Epilepsy in Rett syndrome – notes for talk at ORSA meeting, September 2010

This talk was part of a three-person panel discussion and had two principal objectives:

1) to describe why and how epileptic seizures develop in the human brain
2) to review the main features of epilepsy in Rett syndrome (RTT) – what kinds of seizures occur and at what age; who is more likely to develop epileptic seizures; what treatment strategies are available

Epileptic seizures

An epileptic seizure is defined as an excessive, uncontrolled electrical discharge of cerebral cortical nerve cells (neurons) producing an alteration in behavior or in conscious experience.

All neurons have the capacity to develop and hold an electrical charge. This charge is created by the action of several intricate pump mechanisms that are located in the cell membrane and that have the capacity to push (or briefly allow to pass) a number of charged particles (ions) into or outside the cell. The most important of these ions are sodium (Na^+), potassium (K^+) and chloride (Cl^-); they enter and leave cells through specialized channels (ion channels) around which the "pump" molecules are located. By creating imbalances in ion concentrations between the interior and exterior of neurons (e.g. more Na^+ outside than inside; more K^+ inside than outside), the ion pumps create an overall negative charge inside the cell.

Normal neurons communicate with each other by the propagation down their "exit fibers" (cell processes called axons) of an electrical charge, or action potential. An action potential takes place within a neuron when, as a consequence of electrochemical information collated from other neurons and arriving in the cell via its "input fibers" (or dendrites), the sodium channels in the cell's membrane abruptly open and admit a flood of Na^+ ions into the cell. This influx briefly changes the charge within the cell from negative to positive; the ion pumps then immediately restore the status quo within the cell body. Once created, the action potential rapidly spreads down the axon from the cell body to impinge on other neurons elsewhere in the nervous system – either exciting or inhibiting those cells.

The actual communication point between neurons is a specialized gap, or synapse, that may be located on the downstream cell's dendrites, cell body or even its axon. On arrival at the synapse, the action potential provokes the release of one or more chemical compounds (known as neurotransmitters) that cross the synaptic space and act on specialized receptor sites on the membrane of the downstream neuron. Whether that neuron is excited or inhibited by the message just received depends on both the type of transmitter molecule and the type and location of the receptor.

From the viewpoint of epileptic seizures, the most important neurotransmitter molecules in the cerebral cortex are glutamic acid (glutamate – excitatory) and gamma-aminobutyric acid (GABA – inhibitory).

"Epileptic" (or uncontrolled) electrical discharges from cortical neurons may occur for one or more reasons:

1) the threshold for the creation of action potentials is abnormally low – this is usually a hereditary defect

2) a region of glutamate-producing cortical neurons has been damaged or malformed, and tends to fire outside of normal restraint mechanisms
3) the membrane ion channels are abnormally "leaky" – a mechanism that probably overlaps with (1)
4) there are inadequate numbers of, or a loss of function in inhibitory neurons, either through impaired production of such cells or through acquired brain injury
5) increased glutamate production or decreased GABA formation
6) ion pump failure due to energy insufficiency – as in epileptic seizures in diabetics whose blood sugar has become too low

Depending upon the mechanism(s) of production of epileptic seizures in a given person, a number of different types of epileptic seizures are possible:

a) *focal seizure* (motor – e.g. hand/finger twitching; sensory – e.g. hand/finger numbness; psychic – e.g. groundless fear; autonomic – e.g. vomiting)
   ~ simple type, with no impairment of conscious awareness
   ~ complex type, with partial or complete loss of consciousness
b) *generalized seizure* (tonic – stiffening of all 4 limbs; clonic – rhythmic twitching of all 4 limbs; tonic-clonic; absence – loss of awareness without impairment of ability to stand or sit; atonic – sudden loss of all muscle control with an abrupt fall; myoclonic – bilateral shock-like limb jerks)
c) *focal onset with secondary spread to create a generalized seizure* - as in (b)

Epilepsy in Rett syndrome

In a recent paper published in the journal Neurology, Daniel Glaze and colleagues stated that about 60% of RTT girls are reported by their care-givers to have had epileptic seizures. This reported frequency was the same for girls with atypical RTT phenotypes as it was for those with typical phenotypes. Given that seizure-like episodes in some RTT patients are eventually shown not to be epileptic in nature, Glaze et al postulated that the true incidence of epilepsy in Rett girls is probably closer to 50%, still a high number.

