

CLINICAL FEATURES OF POSTTRAUMATIC EPILEPSY IN CHILDREN

In order to identify clinical-age relationship in children with posttraumatic epilepsy (PTE), 78 patients aged from 3 to 14 years were examined. The mean duration of latent period was 8.9 ± 0.79 months. Studies have shown that the latent period of PTE in children is largely dependent on child's age at the time of traumatic brain injury (TBI) occurrence than on its severity. Moreover, each age group was characterized by certain types of epileptic attacks: polymorphic seizures with predominance of primary-generalized ones prevailed in the younger age-group children (3-6 years), secondary-generalized seizures developed for 52.2% of the total number of paroxysms in the middle age-group children (7-10 years), and partial seizures appeared in the older age-group (63.3 %).

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Keywords: Posttraumatic epilepsy, latent period, electroencephalography, children.

UDC: 616.853-001-053.2-08

Introduction

Traumatic brain injury (TBI) should be regarded as a long, evolving in time process, and not as a cross-sectional effect of mechanical energy. According to Konovalov et al. (2006), the whole dynamics of posttraumatic changes of the moment of injury to the long-term effects can be represented either as a compensation process, culminating in the restoration of existing in the norm of self-regulation mechanisms, or conversely, as a process of not perfect and incomplete compensation which is gradually being depleted and leads to secondary persistent disorders in self-regulation mechanisms. It was long thought that the disturbed functions after undergoing TBI in children and adolescents are more fully than in adults. In particular, Annegers et al. (1980) and DaSilva et al. (1990) believed that the younger the age at which TBI occurred, the greater the probability of complete regression of neurological disorders (Annegers, Grabow, Broover et al., 1980; DaSilva, Vaz, Ribeiro et al., 1990). Nevertheless, recent studies have not been as optimistic. Survival after severe TBI among pediatric patients, according to Akhmediev et al. (2010), is indeed higher than among adults, but there are possible delayed clinical syndromes. In particular, posttraumatic epilepsy (PTE) is one of the most serious consequences of TBI, appeared in childhood and adolescence. Studies conducted by Annegers et al. (2000) showed that PTE occurs in 11-20% of patients after TBI.

According to ILAE experts' recommendations (1997), PTE is one of the most common etiopathogenetic kinds of locally due to symptomatic epilepsy. This means that the etiopathogenetic option is considered in accordance with generally-accepted classification of epilepsy as a disease that arises on the basis of focal cerebral pathomorphological and pathophysiological changes, but the immediate cause of their formation is attributed to previous head injury. In other words, PTE is a type of epilepsy in which the formation of epileptogenic and epileptic focus has reliable causal connection with the previously transferred TBI, and which clinically manifested by repeated unprovoked epileptic seizures. The purpose of this study was to investigate clinical and age relationships in children with PTE.

Materials and methods

We examined 78 children aged from 3 to 14 years old, suffered head trauma, which was further verified the diagnosis of PTE. A total sample of children, the number of boys and girls was 49 (37.2 %) and 29 (63.8 %), respectively. TBI and its severity (according to the

used in our country classification by Caveness, 1979) for all the children included in this study were documented in relevant extracts from the case records. All the necessary studies according to the accepted standards were conducted in the neurosurgical ward, where children have been hospitalized due to TBI.

All patients included in the study, after discharge from neurosurgical hospital, were followed-up in the neurological facilities in the places of their residence. Parents were warned that in some cases after TBI children may have epileptic seizures. The relevant instructions in writing were given. This allowed us to avoid possible “unrecognized” PTE debut. Depending on the type of attacks, children were admitted either to Emergency Care Unit or Pediatric Neurology Unit. EEG was carried on the day of treatment in the hospital for all patients. Further, as required for diagnosis and monitoring the effectiveness of antiepileptic therapy, EEG was repeated, but not less than once a month.

Taking as a basis for neurobiological (neuroanatomical and neurophysiological) approach, all patients were divided into 3 groups: I group - preschool age children (3-6 years, n=18), II group - children of primary school age (7-10 years, n=31), and III group - secondary school age (11-14 years, n=29).

The diagnosis of PTE was based on the definition of the disease formulated by the last revision of the ILAE. All epilepsy cases were classified by the nature of attacks (Kyoto International Classification of Epileptic Seizures, 1981) and the form of the disease (International Classification of Epilepsy, New Delhi, 1989).

The examination included an analysis of medical records, neurological examination, routine EEG and/or video-EEG-monitoring. Bioelectric activity of brain was recorded by “MBN-Neuromapper” (version 4) and “Encephalan-EEP-19/26” computer systems. The electrodes were superimposed on the 10-20 system with reference ear electrode.

Naturally, we expected certain difficulties in verifying the diagnosis of PTE, as even patients with idiopathic epilepsy often had head injuries in the anamnesis, and it was not always possible to differentiate clearly idiopathic, cryptogenic and symptomatic forms of PTE, especially for the debut at young age or in the interictal period. Taking the above into account, in addition to other methods of study, researchers used a set of clinical-genealogical methods. Genealogical method included an analysis of genealogy (pedigrees) of families of epilepsy patients based on examination of parents and the study of medical records. Clinical methods included the analysis of obstetric history, status of children in the neonatal period and in later life, the study of dynamics of psychomotor and speech development, the study of medical history, somatic and neurological status of patients. In case of suspicion of some forms of epilepsy, rather than traumatic, children were excluded from the study.

