L.M. Kuzenkova[1,2], V.M. Shaitor[3], O.V. Globa[1,2], R.F. Tepaev[1,2]
[1] Scientific Center of Children Health, Moscow, Russian Federation
[2] I. M. Sechenov First Moscow State Medical University, Moscow, Russian Federation
[3] Northwestern I. M. Sechenov State Medical University, St. Petersburg, Moscow, Russian Federation

Paroxysmal States of epileptic and non- epileptic Genesis in children. Principles of Diagnosis and Therapy.

Author affiliation:

Globa Oksana Valerievna, a Senior Researcher at the Department of Psychoneurology and Psychosomatic Pathology SCCH
Address: 2 Lomonosovskii pr. bldg. 1B, Moscow, 119991, **tel**.: +7 (499) 134-04-09, **e-mail**: globa@nczd.ru

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Seizures, particularly prolonged, are considered to be an urgent situation, associated with high risk of development of life-threatening complications and frequent development of metabolic disorders, multiple organ failure and severe brain damage. In childhood, one of the first places in prevalence is occupied by paroxysmal states, having both epileptic and non- epileptic origin and a similar clinical picture, which impedes diagnosis and etiopathogenetic therapy selection. The article highlights issues of etiology, clinical picture and differential diagnosis of seizures in children. Recommendations to assist in the development of epileptic and non- epileptic genesis seizures are formulated. The article also describes modern views of status epilepticus as a life-threatening state and principles of a phased therapy depending on seizures epileptic status duration.
Keywords: *seizures, status epilepticus, children, non- epileptic paroxysmal states.*

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INTRODUCTION

In childhood, one of the first places in prevalence is occupied by paroxysmal states, having both epileptic and non- epileptic origin. Diagnosis is often complicated: comprehensive examination coupled with monitoring of patients are required to specify the diagnosis and the question of treatment. It is essential to remember that not all paroxysmal states are convulsions.

GENERAL CHARACTERISTICS OF PAROXYSMAL STATES

Definition

Paroxysm — an unexpected and sometimes recurrent potentially reversible change of organs' activity and the body system.

Seizures – a non-specific reaction of the nervous system on various endo-or exogenous factors: unexpected recurrent involuntary contractions in skeletal muscles, often with impaired consciousness. Generally, they accompany various pathological conditions on the stage of their demonstration, as a primary response during the deterioration of vital body functions.
Epilepsy – a state, which is characterized by recurrent epileptic seizures, unprovoked by a direct certain reason.

Prevalence
According to the literature, convulsive syndrome occurs in 17-20 cases out of 1000; up to 2/3 of seizures in children occur at an early age – the first 3 years of life [1]. Among childhood paroxysmal states epilepsy is the most frequently occurring state: from 41 to 83 cases; among the patients in the first year of life – from 100 to 233 cases out of 100 thousand of child population.

Terminology
In 2001, the International League Against Epilepsy (ILAE) recommended replacing the word "convulsions" to "attacks" because not all attacks manifest as convulsions, which are accompanied by motor phenomena.

However, the most dangerous conditions are the convulsions, which are frequently accompanied by respiratory or cardiac activity disorder, subsequent metabolic changes, central nervous system (CNS) damage and which require active intervention.

Causes
Depending on the age group, causes of seizures can vary. During the neonatal period, the non-specific reaction of the nervous system is most often associated with:

- hypoxic-ischemic lesion of the CNS;
- intracranial birth trauma;
- intrauterine or postnatal infection;
- congenital abnormalities of brain development;
- withdrawal syndrome (in children born to mothers with alcohol or drug dependence);
- metabolic disturbances - transient states or endocrine pathology (hypocalcemia, hypomagnesemia, hyponatremia and hypernatremia, hypoglycemia);
- hereditary metabolic diseases (nonketotic hyperglycemia, urea cycle disorders etc.).

During seizures development in early infancy, infectious diseases predominate: acute respiratory viral infections, pneumonia, inflammatory diseases in ENT organs, sepsis, neuroinfections, post-vaccination complications, craniocerebral injury, post-traumatic acute seizures, post-traumatic epilepsy and various epileptic syndromes.

