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Research Article

Febrile Seizures and Febrile Remissions in Epilepsy in Children: Two Sides of the Same Process?

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Abstract

Background/Introduction: In the article study of hyperthermia impact on appearance and course of seizures in childhood is presented.

Objective/Hypothesis: The object of the current article is desire to bring attention of medical scientific community to such a way of hyperthermic process influence as febrile remissions within the frames of epileptic process, and also to announce several hypotheses of existence of this phenomena.

Materials and Methods: The material for the current studies was statistical analysis of proper clinical observations of 16 patients with hyperthermic remissions.

Results: The results of our statistical processing study of individual patient's history are presented in the current article as the table with the description in the text.

Conclusion: The existing data on mechanisms of hyperthermia impact on paroxysmal activity of brain cells which are described in literature and the data received from proper observations make it possible to draw a conclusion about the same pathogenetic substrate of febrile seizures and febrile remissions in epileptic processes with different types of their realization.

Keywords: *Fever; Febrile; Seizure; Remission; Children*

Introduction

Epilepsy represents chronic brain disease which is characterized as resistant predisposition to appearing of epileptic seizures [1]. Mostly such seizures don't have reflex mechanism of their appearance or any other factors of provocation except some forms of epilepsy (epilepsies with seizures provoked by specific factors-reflex seizures) [2,3]. According to ILAE 1989 [4] classification, febrile seizures are separated as special syndromes, as a group of seizures connected to the situation where diagnosis "epilepsy" cannot be used. At the same time several epilepsies such as generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (Dravet syndrome); contain alongside common seizures those which appearance is provoked by raised body temperature [4]. Such reaction for fever is genetic and is connected to involvement into pathologic process mostly of gene SCN1A, more rarely-other genes (SCN1B, gene of y2-sub-unit of HABA receptor, CACNB4). Such seizures are called forth by hyper-synchronous neuron discharges in response to rising of body temperature which is considered to lead to raising permeability of potential-dependent sodium channels which are in any way excessively permeable due to gene mutation [5,6]. Unlike them, in healthy children the basis of febrile seizures is non-specific organism reaction for hyperthermia outside of primary damage of central nervous system.

Febrile seizures appear in the age of 3 months to 5 years and are considered relatively benign and often end with full recovery. There exist simple (typical) and complex (atypical) seizures. Simple febrile seizures are characterized by generalized form of seizures, their brevity (they last up to 5 minutes), momentariness of a fever period and absence of specific changes on EEG [7,8]. Complex febrile seizures are those which have longer duration than simple febrile seizures-10-15 minutes or longer, certain order of appearance within fever period and/or presence of partial form [9]. Besides, in children with complex febrile seizures there are more often present changes in neurological status and epileptiform activity on EEG [7,8]. It is considered that complex febrile seizures lead to epilepsy more often than simple, and in case of several risk factors of its development it is necessary to lead preventive anticonvulsant treatment [10,11]. Frequency of appearance of epilepsy after febrile seizures is very variable and makes from 2 (after single episode of simple febrile seizure) to 49% (in case of three or more complex febrile seizures) according to the data of different authors [12].

In 1997 I, Scheffer and S Bercovic [13] described the syndrome which was called «generalized epilepsy with febrile seizures plus», (GEFS+). The disease has autosomal-dominant type of inheritance with incomplete penetrance of pathologic gene (70-80%) and is characterized by sufficient heterogeneity of genetic substrate. In the current pathology the etiologic factor is mutation of genes SCN1A and SCN1B which define the defects of alpha-subunits and beta-subunits of neuronal potential-dependent sodium channel correspondingly. In patients with the current forms of epilepsy there are combined febrile and non-febrile seizures which have persistence of febrile seizures after 6 years of age as a common peculiarity. Febrile seizures are usually partial and have tendency to higher appearance frequency. The versions of non-febrile seizures are different: these can be generalized seizures (tonic-clonic, tonic, myoclonic, atonic, absence), partial seizures (hemiconvulsive, temporal and frontal seizures). Non-febrile seizures can start in childhood together with febrile or later, sometimes in patients with no febrile seizures in past history. Combination of seizures can resemble typical generalized idiopathic epilepsies, myoclonic-astatic epilepsy (Doose syndrome) or severe myoclonic epilepsy of infancy (Dravet syndrome), and also cannot correspond to no form of International classification of epilepsies and epileptic syndromes of 1989 [14, 15]. The course of disease is very variable: from mild form when seizures occur rarely and pass in course of age, to severe with developing non-curable drug-resistant epilepsy [13-17].

