Rasmussen’s Encephalitis (RE)

by Alina Ellerington, The Encephalitis Society and reviewed by Dr. Sophia Varadkar, Consultant Pediatric Neurologist, Great Ormond St Hospital for Children NHS Foundation Trust & UCL Institute of Child Health

What is RE?
Rasmussen Encephalitis (RE), also called Rasmussen syndrome, is a rare, progressive, chronic Encephalitis (inflammation of the brain) characterised by seizures, progressive hemiparesis and cognitive loss (learning difficulties). It occurs mainly in children with a peak of incidence at the age of 6-7 years. However adolescent and adult cases have been reported accounting for about 10% of all cases of RE. RE occurs usually in healthy children, adolescents and adults. It is estimated that no more two new cases per year are identified in large epilepsy centres.

RE usually affects only one hemisphere of the brain; bilateral disease (affecting both hemispheres) is very rare.

Symptoms of RE
RE is characterised mainly by intractable seizures, progressive hemiparesis, and unilateral hemispheric atrophy.

- Seizures
Seizures may have different forms and characteristics: simple partial seizures, complex partial seizures, generalised tonic clonic seizures or status epilepticus. But the most notable seizure manifestation of RE is Epilepsia Partialis Continua (EPC) which is continuous twitching of the face, arm or leg on one side of the body. About 50% of patients with RE have EPC.

- Hemiparesis.
Hemiparesis is a weakness on one side of the body. The wiring of the nervous system determines that a lesion on one side of the brain causes problems on the opposite side of the
body. Thus, involvement of the motor cortex in one hemisphere causes weakness on the other side of the body.

- Other characteristics

Clinical features depend on which hemisphere is affected. Over time, patients may develop cognitive impairment, aphasia (difficulties with using language correctly), hemianopia (loss of vision in either the right or left sides of both eyes), sensory deficits, dysarthria (difficulty speaking), dysphagia (swallowing difficulties) and psychiatric problems. Language and cognition disturbances are almost always seen in patients with left-side involvement.

The cause of RE

The exact cause of RE is not known. However, there is increasing evidence of an under-lying immune disorder. Researchers identified a number of different, not mutually exclusive pathogenic concepts:

- Autoimmune cytotoxic T lymphocytes.
- Autoimmune antibodies – a number of different antibodies have been found including anti-GluR3 antibodies.
- Viruses such as Tick-borne Russian Spring Summer Encephalitis virus, Epstein Barr virus, Cytomegaloviruses and Herpes Simplex virus.

Despite all these concepts, the pathogenesis of RE remains obscure. The certainty is that only one hemisphere is affected in most cases and the disease starts focally and spreads across the hemisphere. What triggers such a process is still unknown.

Evolution and Prognosis

Most children are healthy before the onset of Rasmussen Encephalitis. The progression of the symptoms to significant neurological impairment usually occurs within months to a few years. Some patients have a fast evolution with the rapid development of a hemiparesis, while others have a slow evolution with a hemiparesis developing more than 1 year after seizure onset. There are patients who develop only a mild hemiparesis or language disturbance.

In the long-term, the disease is usually expected to ‘burn itself out’ but not before the patient is left with significant hemiparesis, visual field loss, learning difficulties and usually on-going epilepsy. Unfortunately, either quickly or slowly, children begin to show difficulties with learning. At first their academic performance may stabilise and then they fall behind their peers. Supporting education is extremely important. The syndrome can spontaneously stabilize at any time. Very rarely in rapidly progressive cases RE is a cause of death.
**Diagnosis**
Diagnosis is made based on clinical features, neuroimaging (MRI) and electroencephalography (EEG). The most useful investigations are:
- EEG may reveal brainwave patterns which are characteristic of certain types of epilepsy.
- Cerebrospinal fluid (CSF) examination is either normal or shows a mild lymphocytosis.
- Serial Magnetic Resonance Imaging (MRI) show progressive atrophy (shrinkage) and scarring of the affected side of the brain.
Brain biopsies are not usually needed to make the diagnosis and can often be inconclusive.

The differential diagnosis of RE include
- cortical dysplasia (congenital abnormality where the neurons fail to migrate)
- inflammatory and infectious disease of the brain (e.g. Meningoencephalitis and Subacute Sclerosing Panencephalitis -SSPE)
- metabolic diseases
- stroke
- brain tumours.

**Treatment**
The therapeutic strategies have 2 aims:
- an anticonvulsive treatment with as few side effects as possible
- a treatment that stops the brain cells destruction and improves the long term outcome regarding neurological and neuropsychological functions.

Medical therapy should be considered prior to hemispherectomy (HE) in 2 scenarios:
- in patients with minimal or no motor deficits
- in patients with RE involving the dominant hemisphere or bilateral hemisphere.

Early diagnosis and therefore subsequent intervention may contribute to improved responses.

**Anticonvulsant treatment (AED)**
EPC is usually unresponsive to anticonvulsive treatment. However the frequency of focal and secondary generalised tonic clonic seizures in RE may be reduced by anticonvulsive medication. This is the aim of drug treatment rather than trying to achieve seizure freedom.
Immunomodulatory therapy
These treatments target the autoimmune basis of the disease and include steroids, tacrolimus, azathioprine and intravenous immunoglobulin. More recently monoclonal antibody therapies are being trialled (e.g. natalizumab and rituximab). These treatments slow down the rate of MRI damage and emergence of hemiplegia, but they do not stop the disease. Steroids and intravenous immunoglobulin may also reduce seizures.

Hemispheric Surgery
Surgery remains the only cure for the seizures caused by RE. Hemispherectomy (disconnection of the affected side of the brain from the healthy brain) in one of its modern variants offers a very high chance of seizure freedom. However, hemispherectomy has significant consequences:
- irreversible loss of functions located in that affected hemisphere.
- hemiplegia (if there isn't one already from the disease). The patients are expected to walk again but they are not expected to have fine finger function.
- hemianopia (loss of vision for objects coming from one side).
- speech loss if the surgery is on the side of the brain generating language (language dominant side).
- swallowing difficulties.

Despite these concerns, hemispherectomy is less debilitating in children than in adults. Rehabilitation is very important and should begin early in the postoperative period. The decision to go ahead with surgery and choosing the best time is difficult and individual to each child. Careful decisions should be made by the parents and young person in conjunction with a specialist epilepsy surgery service.

Further Information on RE

RE Children’s Project (www.rechildrens.org)
The RE Children’s Project was founded in 2010 to increase awareness regarding Rasmussen’s Encephalitis (RE) for the primary purpose of supporting scientific research directed towards a cure. The organisation also supports research dedicated the recovery process following hemispherectomy surgery.
NORD (The National Organisation for Rare Diseases) (www.rarediseases.org) provides information, advocacy, research, and patient services to help all patients and families affected by rare diseases.

The Hemispherectomy Foundation (http://hemifoundation.homestead.com) provides emotional, financial, and educational support to individuals and their families who have undergone, or will undergo, a hemispherectomy or similar brain surgery.

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