Original article

Refractory and lethal status epilepticus in a patient with ring chromosome 20 syndrome

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ABSTRACT – *Purpose.* The only consistent symptom of ring chromosome 20 syndrome (r(20)) is severe, refractory epilepsy often associated with a characteristic, although not pathognomonic, EEG pattern. Patients suffer from severe seizures with accompanying cognitive decline and frequent episodes of non-convulsive status epilepticus (SE). Other features of this rare disorder, such as dysmorphic changes, mental retardation and behavioral disturbances are variable. Because of the variability of the clinical presentation, some patients with r(20) undergo invasive investigations before being diagnosed. *Case study.* We present the case of a young boy with no dysmorphic traits, who was only diagnosed with r (20) syndrome at the age of 13. His first seizure occurred at the age of four. Later seizures were of various types including non-convulsive SE, with deterioration of the background EEG and severe cognitive decline. Despite multiple trials of anti-epileptic medications, his seizures remained highly refractory, and he died as the result of an uncontrollable, prolonged SE, shortly after the diagnosis was made. *Discussion.* Non-convulsive SE is common in patients with r(20) syndrome and may be caused by a dysfunction in dopaminergic neurotransmission. However, until now, no case of lethal status epilepticus has been reported. This case report suggests that patients with unexplained refractory seizures and episodes of non-convulsive SE should undergo genetic testing early in their disease, even in the absence of any morphologic features or dysmorphic traits suggestive of a chromosomal disease. *[Published with video sequences]*

Key words: status epilepticus, ring chromosome 20 syndrome, refractory epilepsy

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Ring chromosome 20 syndrome [r(20)] is a rare disorder, known to cause intractable epilepsy (Nishiwaki *et al.* 2005). It was first described in 1972 by Atkins and coworkers and about 60 cases have been presented in the literature (Inoue *et al.* 1997, Ville *et al.* 2006, Herrgard *et al.* 2007). While epilepsy seems to be a constant finding, other features may be present, including mild dysmorphic changes, mental retardation and behavioral disturbances (de Falco *et al.* 2006). Seizures typically start between three and five years of age, with progressive severity and concomitant cognitive de-

cline (Nishiwaki *et al.* 2005, Ville *et al.* 2006), and usually remain refractory to anti-epileptic medication (AED) (Parr *et al.* 2006, Herrgard *et al.* 2007). Non-convulsive SE and brief motor seizures are among the most common seizure types (Inoue *et al.* 1997). Non-convulsive SE consists of a prolonged, confusional state and is often associated with EEG changes in the form of long-lasting, high-voltage slow waves with occasional spikes, usually frontal. Other types of seizures include terror, associated with loss of consciousness, automatisms or tonic activity.

Different EEG patterns have been noted in patients with r(20), but some are more common than others. A deterioration of background EEG activity is noted with time (Inoue *et al.* 1997, de Falco *et al.* 2006). Inoue *et al.* (1997) also reported long-lasting, high-voltage, slow wave activity predominating over frontal regions as a consistent finding in all patients they studied. The interictal epileptiform activity often consists of diffuse, 1-3 Hz slow waves and sharp slow waves predominantly over frontal areas, bursts of bilateral synchronous slow spike-and-waves or multifocal polyspike-and-waves during non-REM sleep (Augustijn *et al.* 2001), and in some patients, the EEG changes are clearly lateralized.

Additionally, progressive cognitive delay and behavioral problems are described (Alpman *et al.* 2005). Finally, dysmorphic features are found in only a minority of patients, which might explain the frequent delay in the diagnosis of this rare chromosomal disorder. In most patients, the chromosomal change occurs in the form of a mosaic, which necessitates the analysis of a minimum of 100 mitoses to exclude the disease during, chromosomal testing (Viersbach *et al.* 1997).

We report the case of a 13-year-old boy, who had had refractory epilepsy since the age of four. He had undergone numerous investigations, including intracranial SEEG recording, before being diagnosed with r(20) syndrome. He died shortly thereafter during an episode of severe, refractory SE.

Case study

Our patient was the first child of healthy, non-consanguineous parents. The mother had had one previous miscarriage. A detailed family history did not reveal any neurological disorder. The pregnancy was uneventful. A caesarian section was performed at 41 weeks of gestation for failure to progress, fetal distress and maternal hemodynamic instability. Despite this, the APGAR score was good (8 and 9 at one and five minutes), and there were no neonatal complications.

