Chapter

Neurobehavioral, Cognitive, and Paroxysmal Disorders in the Long-Term Period of Pediatric Traumatic Brain Injury

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Abstract

The consequences of the traumatic brain injury (TBI) in children and adolescents represent a major medical and social problem, as TBI interferes in the normal processes of neuroontogenesis. Brain damage in TBI in children and adolescents occurs during the ongoing processes of its growth and maturation, and therefore the clinical course and outcomes may differ significantly from those in adults. Poor outcomes of TBI sustained in early childhood may be explained considerably by the timing of injury in a period of rapid brain and behavioral development. Thus, TBI has a negative impact on the cognitive function development, behavior, school education, and social skills acquisition. Cognitive and behavioral disorders in children and adolescents in the long-term period of TBI become more prominent in co-occurrence with paroxysmal disorders, including posttraumatic headaches, posttraumatic epilepsy, and subclinical epileptiform activity on the EEG. In general, a favorable outcome is possible in children more often than adults even after severe TBI, due to the high neuroplasticity of the developing brain. Therapeutic and rehabilitation measures in the long-term period of TBI in children and adolescents should be intensively carried out both in the first 12 months after TBI, when the most significant results from their use are expected, and in the long-term period, considering the ongoing processes of morpho-functional maturation and neuroplasticity mechanisms.

Keywords: traumatic brain injury, consequences, children, adolescents, cognitive disorders, behavior disorders, posttraumatic headaches, posttraumatic epilepsy, treatment, neuroplasticity

1. Introduction

Traumatic brain injury (TBI) is the most common and potentially the most deleterious type of injuries in pediatric population [1]. The consequences of TBI in children and adolescents represent a serious medical and social problem.

TBI clinical course and outcomes in children have peculiarities as the damage impacts brain, which growth and maturations are continuing and not yet completed. The complexity of pediatric TBI is due to the heterogeneity of its pathophysiology

and depends on the age of impact, influencing different stages of brain development. TBI interferes with the normal course of neuroontogenesis, disturbing the development of cognitive functions, school education, behavior, and social skills formation. Cognitive and behavioral disorders in children and adolescents in the long-term period of TBI are significantly increased in the presence of paroxysmal disorders: post-traumatic headache, post-traumatic epilepsy, subclinical epileptiform activity on the EEG. Therapeutic and rehabilitation measures in the long-term period of TBI in children and adolescents should be intensively carried out both in the first 12 months after TBI, when the most significant results from their use are expected, and in the long-term period, considering the ongoing processes of morpho-functional maturation and high neuroplasticity of the developing brain.

Despite the importance of the problem, there is no specific treatment for the long-term consequences of childhood TBI, and the available recommendations are mostly extrapolated from studies conducted on adult patients, and thus do not take into account the features of the child's neurodevelopment and brain plasticity [2, 3].

2. Pathophysiology of pediatric TBI

Brain damage in TBI may arise by two mechanisms, including (1) primary (immediate) injury, directly caused by mechanical forces during the initial insult, and (2) secondary (delayed) injury, accompanied by further tissue and cellular damages following primary insult. Primary injury occurs at the time of impact and is mostly irreversible. The immediate impact of different mechanical insults to the brain can cause two types of primary injuries: focal (brain contusions) and diffuse (diffuse axonal injury, diffuse vascular injury, edema). However, the common co-existence of focal and diffuse injuries in patients suffered from moderate to severe TBI was demonstrated [4, 5].

Secondary damages to the brain occur after the initial impact. This is initial injury progression in delayed and prolonged manner, lasting from hours to many years. There are number of factors contributing to secondary injuries, which include hypoperfusion of the penumbral region surrounding the primary injury, excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, edema, neuroinflammation, axonal degeneration and apoptotic cell death [6, 7]. Depending on the age when the TBI happens, the effects of secondary injuries will vary, altering a variety of biological processes of brain development, including myelination, neurotransmitter and neurotrophin development, synaptogenesis and synaptic reorganization, gliogenesis, programmed cell death, blood-brain barrier function and cerebrospinal fluid dynamics. The secondary injury is believed to be an important determinant of outcomes and it may be preventable and more responsive to appropriate and timely medical intervention.

Defining the severity of TBI in the acute period is important as it is predictive of the outcome. The periodization of TBI clinical course could be delineated as follows [8], depending on its initial severity:

1. The acute period lasting 2–10 weeks.

2. The intermediate (subacute) period, from 10 weeks to 6 months post-injury.

3. The long-term (chronic) period, from 6 months to up to 2 years or more.

The factors, defining the long-term impact of TBI on the individual functioning include:

a. the severity of the initial injury in the acute period

b. localization of damage

c. the rate and completeness of physiological recovery

d. the functions affected

e. the meaning of the dysfunction to the individual

f. functions which are not affected by TBI

g. the resources available to aid recovery.