Statistical analysis of research was conducted in the “Primer of Biostatistics 4.03” program. To detect differences in the parameters analyzed ($p < 0.05$), the method of single-factor analysis of variance was used. The correlation was estimated using Spearman’s nonparametric factor. To construct a mathematical model, the data were analyzed based on nonparametric methods of classification and separation of samples of objects surfaces.

Results and discussion

The results of these studies have shown that on the degree of severity of brain injury, the patients in the total sample were divided as follows: 26 (33.3%) children had mild TBI, moderate and severe brain injuries were in 30 (38.5%) and 22 (28.2%) children, respectively. The obtained results are different comparing to the study outcomes of Annegers et al. (1980), Annegers and Coan (2000), according to which it was found that the relative risk of PTE in mild TBI was 1.5 (confidence interval 1.0-2.2) without increasing the frequency of seizures for 5 years, in moderate TBI - 2.9 (CI 1.9-4.1), and in severe TBI - 17.2 (CI 12.3-23.6). This difference can be probably explained by uniqueness of clinics in neurotrauma for children and incorrectness of its identification with TBI in

adults. This is manifested in the typical child's body reactions, reflecting on the one hand hypersensitivity, vulnerability of the child's brain to any harmful exposure, and on the other hand - brain opportunities to functional compensation even in severe TBI. This view is also confirmed in studies of Artaryan (2003) and Midlenko (2004).

Mean duration of latent period (LP) (time between head injury and onset of epilepsy) in the patients was 8.9 ± 0.79 months: for mild TBI - 5.1 ± 1.23 months, moderate TBI - 5.5 ± 1.04 , and in severe one - 7 ± 1.1 months ($p < 0.05$), respectively (Table 1).

TABLE 1. MEAN DURATION OF LATENT PERIOD IN CHILDREN WITH PTE DEPENDING ON AGE AND SEVERITY OF TBI, MONTHS

Degree of injury severity	Total		Patient groups					
			I Group, n=18		II Group, n=31		III Group, n=29	
	N	Mean LP duration	n	Mean LP duration	n	Mean LP duration	N	Mean LP duration
Mild	26	5.1 ± 1.23	Mild	26	5.1 ± 1.23	Mild	26	5.1 ± 1.23
Moderate	30	5.5 ± 1.0	Moderate	30	5.5 ± 1.0	Moderate	30	5.5 ± 1.0
Severe	22	4.7 ± 1.1	Severe	22	4.7 ± 1.1	Severe	22	4.7 ± 1.1
Average for the group			Average for the group			Average for the group		

Our findings do not contradict the view of Makarov et al. (2001) and Broun et al. (2006) who consider that the critical period for appearance of first epileptic attacks is first 18 months after injury. This is the period when 50-60% of patients have epileptic debuts whereas the appearance of first epileptic seizures in the period from 1.5 till 5 years occurs in 2-2.5 times less, and the later development of PTE is defined only in 5-15% of cases. Along with it, according to Hauser et al. (1993), the risk of epilepsy development after severe TBI with skull fractures and intracerebral hematoma formation, as well as gunshot wounds remained high throughout the observation period.

Simultaneously, a more detailed analysis showed that there is a certain relation between LP duration and child's age at the time of TBI occurrence. In particular, in I group, the average duration of LP was 4.5 ± 0.43 months, in II and III groups it was 8.2 ± 0.95 and 11.3 ± 1.15 months, respectively. In contrast to the findings of Swartz et al. (2006), who studied 200 patients with mesial temporal epilepsy and found that the duration of LP inversely related to child's age at the time of TBI, our data suggest that in children there is a direct correlation: the younger the child at time of TBI, the more probable an early PTE debut. Clearly, different outcome obtained from the above is probably explained by other criteria for selection of patients. In addition, our results seem to be explained on the basis of general principles of phase character of the pathogenesis of epilepsy and the formation of so-called epileptic system, as evidence of research by Mazarati (2006). This is probably connected with certain ontogenetic features of the developing child's brain which exposed to the traumatic impact factor. It is known that during ontogenesis child's brain matures unevenly. The increasing complexity of the levels of brain functional organization occurs in a certain chronological order, obeying the law of heterochrony. According to Mukhin et al. (2008), due to specific features of child's brain (incomplete functional determination of cortical fields, cortical organization and myelination), it more than adult brain is prone to paroxysmal events, including as a result of the impact of such initial precipitating injury as TBI. Accordingly, we can assume that the younger the age group, the more clearly seen this pattern.

The clinical picture of seizures in PTE children in the total sample was characterized by predominance of partial forms over generalized, but statistically significant difference between primary and secondary generalized seizures was not detected ($P > 0.05$). At the same time, a more detailed analysis revealed a certain predisposition to a particular type of seizure, depending on age (Table 2).

