

Ring-20-syndrome and loss of telomeric regions

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Abstract – A patient aged 10 years and 8 months with a ring-20-syndrome was studied. Clinically he presented normal psychomotor development until 25 months of age when he began with right simple partial motor seizures. He presented minimal dysmorphism, generalized tonic–clonic seizures refractory to medical therapy and behavioral troubles. He was submitted to a callosotomy when he presented an electric status, subsequently, he was treated with anticonvulsivants and felbamate and the seizures were controlled. The karyotype showed a chromosomal complement 46,XY,r(20)(p13q13.3) with loss of the telomeric regions evidenced by FISH. The mother had normal karyotype. The clinical and cytogenetic features of previous cases described in the literature were compared leading to a better characterization of this syndrome. © 2000 Éditions scientifiques et médicales Elsevier SAS

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1. Introduction

The ring-20-syndrome (RC20) was first recognized in 1976 [3]. Up to date, more than 30 cases have been described, in some of them it has been sustained mosaicism [5–9, 16–20]. This syndrome is characterized mainly by mental retardation, behavioral disorders, epilepsy (age of onset 4–6 years) refractory to treatment and some variable dysmorphic features [2].

The purpose of this paper is to describe the clinical and cytogenetic findings in a patient with RC20 syndrome, which were compared to those reported in the literature, leading to a better characterization of this syndrome.

2. Case report

The propositus aged 10 years and 8 months (*figure 1*), was the product of the first and unique full-term

and uncomplicated pregnancy (APGAR 8–10) from young, healthy and non-consanguineous parents. The psychomotor development was normal until 25 months of age when the patient began with simple partial motor seizures of the right side of the body (with normal EEG). The seizures increased in frequency and, became generalized when he was 3 years old, turning in tonic–clonic, and unsuccessfully treated with difenilhidantoinate, carbamezepine or other anticonvulsivants. Since the onset of the epilepsy all his mental functions began to deteriorate. The frequency of seizures increased (4 per day) and they were associated with mixed dysphasia, hypoglycemia and impossibility to walk. The lack of response to the medical therapy led the neurologist to perform a callosotomy, after which the frequency of the seizures decreased notoriously. During the surgical procedure it was resected an aneurysm of the marginal callosal artery. Since the patient persisted with low frequency seizures despite the treat-

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ment with valproic acid, primidone and acetazolamide, felbamate was aggregated showing with this combination an absolute control of the seizures with notable improvement of the patient. Physical examination at 10 years and 8 months of age showed: a height of 140 cm, a weight of 34.2 kg, an OFC of 52 cm (all the somatometric parameters into normal limits). Clinically he showed wide forehead, telecanthus, prominent eyes, high-arched palate, micrognathia, sialorrhea, high-set nuchal hair, long neck and trunk, low-set and hypertelorism of nipples, microgenitalia, thenar and hypothenar hypoplasia and pes planus. The neurological evaluation revealed hyperreflexia (++++), the cerebral MNR was normal; the EEG previous to the surgery showed an electric status with paroxysms with spike-wave patterns of 2–3 Hertz, with a deorganized base activity. The EEG after the surgery showed non generalized few paroxysms of spike-wave patterns and deorganized base activity. A cerebral biopsy revealed microvacuolar degeneration due to accumulation of lipids in neurones and astrocytes. The psychological evaluation showed a global maturation quotient of 50 % (Gessel Scale). The screening

tests for metabolic defects gave normal or negative results.

3. Cytogenetic studies

The chromosomal analysis was performed after GTG banding on lymphocyte cultures of peripheral blood in the propositus and his mother; in addition, FISH probe, with all the telomeres, (Oncor, Gaithersburg, MD) was done on the patient's chromosomes, yet, telomere-specific probes were not tested.

The propositus' chromosomal complement was 46,XY,r(20)(p13q13.3) (breakpoints defined by GTG banding); out of 100 mitosis scored, 95 presented the r(20), 2 were 45,XY,-r(20), 1 had 2 apparently normal chromosomes 20, 1 presented a double-sized ring, and 1 had a smaller ring (*figure 2*). FISH studies revealed lack of telomeric sequences in the r(20). The maternal karyotype was 46,XX. The propositus' father was not available for cytogenetic study.