The localization of damage for particular types of TBI is rather typical [9]. For instance, the areas predominantly affected by contusions are the frontal and temporal lobes as well as the brain stem—regions located near bony prominences. Brain regions particularly involved in diffuse axonal (or shearing) injury are the corpus callosum, subcortical white matter and the mid-brain.

However, not only the severity of TBI, but also the age at which it occurred, has a significant impact on the clinical manifestations of the consequences of TBI. Research on the response of children's brains to TBI has led to important results on the impact of age on recovery from injury and its functional consequences, and various opinions have been formulated.

Early studies of childhood TBI were largely directed at determining whether there were any long-term sequelae from such injuries. The prevailing view was that as children's brains are more plastic and better able to accommodate the effects of brain insults, children would experience fewer deficits than adults. The developing brain is capable of more significant reorganization and recovery after TBI. In addition, after damage to immature brain, progressive cognitive decline is less likely to develop, and ongoing neurodevelopment may contribute to recovery [10]. Most skills formed by the time of injury are preserved, even if they were temporarily lost or compromised [9]. As a result, children are more likely than adults to have a favorable outcome, even after severe TBI, due to the high neuroplasticity of the developing brain.

On the other hand, studies of Klonoff et al. [11, 12] and Rutter et al. [13] and some others have shown that TBI in childhood does have measurable consequences in terms of functional impairment. Another concept was formulated considering the developing brain as more vulnerable to TBI if it is affected during critical periods of significant growth, formation of brain circuits and functions, which may lead to more serious and persistent physiological changes after a TBI. Brain structures and functions that continue to mature at the time of TBI may be affected to a greater extent than those formed before the injury [14]. Thus, the age of TBI is an important factor influencing its consequences.

Many children who suffered TBI make a good physical recovery and appear outwardly normal. However, even after mild TBI, children may continue to experience problems when faced with the complexities of everyday life, particularly learning, skill acquisition, cognitive and psychosocial functioning [15, 16]. Thus, even a mild TBI suffered in childhood does not always pass without a trace, and its consequences can manifest years after the injury.

Educational and behavioral developments as well as social adaptation are dependent upon the intact capacities of learning, attention, and executive functioning (EF). Many of these skills are impaired as a result of TBI, even while intellectual functioning, as measured by traditional psychometric tests, may appear intact [17].

In general, a favorable outcome is possible in children more often than adults even after severe TBI. Nevertheless, neurological, cognitive, behavioral, emotional, and socio-psychological consequences can be observed in the long-term period of TBI in children and adolescents. The complexity of pediatric TBI is due to the heterogeneity of its pathophysiology and depends on the age of impact, influencing different stages of brain development.

3. Neurobehavioral consequences of moderate and severe closed pediatric TBI

Patients who have suffered moderate or severe TBI exhibit a broad range of possible outcomes, and it is generally not possible to predict the extent of recovery in the initial weeks after the trauma. Traditionally, children have been reported to have better outcomes than adults after TBI. But, unlike in adults, in children the effects of the brain injury on brain function interact with the maturation or development of the child. Skills that are emerging or developing may be affected differently by brain injury from skills that are already established.

However, while fewer focal deficits may be apparent, children appear to develop deficiencies across virtually all areas of higher cognitive functioning. These deficits may not become apparent until later in the child's development. Children with TBI face difficulties because of impaired new learning, inability to take on social cues, and behavioral, educational and schooling problems. Determining the combination of cognitive, behavioral and physical deficits is an important first step in setting goals for rehabilitation.

In our studies of the long-term sequelae of TBI the neurological and neuropsychological assessment of 283 patients aged from 5 to 14 years (201 boys and 82 girls) suffered moderate or severe closed TBI (contusion or diffuse axonal injury) was performed in the period from 6 months to 4 years after TBI [18, 19]. The diagnosis was confirmed during hospitalization in the acute period of head injury. The principal criteria for the severity of the TBI were the Glasgow Coma Scale score and the loss of consciousness duration. Moderate closed head injury was diagnosed in 150 patients (53%) and severe injury in 133 (47%).

During the long-term period of TBI all patients were referred with various complaints, the most common being:

1. frequent headaches (95% of cases)
2. chronic fatigability and decrease in endurance (88%)
3. memory problems (82%)
4. attention deficit and distractibility (74%)
5. learning difficulties at school with academic underachievement (73%)
6. behavioral problems (62%)
7. motor restlessness (60%)
8. sleep disorders (61%).

Secondary nocturnal enuresis developed in 16% of patients post-injury and speech and language disorders in 14%.

There is a direct relationship between general measures of intelligence (IQ) and the severity of TBI, with IQ being depressed for the more severe end of the severe TBI spectrum. In the milder end of severe TBI, and in moderate TBI, measures of IQ usually return to the normal range and may return to pre-trauma levels [20–22]. Despite this, many children who have suffered severe or moderate closed TBI have significant specific neuropsychological deficits that interfere with optimal cognitive functioning, adaptive behavior and academic achievement (**Table 1**).