**TABLE 2. FREQUENCY OF CLINICAL FORMS OF SEIZURES
IN CHILDREN WITH PTE DEPENDING ON AGE**

Clinical forms of seizures	Groups of patients						Total seizures, n=85	
	I Group, n=18		II Group, n=31		III Group, n=29		I Group, n=18	
	Number of seizures		Number of seizures		Number of seizures		Number of seizures	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Primary-generalized	13	54.2±10.17	Primary-generalized	13	54.2±10.17	Primary-generalized	13	54.2±10.17
Secondary-generalized	7	29.2±9.28	Secondary-generalized	7	29.2±9.28	Secondary-generalized	7	29.2±9.28
Partial	4	16.7±7.61	Partial	4	16.7±7.61	Partial	4	16.7±7.61

Note: The total number of seizures is not equal to the number of examined children because some children had several kinds of seizures.

Thus, children in I group in most cases observed polymorphism of seizures with predominance of primary generalized seizures. Moreover, the design of epileptic paroxysms was characterized by blurring the boundaries between the phases, which, in our opinion, can be explained by the lack of brain stable rhythmic cycles. On interictal EEG, the frequency of posterior dominant rhythm (PDR) averaged 5 Hz. In the background there were polymorphic paroxysmal discharges in the form of an irregular diffuse slow-wave activity and occasional bilateral synchronous sharp-wave activity with amplitude of 250 mV and with the focus in frontal parts of brain. This EEG-pattern is caused, apparently, by strengthening the diencephalic synchronizing effects, typical for this age group. Focal activity in most cases (15 patients out of 18) was not detected in routine records and was recorded primarily at video-EEG-monitoring.

In children of II group in the clinical picture of PTE were dominated secondary-generalized tonic-clonic seizures which are, apparently, due to physiological processes of incomplete myelination and determination of cortical fields at the time of TBI. The PDR frequency was an average of 8 Hz. Interictal EEG of this group was characterized by focally located slow waves, spikes and spike-wave complexes in 38.7% of children. However, in other cases the interictal record could be interpreted as relatively normal. It should be emphasized that the speed of propagation of epileptic potential in children was rather high, and consequently, in some cases, focal initiation of seizure had no time to be realized symptomatic and could not be visually identified. In these cases, the decisive method of diagnostics was ictal EEG (7 patients) or video-EEG-monitoring (12 patients).

In PTE clinical picture of patients of III group, partial seizures came to the forefront and were registered in 62.5% of cases. The PDR frequency was on average 16 Hz. In 47.4% of cases, children of this group had fast alpha variant (FAV). The EEG of these patients was characterized by regional localization of epileptiform patterns in the form of sharp waves, spike- and polyspike-wave activity on the background of focal slowing in 52.6% of cases. Apparently, the predominance of partial seizures in children of III group can be explained by sufficient maturity of brain functional systems and weaker synchronizing effect of thalamus which is typical for this age.

Thus, PTE children significantly more often develop primary-generalized epileptic attacks at pre-school age ($p < 0.05$), along with that these attacks are often polymorphic. At the same time, there is a distinct tendency to increase both in the number of simple partial seizures (from $4.2 \pm 4.1\%$ in I group to $33.3 \pm 8.6\%$ in III group) and complex partial seizures (from $12.5 \pm 6.8\%$ in I group to $30.0 \pm 8.4\%$ in III group). Based on these data, we can assume that the change in phenotype of seizures in PTE children is to be expected. In our opinion, this may be due to the ongoing ontogenetic process. In particular, Barry (2001) and D'Ambrosio et al. (2005) described the evolution of neocortical PTE in a typical mesial temporal epilepsy (MTE) both in humans and experimental animals^{5,8}.

With regard to age at the time when TBI occurred, the more we more tend to associate it with a long LP of PTE. In this case, the delayed PTE debut demonstrates individual differences in the rate of epileptogenesis.

An interesting fact is that in our study we found no absences in the structure of posttraumatic epilepsy in children. Apparently, this kind of attacks seems to be hardly expected in PTE because absence seizures (petit mal) are mostly hereditary form of epileptic attacks. Petit mal seizures are the type with the corresponding EEG-pattern, according to Greenberg et al. (2005), are not considered to be typical for PTE, although Caveness (1979) refers to their ability.

Thus, our studies suggest that the duration of LP of PTE latent period in children to some extent depends on the degree of ontogenetic maturity of child's brain at the time of TBI occurrence which demonstrates individual differences in the rate of epileptogenesis. Predisposition to certain types of seizures is based on neurophysiologic processes and is associated with a certain level of development of brain functional systems.

Conclusion

The latent period of PTE in children is largely dependent not on the severity of head injury, but on child's age at the time of TBI appearance, which is directly related to ontogenetic peculiarities of the developing brain.

Clinical-electroencephalographic signs of PTE in children depend on the child's age at the time of the disease onset and are associated with the degree of maturity of brain functional systems.

Conditionally, a normal interictal EEG in children with PTE is not the evidence of intact central nervous system and encourages conducting video-EEG-monitoring to verify the type of seizures and select an adequate therapy.

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