4. Discussion

The ring-20-syndrome is characterized by mental retardation with behavioral disorders and severe epilepsy refractory to medical therapy. The present case shares these clinical characteristics including minimal dysmorphia. The psychomotor development is referred to be normal during infancy until the age of 2 years, when intellectual impairment begins culminating in a mental retardation; in some patients is described arrest of normal mental development presenting progressive features as well as cognitive impairment which is related with the seizure onset [1, 4–7, 11, 15]. From a review of the literature based on 30 patients including the propositus, there were 15 females and 14 males, in one patient, the sex was not specified [4, 7]. In general the epilepsy began between 2–6 years of age, being the first manifestation of the disorder in many cases [2]. The convulsions seem to be complex partial seizures with tendency to become generalized tonic-clonic seizures, although the seizures are described as episodes of altered consciousness with stare gaze, prolonged confusional state and motor seizures or convulsions which also can be manifested as brief motor seizures (16/30) being resistant to drug therapy (27/30) with poor control, also characterized by focal motor symptoms and/or head turning, and in

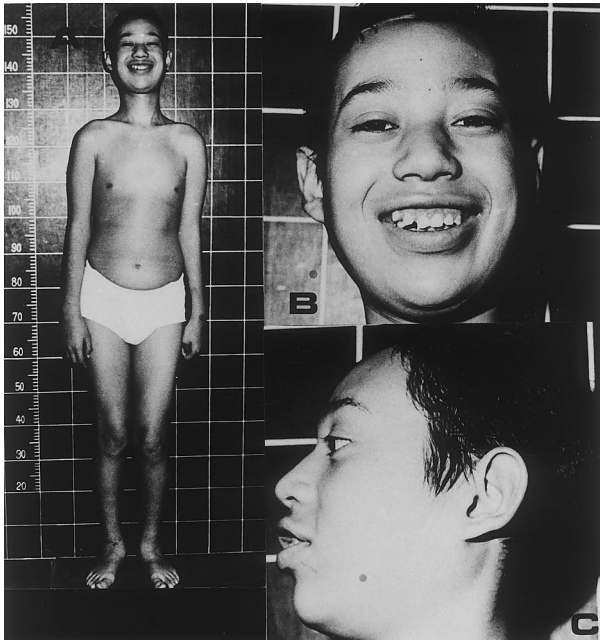


Figure 1. Propositus at the age of 12 years. **a.** General view, see long neck and trunk, low-set and hypertelorism of nipples and pes planus; **b.** Close-up, note wide forehead and telecanthus; **c.** Lateral close-up, showing wide forehead, prominent eyes and micrognathia.

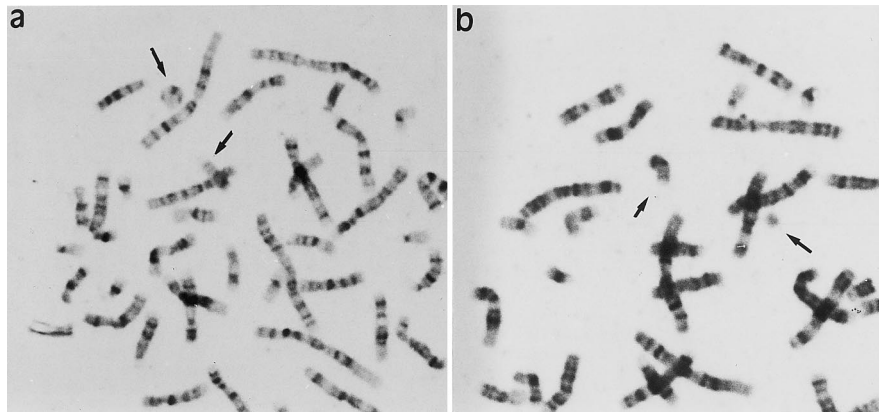


Figure 2. G-bands. **a.** The arrows indicate the normal 20 chromosome and r(20)(p13q13.3). **b.** Normal 20 chromosome and small r(20).

