# Clinical commentary with video sequences

# Ring chromosome 17 epilepsy may resemble that of ring chromosome 20 syndrome

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**ABSTRACT** – A four-year-old boy with ring chromosome 17 presenting with early-onset, pharmacoresistant epilepsy underwent repeated 24-hour video-EEG monitoring and cytogenetic analyses, including fluorescent *in situ* hybridization with telomeric and locus-specific probes of chromosome 17. Epilepsy was characterized by nocturnal motor seizures and by prolonged diurnal electrical status epilepticus. The 46, XY, r (17) karyotype was observed in the majority of cell lines. Fluorescent *in situ* hybridization revealed a deletion at the 17p telomere on the ring chromosome, whereas the 17q telomere and the Miller-Dieker lissencephaly locus were undeleted. The epileptic syndrome observed in this case of ring chromosome 17 resembles the one described in the ring chromosome 20 syndrome, raising the question of the specificity and the pathogenesis of ring chromosome epileptic syndromes.
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**Key words:** ring chromosome 17, epilepsy, ring chromosome 20 syndrome, chromosomal disorders and epilepsy

Ring chromosomes are supposed to be formed by deletion followed by fusion of the telomeric chromosomal regions. This phenomenon has been described for all human chromosomes but only ring chromosomes 14, 17 and 20 are strongly associated with seizure disorders with different phenotypes (Zou *et al.* 2006). More particularly, a specific phenotype consisting of complex partial seizures, nocturnal frontal lobe seizures and non-convulsive status epilepticus (NCSE) has been repeatedly associated with ring chromosome 20 (Inoue *et al.* 1997, Petit *et al.* 1999, Zou *et al.* 2006). We report the case of a child with ring chromosome 17, presenting with clinical and EEG features similar to those observed in ring chromosome 20 syndrome, raising the question of the specificity and the pathogenesis of seizure disorders in patients with ring chromosomes.

## Case report

The patient, a boy born in 2002, was the third child of healthy, unrelated parents with unremarkable family history. Pregnancy and delivery were normal. At birth, the weight, length and occipito-frontal circumference (OFC) were 2550 g (-3.5 SD), 47 cm (-3 SD), and 33 cm (-3.5 SD), respectively. At two years of age, the patient presented with tonic-clonic seizures during sleep. His motor development

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was normal until the age of 18 months, but there was a language delay. Interictal EEG showed a slow background activity with short bursts of temporo-occipital sharp waves with occasional spikes, periodically repeated every two seconds *(figure 1)*. Less frequent discharges persisted during sleep. He was initially treated with valproate monotherapy; lamotrigine and clobazam were added later. However, seizures persisted during sleep and subsequent EEGs showed longer periods of discharges involving parieto-occipital regions and left or right fronto-central regions asynchronously.

At three years of age, the patient was referred to our neuropaediatric clinic. The child had microcephaly and showed delayed growth, but had no dysmorphic features or abnormalities of skin pigmentation. Neurological examination was normal, but WPPSI-III assessment revealed a verbal IQ of 52 and a performance IQ of 47. Brain MRI was normal.

Prolonged video-EEG monitoring showed slow background activity with some generalized or localized (centro-frontal or parieto-occipital) slow spikes which became less frequent during sleep. The different phases and physiological components of sleep were recognizable. Several types of seizure were recorded during sleep. The

first type showed diffuse fast activity, sometimes beginning on the right or left frontal/fronto-central regions and then becoming diffuse; these discharges developed afterwards into slow waves with occasional spikes over both hemispheres, but predominantly on one frontal or fronto-central area and then stopping abruptly. Clinically, as the child awoke, he showed clonic or tonic fits, mainly affecting the axial and proximal muscles. These seizures lasted 60 to 90 seconds (*see video sequence 1*). The child also showed seizures starting as mentioned above and followed by rhythmic, high voltage, 0.5 Hz slow complexes, sometimes with a superposed spike or fast activity, with diffuse spreading or with spreading over bilateral fronto-temporal regions and lasting 3 to 4 minutes. The patient had repeated, brief abduction movements of the shoulders, sometimes associated with a hiccup.

