

Frontal motor seizure following non-convulsive status epilepticus in ring chromosome 20 syndrome

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ABSTRACT

تعد متلازمة حلقة الكروموسوم 20 من الأمراض النادرة حيث يتميز بحالة صرع مستعصية مع ميزات خاصة سريرية و كهربائية للدماغ بما في ذلك حالات صرع مستمر غير اختلاجي يدوم لفترات طويلة ونوبات صرع ليلية ناجمة عن تشنج في الفص الأمامي للدماغ. نستعرض في هذا المقال حالة نادرة لمريضة تبلغ من العمر 17 عاماً وقد كانت تتعرض إلى نوبة صرع ناجمة عن تشنج في الفص الأمامي مع حالة صرع مستمر غير اختلاجي في نفس الحلقة أكدته التخطيط الدماغي المصاحب. أظهرت دراسة النمط النووي وجود الكروموسوم 20 في شكل حلقة في 70% من الخلايا اللمفية، ولم تكشف دراسة الجينات CHRNA4 و KCNQ2 عن وجود خبن صبغي. لقد أظهر التخطيط الكهربائي للدماغ وجود صرع غير تشنجي قد استمر لأكثر من 20 دقيقة، وقد تبعه تشنج في الفص الأمامي. إن مثل هذه العلاقة لم يتم التطرق لها سابقاً في الأدب الطبي، كما كان سببها على الأرجح اضطراباً في الكروموسومات.

The ring chromosome 20 syndrome is a rare syndrome characterized by intractable epilepsy with particular electro clinical features including episodes of prolonged confusional state and nocturnal frontal lobe seizures. We report a 17-year-old girl who had intractable epilepsy with frontal seizure and prolonged confusional state secondary to non-convulsive status epilepticus. The diagnosis of ring chromosome 20 was suspected and confirmed by karyotype. The cytogenetic study of CHRNA4 and KCNQ2 genes did not detect deletion in the ring chromosome 20. During video-EEG recording, this girl presented a non-convulsive status epilepticus that lasted more than 20 minutes followed by typical frontal lobe seizure. This association was not previously described, and was probably caused by chromosomal instability.

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The ring chromosome 20 [r(20)] syndrome is a rare syndrome first described by Atkins and co-workers in 1972,¹ and around 60 cases have been presented. This syndrome is characterized by intractable epilepsy, mild to moderate mental impairment, facial dysmorphism, and microcephaly. Patients generally show mosaicism in 1-100% of lymphocytes with r(20).² Subsequent reports disclosed that epilepsy constitutes the main clinical feature of this syndrome.^{3,4} Distinct electroclinical features suggesting a fronto-temporal origin of the seizures have been described. Typical features of epilepsy in r(20) syndrome are drug-resistant epileptic seizures and periods of non-convulsive status epilepticus (NCSE).^{1,5,6} A particular electrical pattern has been reported in these patients including episodes of long-lasting bilateral paroxysmal high-voltage slow waves over the frontal lobes.⁵ The mechanism underlying the seizure disorders remains unknown.³ Cognitive problems are common, and vary from mild learning disabilities to moderate mental retardation.^{2,5,6} We report a patient with r(20) previously identified genetically,⁷ who had 2 seizures types occurring in the same ictal event confirmed by video-EEG recording. Our objective in presenting this particular case is to highlight the phenotypic variability of epilepsy in the r(20) syndrome.