He had normal developmental milestones in the first two years of life. However, at age three, he started to show hyperactive and aggressive behavior and was diagnosed with ADHD. He was treated with methylphenidate. Neuropsychological testing showed a low-average IQ (# 82).

Seizures started at age four. From very early, his parents noted prolonged and frequent, atypical absences with decreased responsiveness, and discrete facial or manual automatisms. Soon after, generalized tonic-clonic seizures occurred. Initial EEGs showed normal background activity with occasional diffuse slow waves and spike-and-slow waves activity, predominating over the frontal regions. MRI studies were normal. Valproic acid temporarily reduced seizure frequency, but he continued to have 10 to 20 attacks a month. He then rapidly developed additional multiple seizure types including focal motor attacks, diurnal and nocturnal hypermotor seizures and focal seizures with automatisms suggesting temporal involvement. All available AEDs were used, in several combinations, without success; neither steroids nor the ketogenic diet improved his condition.

The patient was referred to the Montreal Neurological Institute when he was nine years of age. The etiology of his difficult-to-treat epilepsy was unclear. He was slightly obese, with a short attention span and slow reactions. The ears were large and cauliflower-shaped. No other dysmorphic or cutaneous features were present. He had a slight, left hemiparesis and appeared clumsy, with reduced fine motor skills. Muscle strength, gross motor skills and cranial nerve function were normal. The parents had noted progressive cognitive decline in their son confirmed by neuropsychological retesting, showing a clearly below average IQ (# 71). Behavioral problems were usually controlled with methylphenidate, but occasional aggressive outbursts persisted.

The patient experienced up to 30 seizures a day there being four recognizable types: 1) prolonged atypical absences; 2) tonic posturing of the arms, extension of the neck and head turning to the left; 3) nocturnal hypermotor seizures with agitation *(see video sequence)*; and 4) focal seizures with terror, visual hallucinations and impaired consciousness. Interictal EEGs had deteriorated and there were marked background changes, with generalized rhythmic slow waves predominantly over frontal areas, and very active widespread spike-and-slow wave activity, more prominent over the right hemisphere *(figure 1)*. The most common ictal EEG changes were observed during his prolonged absences and consisted of a generalized suppression, followed by 2-3Hz rhythmic slow waves and then by a 1Hz spike and slow wave activity seen over both hemispheres, but again more prominent on the right.