In moderate or severe cases of TBI, the cognitive functions that are most vulnerable are memory, attention, speed of information processing, visuospatial and perceptual abilities, language skills, EF in particular. **Table 2** outlines the peculiarities of the TBI effects on the cognitive functioning and development of children (**Table 2**).

Some of the cognitive disorders are attributable to the specific focus of damage. But residual problems are commonly the consequence of diffuse damage or involvement of axial brain structures that modulate cortical functions. This combination of specific cortical damage and diffuse damage to axial and subcortical structures is responsible for deficits in different higher cerebral functions. Neuropsychological assessments can help to delineate the extent and type of cognitive disability that a child may experience.

Memory is easily damaged by TBI because several brain structures are involved in information-processing, storage, and retrieval. Short-term memory loss is the most common and most troublesome type of memory problem. This can manifest itself as forgetting new information, difficulties in scholastic learning and mastering new skills, repeating the same question over and over, getting details mixed up, forgetting a change in routine and forgetting where things have been placed.

Speed of information-processing. Slowing down the speed at which the brain performs information-processing is often due to diffuse axonal damage of the brain pathways. This results in problems such as not understanding fast speech, being unable to absorb instructions first time around, and not being able to quickly formulate a reply to a question.

Attention and concentration. A reduced concentration span after TBI is very common, as is a reduced ability to pay attention to more than one task at the same time. These problems are usually caused by damage to the frontal lobe. Attentional problems tend to get worse when the person is tired, stressed, or worried. When there are problems with concentration, it is difficult to follow instructions, plan ahead, or be organized.

EF: planning, organizing and problem-solving. EF is associated with the frontal lobes, which are especially fragile in TBI. EF includes goal-orientated behavior, initiation, attention control, flexibility, social learning, and self-control.

In general, executive skills are required in novel and complex situations, where routine responses do not exist. Damage to the frontal lobe can affect these skills, resulting in a subtle set of deficits which have been called "dysexecutive syndrome." This covers problems in making long-term plans, goal setting, and initiating steps to achieve objectives. The ability to stand back and take an objective view of a situation may be lacking, as may the ability to see anything from another person's point of view.

A number of studies have shown persistent cognitive and behavioral deficits following pediatric TBI [17, 23, 24]. A 2-year follow-up suggested that children sustaining severe TBI are particularly vulnerable to impairments in EF. While some recovery took place with time since injury, deficits remained 2 years post-injury and were suggested to have an impact on ongoing development [24].

In our clinical sample, the majority of patients who had suffered traumatic frontal lobe lesions demonstrated various manifestations of dysexecutive syndrome,

Behavior	School education	Social contacts and relations with peers
a. Irritability, temper tantrums, episodes of aggressive behavior	a. Academic underachievement, accumulated knowledge is dissimilar and fragmentary	a. Difficulties in co-operating with others and in understanding the rules of social interactions
b. Impulsivity, disinhibition, physical restlessness	b. Difficulties in entering schoolwork, poor performance with inconsistency and inflexibility	b. Poor judgment and deficient self-control leading to mistakes in contacts with others
c. Fluctuations of mood	c. Slowed thinking, difficulties in remembering new information and sustaining attention on tasks, distractibility	c. Limited social activity due to becoming easily tired, lack of energy, residual neurological deficit, ongoing treatment
d. Impaired goal-directed behavior, decreased interest in the achievement of good results in different tasks and activities	d. Inaccurate, makes a lot of careless mistakes, fails to finish assignments	d. Social activities (such as hobbies, games, sports, trips etc.) are limited or avoided due to behavioral and cognitive difficulties
e. Indecision, restraint, feelings of inferiority and failure	e. Unable to use other people's help to complete schoolwork or other assignments	e. Is behind peers in the acquisition of independent behaviors and skills socially valued for age
f. Dependent on others, unable to stick up for self	f. Difficulties with use of acquired information and skills, drawing conclusions and generalizations	f. Loss of friends, increased risk of social isolation
g. Does not perceive entirely the results of his/her behavior, does not modify his/her reactions		

Table 1.
Impairments in behavioral adjustment, school education, and social competence in the long-term following traumatic brain injury.

including poor planning and organizational skills, problems with initiation/inhibition, impaired problem-solving skills, inability to shift mental sets (inflexibility, perseverations), attention disturbances and impulsivity, impaired working memory, impaired temporal organization of behavior, impaired social behavior and affective changes, and disturbances of motor control.

Children with moderate to severe TBI have displayed poorer outcomes compared to children with orthopedic injuries in all neuropsychological domains at an extended follow-up (mean 4 years). Some recovery occurred during the first year post injury, but recovery reached a plateau after that time. Further recovery was uncommon after the first year [25]. Deficits in EF, pragmatic language skills and social problem-solving were the long-term social outcomes [26].

