR. The effect of the botulinum toxin on spastic muscles of the lower extremity, due to a central motor neuron lesion in children with cerebral palsy, cannot be disputed (35 – 37). It is certain that the lack of randomized homogenized studies is the reason why the recommendation refers only to the upper extremities and why combination therapy is not recommended, since the mechanism of spasm occurrence is identical in children after PS and in children with spastic form of cerebral palsy, but the recommendations should nevertheless be based on evidence.

Another reason why RNR in children with PS is still insufficiently recognized as an important and advanced therapeutic modality is the design of RNR devices. It is known that RNR devices are designed for specific high intensity exercises that lead to long-term neuroplastic changes. However, most robotic devices for neurorehabilitation have been designed for use on adult patients, i.e. they have a limiting potential in pediatric populations. Analyses showed that safety, operability, and motivation are the decisive factors for a successful design of devices for RNR of children (38).

CONCLUSION

Neuroplasticity is the ability of the brain to modify functional organization as the result of acquired experience. RNR in combination with virtual reality in children with PS is able to effectuate key factors necessary for brain neuroplasticity activation, through high therapeutic doses (number of movements), high intensity (movements per unit of time), and self-correction capability. It is interesting, motivating for children, and enables through play the realization of often long and tedious neurorehabilitation treatments in children with PS. The therapeutic approach can be individually adapted to every child through the realization of functional goals in all domains of health. The use of RNR is delayed in children with PS compared to adult populations, which cannot be justified, and we have identified two main reasons for that. The first is the lack of randomized, controlled studies, with a clear recommendation concerning the treatment protocol and recommended evaluation indices – tests and scales – for the purpose of assessment of rehabilitation success, which would open the door to future studies. The second reason is the fact that most robots have been designed for use in adults, disregarding the specific aspects and needs of pediatric populations. The use of robotics cannot replace the usual individual exercise techniques in children, however, it has been proven that it contributes to functional recovery.

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Robotska neurorehabilitacija kod dece sa cerebrovaskularnim insultom: zašto se kasni?

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SAŽETAK

Uvod. S obzirom na to da ima globalnu incidenciju od 1,2/100.000 do 13/100.000, pedijatrijski cerebrovaskularni insult (PCI) predstavlja retku bolest, ali je istovremeno i značajan uzrok pojave invaliditeta kod dece. Alarmantni porast prevalencije od 35% čini ga izazovnim predmetom istraživanja. Najzastupljeniji motorički deficit je hemipareza, koja se javlja kod 50% – 80% dece sa PCI-jem.
Pregled literature. Korišćene su naučne baze podataka *PubMed*, *Medline*, *Scopus* i *Google Scholar*. Asimptomatska klinička slika i vrlo retka primena indikovane hiperakutne rekanalizacione terapije čine rehabilitaciju primarnom terapijom dece sa PCI-jem. Trenutna istraživanja ukazuju na to da povećan kapacitet neuroplastičnosti mozga dece može biti od značaja u oporavku, ali takođe ukazuju na neke specifične posledice povreda mozga u razvoju. Robotska neurorehabilitacija (RNR) aktivira neuroplastičnost mozga, tj. stimuliše novo motoričko učenje, koje doprinosi motoričkom oporavku nakon oštećenja mozga. RNR u kombinaciji s virtuelnom stvarnošću može proširiti efekte konvencionalne rehabilitacije. Takođe, zanimljiv je deci i motiviše ih da aktivno učestvuju u dugotrajnim, specifičnim vežbama visokog intenziteta. Motorički oporavak intenzivira se učenjem i ponavljanjem zadataka; pritom, robot omogućava dodatnu snagu u izvođenju pokreta, uz stalno merenje objektivnih parametara.
Zaključak. Preporuke o primeni RNR-a kod dece nakon PCI-ja zasnivaju se na stručnom konsenzusu ili slabim dokazima zbog nedostatka randomizovanih, kontrolisanih ispitivanja.

Ključne reči: **cerebrovaskularni insult, dete, neuroplasticitet, robotska neurorehabilitacija**