At age four, the patient showed a few seizures during wakefulness, characterized by sudden fall of the head or of the entire body, with rare, generalized, tonic-clonic seizures. Nocturnal seizures persisted. At that time, the treatment was a combination of valproate, topiramate and clonazepam.

Video-EEG during wakefulness showed continuous, irregular, diffuse slow spike-and-wave complexes, pre-



**Figure 1.** EEG recorded at age 2 years showing posterior burst of sharp waves with occasional spikes periodically repeated.
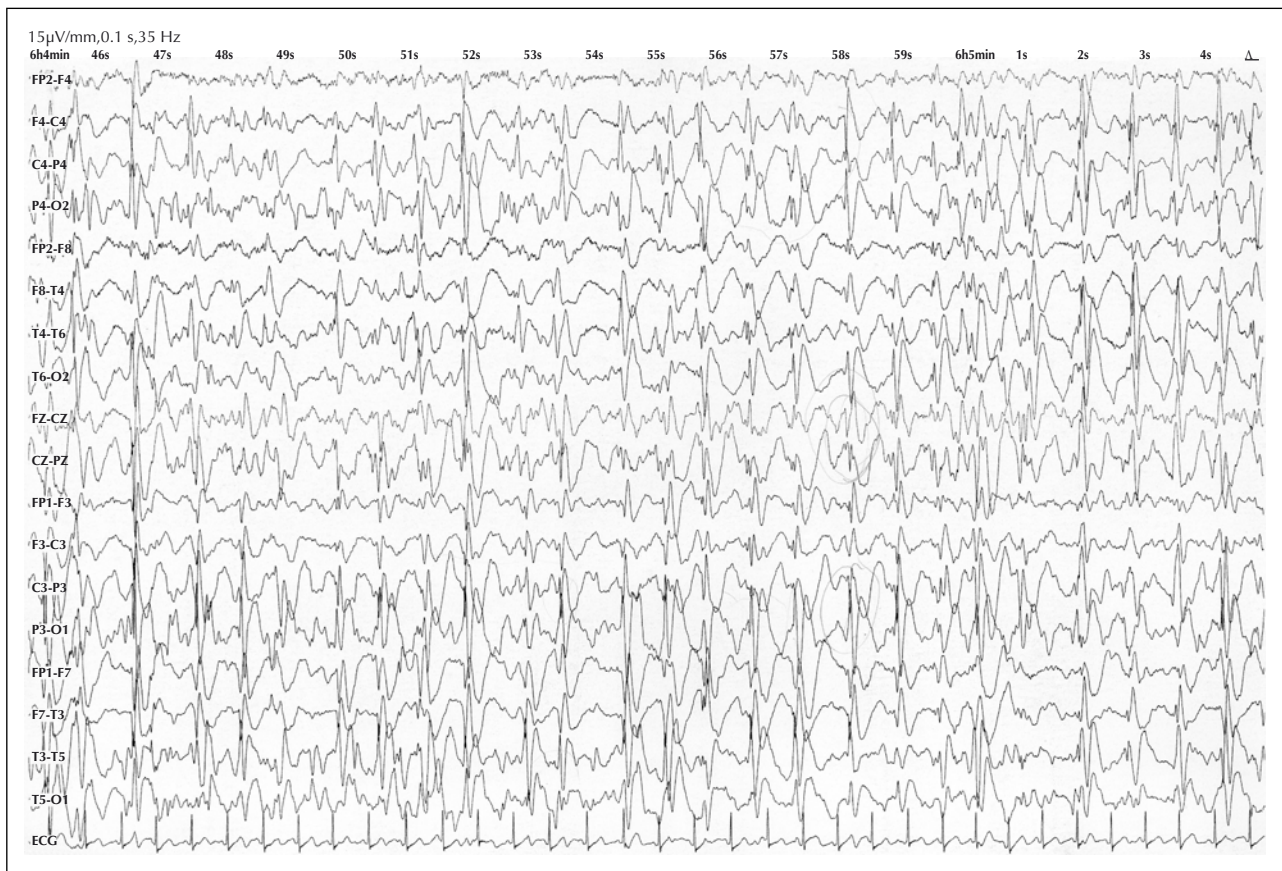
**Figure 2.** EEG recorded at age 4 years showing continuous, high voltage, 1-2 Hz, diffuse spikes-and-waves without any change in the child's behaviour.

dominantly on the central right or left regions or occurring bilaterally with a variable frequency (0.5 to 3 Hz) over several hours *(figure 2)*. Clinically, there was no change in the child's behaviour, as he kept on playing (*see video sequences 2 and 3*), but sometimes there were rare brief head falls. During sleep, the spike-and-wave discharges became rare and more localized in various regions. During the periods of arousal, an activation of the spike-and-wave complexes occurred. Motor seizures persisted.