Severe myoclonic epilepsy of infancy (Dravet syndrome) represents a rare form of genetically determinated progressive encephalopathy which is characterized by tetrad of seizures: early clonic febrile seizures; myoclonic; atypical absence seizures; complex-partial seizures. There are also marked resistance to anticonvulsant therapy taken, progressing of intellectual and neurological abnormalities. Another common thing is strengthening of seizures and neurological abnormalities in time of infectious diseases which occur with fever [18-20].

All the above-mentioned pathologic processes are widely described in epileptology. At the same time not many epileptologists pay attention to the situation when raising body temperature in patient leads to reduction of frequency of seizures (or even temporary full remission) for the moment of fever.

Materials and Methods

We made statistical analysis of 16 case histories of children (9 boys and 7 girls), which were taken under observance for the reason of epileptic pathology within 1997 and 2014 год. The current selection had the following criteria of including into studies: presence of stated epilepsy diagnosis; dependence of grade of expression and frequency of epileptic seizures on temperature in such a way that when it raises to fever level reduction of seizure frequency occurs not less than by 50% till full disappearance of seizures; stating not less than 2 episodes of febrile remission of seizures in a row from the moment of discovering of such phenomena in every single case; duration of remission through the whole period of temperature raise and several more days after it gets back to normal; recurrence of seizures with prior strength and frequency after the episode. As a rule, the reason of appearance of febrile temperature didn't matter (Table 1).

The criteria of excluding from the current study were the following: absence of the stated diagnosis; decrease of seizure frequency when body temperature was raised till fever level by less than 50%; single episode of febrile remission in a patient (Table 1).

Sign	Frequency (n=16)
Debut in the age before three years	100% (16)
Changes in neurologic status:	
-ataxia	75% (12)
-paresis (hemiparesis, tetraparesis)	25% (4)
-pyramidal symptoms	37.5% (6)
Intellectual and mnestic insufficiency	81.5% (13)
Attention deficit and hyperactivity syndrome	33.3% (7)
Changes on EEG:	
-slow-wave type disorganizing	12.5% (2)
-hypsarrhythmia	25% (4)
-focal sharp waves	25% (4)
-spike-wave activity less than 2, 5 Hz	18.75% (3)
- multiregional sharp waves	18.75% (3)
Changes on CT/MRI:	
- diffuse cystic-atrophic changes	75% (12)
- calcinosis	12.5% (2)
- no changes	12.5% (2)
Types of seizures:	
-infantile spasms	31.25% (5)
-generalized tonic-clonic	25% (4)
-versive focal	12.5% (2)
-myoclonic generalized	56.25% (9)
-tonic focal	18.75% (3)
-atypical absence	18.75% (3)
-clonichemiconvilsive	12.5% (2)
Resistance to therapy	100% (16)
Decrease of seizure number for the period of febrile temperature	100% (16)
Decrease of seizure number in course of time	31.25% (5)
Febrile seizures in anamnesis	12.5% (2)

Table 1: *Signs of epilepsy with febrile remissions (a single child can have a combination of several signs).*

Results

The age of seizure appearance in the patients under observation was in the range of birth till 34 months of life. In all children epileptic seizures developed quickly and intensively and became stubborn and cure-resistant almost at once. Seizures had different forms and included the following types: generalized tonic-clonic seizures, myoclonic, alternating hemiconvulsions, infantile spasms, focal motor, tonic, episodes with apnea. In five cases there was periodic course of epilepsy in form of periods of elevation of seizures (averagely for a week) and decrease of their frequency and intensiveness which lasted for three to five weeks. Such cyclicity did not depend on prescribing anticonvulsants and was interrupted only by infectious disease with fever.

