EPILEPSY IN IEM

WHAT IS A SEIZURE?

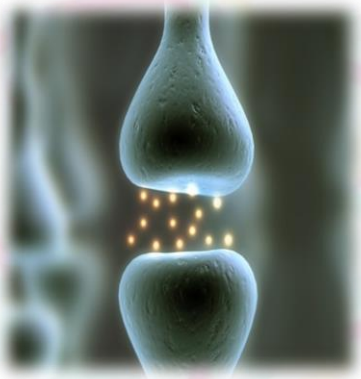
A **seizure** is a sudden and limited brain process that consists in a synchronized and excessive activity of a group of neurons. This discharge may be focal or spread to other regions through a propagation process. When a seizure is focal, the patient is usually conscious. When a seizure is generalized, there tends to be an environmental disconnection and the patient loses all memory of the episode. Seizures may be associated with convulsive movements, muscle stiffness, loss of muscle tone, tremor, myoclonus, or generalized jerks. In other cases, seizures may consist simply in a cessation of activity without causing convulsive movements. We talk about **epilepsy** when the brain, for one reason or another, has a predisposition to have recurrent seizures.

DIAGNOSIS

The diagnosis of a seizure is made through theanamnesis or clinical interview (the patient's symptoms are essential, as well as personal and family history) and relies on the electroencephalogram or EEG. The EEG is a recording of the electrical activity of neurons. There are external factors that affect the incidence of EEG abnormalities, and are applied systematically over the registers to optimize the results and validity of the test. These favorable factors are: perform a sleep registration, hyperventilation maneuvers (breath deeper and more frequently), intermittent light stimulation, visual or auditory stimuli, etc… Performing an EEG register in these conditions improves its diagnostic possibilities.

There are many different types of seizures, as there are different types of EEG findings according to the type of crisis that the patient presents, the base disease, use of antiepileptic medication…

MECHANISMS OF EPILEPSY IN IEM



Epilepsy is a relatively common symptom in the IEM. The mechanisms by which the different IEM can produce seizures are varied:

(1) They may interfere with the metabolism of substrates (necessary substances) for the normal function of neurons, the best example would be in the mechanism of obtaining energy (defects in creatine metabolism, defects in glucose transport, mitochondrial diseases).

(2) They can produce an alteration on the necessary function coupled between neurons and astrocytes (astrocytes have important roles in maintaining and protecting neurons, if this fails, the neuron function may be altered).

(3) IEM directly altering neurotransmitter pathways (neurotransmitters are substances produced by nerve cells that allow communication between them). There are excitatory neurotransmitters (causing an increase in the activity of neurons) and inhibitory neurotransmitters (which decrease the activity of neurons).

AGE OF EPILEPSY ONSET

There are IEM that present epilepsy during the neonatal period: Nonketotic hyperglycinemia, defects of purine synthesis, causes of hypoglycemia, deficiency of holocarboxylase synthase, deficiency of PNPO and antiquitine, congenital hypophosphatasia, some forms of CDG, defects of the O-glycosylation, deficiency of the molybdenum cofactor/ sulfite oxidase, peroxisomal diseases, glutamate transporter deficiency, congenital deficiency of glutamine, GABA transaminase deficiency, neonatalneuronal ceroidolipofuscinoses, among others.

Other manifest during **infancy**: Causes of hypoglycemia, urea cycle disorders, organic aciduries, phenylketonuria, BH4 deficiency, biotinidase deficiency, folic acid metabolism (MTHFR, FOLR1), some forms of CDG, deficiency of GLUT1, defects in the metabolism of creatine, defects of oxidative phosphorylation (mitochondrial cytopathies), neuronal ceroidolipofuscinoses, type 1 sialidosis, infantile Krabbe disease, among others.

In general terms, seizures can occur at any time during childhood, depending on the clinical onset of IEM, which can be highly variable between different patients.

FINDINGS IN THE EEG

The EEG findings serve to guide the doctor about what type of antiepileptic drug (AED) may be useful to control epilepsy in patients, being metabolic diseases or diseases from other sources.

Overall, the findings that can be found in the EEG are not specific to any IEM, although sometimes very specific ones may suggest a specific IEM.

TREATING EPILEPSY IN INBORN ERRORS OF METABOLISM

There are IEM presenting refractory epilepsy, such as nonketotic hyperglycinemia, sulfite oxidase deficiency or Menkes disease. In other cases, seizures may occur in the context of metabolic decompensation with little risk of recurrence when the patient is controlled. This is the case of glutaric aciduria type I.

There are a large number of AEDs and pharmaceutical research in AEDs is profuse, and thus this number is growing.

Certain AEDs are contraindicated, as a rule, in certain IEM, such as valproic acid in mitochondrial diseases (since it produces a mitochondrial metabolism inhibition), or the phenobarbital defects in Glut-1 (since it inhibits the glucose transporter).

With some exceptions as mentioned above, the type of AEDs indicated for each patient depends on the type of seizures, EEG abnormalities, the patient's clinical situation, if the patient is already receiving other AEDs, side effects… and not from the IEM presented by the patient. However, antiepileptic drugs are not the only way to control epilepsy, as there are other options such as ketogenic diet (the first choice in some IEM as GLUT1 deficiency), the vagus nerve stimulator (it is a small generator pulse that sends electrical signals to the brain via the vagus nerve and is placed at the level of the clavicle from behind) and neurosurgery. Epilepsy surgery is indicated in focal epilepsies with a brain injury affordable for deletion. In general, IEM are not candidate diseases for epilepsy surgery because it does not usually produce focal lesions but a diffused dysfunction of the central nervous system.

Furthermore, there are IEM that respond to specific treatments different from the classic AEDs. Pyridoxine-sensitive crises caused by defects in the antiquitine gene are a clear example, since the treatment is based on the administration of pyridoxine. Seizures associated with cerebral folate deficiency respond to folinic acid and seizures deficits in thiamine transport operator respond to the administration of thiamine.

In general, those IEM with an effective treatment may benefit from such treatment to improve all aspects of their disease, including seizures.

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