Speech and language disorders. Motor speech disorders are common in the acute period of TBI but tend to show considerable improvement with time. They include oral-motor apraxia, dysarthria, and difficulties with breath control resulting in short length of utterance, whispering, or a monotonous voice [27].

Language function may be impaired secondary to cognitive dysfunction or specific language deficits. Disorganized language secondary to impaired cognition is most common following TBI in its acute period. Although classic aphasias are rarely seen in pediatric TBI, aphasic symptoms are. These include the inability to name objects or remember names, word-retrieval problems, and auditory and reading comprehension deficits [28].

Processing speed	a. Decrement in processing speed which can be mistakenly attributed to lack of concentration. b. This impairment will have a pervasive effect on education as the pace of learning required in school increases.
Attention	a. Deficits in the focus, division, and ability to sustain attention may mean distractibility from play, study, or road safety. b. Child may have difficulty developing attentional control.
Memory	a. Young children are unlikely to report a difficulty spontaneously. b. The younger child has acquired less knowledge previously. c. New learning deficits can have a cumulative effect as the child fails to keep up—a minor problem can develop into a major difficulty. d. The task is to acquire skills.
Language	a. Language is central to the child's sociocultural and intellectual development. b. Children losing language due to left hemisphere damage before the age of 5–6 years are likely to regain these skills due to plasticity. c. Complete recovery is less likely with injury after the critical period of language development.
Perceptual and motor skill	a. Problems are common in the acute period of TBI. b. Psychomotor slowness and dyspraxia may develop after TBI, which can adversely affect social and scholastic functioning.
Executive functioning	a. Longer term difficulty with executive skill development. b. Frontal lobes are still developing late into the second decade of life. c. Difficulties may become apparent in later childhood and adolescence.

Table 2.
Effects of traumatic brain injury on cognitive functioning and development in children.

Among our pediatric patients, in the long term after moderate or severe closed TBI only 14% had speech and language problems, including aphasic symptoms in 8% and dysarthric symptoms in 6% of cases. Impairments in communication may include slowed speech, dysfluency, word-finding difficulties, insufficient quality of conversation (producing fewer words or sentences with simple structures, tendency to use gestures while speaking), and poor comprehension of complex or long expressions. Thus, a clear difference between children and adults is that while the effects of the TBI are immediately obvious in adults, children's development is disordered after injury and some deficits may take a considerable time to appear.

Motor disorders. Severe motor deficits, including hemiparesis and impaired balance and steadiness are common in the acute period of TBI in children, with rapid recovery occurring in the first weeks or months post-injury. It is only in children who sustain very severe TBI that such motor deficits persist. Although motor outcome in the mild end of the severe TBI group is generally good, abilities rarely return to normal. Even if a classic motor examination appears normal, there will usually be deficits related to speed of performance [29]. Balance problems are also very common after TBI.

In our cohort of patients, neurological assessment revealed hemiparesis in only 4% and symptoms of ataxia in 46%. The severity of these motor disorders was defined as mild or moderate. However, 100% of children in the long-term period following moderate or severe closed TBI manifested balance problems and subtle neurological signs when examined using Denckla's battery for gross and fine motor functions [30]. Like children with ADHD, they demonstrated poor performance in both types of this battery tasks, including walking a line and sustaining postures/stations, or repetitive or successive movements for hands and feet (fine motor proficiency).

Psychiatric disorders. Pediatric TBI is associated with increased risk for the development of psychiatric disorders. The rates of newly diagnosed psychiatric disorders among pediatric patients suffered TBI were as high as 49% compared with 13% in samples of children with orthopedic injury [31]. The psychiatric sequelae of TBI, both behavioral (externalizing) and emotional (internalizing), vary with the severity and location of injury, the phase of recovery, the premorbid conditions and personality of the patient, and the psychosocial environment [9, 32].

Our study included 104 adolescent patients (58 male and 46 female) aged 12 to 19 years, who were examined within 6 months to 4 years after undergoing closed TBI of moderate and severe degrees [19]. The presence and severity of psychiatric disorders was evaluated before and after the TBI. In the long-term period of TBI, emotional and behavioral disorders were diagnosed in 55% of the adolescent patients (**Table 3**). Among internalizing disorders, a high percentage (30%) of patients with anxiety disorders (simple phobias, obsessive-compulsive and generalized anxiety disorders) was found. Mood disorders in the form of depressive states (17%) were two times more common in girls than in boys. In the majority of cases mood disorders and anxiety disorders developed after TBI—that is, TBI served as a causative factor for their development.