Case Report. Our patient is a 17-year-old girl born by normal vaginal delivery after uneventful pregnancy. There were no initial concerns about her growth and development until the age of 3 years when she started to experience nocturnal paroxysmal attacks with intense fear and visual symptoms. She described seeing monsters, snakes, or spiders. She was diagnosed to suffer nightmares and received no medication. At the age of 4 years, she started to suffer diurnal episodes of brief tonic seizures. An epilepsy diagnosis was made at that time,

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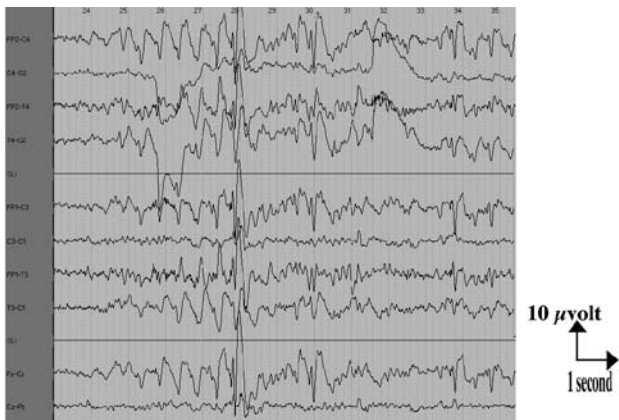


Figure 1 - Inter-ictal EEG with bilateral paroxysmal high-voltage slow-waves with occasional spikes in the anterior regions.

and she was treated by valproate and carbamazepine. Her condition remained stable until the age of 6 years; she used to have one or 2 seizures per month, yet she started to have learning difficulties. At the age of 10 years, the frequency of seizures increased dramatically following poor compliance by her parents. She started to suffer

from prolonged episodes of altered consciousness with staring, prolonged confusional state followed by motor seizures (crying with intense fear and tonic stiffening of the limbs). The interictal EEG showed bilateral paroxysmal high-voltage slow-waves with occasional high-voltage spikes in the anterior regions (Figure 1). At the age of 13 years, video-EEG monitoring identified diurnal seizure. At the beginning, she presented a mental slowing. During this episode, she remained responsive but manifested considerable mental slowing, loss of facial expression, and perseveration (she draws lines when we asked her to write her name). The EEG showed recruiting generalized spike activity (Figure 2a) followed by long-lasting bilateral paroxysmal high-voltage slow spike-waves at 2-3 Hz lasting 20 minutes (Figure 2b). Then, she started to manifest intense fear and tonic stiffening of when limbs, when the EEG record showed attenuation and low-voltage fast activity evolving into high-voltage rhythmic slow waves lasting for 10 minutes (Figure 3a). At the end, she remained confused for one hour during which the EEG showed progressive fragmentation of the rhythmic spike-waves with global slowing activity (Figure 3b). Her clinical examination showed mild mental deficiency

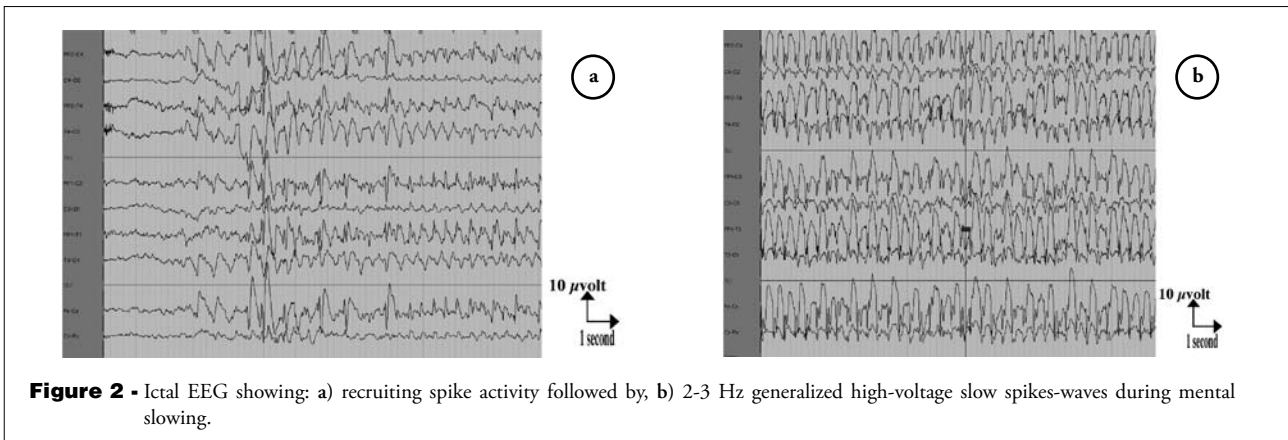


Figure 2 - Ictal EEG showing: a) recruiting spike activity followed by, b) 2-3 Hz generalized high-voltage slow spikes-waves during mental slowing.