Vigabatrin and hydrocortisone were added to the treatment. Episodes of prolonged and continuous slow spikes-and-waves persisted, but motor seizures became rare and were no longer followed by the repeated brief adduction movements of shoulders.

## Cytogenetic and fluorescent *in situ* hybridization (FISH) analyses

R- and G-banded karyotyping were performed on blood lymphocytes and skin fibroblasts. The 46, XY, r(17) karyotype was observed in lymphocytes in the majority of cell lines (n = 36), whereas the 45, XY,-r (17) karyotype, *i.e.* with the absence of ring 17, was observed in a single cell line. In fibroblasts, 46, XY, r (17) and 45, XY, -r (17) karyotypes were observed in 39 and three cell lines respectively.

Telomeric regions of chromosome 17 were studied by FISH using the common human telomeric probes (Qbiogene®) and specific subtelomeric probes for regions 17p (D17S643) and 17q (D17S724). On the ring chromosome, a telomeric deletion was observed with the 17p probes but not with the 17q probes. The same results were obtained by FISH analysis on buccal smears (56 nuclei studied) using the same subtelomeric probes *(figure 3)*.

In addition, FISH studies, using specific probes for the Miller-Dieker lissencephaly region (17p13) and the Smith-Magenis syndrome (17p11.2) (Qbiogene®), showed no deletion on ring 17 *(figure 3)*.

Finally, normal karyotypes were found in both parents of the patient.

## Discussion

Ring chromosome 17 is a rare, cytogenetic abnormality resulting in variable phenotypes depending on the size of
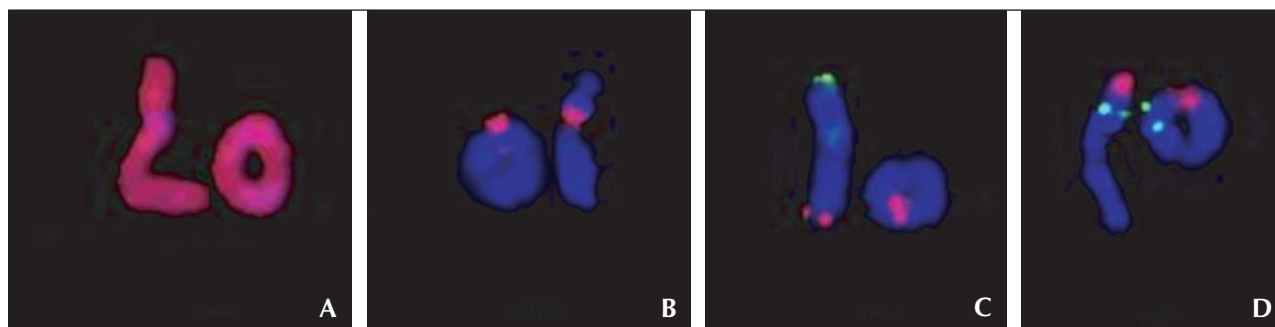
**Figure 3.** FISH study on chromosome 17. A: whole chromosome 17 painting. B: with a centromeric probe, both centromeres showed signals. C: FISH using subtelomeric probes 17pter (green) 17qter (red): the 17pter probe is missing on the ring chromosome. D: FISH using the Smith Magenis locus probe (green) and the Miller-Dieker LIS1 locus probe (red), showing signals on both chromosomes.

the deletion on the ring chromosome (Shashi *et al.* 2003). One group of patients with the more severe phenotype have deletions of the 17p13 region encompassing the LIS1 gene, resulting in Miller-Dieker lissencephaly syndrome. Another group includes patients harbouring ring chromosome 17 without the LIS1 deletion; our patient belongs to this second group.