Attention deficit hyperactivity disorder (ADHD) occurred in 30% of the examined patients, with less frequent conduct disorder (9%) and oppositional defiant disorder (6%). It should be noted that the manifestations of ADHD in all cases were observed even before TBI, as well as most cases of conduct disorder and oppositional-defiant behavior. Thus, the presence of externalizing disorders before TBI demonstrates their role as premorbid and predisposing conditions and a serious risk factor for TBI. On the other hand, in all those cases a significant deterioration of behavior was observed after the TBI compared with degree of behavioral problems before the injury.

ADHD, defined by developmentally inappropriate and impairing levels of inattention and/or hyperactivity-impulsivity in multiple settings, is reported to be the most common externalizing psychiatric disorder among children with a history of TBI, with a prevalence of about 20–30% [31, 33], compared with the pediatric population prevalence of 5–8%. The studies have demonstrated that children with a history of TBI, even those with less severe injuries, have an increased risk for the development of new-onset attention problems even many years after injury. TBI severity was correlated with increased risk of secondary ADHD with strongest associations in severe TBI. Additional findings about the association of poor family functioning with the development of attention problems after TBI support the importance of allocating resources to the injured child's family throughout recovery [33].

Neurobehavioral effects from TBI differed by age at injury. Preschool children showed increasing ADHD and affective problems during the first year after injury [34]. Younger age at TBI was found to be a risk factor for adverse outcomes in specific psychosocial and EF domains. Preschoolers and school-age children were vulnerable to TBI adverse effects in terms of reduced emotional control, elevated emotional and affective symptoms, and behavior problems [35]. These

Emotional and behavioral disorders	Total (%) of patients with the disorder	% of patients with the disorder	
		Before the TBI	After the TBI
Anxiety disorders	30	5	25
Mood disorders	17	2	15
Attention deficit hyperactivity disorder	30	30	—
Oppositional defiant disorder	6	5	1
Conduct disorder	9	7	2

*Note: The gray shade in **Table 3** illustrates prevailing of firstly diagnosed externalizing psychiatric disorders in patients before the TBI and internalizing psychiatric disorders after the TBI.*

Table 3.
Emotional and behavioral disorders in adolescents aged 12–19 years, developed before and after closed traumatic brain injury.

findings regarding attention and emotional control are of particular importance for later self-regulation of behavior and academic achievements after TBI [36]. Executive dysfunction and psychosocial difficulties are likely to contribute to the lower functional academic skills in younger children and emergence of increased academic problems years after TBI [37].

Thus, TBI is a major cause of neurobehavioral disability among children and adolescents. Studies of outcomes 1 to 3–4 years post-injury reveal that moderate or severe pediatric TBI leads to difficulties in adaptive functioning, behavioral problems, deficits in academic and cognitive skills [9, 11–13, 15–29, 31–33]. Neurobehavioral sequelae frequently fail to resolve completely over time and thus are of particular concern to children's parents, teachers and health care professionals.

Poor outcomes of TBI sustained in early childhood may be explained considerably by the timing of injury in a period of rapid brain and behavioral development [24, 38]. Identification of vulnerability periods to the effects of TBI is crucial to promote awareness of appropriate referral for rehabilitation and school-based services [38].

4. Paroxysmal disorders in the long-term period of pediatric TBI

The vulnerability of structures of the immature brain associated with TBI can be also manifested in paroxysmal disorders: post-traumatic headache, post-traumatic epilepsy, subclinical epileptiform activity on the EEG. It is noteworthy, cognitive and behavioral disorders in children and adolescents in the long-term period of TBI significantly increase in the presence of paroxysmal disorders.

Post-traumatic headache (PTH). Headache following traumatic brain injury (TBI) of any severity has been the most common physical symptom described and is a focus of research and clinical attention [39–41].

It is easy to establish the relationship between a headache and TBI when the headache develops immediately or in the first days after trauma has occurred. On the other hand it is very difficult when a headache develops weeks or even months after trauma, especially when the majority of these headaches have the pattern of tension-type headache and the prevalence of this type of headache in the population is very high. Frequently, headache that results from head trauma is accompanied by other symptoms such as dizziness, difficulty in concentration, fatigue, anxiety and insomnia. This constellation of symptoms is known as the post-traumatic or post-concussion syndrome; among them, headache is usually the most prominent [42].

In the International Classification of Headache Disorders (3rd edition) [43], PTH is considered a secondary headache defined by the onset of headache "within 7 days following trauma or injury, or within 7 days after recovering consciousness and/or within 7 days after recovering the ability to sense and report pain" [43]. PTH is further subdivided into "acute headache attributed to traumatic injury to the head" and "persistent headache attributed to traumatic injury to the head." If the headache resolves within 3 months of onset, it is characterized as acute PTH, whereas headaches that occur beyond 3 months are defined as persistent PTH.