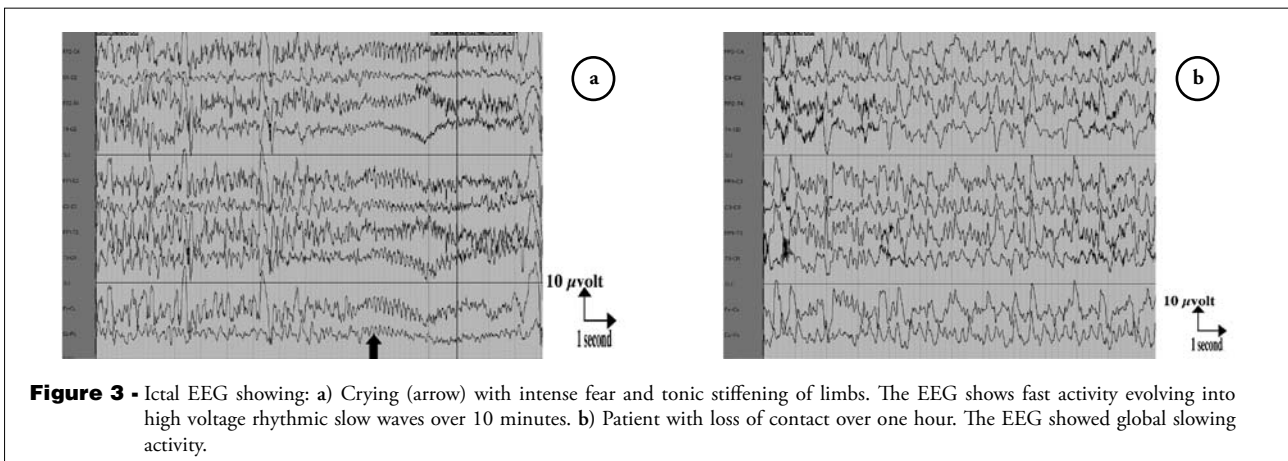


Figure 3 - Ictal EEG showing: a) Crying (arrow) with intense fear and tonic stiffening of limbs. The EEG shows fast activity evolving into high voltage rhythmic slow waves over 10 minutes. b) Patient with loss of contact over one hour. The EEG showed global slowing activity.

with no dysmorphic features. Her brain MRI imaging was normal. The karyotype showed the presence of ring chromosome 20 in 70% of the studied lymphocytes: 46, XX, r(20) (p13q13.3). Interphasic fluorescence in situ hybridization (FISH) using centromeric probe of chromosome 20 detected the presence of a chromosome 20 monosomy in 7%, and a duplicated ring chromosome 20 in 8% of studied cells. Metaphase FISH using chromosome 20 telomeric probes and specific probes of CHRNA4 and KCNQ2 genes detected the absence of any deletion in the ring chromosome 20.⁷

Currently, she still presents prolonged episodes of non-convulsive status epilepticus (NCSE) several times a day despite polytherapy (valproate, lamotrigine, carbamazepine, and levetiracetam) with a long sequence of bilateral paroxysmal high-voltage spike and wave in the anterior regions on EEG.

Discussion. We report a patient with r(20) syndrome who presented with typical NCSE that occurred over 20 minutes with the characteristic EEG pattern, followed by typical frontal lobe seizure in the same episode and was confirmed by EEG. This association in the same ictal episode is rarely described.

