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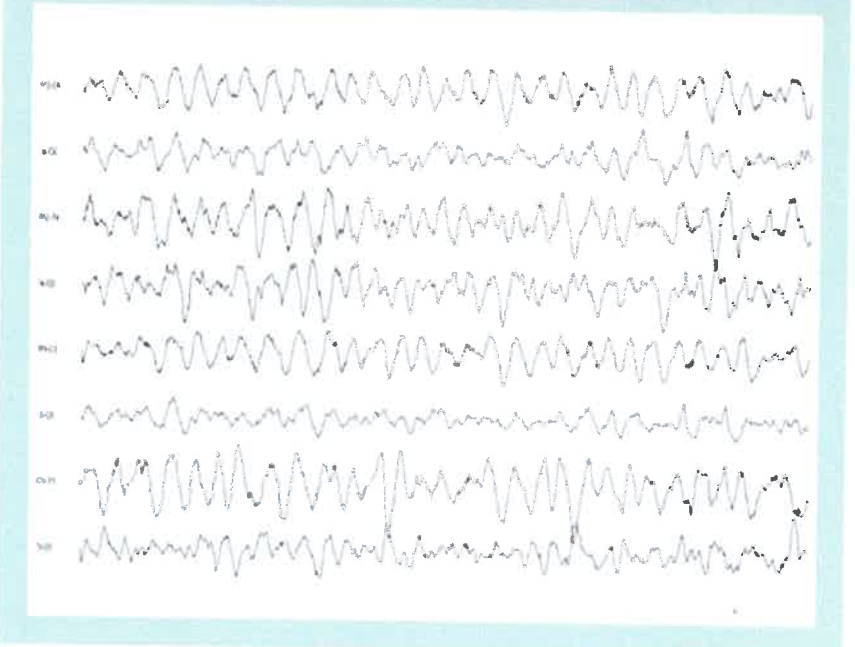
20 questions

Ring chromosome 20 syndrome

In conjunction with the Ring Chromosome 20 Foundation, *Epilepsy Professional* presents a special edition booklet, containing both parts of the recent feature article, *20 questions*. Specialists from the Ring Chromosome 20 Foundation describe this rare genetic form of epilepsy and outline common problems with diagnosis and treatment.

Figure 1 – Interictal EEG showing mild diffuse slowing



A definitive diagnosis of r(20) syndrome can only be made by chromosomal analysis with mosaic screening

outward signs makes the syndrome very difficult to notice early on. Additionally, chromosomal testing is rarely considered in a patient with severe early onset epilepsy who does not have dysmorphic features. This is frustrating, given that this situation reflects the usual form that r(20) syndrome takes.

A definitive diagnosis of r(20) syndrome can only be made by chromosomal analysis with mosaic screening. By a 'mosaic' or 'mosaicism', we refer to a case where the person may carry both normal cells and cells containing the ring 20 abnormality. Both age of seizure onset and severity of seizures may be linked with the degree of mosaicism. By this, we refer to what percentage of a person's cells contain the abnormality.

Chromosomal analysis is a relatively simple and inexpensive test that may save complex and unnecessary evaluations at a later date. Cytogenetic chromosomal karyotyping is the most common method of performing this analysis. This is where dyes are used, which bind to particular bands of DNA on the chromosome. Each chromosome has a specific pattern of coloured bands – allowing them to be identified. If chromosomal karyotyping was used more often in cases of refractory epilepsy without an obvious cause, more cases of r(20) syndrome would undoubtedly be recognised.

Borgaonkar and colleagues at Johns Hopkins University catalogued r(20) syndrome as a genetic syndrome in 1976. Since then, more than 60 cases of r(20) syndrome have been reported in literature. Despite this, we still know relatively little about it. To date, there are still no published data on the incidence and prevalence of this syndrome. Cases have been identified in different parts of the world, involving different ethnicities. The syndrome would also appear not to be gender-specific. Most reported cases are

sporadic apart from a few exceptional reports of families. This suggests that formation of the ring is a 'de novo' event, reflecting a spontaneous mutation, and is not familial.

Phenotypic characteristics

Epileptology

By a 'phenotype', we refer to the visible characteristics of an organism, which are particularly relevant here due to their genetic basis. Epilepsy is a constant feature – or phenotypic characteristic – of r(20) syndrome and typically starts in early childhood. In the 60 or so reported cases of r(20) syndrome, seizure onset has been reported between 6 months and 17 years of age. In many of these cases, the epilepsy is intractable and drug resistant.

Seizures are often complex partial in type and are reported as episodes of altered consciousness with staring and oral automatisms (such as lip-smacking). Other unspecified automatic behaviour is also commonly reported. Periods of intense fear and sometimes prolonged confused states (lasting from several minutes to hours) are described. Such states are often referred to as non-convulsive status epilepticus.