Less common causes of seizures in this age are congenital malformations of brain development, neoformations, brain abscesses. Seizures sometimes occur during heart rhythm disorders, poisoning and intoxication.

It is essential to distinguish motor manifestations associated with seizures from non-epileptic motor response – tremor, hyperkinesia, hypoxic convulsive manifestations following syncopal states, affective-respiratory paroxysms, heart rhythm disorders, hypoglycemia and

other metabolic disorders [1]. Febrile and nonfebrile seizures at children should be also distinguished.

Diagnosis

During the beginning of a seizure, it is essential to take into account, whether it is febrile, which means, occurring during or after fever, or nonfebrile.

Nonfebrile seizures can be the first epileptic paroxysm, symptomatic neonatal convulsions, isolated epileptic attack and non-epileptic paroxysms, arising from heart rhythm disorders, asphyxia, psychogenic paroxysms.

Febrile seizures can be simple febrile seizures manifestation, systemic or neuroinfections, febrile provoked epileptic attacks.

However, in urgent clinical situation for the relief of convulsive seizures it is necessary to resort to symptomatic therapy. Diagnostic measures can be delayed.

Seizures in children can be both epileptic and non-epileptic paroxysms as well as states, which do not require the definition "epilepsy".

Non-epileptic convulsive and other paroxysmal states

1. Seizures as the non-specific reaction of the brain in response to various endo-or exogenous factors, i.e. acute symptomatic attacks:

- febrile (amid fever);
- amid intoxication;
- hypoxic (amid diseases of the respiratory system, e.g. bronchial asthma, asphyxia etc.);
- affective-respiratory paroxysms;
- exchange and metabolic (spasmophilia syndrome and hypervitaminosis of vitamin D in rickets and so on, hypoglycemia, hypokalemia and hyperkalemia);
- during violation of the vegetative system;
- cardiac syncope (heart rhythm disorders) etc.

2. Symptomatic seizures in brain diseases including:

    - tumors;
    - abscesses;
    - ischemic or hemorrhagic strokes;
    - malformation of the brain;
    - cerebrovascular malformation (aneurysms, Moya-Moya disease etc.).

The features of paroxysmal states

- In accordance with the nature of motor manifestations, seizures are divided into:

    • tonic;

    • clonic;

- tonic-clonic;
- clonic-tonic;
- atonic;
- myoclonic.

♦ For duration of release:

- self-limiting – focal, generalized;
- continuing attacks – generalized epileptic status, focal epileptic status.

FEBRILE SEIZURES

Febrile seizures arise from the fever in 2-5% of children and are the most frequent type of seizures in children under 5 years old.

Terminology

Metabolic disorders – hypoglycemia and hyperglycemia, as well as electrolyte metabolism disorders (In particular, sodium) - are mostly factors in disorders of consciousness, sometimes accompanied by muscle contractions. These states require urgent therapy.

Cardiac syncope associated with heart rhythm disorders, paroxysmal tachycardia, disorders of congenital heart disease may also be manifested by loss of consciousness, sometimes accompanied by muscle contractions due to developing cerebral hypoxia. This condition is life-threatening and requires emergency intervention of anesthesiologist-resuscitator!

Affective-respiratory attacks. The cause of such states is autonomic (vegetative) nervous system dysregulation. Affective-respiratory paroxysms proceed with loss of consciousness in approximately 5% of patients [1]. These states often do not require therapeutic intervention.

Causes

1. Infectious process involving the central nervous system, or convulsions in encephalitis, meningitis. In neuroinfections, consciousness is often not fully recovered after seizures [2].
2. Fever as a provoking factor of an existing neurological disease (e.g., febrile-provoked epileptic seizure).
3. Simple febrile seizures – age dependent (from 6 months to 5 years) genetically determined seizures occurring only at fever, and in the absence of infection in the CNS.

Clinical manifestations

Simple febrile seizures are characterized by the following clinical manifestations:

- usually develop at body temperature above 38 ° C in the first hours of the disease;
- tend to have a generalized nature;
- the seizures duration – less than 15 minutes;
- do not repeat within 24 hours;
- family history often contains indications of the presence of febrile convulsions in relatives.