Repeated MRI studies suggested a slight atrophy of the right hemisphere, with an area suspicious for cortical dysplasia over the right temporo-occipital region. An interictal FDG-PET study showed diffuse hypometabolism over the right hemisphere and an ictal SPECT revealed tracer enhancement over the right temporo-parietal area. Because of the unusually refractory and progressively catastrophic picture, intracerebral SEEG investigation was undertaken exploring the right parietal, occipital and temporal areas. The intracranial investigation confirmed
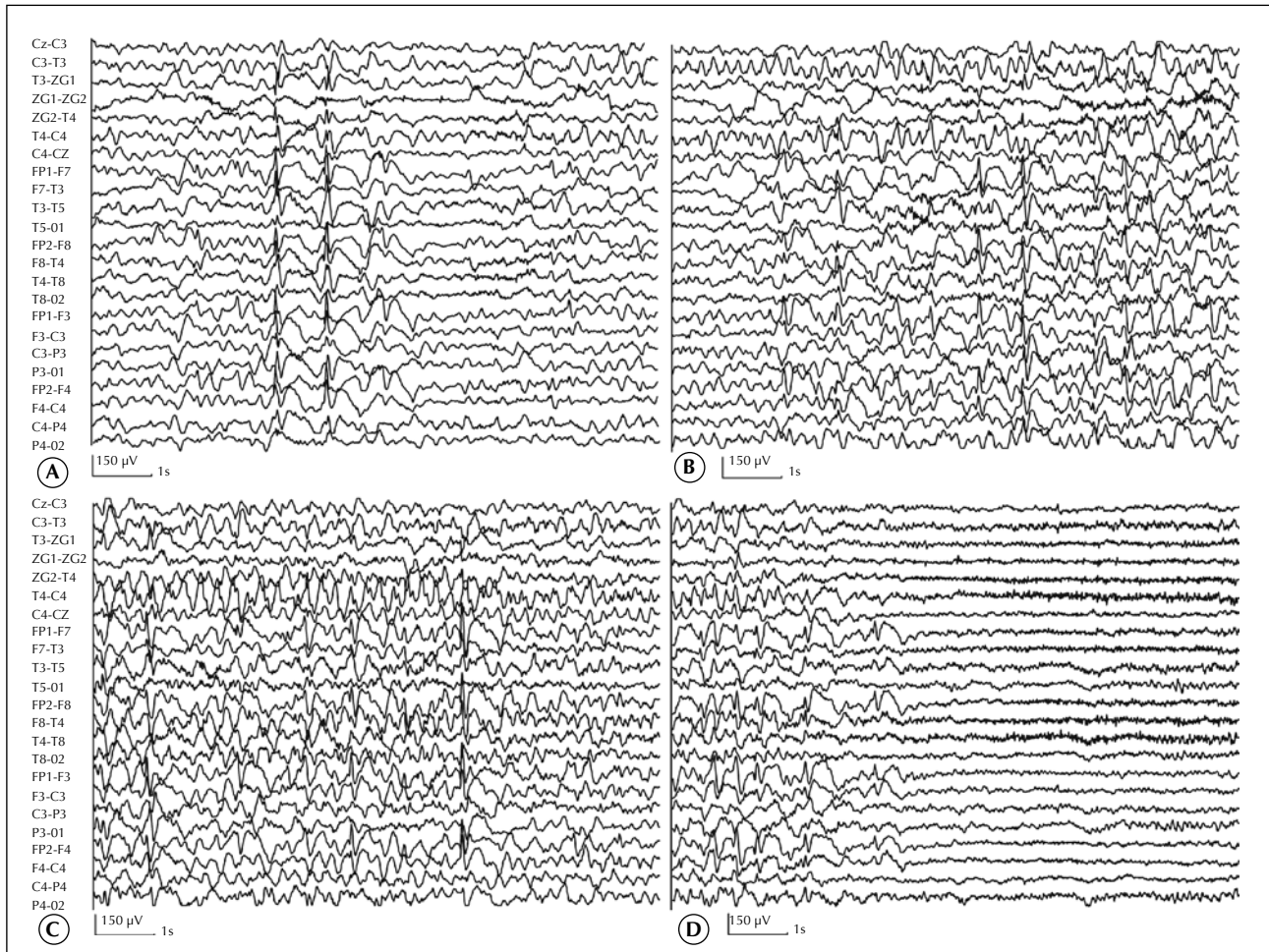
Figure 1. A and **B**) Interictal EEG of the patient at 9 years of age. He was fully responsive and oriented at the time of this recording. Severe deterioration of the background, with general slowing and rhythmic theta waves, is observed. Additionally, the EEG shows spikes and sharp slow-waves with predominance over the frontal areas, which mostly occurred in trains and often continuously. **C** and **D**) Ictal EEG recorded at the same age. During the seizure, rhythmic slow waves and spike and slow waves were recorded with predominance over the right hemisphere. This was followed by low voltage fast activity (**D**) during the tonic phase of the seizure.

extensive epileptogenesis, with epileptic discharges seen over the brain areas explored and some accentuation over the right temporal neocortex.

Before surgical intervention could be considered, the patient developed an intractable and irreversible non-convulsive SE, refractory to intravenous treatments with propofol, phenobarbital and midazolam, and induction of a coma with thiopental and pentobarbital. Before the induction of a deep coma, the EEG showed continuous generalized 2.5Hz spike and wave activity maximum over frontal regions *(figure 2)*. After several weeks of coma, and persistent relapse of continuous epileptic activity, the decision was taken, with the parents, to withhold all extraordinary therapeutic measures. The patient soon died of cardiovascular collapse. During his last hospitalization, blood was drawn for additional genetic and metabolic

testing. Karyotyping revealed a 46 XY, r(20). Forty-four lymphocytes were analyzed and the chromosomal abnormality was found in all cells. The autopsy revealed no specific brain changes.