The prolonged seizure episodes with subtle complex behavioural impairment appears to be a very specific type of seizure pattern in r(20) syndrome. Subtle, nocturnal behavioural changes have also been observed. These include stretching, rubbing and turning, which often resemble normal arousal behaviour.

Generalised tonic-clonic seizures are rarely reported. Meanwhile, subtle nocturnal seizures (SNS) and nocturnal frontal lobe seizures (SNFLS) are sometimes reported. In many instances of r(20) syndrome, many seizures can be easily mistaken for non-epileptic events, although features of frontal lobe epilepsy are often recognised.

Cognition and behaviour

Some people living with r(20) syndrome may have normal cognition, despite periods of poorly controlled epilepsy. Meanwhile, others may have profound learning disabilities and will require help with all aspects of daily life. Behavioural problems can vary from minor concentration and attention difficulties with high levels of activity, to profound problems.

Several of the children reported in medical literature have been described as having periods of very difficult behaviour, often associated with poor seizure control. The behaviour and cognitive difficulties do vary with time and may worsen with increasing seizure frequency. However, impairments may not be permanent – some children may regain lost skills with improved seizure control.

Physical Features

Major and minor malformations that are signatures of chromosomal abberations – including facial dysmorphism – are usually subtle or entirely absent in r(20) syndrome. Rare cases of r(20) syndrome with dysmorphic features published in the literature demonstrate particular physical abnormalities. These include microcephaly, plagiocephaly, dental malocclusions, micrognathia, cauliflower-shaped ears, and coarse facial features with slanting eyelids (obliquely downward and outward).

Investigations

EEG features cannot always distinguish r(20) syndrome from other refractory epilepsies, therefore EEG results alone cannot provide a foundation for diagnosis. A wide spectrum of EEG abnormalities has been described in cases of r(20) syndrome.

An interictal EEG (performed between seizures) may be normal to mildly slow. Many cases described in literature have shown interictal bifrontal spikes and sharp wave discharges – see Figure 1). These frontal epileptiform patterns often raise the possibility of a frontal lobe seizure focus, and may represent a distinct EEG pattern. The EEG pattern seen in r(20) has similarities with other epileptic conditions such as Lennox-Gastaut syndrome (LGS) and Landau-Kleffner syndrome (LKS).

Differential diagnosis

We have established that r(20) syndrome is rarely reported, although it seems very likely that there are many more cases that have simply not been recognised. The syndrome in many instances may be misdiagnosed as some other form of epilepsy. Both clinical and EEG findings in patients with r(20) syndrome can be confused with other refractory epilepsy syndromes.

This syndrome can be misdiagnosed as Lennox-Gastaut syndrome (LGS), which is characterised by medically refractory seizures. The tonic and atonic seizures characteristic of LGS, however, are rarely seen in r(20) syndrome. The diagnosis may be missed in cases where no cause is found, especially if the clinical and EEG features are of frontal lobe epilepsy. Identifying r(20) syndrome in patients suspected of intractable frontal lobe epilepsy is critical to avoid unnecessary investigations and treatments.

There are also some similarities between r(20) syndrome and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). The nocturnal EEG pattern in r(20) syndrome may show similarities with those observed in someone with ADNFLE. However, unlike those associated with r(20) syndrome, the seizures in ADNFLE may be more easily controlled with anti-epileptic drugs (AEDs) and are primarily nocturnal. These features also overlap with rare severe epilepsies of childhood, such as epilepsy with continuous spike and wave discharges in slow wave sleep (ECSWS) and electrical status epilepticus in sleep (ESES). Early chromosomal testing to look for ring chromosome 20 mosaicism (below) may avoid misdiagnosis.

Diagnosis and genetics

An r(20) syndrome diagnosis can be made by recognising certain characteristic clinical features, although definitive diagnosis requires chromosomal testing to identify the presence of an abnormality. In some patients with the ring chromosome 20, the ring chromosome will be present in every cell (these cases are non-mosaic). In others, some percentage of cells can be normal and other will have rings (cases referred to as mosaic).

Cytogenetic analysis will diagnose the ring chromosome 20. However, because some patients may be mosaic for the ring, at least 50 cells should be analysed to maximise the chance of catching the abnormality. If no rings are identified in the first 50 cells, it is recommended that 100 should be counted if clinical suspicion is high. Chromosomal analysis is most often carried out on white cells from peripheral blood. However, any other tissue – including skin – could be examined.

As we've established, chromosomal analysis is not a routine investigation when epilepsy first presents, often delaying the diagnosis of r(20) syndrome. Recently, new technologies designed to analyse genes and chromosomes have emerged and can aid diagnosis. These

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technologies scan the genome for deletions (missing sections of genetic material) or duplications.