Atypical (complex) febrile seizures are characterized by the following clinical manifestations:

- • a focal component;
- • last for more than 15 minutes, febrile convulsive status may occur;
- • may recur within 24 hours.

During atypical febrile seizures, there is a high probability infection or epilepsy in a child.
Electroencephalographic examination for typical febrile seizures usually fails to identify epileptic changes in atypical febrile attacks; in contrast, both non-specific paroxysmal changes and epileptic patterns can be seen.
About 1/3 of patients with febrile attacks have repeated convulsions.
The most important criteria of possible febrile epileptic seizures is a change in neurological status and/or violation of the neuropsychological development.

Metabolic seizures in spasmophilia are characterized by the following clinical manifestations:

- paroxysm starts with apnea – when inhaling the original condition is restored;
- cyanosis of nasolabial triangle is often identified;
- predominantly clonic seizures nature;
- paroxysms can be triggered by external stimuli – a sharp thud, a sound, a cry, etc.;
- tend to repeat throughout the day;
- are nonfebrile;
- focal neurological symptoms are usually absent;
- symptoms of somatic inflammatory processes are absent;
- positive signs of Chvostek, Trousseau, etc., bone symptoms of rickets can be observed.

Affective-respiratory "blue" type paroxysms are not epileptic paroxysms; they are characterized by the following clinical manifestations:

- can be observed from the age of 4 months;
- provoking factors are negative emotions, fear, discomfort;
- apnea arises amid a prolonged cry;
- about 5% of cases are accompanied by loss of consciousness;
- amid a prolonged apnea clonic or tonic-clonic seizures are sometimes observed;
- paroxysms are short-term;
- after the attacks there is weakness, drowsiness;
- can occur several times a day, however, sometimes – 1-2 times in a lifetime.

Affective-respiratory "white" type paroxysms are characterized by the following clinical manifestations:

- are the result of a reflex asystole;
- often triggered by pain impact;
- the child is rarely crying for a long time, skin paleness appears quickly, there is a loss of consciousness, the paroxysm is from a few seconds to a few hours long;
- after the paroxysm the child often falls asleep, after waking up the normal vital activity is retained;
- in heart disease, heart rhythm disorders these states can be life-threatening.

STATUS EPILEPTICUS

Terminology

Status epilepticus (SE) – the most threatening pathological condition that requires urgent intervention – it is characterized by seizures up to 5 min and longer or recurring seizures with the function of the central nervous system not fully recovered between these seizures.

In 2015, E. Trinka et al. proposed a new definition of status epilepticus as a state, resulting from the depletion of the mechanisms responsible for the cessation of attacks or initiating mechanisms leading to abnormal sustained attacks. The result of the prolonged effect, is that this condition can lead to neuronal damage, neuronal death, disruption of neuronal circuits - depending on the type and duration of seizures [3]. Time intervals and types of treatment are important for prediction of a pathological condition.
In an urgent situation, SE in epilepsy and symptomatic SE during the current cerebral processes should be distinguished [4].
Convulsive status is the most unfavorable in terms of predictions and requires urgent measures. Non-convulsive epileptic status is difficult to diagnose, however, it is more favorable in terms of maintaining vital functions.

Classification [2, 4].

1. SE in newborns:
   - neonatal status epilepticus;
   - status epilepticus in epileptic syndromes in newborns.
2. SE in the childhood age:
   - infantile spasms;
   - febrile status epilepticus;
   - status epilepticus in children with myoclonic syndromes;
   - status epilepticus in partial benign epileptic syndromes in children;
   - electrical status during slow-wave sleep;
   - acquired epileptic aphasia syndrome.
3. SE in childhood age and in adults:
   - tonic-clonic status;
   - absence status;
   - epilepsia partialis continua;
   - myoclonic status in a coma.
4. specific forms of SE in mental delay:
   - myoclonic status in other epileptic syndromes;
   - non-convulsive status in simple partial seizures;
   - epileptic status of complex partial seizures.