Discussion

We report a patient with sporadic r(20) syndrome who presented with very severe and eventually lethal epileptogenic encephalopathy. Catastrophic epilepsy, in addition to the slight EEG asymmetry suggesting a possible right hemispheric focus, the suspicious area on MRI in the same region and the results of SPECT studies, led to an SEEG investigation. Later, cytogenetic studies revealed that 100% of the lymphocytes tested carried a ring chromosome. Until now, no fatal SE has been described in patients
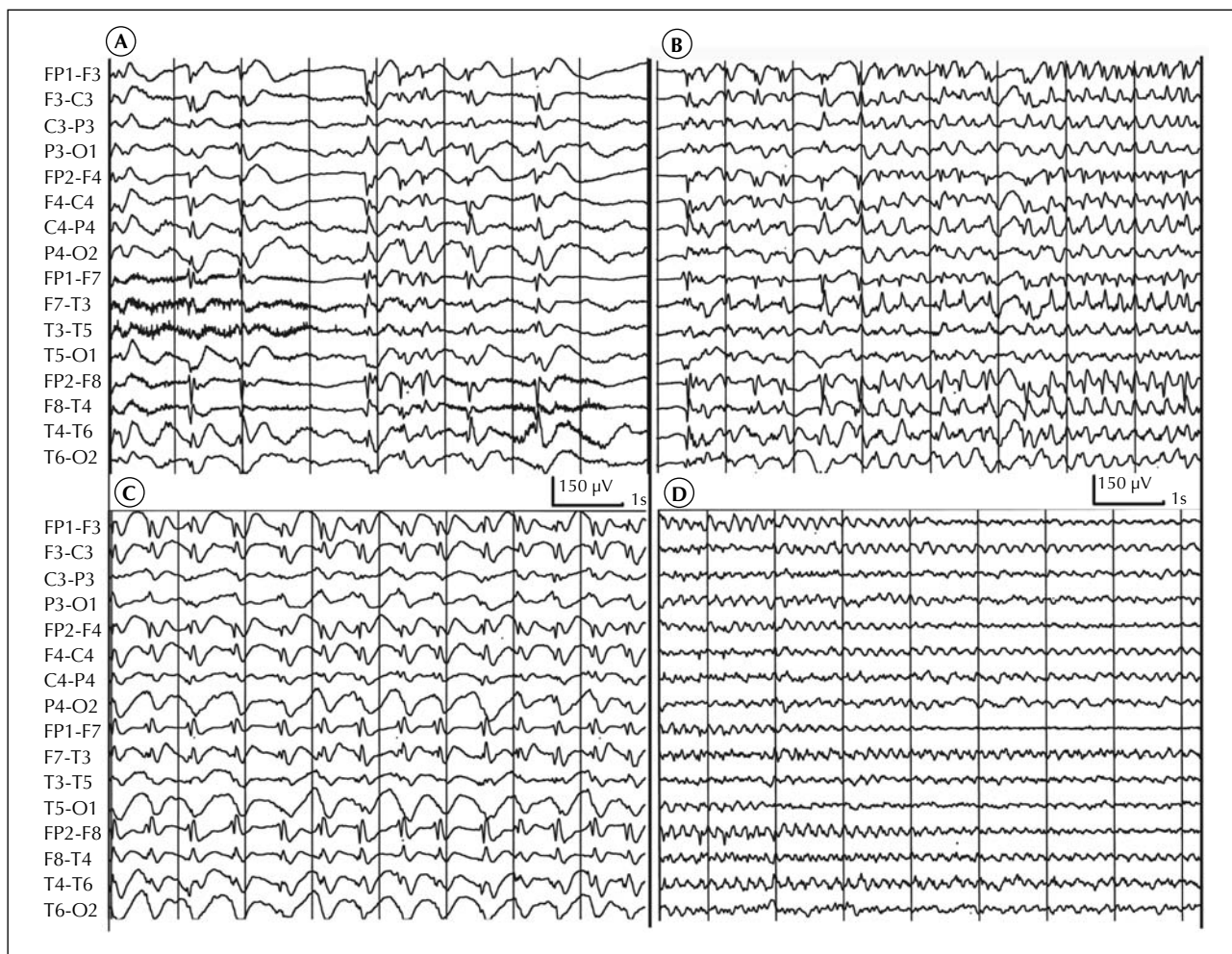
Figure 2. Variable EEG patterns during non-convulsive status epilepticus. Despite intravenous medication with propofol, phenobarbital, midazolam, and induction of coma with thiopental and pentobarbital, the SE could not be controlled.

with r(20). We want to stress the importance of early cytogenetic testing when patients present with unexplained refractory seizures and repetitive non-convulsive SE, even in the absence of any morphologic features suggestive of a chromosomal disorder.

While our patient showed chromosomal changes in all of the lymphocytes analyzed, in many patients only a mosaic is seen. Higher levels of mosaicism correlate with a lower age of seizure-onset, more severe cognitive impairment and usually, more prominent dysmorphic features (Nishiwaki *et al.* 2005, Herrgard *et al.* 2007). The non-mosaic condition of our patient may explain the severity and lethal outcome of the disease in our patient. Behavioral problems are typically found and can precede the actual seizure disorder (Ville *et al.* 2006). In many patients, specific treatment has been less effective than in

our patient, whose behavior, in spite of the severity of his seizure disorder, improved with methylphenidate (Alpman *et al.* 2005).