many cases simultaneously with oral automatisms and unspecified automatic behavior (see *Table I*) [5, 8]. Other symptoms such as frightened expression were seen in 2/30 [5], and others like expressionless face, muteness, inattentiveness and perseveration less frequently [8]. On the other hand, episodes of status epilepticus were present in 4/30 patients [5, 8]. Clinical dysmorphism varied from microcephaly, facial dysplasias and growth retardation which were more consistent; other features such as muscular hypotonia, minor dysplasias, scapula alata and bilateral epicanthi have been described less frequently [2]. Canevini et al. [5] described a boy with slight generalized obesity, bilateral genu valgum and small hands; in another patient was described short stature due to hypophthalamic dysfunction [8]. Our patient presented wide forehead, telecanthus, prominent eyes, high-arched palate, micrognathia, high-set nuchal hair, long neck and trunk, low-set and hypertelorism of nipples, microgenitalia, thenar and hypothernar hypoplasia and pes planus, clinical features that were not previously described, as well as the aneurism of the marginal callosal artery, and the features found in the cerebral biopsy (microvacuolar degeneration due to accumulation of lipids in neurons and astrocytes). In respect to the electrophysiological features the ictal EEG showed long-lasting high-voltage slow waves with occasional spikes which usually are unilateral in the frontal region, becoming bilateral [8, 10]. On the other hand, Canevini et al. [5], referred that the EEGs described in the literature may be related to the presence of frequent bursts of theta waves, this finding was found in 11/30 cases (see *Table I*) [5, 8].

There are two cases reported with absence of epileptic seizures: a patient of 15 months of age [13]

who probably had not reached the age of onset, and a woman carrier of a familial RC20 mosaicism [2]. Other cases of RC20 mosaicism have been described as a supernumerary RC20 with mosaicism [1, 5, 19, 20]. On the other hand, five cases have been described with normal cells, as well as cells in which a normal chromosome 20 is replaced by a RC20 chromosome [6, 7, 15, 16, 18]; also 4 instances of familial RC20 mosaicism are known [2, 5, 17, 21]. Our review of the literature showed that 21/30 patients

Table I. Clinical, electrophysiological and cytogenetic findings in patients with ring-20-syndrome.

Clinical findings	Total cases
Motor seizures or convulsions*	16/30
Focal motor symptoms* and/or head turning	5/30
Myoclonia	3/30 ^a
Episodes of altered consciousness with stare gaze	14/30
Prolonged confusional state	8/30
Unspecified automatic behavior	3/30 ^b
Oral automatisms	5/30
Other automatisms	3/30 ^c
Episodes of status epilepticus*	5/30
Drug-resistant epilepsy*	27/30
EEG	
Bursts of long trains of theta waves*	12/30
Ictal EEG: Long lasting high-voltage slow waves. Occasional spikes localized to a unilateral usually frontal region but easily became bilateral*	14/30
Normal EEG	3/30
Mosaic r(20)p13q13, p13q13.3 or p13q13.33	21/30

* Present in the proband.

^a Eyelid myoclonia.

^b Bizarre behavior.

^c Complex motor automatisms.

EEG, electroencephalography.

Based on reviews of Inoue et al. [8] and Canevini et al. [5].

presented mosaic r(20)p13q13. p13q13.3 or p13q13.33, the percentage of RC20 varied from 10 % to 100 % in lymphocytes [8]. The remaining cases reported in the literature did not demonstrate mosaicism, although conventional cytogenetic studies were not performed in two different cellular lines [4, 12]. Recently, Roubertie et al. [14] described two new cases with non convulsive status epilepticus, typically EEG features and RC20.

Human ring chromosomes are originated by deletions in both telomeric regions. If the loss of genetic material is large enough the carriers can exhibit phenotypical similitudes corresponding to the deletion involved [2]. Although in 3 patients reported by Canevini et al. [5], FISH with chromosome specific telomeric probes demonstrated the integrity of the ring chromosome concluding that the clinical picture probably be related to the instability of the r(20), thus are generated monosomic cells for chromosome 20 and haplo insufficiency for a gene.

Recently, Stevens et al. [15], proposed that the fusion of a ring chromosome is possible if only one telomere is defective. The mitotic stability of the r(20) in the present case is probably related to the length of the 20-chromosome since it seems that the stability of the ring is a function of its length; if it is longer, the probability of sister chromatid exchanges will increase [3].

The loss of the telomeric sequences in the propositus agree with other observations [11]. Furthermore, as it is recommended by other authors, in those cases with mild dysmorphism, mental retardation and seizures refractory to medical therapy, a cytogenetic study is aimed to demonstrate a RC20.

From our review of the literature, it can be concluded that the clinical and electrophysiological picture in RC20 syndrome, in order of frequency is characterized by brief motor seizures or convulsions resistant to drug therapy, episodes of altered consciousness with stare gaze, prolonged confusional state, focal motor symptoms and/or head turning, oral automatism or other automatism, unspecified automatic behavior, and in some cases episodes of status epilepticus; electrophysiologically by bursts or long trains of theta waves (*table I*) [5, 8].

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