Clinical manifestations

Epileptic convulsive status is characterized by the following clinical manifestations:

- usually triggered by violation of the dosage of antiepileptic drugs or the termination of their admission if the child has epilepsy, acute infections, etc.;
- characterized by recurrent seizures with impaired consciousness;
- full recovery of consciousness between seizures does not occur;
- seizures are generalized tonic-clonic in nature;
- clonic jerking of the eyeballs and nystagmus are observed;
- attacks are accompanied by respiratory failure, hemodynamic, metabolic disorders and the development of cerebral edema;
- the increasing depth of impaired consciousness and the appearance of paresis and paralysis after seizures are prognostically unfavorable.

Treatment

Status epilepticus is distinguished by stages; status treatment protocol is strictly regulated according to the time flow of seizures.

Urgent help

During seizures, urgent care is provided in the following stages:

- it is necessary to ensure in the airway patency;
- humidified oxygen inhalation is obligatory;
- the patient should be laid on a soft surface and the head should be turned to one side in order to prevent injuries to the head, limbs, biting the tongue and tongue retraction, aspiration of vomitus;
- glycemia monitoring, ECG;
- if the child is taking anticonvulsant therapy – measurement of anticonvulsants concentration;
- medical history with description of the paroxysm; if it has ended by the time of inspection – the situation preceding the paroxysm should be clarified: whether similar states were observed previously; if possible, family history of similar or other paroxysmal conditions in relatives.

Anamnestic data enables to assume epileptic/non-epileptic nature of paroxysm in many cases.

Medicamental therapy

- Introduction of diazepam 0.5 mg per 1 kg of body weight intravenously or intramuscularly, but not more than 10 mg per dose.
- With a partial relief of seizures or absence of response to the initial administration of diazepam dose introduction may be repeated after 5-10 minutes, the total dose should not exceed 20 mg.
- If hypoglycemic seizures are suspected, 20% dextrose solution at a dose of 2.0 ml/kg is intravenously administered.
- If hypocalcemic convulsions are suspected, 10% calcium gluconate solution at a dose of 0.2 ml/kg (20 mg/kg) diluted to 20% dextrose solution twice is slowly administered intravenously.
- In case of prolonged febrile seizures and inability to take fever-reducing drugs intravenously, paracetamol solution at the rate of 10 mg per 1 kg of body weight is administered, physical cooling methods are used.

Table. Two-stage scheme of administration of the freeze-dried sodium valproate

Stages	**Administration method**	**Dosage**	**Preparation before administration**	
1	Intravenous bolus (during 5 min)	15−30 mg/kg	Dissolve each 400 mg in 4,0 ml of solvent (water for injection)	
2	Prolonged infusion	1−5 mg/kg per hour	1st option: dissolve each 400 mg of lyophilisate in 0,9% sodium chloride solution	2nd option: dissolve each 400 mg of lyophilisate in 20% dextrose solution

Drug therapy of status epilepticus is conducted in the following stages.

1. Stage 1 (5-10 min) - early status epilepticus:
   - diazepam – 0.5% solution is administered slowly intravenously (for children in the age of 3 years and older at 0.3 mg/kg, for children younger than 3 years the dosage may be increased up to 0.5 mg/kg);
   - midazolam, 0.2 mg/kg (in the absence of reaction to diazepam);
   - if it is ineffective – intravenous administration of sodium valproate liofilizata (table.).

2. Stage 2 (10-30 min) – established status epilepticus:
    - valproic acid administered intravenously in a bolus dose of 15-30 mg/kg, followed by a maintenance dose of 2.5-5 mg/kg per hour.
3. Stage 3 (30-60 min) – refractory status epilepticus:
    - sodium thiopental is used in status epilepticus which is refractory to other treatments, in a bolus dose of 3-5 mg/kg, followed by microfluidic infusion of 1-3 mg/kg per hour; the maximum dose of 5 mg/kg per hour (contraindication - shock) under strict control of blood pressure. Introduction of sodium thiopental requires monitoring of blood pressure, electrolyte content, especially sodium, as it can lead to hypotension, hypernatremia and prolonged time for getting out of the drug coma;
    - midazolam in a dose of 100-200 mkg/kg as a bolus loading sample, followed by 1-2 mkg/kg per minute with an increase of 1-2 mkg/kg per minute every 15 minutes if seizures are unrelieved;
    - propofol in initial dosage of 2 mg/kg.