Patients with r(20) usually start having seizures between the age of three and five, but some experience early neonatal onset, and in others, seizures start only in their twenties (Ville *et al.* 2006, Herrgard *et al.* 2007). Typically, they have repetitive and prolonged episodes of non-convulsive SE (Garcia-Cruz *et al.* 2000, Inoue *et al.* 1997), with tonic and hypermotor seizures, drop attacks and generalized tonic-clonic seizures being frequently observed. Our patient also had focal seizures with intense terror and visual hallucinations, which have been described in other patients and often misinterpreted as psychogenic or behavioral changes (Alpman *et al.* 2005, Ville *et al.* 2006). Finally, many "subtle nocturnal seizures" can

occur and are accompanied by bursts of high voltage fast activity followed by bi-frontal high voltage slow waves as observed in our patient (Augustijn *et al.* 2001). Seizures are usually highly refractory to medication and accompanied by a progressive cognitive decline.

It remains unclear whether the observed progression of the disease, which in our patient included cognitive decline, behavioral problems and seizures, is a result of the refractory epilepsy or a direct symptom of the chromosomal disease. On the one hand, some changes, such as the behavioral problems in our case, might be present before the onset of epilepsy. The severity of not only the epilepsy disorder, but also the dysmorphic features and psychomotor developmental delay, are highly correlated with the ratio of mosaicism. On the other hand, many patients develop normally until the onset of epilepsy and some are affected only very slightly by the disease (Viersbach *et al.* 1997, Nishiwaki *et al.* 2005). In our patient, the progression of the clinical symptoms was directly reflected by the EEG changes; the patient's development, disease, and outcome were majorly determined by the progression of the epilepsy. Nevertheless, given his non-mosaic state, it is likely that the severe progression of the disease was also linked to the genotype of the syndrome.

The diagnosis of r(20) syndrome can be complicated not only by the lack of a clear phenotype, but also by clinical findings that suggest focal epilepsy. Focal and lateralizing features of the surface EEG have been described, as in our patient (Augustijn *et al.* 2001), and in whom even intracranial EEG suggested focality. The MRI and other neuroimaging studies in patients with r(20) are usually reported to be normal, and only in occasional cases have nonspecific, anatomical changes been described (Gomes Mda *et al.* 2002, Inoue *et al.* 1997). These non-specific changes, particularly if they co-localize with the EEG changes, can provide additional support for the hypothesis of focality, and thereby delay the diagnosis.

This case report raises three important questions: *i)* what is the mechanism of the recurrent, non-convulsive SE; *ii)* how should these patients with r(20) be treated; and *iii)* should patients with epilepsy undergo chromosomal studies even if they show no dysmorphic features.

Non-convulsive SE has frequently been described in patients with r(20), although, to our knowledge, no fatal SE has been described thus far. Moreover, the pathophysiology of this catastrophic epilepsy syndrome is not well understood. Some authors have suggested that it could be a channelopathy. In fact, for the formation of the ring chromosome, the two telomeric regions of the chromosome must fuse and this could lead to loss of genetic material. Two channels known to cause epilepsy syndromes are located in these regions. The first is the gene encoding for one subunit of the acetylcholine receptor, known to cause "autosomal dominant nocturnal frontal lobe epilepsy". Some authors hypothesized that the epilepsy mechanisms in r(20) might be similar to those in familial frontal lobe epilepsy (Steinlein *et al.* 1994, Philipps *et al.* 1995). Yet the epilepsy observed in r(20) is much more severe and intractable, and patients often show a protracted course. However, another gene encoding for one subunit of a potassium channel is also located in this critical and possibly deleted chromosomal region. This gene is mutated in benign familial neonatal epilepsy. Again, this mechanism by itself cannot explain the intractability of the r(20) syndrome. However, it may be hypothesized that the deletion of these two genes, already known to cause epilepsy syndromes, possibly in combination with the deletion of other important genes, may explain the pathophysiology of this poorly understood epilepsy syndrome.

Another hypothesis suggests a dysfunction in dopaminergic neurotransmission in these patients (Biraben *et al.* 2004). PET studies using [^{18}F]fluoro-L-dopa showed that the dopaminergic uptake in the putamen and caudate nuclei is reduced in patients with r(20), and it has been proposed that this dysfunction impairs the mechanism of seizure interruption. If this mechanism explains the impaired seizure interruption in r(20) syndrome, treatment with dopaminergic agonists could improve the course of the epilepsy and possibly prevent an outcome such as that described in our case.