The most common headache phenotypes in PTH are tension-type-like headache and migraine-like headache. In our cohort of patients suffered closed TBI of moderate and severe degrees persistent PTH were observed in 268 of 283 patients (95% of cases) recurring from one episode in a week to daily attacks [18, 19]. Headaches usually affected the lifestyle of the children, resulted significantly on their mood, behavior, intellectual and physical endurance, school learning. Headaches causation was established by their onset in temporal relation to TBI and persistence for more than 3 months after head trauma. The most commonly seen pattern, resembling tension-type headache, occurred in 72.4% of patients. Headache associated with the increase of intracranial pressure due to long-lasting disorders of cerebrospinal fluid circulation was confirmed in 12.3% of cases. Migraine-like headaches were diagnosed in 11.9% and neuralgic pains in the frontal or occipital regions in 3.4%. Thus, our data evidence for the involvement of different causative mechanisms in PTH in children.

PTH pathophysiology remains largely unclear, but several possible mechanisms have been proposed, including impaired descending modulation, neurometabolic changes and activation of the trigeminal sensory system [39]. When indicating severe brain damage due to TBI and persistent PTH, it is necessary to exclude the epileptic origin of paroxysms. The combination of PTH and epilepsy, as well as epileptiform activity on the EEG in patients with PTH was firstly reported in 1963 by D.W. Cooper and D.C. Cavicke based on two cases [44]. Formisano et al. [45] revealed a high incidence of paroxysmal abnormalities on the EEG with the presence of sharp waves in 84.6% of patients with chronic PTH, which was also associated with the presence of fractures or damages to the skull and dura mater, either due to TBI or as a result of craniotomy.

Not only routine EEG, but also video-EEG monitoring with the recordings in different functional states (especially all phases of sleep) should be used in the examination of patients with chronic PTH. Studies on the use of multichannel EEG monitoring in combination with evoked brain potentials to assess the disruptions and delay of activation of neuronal networks in PTH, especially in posttraumatic migraines, is promising [46].

Post-traumatic epilepsy is one of the most threatening consequences of TBI. High risk of post-traumatic epilepsy is characteristic for patients with penetrating head injuries—as much as 50% of them develop seizures. Patients with focal neurological deficit and large cerebral lesions immediately after injury have the greatest risk for post-traumatic epilepsy. It is believed that post-traumatic epilepsy is much less common with closed head injuries.

We have determined the incidence of post-traumatic epilepsy in our cohort of children suffered moderate or severe closed TBI. A total of 18 cases of epilepsy were revealed in a total of 283 patients. A total of 16 patients (10 boys and 6 girls) or 5.7% developed secondarily generalized seizures, all in the period from 4 to 12 months post-injury; the severity of head injury was moderate in 12 and severe in 4 of them. In 2 of 18 patients head injury precipitated idiopathic generalized epilepsies: childhood absence epilepsy in a boy of 7 years of age and idiopathic epilepsy with grand mal seizures on awakening in a boy of 10 years of age. Although symptomatic post-traumatic epilepsy developed in 5.7% (16 of 283) of children suffered closed TBI of

moderate or severe degree, this incidence appears to be rather high. The findings are indicative of long-term follow-up in cases of moderate or severe TBI with the necessity of repetitive EEG recordings.

One of the most well-known population studies on post-traumatic epilepsy risk factors conducted to date [47] included 4541 patients who were divided into four age groups: from birth to 4 years (n = 542), from 5 to 14 years (n = 1184), from 15 to 64 years (n = 2546), 65 years and older (n = 269). The total 5-year probability of developing epileptic seizures was 0.5% among patients with mild TBI (loss of consciousness or amnesia lasting less than 30 minutes and no skull fractures), 1.2% for those with moderate TBI (loss of consciousness for 30 minutes to 24 hours or a skull fracture), and 10% among patients with severe TBI (loss of consciousness or amnesia for more than 24 hours, brain contusion or subdural hematoma). Thirty years post-injury, the corresponding figures were 2.1% for mild TBI, 4.2% for moderate TBI, and 16.7% for severe TBI. Thus, the increased risk of seizures after TBI varies greatly according to the severity of the injury and the time since the injury. The probability of developing epilepsy after a mild TBI does not exceed the average population risk, but severe or moderate TBI with focal damage to the cerebral cortex leads to formation the substrate of post-traumatic epileptogenesis.

The complexity and polymorphism of clinical manifestations of post-traumatic epilepsy are determined by the variety of injuries in TBI, which include both focal and diffuse components, blunt closed head injuries with or without a skull fracture, contusions, hematomas, and penetrating injuries to the brain [48]. Mostly focal injuries are accompanied by contusion of the hemispheric surface structures and the involvement of various epileptogenic zones of the brain. The subcortical structures are affected by strong mechanical impact; the superficial focal injuries often damage the frontal and temporal lobes, which have high epileptogenic potential. Therefore, the epileptic syndromes that occur with these lesions will correspond to frontal or temporal lobe epilepsy. During the course of post-traumatic epilepsy seizures remain focal in about one quarter of patients, in half they become secondary generalized with a focal onset, and in another quarter they are manifested by generalized convulsions only (after a closed TBI with diffuse damage to the deep brain structures) [49].

