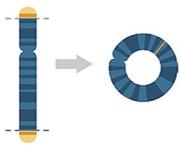


Ring Chromosome 20 Syndrome

Also known as: *r(20) syndrome, r(20), Ring 20, RC20*

Overview

Fig 1: Ring chromosome



In *r(20)* syndrome one of the two copies of chromosome 20 has formed a ring rather than the typical linear chromosome structure (figure 1). Why the tips of the chromosome join together to form the ring is not understood and how the

formation of the ring affects the function of genes on chromosome 20 and elsewhere is not understood. The consequence of the ring formation is a drug-resistant epilepsy, typically with onset in early childhood and associated with multiple seizure types, characteristic EEG features, intellectual disability and behaviour problems which may be progressive. Behavioural problems may present to psychiatry or psychology before onset of the epilepsy.

The diagnosis of *r(20)* syndrome is often delayed because physicians have not considered checking chromosomes in people who have no intellectual disability prior to epilepsy onset. Another reason for diagnostic delay is that chromosome microarray, gene panels, exomes or genomes requested when a genetic epilepsy is suspected will not detect the formation of rings as no DNA material may be lost or duplicated. A karyotype is required to make the diagnosis.

The majority of individuals with *r(20)* syndrome are mosaic for the ring. Levels of mosaicism may vary in tissues. In general, a higher proportion of abnormal cells is associated with earlier age of onset of seizures but this not true for everyone. If cells have a ring chromosome 20 the individual tends to be more severely affected. *r(20)* syndrome is not usually inherited, but affected individuals and families should be referred for a clinical genetic opinion and counselling.

Incidence and prevalence

r(20) syndrome is a rare disorder and estimates for incidence and prevalence are unknown as there have been no population based studies of karyotype testing in drug resistant epilepsy in the relevant age groups. There are likely to be people with epilepsy in which the syndrome remains undiagnosed or misdiagnosed.

Diagnosis of *r(20)* syndrome

Diagnosis requires clinical suspicion based on the electro-clinical phenotype detailed below and karyotype testing. Mosaicism in lymphocytes may be as low as 0.5% in severely affected individuals therefore it is recommended that at least 100 cells are looked at if there is a clinical suspicion of the syndrome. Many labs will examine 30 cells in routine karyotype analysis.

Age of onset

Usually seizures begin in early childhood, typically around the time children start school however symptoms may also present earlier in childhood, in adolescence or early adult life. *r(20)* syndrome is not associated with dysmorphic features and individuals do not have intellectual disability before the epilepsy onset. There is usually a sudden onset of seizures without a clear trigger. Many people experience a change in behaviour before or around the seizure onset manifested by poor attention and concentration, impulsivity and other behavioural problems

Seizure types at presentation

Features characteristic of *r(20)* syndrome are:

Focal seizures with impaired awareness

- At onset these are often from sleep, may manifest as brief arousals with posturing of limbs with or without hyperkinetic movements. The person may rouse suddenly sit up and have brief abnormal movements (stiffening or abnormal postures) of their arms and legs and may shout out before settling to sleep. These may occur several times a night and can be mistaken for night terrors. They are often described as frontal lobe seizures though more widespread networks are likely to be involved. Events may be hypermotor or characterised by arousal and subtle motor features or brief episodes of arousal, fear and confusion.
- Events in the daytime where the individual appears frightened, confused and does not respond normally.
- A feature characteristic of focal seizures in *r(20)* syndrome is frightening hallucinations. Examples include seeing sharks swimming above them, fire, spiders or large black holes. These may be mistaken for non-epileptic events. Patients may not report these symptoms if they are not asked directly about such symptoms.
- Sometimes people may have clusters of seizures with brief periods of apparently normal awareness between several events.

Tonic clonic seizures – These can occur in isolation or evolve from focal seizures

Non-convulsive status epilepticus – These are prolonged focal seizures with impairment of awareness which may last many minutes to hours (rarely days). They often occur in the late afternoon and early evening.

Other seizure types include **myoclonic** or **atonic** seizures – both seizure types may result in sudden drops or falls.

How do seizure types change over time?

Nocturnal focal seizures are often the first seizure type. People with r(20) syndrome can go through periods where they have multiple very difficult to control seizures of different types on a daily basis. This may be associated with significant intellectual and behavioural decline, an epileptic encephalopathy - r(20) syndrome. These periods tend to be more of a problem in the first few years after presentation. Later in the course of epilepsy the seizures may be less frequent and may change over time with a more predictable pattern specific for that individual. Complete seizure freedom for prolonged periods (years) appears to be exceptional with most people having seizures in adult life.