These tests are very powerful at identifying many cytogenetic (chromosomal) abnormalities. However, they cannot identify abnormalities such as balanced translocations, inversions or rings. In these cases there is the correct amount of genetic material, but the material is structured abnormally. In most patients with r(20) syndrome, the ring formation results from a fusion of the short and long arms of chromosome 20 (referred to as the p and q arms respectively). The fusion generally presents without any loss or gain of genetic material (deletion or duplication). However, in some patients deletions in the short or long arms have been identified. Therefore, traditional cytogenetic analysis, rather than these new technologies, is recommended to reliably identify r(20) syndrome.

Patients with mosaicism for the ring chromosome 20 have been studied to determine if the percentage of mosaicism – meaning the proportion of cells that contain the abnormality – may predict the phenotype. In general, a higher proportion of abnormal cells is associated with earlier age of seizure onset and malformations. However, if we analyse data from several patients with the same percentage of mosaicism, the age at which they developed seizures will vary widely. The degree of mosaicism also does not appear to determine a patient's response to drug treatment. Any prediction of phenotype from the mosaicism ratio should be done with caution, for example in genetic counselling.

There are several genes found on chromosome 20 that have been associated with other distinct epilepsy syndromes. Specifically, these syndromes are autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and benign familial neonatal convulsions (BFNC). The particular genes linked with these syndromes have been suggested as candidates for causing seizures in r(20) syndrome. However, not all r(20) syndrome patients have deletions of these genes. An alternative hypothesis – that these genes are aberrantly expressed in individuals with the ring chromosome – requires further research.

The recurrent genetic risk for r(20) syndrome within a family is very low, as the chromosomal ring formation is usually a spontaneous event. However, analysis of parental chromosomes is recommended, especially in patients with mosaicism. This can rule out the possibility that one of the parents is also a mosaic.

Treatment and outcomes

Managing children with r(20) syndrome – as is almost always the case with any epilepsy – is a case of managing symptoms. Seizures are typically difficult to treat. There are no useful studies to compare the value of different AEDs against seizures due to r(20). Patients are frequently exposed to multiple AEDs, with limited benefit.

Alternative treatments may be worth considering. Epilepsy surgery has proved unsuccessful in the few r(20) patients for whom it has so far been tried. Vagus nerve stimulation (VNS) has been reported as effective in a few cases. There are no published reports on using the ketogenic diet in patients with r(20) syndrome. However, its efficacy and safety is well established in treating other intractable childhood epilepsies such as Lennox-Gastaut syndrome and other symptomatic epilepsies.

The long-term outcome of r(20) syndrome is not known, although it is not

Further reading

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Managing children with r(20) syndrome – as is almost always the case with any epilepsy – is a case of managing symptoms

in itself believed to be fatal. However, r(20) syndrome patients are at risk of potentially dangerous epilepsy-related complications. These include status epilepticus and sudden unexpected death in epilepsy (SUDEP). The best predictor of outcome of r(20) is likely to be the degree of seizure control.

Conclusions

In summary, r(20) syndrome causes refractory epilepsy and in many patients this syndrome remains undiagnosed. The diagnosis of this syndrome is often delayed, as chromosome testing is not routinely requested in epilepsy patients without dysmorphic features and malformations. Many patients may be subjected to other unnecessary investigation and epilepsy surgery workup. Several patients have been subjected to epilepsy surgery without any reported improvement.

The diagnosis of r(20) syndrome should be considered in non-lesional refractory epilepsy patients with frontal lobe type complex partial seizures. It should also be considered in patients with prolonged seizures with intense fear and confusional states. Nocturnal seizures are also common in patients with r(20) syndrome. EEG often, but not always, shows bilateral frontal spikes. The absence of this finding does rule out r(20) syndrome.

Patients with these seizure patterns and EEG findings should be tested for r(20) syndrome. The definitive diagnosis of r(20) syndrome can only be made by requesting chromosome testing with mosaic screening.

Ring Chromosome 20 Foundation

For more information, visit www.ring20.org

The Ring Chromosome 20 Foundation

The Foundation has had a busy year, collaborating with a number of medical professionals in France, Spain, Italy, UK, Australia, and in the US. Our website – *ring20.org* – received a record number of hits from medical professionals and individuals. The site is now updated with multiple translations of key information. Ring 20 Foundation can also be found on *facebook.com* giving individuals, families, or medical professionals a great new way to share their experiences.

Two ongoing r(20) syndrome research studies have been supported by the foundation over the past year, involving over 30 participants. A genetic study was conducted at the Children's Hospital of Philadelphia (CHOP), and a clinical research study at the foundation's medical centre in New York City.

For further details regarding the foundation's work, or if you would like more information please contact us at *info@ring20.org*

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