The clinical presentation and EEG patterns of r(20) are well described. In general, epilepsy begins between 2-6 years of age, being the first manifestation of the disorder in many cases. Several types of seizures are described in this syndrome such as nocturnal frontal lobe seizures (subtle nocturnal seizures: SNS), NCSE, complex partial seizures, "absence like" and generalized tonic-clonic seizures.^{1,5,8} Nocturnal frontal lobe seizures are characterized by awakening, staring, some tonic stiffening followed by clonic movements of eyelids and extremities, then by agitation, and disorientation. They can manifest as minimal motor activity like subtle stretching, turning, or rubbing movements.^{1,5} The NCSE usually present as episodes of an altered state of vigilance with stare gaze, loss of emotional facial expression, diminished spontaneous behavior and speech, and a slow response to questions. Focal motor symptoms like myoclonia, head turning, oral automatisms, and frightened expressions were also seen during this period.^{1,5,8} So, in our patient, the motor symptoms occurring during the episodes are different and are closer to the frontal lobe seizures semiology. In fact, the association of NCSE with partial seizures in the same episode is well known, but the association with frontal lobe seizures in the same ictal episode is rarely described. Augustijn et al⁵ described one patient with multiple nocturnal and diurnal frontal lobe seizures, but without NCSE.

From the physiopathological point of view, most ring chromosomes are formed by fusion of the deleted telomere of both chromosome arms. Epilepsy can be caused by the terminal deletion of the long arm, or by a

disordered equilibrium of the residual genes.⁹ We know that 2 epilepsy genes mapped to 20q13.2-13.3 have been identified: CHRNA4 that codes for the alpha4 subunit of the neuronal nicotinic acetylcholine receptor and leads to "autosomal dominant nocturnal frontal lobe epilepsy: ADNLFE," and KCNQ2 that encodes a voltage-gated potassium channels and leads to "benign familial neonatal epilepsy: BFNE." Therefore, epilepsy can be caused by loss of CHRNA4 and KCNQ2.² However, the clinical seizure phenotypes caused by mutations or deletions of these genes are different from those reported in the r(20) syndrome.³ However, our patient who does not express terminal deletion of the chromosome 20,⁷ has severe epilepsy. The predominance of SNS suggests a possible relationship with other epilepsy syndromes related to the distal long arm of chromosome 20.^{2,5}

Therefore, the severity of clinical expression depends not only on the extent of chromosomal deletion, but also on the haploinsufficiency of other important related genetic loci due to ring instability.^{3,4,6,9} The results of a recent study on molecular analysis of 28 patients with r(20) do not agree with this; since the majority of patients do not have any detectable deletions of chromosome 20, and those with deletions have heterogeneous affected genes.⁹

Using ictal magneto-encephalography, the source of the ictal discharge in r(20) was localized to the medial frontal lobe.¹⁰ It was suggested, however, using positron emission tomography scanning, that seizures may be associated with dysfunction of striatal dopamine neurotransmitter.⁶ Therefore, we can assume that the prolonged seizures duration and the association of 2 seizures types in the same episode is linked to an inability to inhibit epileptogenesis. In fact, striatal dopamine is modulated in r(20) epilepsy; dysfunction of this neurotransmission may impair the mechanisms that interrupt seizures.⁶

Conlin et al⁹ recently demonstrated that r(20) syndrome is a heterogeneous disorder with both mosaic and non-mosaic rings, however, there is a genotype-phenotype correlation between the 2 groups. Mosaic rings patients have later seizure onset than non-mosaic ones, and a lower likelihood of additional findings such as intellectual disability and dysmorphic features.

In conclusion, the profile of a patient with ring 20 chromosome syndrome includes complex partial seizures and repetitive NCSE resistant to antiepileptic drugs, EEG findings of slow waves and spikes in anterior regions, and normal brain imaging studies. The association of NCSE with partial seizures in the same episode is well known, but the association in the same ictal episode with frontal lobe seizures is rarely described.

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CASE REPORTS

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