To date, only eight patients have been reported in this more mildly affected group (Qazi *et al.* 1979 ; Chudley *et al.* 1982 ; Charles *et al.* 1991 ; Gass and Taney, 1994 ; Endo *et al.* 1999 ; Shashi *et al.* 2003). With the exception of one patient who was too young at the time to be fully evaluated (Endo *et al.* 1999), all these patients shared consistent features such as short stature, mental retardation and seizures. However, literature data present only brief descriptions of the epileptic episodes. To our knowledge, the present case report offers the first detailed description of the epileptic phenotype associated with ring chromosome 17.

Interestingly, the electroclinical features presented by our patient resemble those described as being specific to ring chromosome 20 syndrome. Firstly, interictal activity shows similarities. The slow background activity observed in our case has been previously described in children (Ville *et al.* 2006), although it is usually normal in adults. At the beginning, we observed temporo-occipital bilateral discharges which became more diffuse during the first two years of the clinical course. This evolution has been reported in children with ring chromosome 20 syndrome, as well as in some generalized epileptic syndromes of childhood (Ville *et al.* 2006). Next, continuous paroxysmal activity with diffuse, asymmetrical, synchronous spike-and-waves of various frequencies occurred during wakefulness with no clear clinical manifestations. This electroclinical dissociation has been previously described in adults (Inoue *et al.* 1997, Biraben *et al.* 2001, Latour *et al.* 2002, Canevini *et al.* 1998) as well as in children (Ville *et al.* 2006, Augustijn *et al.* 2001) with ring chromosome 20 syndrome. In our patient, this activity disappeared during sleep, something that has been described in cases of ring chromosome 20 (Kobayashi *et al.* 1998, Ville *et al.* 2006). This pattern does not exactly correspond to "non-convulsive status epilepticus", where an altered level of consciousness is observed. The term "electrical status during wakefulness" seems to be more accurate to describe these particular features. Besides this, the nocturnal seizures with motor components associated with fast rhythms, either diffuse or with frontal initiation and followed by diffuse slow waves, seem to be identical to those described by Augustijn *et al.* (2001) in paediatric cases with ring chromosome 20 syndrome. However, in our case, some of these seizures were followed by a symptomatology evoking clusters of spasms; unfortunately, the conditions of the video-EEG monitoring at this moment did not allow accurate recording.

Epilepsy associated with ring chromosome 20 syndrome has been hypothesized to be related to the loss of the function of both epilepsy genes located at 20qter, namely *CHRNA4* and *KCNQ2*, which could be deregulated during the formation of the ring (Zou *et al.* 2006).

Similarly, epilepsy genes may be involved in ring chromosome 17 syndrome. More particularly, a putative epilepsy gene could be located in 17p since in our case, a deletion of the subtelomeric region of the 17 short arm was observed in the ring chromosome. To our knowledge, no epilepsy genes have been identified so far on chromosome 17 and more particularly in the 17p region (Online Mendelian Inheritance in Man). Moreover, cases of 17pter deletion have been reported either in patients with an apparently normal phenotype (Martin *et al.* 2002) or as a benign familial variant (Ravnan *et al.* 2006).

Another possible explanation of the epileptic phenotypes observed in ring chromosome 20 and 17 is that seizure disorders might occur as a result of structural instability of the ring chromosome in mitoses during brain development (Shashi *et al.* 2003). However, it is difficult to understand why such a typical epilepsy phenotype would occur only in ring chromosomes 20 and 17 while it is absent in the majority of other ring chromosomes (Shashi *et al.* 2003).

Finally, the fact that striking similarities exist between the phenotypes of ring chromosome 20 and 17 syndromes raises the possibility of common genes, close to the telomeric region, which could be deregulated during the formation of the ring. □

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### Legends for video sequences

*Sequence 1.* A recording made while the four-year-old child was asleep. The seizure lasted 60 seconds with tonic arm elevation, followed by a few clonic shoulder fits. The EEG shows diffuse, fast activity, followed by diffuse, but predominantly central, spike-and-wave activity, and finally followed by diffuse, slow waves.

*Sequence 2.* Diffuse, high-voltage, slow spike-and-wave activity, predominantly in the right central region, with a variable frequency. The child continued playing.

*Sequence 3.* Continuous, high-voltage, 1-2 Hz, diffuse spike-and-wave activity. The child was awake and calling for his mother.

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