Meanwhile, in recent years, the use of long-term video EEG monitoring allows to identify subclinical forms of seizures, as well as epileptic status in some patients with post-traumatic epilepsy [50].

5. Treatment of neurobehavioral consequences of pediatric traumatic brain injury

The long-term consequences of TBI are often more obvious in children because their longer life span and need for schooling make such deficits all the more apparent. The overall disability in children is often less than that in adults suffered TBI. However, in the majority of head-injured children neuropsychological studies have shown deficits in cognitive functions and learning skills ranging from subtle to obvious. Special supportive measures, including educational intervention, behavioral modification and medical treatment, are therefore important issues. Thus, the treatment of TBI cognitive and behavioral sequelae must be planned as multimodal.

The study of cognitive functioning and recovery 10 years after TBI in young children by Anderson et al. [51] confirmed the high risk of persisting functional deficits associated with severe early brain insult but demonstrated an "injury threshold" beneath which children may escape serious sequelae. In contrast to the "severity"-specific recovery observed in acute and subacute periods, findings

illustrate that recovery trajectories plateau from 5 to 10 years for all groups, regardless of injury severity. This result is important because it questions previous speculation that children with severe brain insults "grow into deficits" with time since injury. After a protracted recovery period, these children gradually stabilize and begin to make some developmental gains, suggesting that even many years post-injury, intervention may be effective [51].

Children with TBI represent a challenge to pediatric rehabilitation professionals as they may improve neurologically for months or years after the injury and may recover much of the knowledge and skills acquired before their injury despite substantial new problems of learning and behavioral self-regulation.

A child with a TBI is unique not only in comparison with peers of the same age, but also to other children with brain injuries. Each child's recovery process and outcomes are different and individual. Outcomes from pediatric TBI are rarely predictable and neither is the student's progress in school. Therefore, before the child returns to school, it is necessary for him, his parents, educators and rehabilitation professionals to develop an Individual Education Program (IEP). An IEP is essential for the successful academic progress of a child suffered TBI. An IEP is an educational plan outlining the special learning needs of a child, including:

a. The amount of special education or resources which needs to be provided

b. The educational and learning goals

c. The frequency of the interventions within and without the school (usually revised yearly)

Cognitive rehabilitation refers to the process of retraining individuals in the way they take in, store, and use information. Cognitive rehabilitation therapy is sometimes provided through hospitals or rehabilitation facilities immediately following acute hospitalization. When the student is reintegrated into school, it is necessary to continue some form of cognitive training. Cognitive rehabilitation and training help the student function within the environment. Although this treatment may initially be coordinated between an outpatient rehabilitative program and school, eventually it will become a school-based intervention program.

Cognitive training focuses on the foundation skills necessary for learning. The treatment goals are improvement in these skills as well as development of compensatory strategies. Skill development should be addressed both in individual and group settings where abilities such as social/verbal pragmatic competence can be addressed more suitably. Academics as well as functional life activities need to be included within the treatment to aid with generalization of identified skills.

The home environment and parenting style have long-term impacts on functional outcomes of children recovering from TBI. Interventions to promote more effective parenting may be useful for preventing or ameliorating morbidity following TBI [52].

The brain preserves a capacity to recover and adapt secondary compensatory mechanisms when neural tissue is compromised. This capability is due to neuroplasticity, a unique feature that makes the neural circuits malleable and is at the basis of memory formation and learning as well as in adapting to injuries and traumatic events throughout life [53–56].

Neuroplasticity is a process of biological adaptation based on brain structural and functional reorganization, aimed at restoring lost or impaired functions after brain damage [54, 55]. Neuroplasticity can be implemented at the molecular,

synaptic, neuronal or multiple levels. It is based on modulating the functioning of neurons, restoring synaptic transmission, and activating inter-neuronal connections. To varying degrees, activation of neuroplasticity is accompanied by stimulation of the expression of certain genes, biosynthesis of receptor and ion channel molecules, filamentous proteins of the synaptic cytoskeleton, neurotransmitter, synaptic membrane components, intercellular adhesion molecules, formation of immature contacts, their maturation, activation, hypertrophy, and reorganization of active synapses [54]. Reparative neuroplasticity provides restoration of functional systems of the brain after their damage and is implemented by the entire spectrum of increasing the efficiency of the synaptic pool, from activation of preserved synapses to neosynaptogenesis and growth of nerve processes-a phenomenon of synaptic sprouting [54, 55].