Partial and generalized seizures (see previous section) occur with equal frequency, the most common seizure patterns being complex partial, tonic-clonic and myoclonic. 30% of RTT girls with epilepsy have multiple seizure types.

The peak age of epilepsy onset in RTT is 3-4; it is very rare for patients with MECP2 mutations to develop epilepsy prior to age 2; in contrast, girls with RTT phenotypes caused by CDKL5 mutations develop epilepsy in the first few months of life. Over time, epileptic seizures in Rett girls tend to decrease in frequency by the teens, often disappearing in adult life.

The mechanism of production of epileptic seizures in RTT is not clear. Possibilities include an over-development of glutamate (excitatory) receptors on cortical neurons and a defective development of GABA-producing neurons. In regard to the latter possibility, Dlx5 – one of the genes controlled by MeCP2 – is present in GABA-producing neurons and stimulates the synthesis of GABA.

In general, girls with a greater degree of impairment in walking, hand use and communication are more likely to develop epilepsy. Nevertheless, girls with mild phenotypes still have a significant risk, depending upon the type of MECP2 mutation. In the Glaze et al study, the highest incidence of epilepsy was seen in RTT patients with

T158M (74%) and R106W (78%) mutations. Incidences were lower for the R306C (49%), R255X (49%) and R133C (50%) mutations, the last of these nearly always having a "mild" phenotype.

One does not automatically start patients with epileptic seizures on antiepileptic drugs (AEDs). The decision to start AEDs is made on the basis of seizure severity and frequency. A medication is typically not introduced after a first seizure (unless that seizure lasted for over 30 minutes) as the patient might never have a second seizure, or have the next attack 1-2 years after the first. A Rett girl with generalized tonic-clonic seizures once or twice a month would nearly always be started on an AED; in contrast, a patient with several minor seizures a day (e.g. 10 seconds of inattention and eye deviation to one side) and no other seizure types is probably better off without medication. Clearly, the decision as to whether or not to start an AED has to be individualized, and based on the risk to the patient, the degree of disruption to the family and a careful consideration of known drug side-effects.

AEDs work in a number of different ways. Some (phenytoin, carbamazepine, oxcarbazepine, topiramate) reduce seizures by stabilizing "leaky" neuronal membranes. Others (phenobarbital, divalproex, benzodiazepines, vigabatrin) primarily work by enhancing inhibitory (GABA) neurons. Lamotrigine is thought to reduce seizures by inhibiting excitatory (glutamate) neurons. Many drugs (e.g. topiramate) operate by several different mechanisms at once. Since mechanisms of action, patients with difficult-to-control epilepsy typically wind up on a combination of drugs, each having a different main mechanism of action.

AEDs are also chosen based on the type of seizure being treated. Generalized tonic-clonic seizures, for example, respond best to divalproex, topiramate, benzodiazepines and phenytoin (although phenytoin, because of its serious cosmetic side effects – acne, puffy gums, increased body hair – is usually only employed as a simple loading dose to stop prolonged seizures). Focal-onset seizures, on the other hand, tend to respond best to lamotrigine, levetiracetam, topiramate, carbamazepine and oxcarbazepine.

While most patients taking AEDs have a partial reduction or complete cessation of their epileptic seizures, some (15-20%) do not respond to medications of any kind. For RTT girls failing to respond to AEDs, there are two other options: the ketogenic diet and vagus nerve stimulation.

The diet is a complex high fat, low carbohydrate, adequate protein diet that requires close supervision by an experienced dietician and, at least initially, a great deal of training and hard work on the part of the care-givers. In some cases, the response to the ketogenic diet is dramatic. The diet is potentially dangerous, however, and should never be undertaken without supervision.

A vagus nerve stimulator is an implanted device somewhat like a cardiac pacemaker that reduces the number and severity of epileptic seizures by regular, intermittent stimulation of the left vagus nerve in the neck; the precise mechanism of action within the brain is unknown. Typically it takes a year or so following the commencement of vagus nerve stimulation for the improvement in seizure control to occur; complete cessation of seizures is unusual.

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