

Ring Chromosome 20 Epilepsy Syndrome



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Acknowledgements

I am very grateful to Dr Nancy Spinner (Professor of Human Genetics at Children's Hospital of Philadelphia) for her valuable personal input regarding cytogenetic testing in patients with Ring chromosome 20 epilepsy syndrome. Ring Chromosome 20 Foundation for supporting research (www.ring20/research) and providing support to families and patients suffering from this disorder.

Ring chromosome 20 epilepsy syndrome [r(20)], has a striking association with seizures, whereas in other aberrations of chromosome 20 seizures are infrequent. This syndrome is characterised by medically intractable complex partial epilepsy, nocturnal subtle seizures, behavioural problems and mild mental impairment. Chromosomal abnormalities are rarely considered in patients with severe, young onset epilepsy with no dysmorphism or intellectual impairment, but this is the usual phenotype of ring chromosome 20. Chromosomal analysis, relatively simple and cheap, may save complex and unnecessary evaluation at a later stage. This syndrome is undoubtedly an under-diagnosed condition as chromosomal testing is not routine in epilepsy patients. Diagnosis is often delayed for many years after onset of seizures.

Borgaonkar and colleagues at Johns Hopkins University catalogued ring chromosome 20 syndrome as a genetic syndrome in 1976. Since then, over 60 cases of r(20) have been reported in the literature. To date there is still no published data on the incidence and prevalence of this syndrome. This disorder appears to be pan-ethnic and non-gender specific. Cases of this syndrome have been reported from many different parts of the world involving different ethnicities. Almost all cases reported are sporadic except a few with known family history. With more widespread cytogenetic chromosomal karyotyping in non-aetiological cases of epilepsy, more cases of r(20) will undoubtedly be recognised.¹

Phenotypic characteristics

Epileptology

Epilepsy is a constant feature of this syndrome and typically starts in early childhood and in many cases is intractable and drug resistant. Seizure onset has been reported between 1 and 17 years of age. Seizures are often complex partial in type and reported as episodes of altered consciousness with staring, oral automatisms, unspecified automatic behaviour, focal motor symptoms and/or head turning. Periods of intense fear and sometimes prolonged confused states lasting for several minutes to hours are described (non-convulsive status epilepticus). Subtle nocturnal behavioural changes such as stretching, rubbing and turning have been observed which resemble normal arousal behaviour. Generalised tonic-clonic seizures are rarely reported. In addition, subtle nocturnal seizures (SNS) and nocturnal frontal lobe seizures (SNFLS) are also reported. Seizures can be easily mistaken for non-epileptic events. Features of frontal lobe epilepsy are often recognised. Seizures are difficult to control with antiepileptic medications and if the diagnosis of

r(20) has not been made patients are subjected to epilepsy surgery workup and unnecessary investigations.^{2,3,4,5}

Cognition & Behaviour

Cognition is usually normal before the onset of epilepsy; however, there is the possibility of mental impairment if seizures are frequent and persistent. Individuals may have normal cognition despite periods of poorly controlled epilepsy and others may have profound learning disabilities and 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 the medical literature have been described to have 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 seizures. However, the child may regain these lost skills with improved seizure control.⁶

Physical Features

Abnormal physical features are often lacking. Major and minor malformations including facial dysmorphism are subtle or absent. This lack of dysmorphic features and often omission of chromosomal testing in patients with refractory epilepsy leads to delayed diagnosis. Rare cases of r(20) syndrome with dysmorphic features published in the literature consist of microcephaly, plagiocephaly, dental malocclusions, micrognathia, cauliflower-shaped ears, and coarse facial features with slanting eyelids (obliquely downward and outward).⁷ Occasional renal and cardiac abnormalities are also reported in the syndrome.

Neurophysiology

Electroencephalography (EEG)

No characteristic electroencephalographic (EEG) features distinguish r(20) syndrome from other refractory epilepsies, therefore diagnosis alone cannot be suspected by EEG. A wide spectrum of EEG abnormalities has been described. Interictal EEG (Figure 1) may be normal to mildly slow, and in some cases bifrontal spikes and sharp waves may be seen. Burst of sharply contoured theta activity has also been described. Interictal patterns are often more pronounced in sleep and may share similarities with other epileptic encephalopathies such as Lennox-Gastaut syndrome (LGS) and Landau-Kleffner syndrome (LKS).