The goal of TBI treatment is to restore normal neuroplasticity. Important tasks of neuroprotection in patients with TBI are prevention of secondary damage processes, blocking of biochemical cascades that lead to the death of neuronal cells, as well as stimulation and maintenance of neuroregeneration and neurogenesis. The discovery of neurotrophic peptide factors served as a justification for peptidergic neurotrophic therapy of many brain diseases and the consequences of TBI in particular [55, 56]. The pharmacological potential of neuropeptides is linked with the treatment of cerebral diseases associated with secondary brain damage, including TBI. Specifically, in the area of "traumatic penumbra," neurotrophins may offer protection from a secondary injury by stimulating growth and differentiation and promoting recovery of injured brain neurons [53].

Novel therapeutic strategies for TBI should attempt to stimulate endogenous repair-regeneration mechanisms while antagonizing deleterious processes. Peptide extracts from animal brains have been used as the basis for several multicomponent organ-specific medicinal formulations which are currently use in the treatment of brain diseases, including TBI [55–58]. These formulations have one very important property in common: they contain hundreds of potentially active peptide components extracted from the brain. The complex peptide formulations from the brain are optimal for simultaneous actions on different targets in the brain maintaining optimal neuroplasticity, which can in turn be regarded as a global multicomponent target.

Cortexin is a complex of polypeptides and L—amino acids with a mass of 1 to 10 kDa. Mechanisms underlying the neuroprotective properties of cortexin as well as its numerous positive effects in cerebral diseases in clinical and experimental studies have been reported [56–62]. Experimental studies have shown that cortexin's neuroprotective and nootropic actions are based on its ability to reduce neuroapoptosis and mitochondrial dysfunction, which are complex pathological processes leading to persistent cognitive disorders [57, 58].

The neuroprotective and neuroregenerative properties of this peptidergic drug are based on the ability to influence the neurotrophins system and, indirectly, neuroplasticity, neurogenesis, and degenerative changes in neurons [58, 59]. The potential molecular mechanisms of cortexin's neuroprotective properties are diverse and relate to key processes underlying neuroplasticity: signal transduction, energy metabolism, protein proteolytic modification, brain cell structure, and neuroinflammation processes. Tissue specificity is important, as well as the multicomponent nature of the drug's action, which determines its potential beneficial effect on different targets in the brain simultaneously [56].

Since neuroinflammation is a significant factor in the pathogenesis of TBI consequences, the results of animal experiments that confirmed the anti-inflammatory effect of cortexin, which had both a systemic and tissue-specific character, are of particular interest [60]. At the CNS level, its action led to normalization of free

radical balance and prevention of excessive inflammatory processes, which is the basis for potential optimization of neuroplasticity.

Another study identified four brain proteins that interact with cortexin peptides [61]. The identified molecular partners of cortexin peptides are the cytoskeletal proteins actin and the brain-specific isoform of tubulin, the brain-specific adaptive protein 14-3-3 and creatine kinase—the first potential primary targets of the drug. All these proteins are involved in fundamentally important processes. The actin cytoskeleton is known to regulate important cellular processes in the brain, including division and proliferation, cell migration, cytokinesis, and differentiation. The neuron-specific protein tubulin β5, a component of the cytoskeleton microtubules, is critical for the emergence and maturation of neurons, their migration, differentiation, and integration into neural networks. Protein 14-3-3 (alpha/beta) is the important adaptive protein of the brain that interacts with a large number of proteins, determining their localization and function in the cell, and thereby affecting a variety of cellular and physiological processes. Regulating the activity of enzymes, protection from dephosphorylation of proteins, the formation of triple complexes and sequestration processes, protein 14-3-3 participates in pathogenesis and performs neuroprotective functions in neurodegenerative diseases and other neurological and mental disorders. If we assume that binding to cortexin peptides modulates the activity of creatine kinase type B, another molecular partner identified in this study, then the positive effect of the drug on the energy supply of brain tissue becomes clear [61].

Cortexin was demonstrated to be effective in the treatment of neurological, cognitive consequences of TBI and PTH in both pediatric and adult patients [56, 58]. Taking into account the risk of post-traumatic epilepsy in the long-term period of TBI, data on the dose-dependent antiepileptic activity of cortexin obtained in experiments in animals when modeling chronic convulsive activity (model of temporal epilepsy) are important [59, 62].

The potential multicomponent nature of cortexin, containing a multitude of different neuropeptides, may be favorable for simultaneous actions on multiple targets [58, 59]. The brain tissue specificity of these molecular mechanisms is important, as to a significant extent it determines the efficacy of the formulation in cerebral diseases, including consequences of TBI.

6. Conclusions

Childhood and adolescence are periods of rapid physical and psychological growth, endocrine adjustment, and, at the same time, high risk of injuries. TBI is the most common and potentially the most deleterious type of injury in pediatric population. The consequences of TBI in children and adolescents can be represented in cognitive, behavioral, and paroxysmal disorders. These disorders may have a long-term and significantly negative impact on the success of school education and social adaptation in pediatric patients. Meanwhile, high levels of neuroplasticity in children and adolescents may determine favorable outcomes of TBI.

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.93733

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