4. Stage 4 (> 24 h) – super-refractory status epilepticus – characterized by total hypothermia with a temperature decrease to 34°C:
    - continued therapy of the 3rd stage;
    - identification of possible causes of resistance: if there are structural, metabolic disorders or infectious cause of long-continued convulsions;
    - pyridoxine (for suspected pyridoxine-dependent seizures) in a dose of 20-100 mg/kg intravenously;
    - steroids in a dose from 1 to 10 mg per kg of body weight.

During the development of status epilepticus

Assessment of the patient's condition, carrying out cardiopulmonary resuscitation, if necessary, as recommended by the Pediatric Advanced Life Support (PALS) [5], and assessment according to Glasgow coma scale (GCS).

Inhalation conducted with 100% oxygen and determining the need for immediate tracheal intubation and mechanical ventilation (MLV). Indications for tracheal intubation and mechanical ventilation include:

- violation of consciousness (GCS <9 points);
- clinical manifestations of growing intracranial pressure;
- absence of pharyngeal and laryngeal reflexes;
- hypoventilation;
- hypoxemia;
- shock.

Furthermore, it is advisable to monitor the laboratory tests (with the assessment of the level of creatine kinase, glucose, electrolytes, blood gas composition, lactate, acid-base status). Seizures do not always require intubation, if the airway is not broken and hypoxemia is not developing. However, intubation is required especially in the ongoing convulsive status epilepticus, and is performed after the intravenous induction or general anesthesia. During prolonged seizures hyperkalemia may develop, that is why it is better to use fast-acting nondepolarizing muscle relaxants (e.g., rocuronium bromide), and avoid the use of suxamethonium iodide, which is depolarizing muscle relaxant of peripheral effect.

Prolonged infusion of muscle relaxant should not be performed, because it masks the motor manifestations of seizure activity. It is used only in pronounced muscular activity, which may impede the intubation, providing adequate respiratory support, and causes lactic acidosis. Nasogastric tube installation is recommended for prevention of the development of aspiration pneumonia. Cooling to normal temperature is conducted in the presence of hyperthermia.

Measures are carried out to restore arterial pressure indicators, the content of oxygen and carbon dioxide, glucose, electrolyte status, etc.
All the mechanical ventilator patients should be connected to the monitor of the assessment of the cerebral cortex functions. Drugs titration is carried out, until the pattern "flash-suppression" in the EEG recording appears. Further deepening of sedation is unfavorable, because it leads to brainstem anesthesia, which is characterized by low-voltage "native" EEG on the monitor and oppression of pupils' photoreaction [3, 6-9].
In the absence of timely and adequate treatment, status epilepticus leads to neurological disability in patients, as well as to high mortality. Permanent EEG recording is of great importance for both keeping control of convulsive status relief measures and performing differential diagnostic measures with non-convulsive status epilepticus, which is often impossible to diagnose without neurophysiological monitoring.

In the treatment of the first SE occurrence, it is necessary to prescribe basic antiepileptic therapy or clarify anticonvulsants concentration in blood serum, if a child is suffering from epilepsy and receiving long-term therapy. One possible reason for the development of SE in children can be low concentration of anticonvulsants in blood.

CONCLUSION

It should be noted, that in case of seizures development, the fundamental factor of success of the therapy is adequate diagnosis. Somatic, endocrine, metabolic causes of seizures suggest an appropriate etiopathogenic therapy. Paroxysmal "neurological" non-epileptic disorders often do not require treatment. That is why, in case of the development of seizures, particularly of convulsive status epilepticus, an integrated approach to the examination and treatment with specialists - neurologists, cardiologists, endocrinologists, infectious disease doctors, ENT doctors, and possibly geneticists, is necessary.

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