EEG features

r(20) syndrome is associated with a characteristic EEG signature. This comprises long runs of rhythmic theta activity most prominent over frontal and temporal regions and often associated with sharp waves and spikes. This activity may be unilateral or over both hemispheres. There may be brief runs of higher amplitude spike and slow wave activity over the frontal region without any obvious clinical accompaniment. During periods of non-convulsive status epilepticus this activity may increase in amplitude and become more widespread over both hemispheres.

Treatment

Seizures do not typically respond to medical, dietary or neurostimulation and there is currently no recommended treatment for r(20) syndrome. There are reports of efficacy of the ketogenic diet and vagal nerve stimulation in individual cases however other cases do not respond to these treatments and there is insufficient evidence.

Polytherapy should be avoided as this increases the risk of side effects and is not likely to improve seizure control.

It is often unnecessary to treat all episodes of NCSE which may last for minutes, hours or even days as patients will typically recover spontaneously. Use of rescue (emergency) medication may be ineffective and if used regularly may cause sedation and significantly impair quality of life.

Sudden unexpected death has been reported in this syndrome and therefore decisions not to prescribe medication must take this into account.

Individualised emergency protocols

Individualised treatment plans for prolonged seizures, convulsive status epilepticus, non-convulsive status epilepticus.

Comorbidities

Until the onset of seizures, childhood development appears to be normal, however there often follows a rapid decline in intellectual function. Skills previously attained may be lost. This decline in ability varies from losing some skills but remaining in the normal range for intellectual function to a significant loss in skills including difficulties with mobility and loss of speech and language functions. r(20) syndrome is associated with an epileptic encephalopathy at times of poor seizure control.

Support is likely to be required at school/college and in the workplace. Behavioural issues such as bouts of aggression before and/or after a seizure are reported. Many individuals develop autistic features. Predicting how severe learning and behaviour problems will be in the future is not possible at the onset of the epilepsy.

Overall about half the patients may have intelligence quotient assessed as in the normal range as adults but many of these may have had a relative decline in their cognitive abilities through childhood.

Review the impact of seizures, drugs & comorbidities on:

- Day-to-day activities
- Overall well-being
- Mental health
- Physical health
- Independence
- Biological and psychiatric health
- Behaviour

Provide patient and/or carer with:

- Safety advice especially re the 'confusional state' associated with episodes of NCSE
- SUDEP risk management
- Genetic counselling
- Patient, carer & employer support requirements (neuropsychological evaluation, guidance, potential psychiatric support)

For Patient Support contact:

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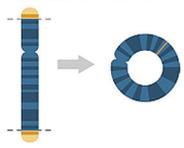
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The European Commission support for the production of this publication does not constitute endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

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In Ring Chromosome 20 Syndrome one of the two copies of chromosome 20 has formed a ring rather than the typical linear chromosome structure (figure 1). Why the tips of the chromosome join together to form the ring is not understood and how

the formation of the ring affects the function of genes packaged on chromosome 20 is also not understood. The consequence of the ring formation is a difficult to control epilepsy, typically with onset in early childhood and associated with intellectual disability and behaviour problems which may be progressive. Sometimes the behavioural problems may present before the epilepsy. The diagnosis of *r(20)* syndrome is often delayed because physicians may not consider checking chromosomes in people who have no intellectual disability before the epilepsy begins.

Another reason for diagnostic delay is that modern methods of testing for chromosome abnormalities, such as chromosome microarray, are better at picking up small changes in chromosomes but can miss the formation of rings. An older test (a karyotype test) where the chromosomes are looked at under a microscope must be requested to diagnose the condition. Not all the cells in the body may have a ring chromosome. When only a percentage of cells have a ring chromosome 20 this is called mosaicism. In general, a higher proportion of abnormal cells is associated with earlier age of onset of seizures, but this not true for everyone. If all the cells in the body have a ring chromosome 20 the individual tends to be more severely affected. *r(20)* syndrome is not usually inherited, but affected individuals should seek genetic counselling if wishing to start a family of their own.

1. How common is *r(20)* syndrome?

This is a rare disorder and we do not know how common it is. There are likely to be people with epilepsy in which the syndrome remains undiagnosed or misdiagnosed.