Ictal EEGs (Figure 2) may show prolonged runs of diffuse slowing with frontal dominance intermixed with bifrontal sharp wave discharges. Ictal

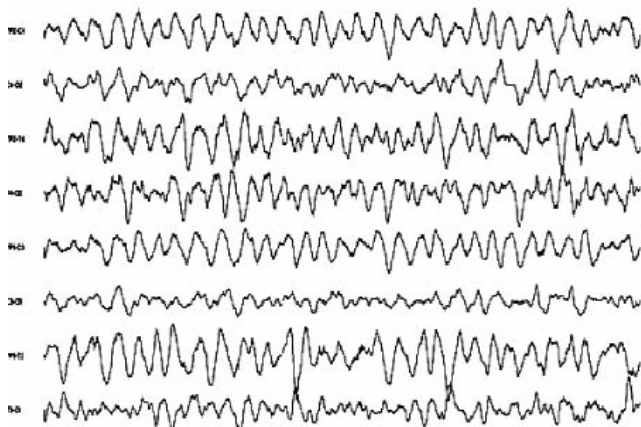


Figure 1: Interectal EEG showing rhythmic sharp theta burst.



Figure 2: Ictal EEG showing predominant bifrontal slowing and sharp wave discharges.

r(20) karyotype

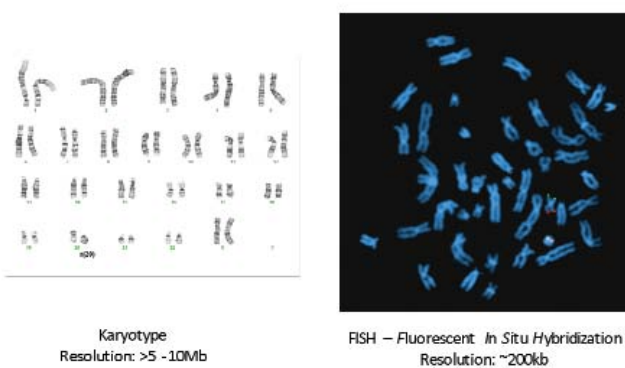


Figure 3: Diagnosis of r(20) syndrome.

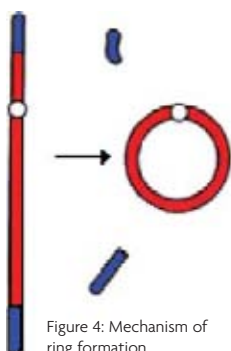


Figure 4: Mechanism of ring formation.

Early chromosomal testing to look for ring 20 mosaicism may avoid misdiagnosis

patterns often raise the possibility of a frontal lobe focus. In patients with non-convulsive status epilepticus the above described patterns may be combined with large portions of normal appearing EEG activity.^{8,9}

Magnetoencephalography

Ictal magnetoencephalography (MEG) has been performed on one patient with r(20) syndrome. MEG and EEG were simultaneously recorded and the equivalent current dipoles (ECD) of ictal discharges on MEG were localised to the medial frontal lobe. The authors suggested that the mechanism of underlying epilepsy in r(20) syndrome may be similar to medial frontal lobe epilepsy.¹⁰

Neuroimaging

A wide spectrum of structural and functional neuroimaging studies has been performed in patients with r(20) syndrome. In the majority of the patients structural abnormalities are not seen. In a few patients minor structural abnormalities have been reported. A recent [18F] fluoro-L-DOPA PET study in patients with r(20) showed decreased uptake in the basal ganglia bilaterally. The authors discussed the possible role of subcortical structural abnormalities in epileptic mechanisms.¹¹

Differential diagnosis

Both clinical and electroencephalographic 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 mixed intractable seizures. Tonic and atonic seizures characteristic of LGS are rarely seen in r(20) syndrome. Non-aetiological frontal lobe epilepsy is another frequent consideration and has phenotypic and EEG similarities with r(20) syndrome. Identifying r(20) syndrome in patients suspected of intractable frontal lobe epilepsy is critical to avoid unnecessary investigations and treatments. Unlike r(20) syndrome, the seizures in autosomal dominant nocturnal frontal lobe epilepsy (ADNFE) are predominantly nocturnal and rarely refractory. The nocturnal EEG pattern in r(20) may also have overlapping features of continuous spike and wave discharges in slow wave sleep (CSWS) and electrical status epilepticus in sleep (ESES). Early chromosomal testing to look for ring 20 mosaicism may avoid misdiagnosis.¹²

Diagnosis and genetics

Diagnosis of ring chromosome 20 syndrome can be made by recognition of certain characteristic clinical features, however definitive diagnosis requires chromosomal testing. This is most easily done by looking at the chromosome pattern (karyotype) in blood cells but any other tissue including skin could be examined (Figure 3).

At least 50-100 cells should be cytogenetically analysed to diagnose mosaic ring 20. Analyses of fewer than 50 cells may not reveal ring mosaicism. Cytogenetic testing is most easily done by looking at the chromosome pattern (karyotype) in blood cells but any other tissue including skin could be examined. Since chromosomal analysis is not a routine investigation when epilepsy first presents, the diagnosis of r(20) syndrome may be delayed or go unrecognised. Almost all parents of individuals with r(20) syndrome have no evidence of r(20) syndrome in their own blood chromosome analysis (personal communication – Spinner laboratory – Children’s Hospital of Philadelphia). A few individuals, typically relatives of affected children, have been found to have a ring chromosome 20 without any evidence of symptoms.