For the moment of examination in all children there were organic neurologic symptoms, and though by the time of seizure appearance in eight children psychic and motor development was normal, in course of disease all of them formed psychic and neurologic pathology. Among neurologic abnormalities there was ataxia which was dominating in relation to other motor abnormalities, pareses, delay of infant reflexes, psychic and motor developmental delay. In 5 children in the course of disease cognitive dysfunction and attention deficit with hyperactivity syndrome became dominating in clinical presentation which was especially noticeable on the background of gradual and spontaneous decrease of frequency and expressiveness of seizures without dependence on the taken anticonvulsant therapy. The data of electroencephalographic examination was characterized with more diversity. Both epileptiform and non-specific changes without patterns which are common for epileptic process were registered.

Neurovisualizing according to the data of computer tomography (CT) or MRI discovered picture of almost the same type in form of diffuse-atrophic changes of brain substance mostly in frontal and temporal zones. Only on one case there was found burdened hereditary anamnestic record in epilepsy. And perinatal anamnesis was burdened in four children in form of pregnancy pathology in their mothers; the pregnancy lasted with the threat of interruption in the second and third trimesters. One child was taken to intensive care department in neonatal period for the reason of fetal infection (sepsis).

Rather significant sign was almost full resistance of seizures to therapy. The following medicines were used: valproic acid, benzodiazepine, barbiturate, carbamazepine, lamotrigine, ethosuximide, levetiracetam, acetazolamide, hormonal therapy. As a rule, it was temporary recovery in the beginning of therapy with the loss of effect in the first month of medicine taking. At the same time, as it was mentioned before, in all children without dependence on taking anticonvulsants there took place the decrease of frequency or disappearance of seizures for the period of body temperature raise to febrile level.

By the character of epilepsy course among the described patients with hyperthermic remissions there could be singled out two almost homogeneous groups: with West syndrome and with some elements of Dravet syndrome (at that with exclusively paradox reaction on raising body temperature). In the first group there were 6 children, and 4 children were in the second one. Children with clinical West syndrome corresponded to all the criteria of its course: presence of epileptic infantile spasms, psychic and motor developmental delay and hypsarrhythmia on EEG. And in children with Dravet syndrome elements there were the following signs: unburdened obstetric anamnesis, start of febrile seizures in two of the patients, presence of many types of seizures- atypical absence seizures, generalized tonic-clonic, myoclonic (though without precise stages of their delayed debut), cyclicity of seizure course, predomination of coordination abnormalities in neurological status, evident hypersalivation strengthened in period of aggravations, progressive disorder of psychic and speech development, relative decrease of seizure number in course of time. At the same time the main clinical criteria which refuted this diagnosis was decrease of severity of symptoms under influence of febrile temperature. Such peculiarity of course of disease in several patients with its genetically determinated etiology taken into account, as well as etiology of some other forms of epilepsy demands further study with the purpose to define the ways of mutation realizing of some genes, in particular, SCN1A, SCN1B, CACNB4, gene of y2-subunit of GABA receptor.

Discussion

Functional activity of brain is regulated by nuclei of stem, diencephalic and limbic structures. These formations make multiply neuronal systems among which there are singled out ascending activating (situated basically on the level of reticular formation of middle and partially frontal brain) and inhibitory somnogenic (situated in thalamus, lower sections of pons cerebelli and medulla oblongata). Because of their net-like organizing excitation of one section of the net leads to distribution of the impulse to all sections of the brain. The most stable balance level between excitation and inhibition of hyper-synchronic neuron activity is in striatal complex and cerebellum, the less stable which is easily moved to the excitation range is sensomotor section and especially hippocampal. It leads to the fact that any non-specific impact in the section of hippocampal structures (and most epilepsies defined by perinatal abnormalities are related to temporal) leads to distribution of excitation to all the sections of the brain [17].