2. When do symptoms first appear?

Usually seizures begin in early childhood, typically around the time children start school however symptoms may also present

earlier in childhood, in adolescence or early adult life. Unlike many chromosomal disorders people with *r(20)* syndrome have a normal appearance and do not have intellectual disability before the epilepsy onset. There is usually a sudden onset of seizures without any clear trigger. Many people experience a change in behaviour before or around the seizure onset, manifested by poor attention and concentration, impulsivity and other behavioural problems

3. What are the types of seizure(s) seen in *r(20)* syndrome?

Several different seizure types may be seen. For accepted definitions of seizure types see EpiCARE seizure types leaflet or www.epilepsydiagnosis.org. Features characteristic of *r(20)* syndrome are:

Focal seizures with impaired awareness

- At onset these are often from sleep. The person may rouse suddenly, sit up and have brief abnormal movements (stiffening or abnormal postures) of their arms and legs and may shout out before settling to sleep. These may occur several times a night and can be mistaken for night terrors.

- Events in the daytime where the individual appears frightened, confused and does not respond normally.

- A feature characteristic of focal seizures in *r(20)* syndrome is frightening hallucinations. Examples include seeing sharks swimming above them, fire, spiders or large black holes. These may be mistaken for non-epileptic events.

- Sometimes people may have clusters of seizures with brief periods of apparently normal awareness between several events.

Tonic clonic seizures – These can occur in isolation or evolve from focal seizures

Non-convulsive status epilepticus – These are prolonged focal seizures with impairment of awareness which may last many minutes to hours (rarely days). They often occur in the late afternoon and early evening.

Other seizure types include **myoclonic seizures** (rapid jerks of muscles) or **atonic seizures** (loss of muscle tone) – both seizure types may result in sudden drops or falls.

4. Is r(20) syndrome linked to any other epilepsy syndromes?

Epilepsies can be defined as syndromes based on the different seizure types, EEG patterns, age of onset or based on the cause, if known, as well as associated co-morbidities (see other problems below). r(20) syndrome is an epilepsy syndrome in its own right as it has characteristic features with a specific genetic cause.

5. How frequent are seizures typically in r(20) syndrome?

Seizures may become very frequent with multiple events per day.

6. How may seizures change over time?

Nocturnal focal seizures are often the first seizure type. People with r(20) syndrome can go through periods where they have multiple very difficult to control seizures on a daily basis and this may be associated with significant intellectual and behavioural decline. These periods tend to be more of a problem in the first few years after presentation. Later in the course of epilepsy the seizures may become less frequent and may change over time with a more predictable pattern specific for that individual. Complete seizure freedom for prolonged periods (years) appears to be exceptional with most people having seizures in adult life.

7. What other problems apart from epilepsy, affect people with r(20) syndrome?

Until the onset of seizures childhood development appears to be normal, however there often follows a rapid decline in intellectual function. Skills previously attained may be lost. This decline in ability varies from losing some skills but remaining in the normal range for intellectual function, to a significant loss in skills including difficulties with mobility and loss of speech and language functions. When this decline is associated with epilepsy it is called an epileptic encephalopathy. When very severe, r(20) syndrome may manifest in some people as a form of childhood dementia.

Support is likely to be required at school/college or even in the workplace. Behavioural issues such as bouts of aggression before and/or after a seizure are commonly reported. Individuals may also receive a diagnosis of autism. Predicting how severe these learning and behaviour problems will be in the future is not possible at the onset of the epilepsy.

8. What are the treatment options for r(20) syndrome?

Seizures do not typically respond to treatment and there is currently no recommended treatment for r(20) syndrome. Treatment usually comprises use of anti-epileptic drugs (AED's), although Vagus Nerve Stimulation (VNS) and/or Ketogenic Dietary Therapy (KDT) have proven useful in some cases. r(20) syndrome is not suitable for brain surgery.

9. What is the emergency protocol for seizures?

Your doctor may advise special treatment for emergency situations as prolonged seizures may be dangerous to health and must be treated immediately. It is important that every person has an individualised treatment plan for emergencies.

10. What could I ask my doctor or specialist epilepsy nurse about?

- Safety advice especially re the 'confusional state' associated with episodes of NCSE
- A personalised rescue medication plan for prolonged or cluster seizures
- The side effects of medication particularly when changing treatment
- Genetic counselling
- Liaison with school or college for support during education
- Patient, carer & employer support requirements including neuropsychological evaluation, guidance, potential psychiatric support
- Sudden Unexpected Death in Epilepsy (SUDEP) risk management



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