The lack of clear dysmorphic features in our patient explains why early chromosome studies had not been suggested. Even in those patients with r(20) and a dysmorphic trait, the changes tend to be nonspecific and of a wide variety, such as microcephaly, growth retardation, slanting eyelids and high palate (Garcia *et al.* 2001, de Falco *et al.* 2006), and the diagnosis therefore depends on a very high degree of suspicion. As described above, the diagnosis is additionally complicated by findings for MRI, EEG and seizure semiology, which all suggest a focal etiology of the epilepsy. However, some features of the disease such as repetitive, prolonged, non-convulsive SE, the unusual behavioral disturbances and the protracted course of the refractory epilepsy with cognitive decline, might provide clues to the diagnosis. Genetic testing should be performed early in children with these features, even if no dysmorphic trait is present. □

Legend for video sequence

The video-EEG sequence shows a clinical seizure of the patient. Symptoms start with agitation, pedaling of the legs and vocalization ("arrête"= "stop"), later manual automatisms. This is followed by a tonic phase with posturing of both arms and legs. Ictal EEG changes consist of bi-frontal spike slow waves and rhythmic slow waves.

References

Atkins L, Miller WL, Salam M. A ring-20 chromosome. *J Med Genet* 1972; 9: 377-80.

Alpman A, Serdaroglou G, Cogulu O, *et al.* Ring chromosome 20 syndrome with intractable epilepsy. *Dev Med Child Neurol* 2005; 47: 343-6.

Augustijn PB, Parra J, Wouter CH, *et al.* Ring chromosome 20 epilepsy syndrome in children: Electroclinical features. *Neurology* 2001; 57: 1108-11.

Biraben A, Semah F, Ribeiro MJ, *et al.* PET evidence for a role of the basal ganglia in patients with ring chromosome 20 epilepsy. *Neurology* 2004; 63: 73-7.

de Falco FA, Olivieri P, de Falco A, *et al.* Electroclinical evolution in ring chromosome 20 epilepsy syndrome: A case with severe phenotypic features followed for 25 years. *Seizure* 2006; 15: 449-53.

Garcia DM, Ortiz R, Gómez A, *et al.* Ring 20 chromosome syndrome with epilepsy and dysmorphic features: a case report. *Epilepsia* 2001; 42: 1607-10.

Garcia-Cruz D, Vasquez AI, Perez-Rulfo D, *et al.* Ring-20-syndrome and loss of telomeric regions. *Ann Genet* 2000; 43: 113-6.

Gomes Mda M, Lucca I, Bezerra SAM, *et al.* Epilepsy and Ring Chromosome 20. *Arq Neuropsiquiatr* 2002; 60: 631-5.

Herrgard E, Mononen T, Mervala E, *et al.* More severe epilepsy and cognitive impairment in the offspring of a mother with mosaicism for the ring 20 chromosome. *Epilepsy Res* 2007; 73: 122-8.

Inoue Y, Fujiwara T, Matsuda K, *et al.* Ring chromosome 20 and nonconvulsive status epilepticus. A new epileptic syndrome. *Brain* 1997; 120: 939-53.

Nishiwaki T, Hirano M, Kumazawa M, *et al.* Mosaicism and phenotype in ring chromosome 20 syndrome. *Acta Neurol Scand* 2005; 111: 205-8.

Parr JR, Pang K, Mollett A, *et al.* Epilepsy responds to vagus nerve stimulation in ring chromosome 20 syndrome. *Dev Med Child Neurol* 2006; 48: 78-80.

Philipps HA, Scheffer IE, Berkovic SF, *et al.* Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q13.2. *Nat Genet* 1995; 10: 117-78.

Steinlein O, Smigrodzki R, Lindstrom J, *et al.* Refinement of the localization of the gene for nocturnal nicotinic acetylcholine receptor alpha subunit (CHRNA 4) to human chromosome 20q13.3. *Genomics* 1994; 22: 493-5.

Ville D, Kaminska A, Bahi-Buisson N, *et al.* Early Pattern in the Ring Chromosome 20 Syndrome. *Epilepsia* 2006; 47: 543-9.

Viersbach R, Engels H, Schwanitz G. Identification of supernumerary der(20) chromosomes by FISH in three patients. *Am J Med Genet* 1997; 70: 278-83.