If hypothalamus and thermal regulation centres situated in it are involved into the process it appears that seizures are linked to body temperature. In children - for the reason of age-related peculiarities of functioning of central nervous system - inhibition processes are lower, thus it is more often seen that hypothalamic thermal regulation structures are involved into epileptogenesis much more often than in adults, especially with genetic base.

Due to the fact that in the cases described in our study all the patients finally developed intellectual and mnestic dysfunction, we wanted to look in details at pathogenetic basis of forming epileptic encephalopathies. In the genesis of their development the major role belongs not to pathologic epileptic focus itself, but to functional instability and hyperexcitability of neurons with development of reciprocal self-supported epileptic thalamocortical and/or corticothalamic closed circles [21]. For such disorders the definite level of neurons' maturity is needed which are able not only to generate epileptiform activity, but to support it protractedly with the definite rhythm. At the same time, this destructive epileptic activity represents specific, age-determined reaction of increased neocortical excitability with possible self-induction and circulation of epileptiform activity in form of «re-entry» mechanism in response to different pathologic states [1]. As a rule, if definite genetic substrate is present the hyperthermic reaction of organism accompanied by production of cytokines, leukotrienes and prostaglandins makes additional stimulating impact on the increased excitability of neocortex neurons. Nevertheless, in our studies the opposite, suppressing influence of hyperthermia on epileptogenic activity was marked. We suppose that in definite conditions there takes place paradox reaction of genetic substrate in form of such transmembrane ionic channels work disorder in neurons, when the action of hyperthermic cytokines leads to decrease of ability of neurons to generate stimulant action potentials. But these conditions are subject for further detailed research.

Fever has multidirectional impact on epileptogenic process in organism. Dravet syndrome is the most studied in this regard. Its etiological marker is discovering the gene mutation of α 1-subunit of sodium channels (SCN1A) in most of the patients. Mutations of gene SCN1A were discovered in generalized epilepsy with febrile seizures plus- GEFS+ alongside with mutations of gene SCN1B, and are associated with the grade of inheritance anamnesis in epilepsy and febrile seizures higher than in population [22]. By now there are found more than 700 mutations linked with Dravet syndrome. The most distributed among them is mutation of gene SCN1A which is found in 85% of patients with such syndrome. Mostly they are mutations de novo, hereditary form is found only in 5-10% of patients; it should be noted that in case of burdened family anamnesis a child with Dravet syndrome suffers in higher extent in relation to other family members whose clinical presentation can be «milder» as GEFS+ [23]. In case of clinical symptoms of Dravet syndrome the negative genetic analysis for SCN1A mutation does not refute the diagnosis, because exonic deletion or chromosome translocation with involvement of this gene may take place. The range of such genome alterations is very wide and varies from breach of an exone inside of SCN1A gene to alteration of huge number of adjacent genes. Seldom there can develop duplication and amplification of this gene, even more seldom molecular mechanism lies in the base of its breach. As it was mentioned above, mutations of other genes are also possible which lead to clinical presentation of Dravet syndrome- protocadherin 19 (PCDH19), changes in α-2 subunit of $GABA_A$ receptor (GABRG2), homozygote mutation of SCN1B etc [24].

Due to the variety of possible embodiment's aforementioned gene mutations, and in particular, a large diversity of phenotypic manifestations of SCN1A mutation, described in international studies, we expect them to participate in the development of epileptic febrile remissions in children. This hypothesis requires close attention and collaboration of experts in neurology and genetics.

Conclusion

On the ground of argumentation mentioned above and proper clinical observation experience the following conclusion can be made: febrile seizures and febrile remissions in epilepsy in children are really linked processes with common genetic substrate, but different pathophysiological mechanisms of its realization. But due to small amount of studies about febrile remissions, further detailed investigation of such mechanisms is required at molecular-genetic level to make them more precise.

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