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EPILEPSY AND RING CHROMOSOME 20

Case report

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ABSTRACT - We present the clinical, electroencephalographic, neuroimaging (brain magnetic resonance image - MRI and spectroscopy by MRI) and cytogenetic findings of a young male patient with a rare cytogenetic anomaly characterised by a *de novo* 46,XY,r(20)(p13q13.3) karyotype. He presents with mental retardation, emotional liability, and strabismus, without any other significant dysmorphies. There are brain anomalies characterised by corpus callosum, uvula, nodule and cerebellum pyramid hypoplasias, besides arachnoid cysts in the occipital region. He had seizures refractory to pharmacotherapy and long period of confusional status with or without a motor component. The authors recognised that the EEG pattern was not fixed but changed over time, specially for bursts of slow waves with great amplitude accompanied or not by sharp components, and bursts of theta waves sharply contoured. Previously, epilepsy solely has been assigned to region 20q13. However, the important structural cerebral alterations present in our case has not been reported associated to such chromosomal abnormality and may indicate possible new chromosomal sites where such atypical neurological characteristics could be mapped

KEY WORDS: ring chromosome 20, epilepsy, mental retardation.

Epilepsia e cromossomo 20 em anel: relato de caso

RESUMO - Apresentamos os achados clínicos, eletrencefalográficos, de neuroimagem (ressonância magnética nuclear - RMN e espectroscopia por RMN) além de achados citogenéticos de um menino com uma anomalia citogenética rara caracterizada por um cromossomo 20 em anel não herdado, cariótipo 46,XY,r(20)(p13q13.3). Ele apresenta retardo mental, labilidade emocional, estrabismo sem outras alterações dismórficas externas significativas. Existem alterações cerebrais caracterizadas por hipoplasias do corpo caloso, úvula, nódulo e pirâmide cerebelares, além de cisto aracnóide na região occipital. Ele tem crises epilépticas refratarias à farmacoterapia e períodos longos de estado confusional com ou sem componente motor. Destacamos que o padrão EEG não é fixo mas muda com o período da vida, existem paroxismos de ondas lentas de grande amplitude acompanhados ou não por componentes agudos e paroxismos de ondas tetas pontiagudas. As importantes alterações morfológicas cerebrais não foram relatadas previamente associadas ao cromossoma 20 em anel, exceto epilepsia mapeada em 20q13. A anormalidade estrutural do cromossomo 20 pode indicar possíveis *loci* no cromossomo 20 onde tais características neurológicas atípicas possam ser mapeadas.

PALAVRAS-CHAVE: cromossomo 20 em anel, epilepsia, retardo mental.

Patients carrying a *de novo* chromosomal anomaly characterised by a ring chromosome 20 have neurological abnormalities expressed by moderated mental retardation, behavioural disorders, different type of seizures refractory to pharmacotherapy, mainly consisting of prolonged confusional state with or without additional motor seizures, and visceral dysmorphies, usually renal and cardiac anomalies[1-6]. Apparently, the psychomotor development is normal during the infancy until the age of 2 years, with no sex predominance, as referred by Garcia-Cruz et al.[7]. The ring chromosome 20 is originated by chromosomal breaks on each arm resulting in deletions in both telomeric regions, but there are reports of cases in which there was integrity of both chromosome ends[7-9]. Borgaonkar et al. catalogued this type of

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abnormality for the first time in 1976 as a genetic syndrome (apud Porfírio et al.[2]), and Herva et al.[10] confirmed it considering that should be considered a specific ring-20 syndrome. It is attributed to Atkins et al.[11] the first clinical description of a case of a mentally retarded boy with behavior problem, seizures, microcephaly associated to a ring chromosome 20.

The lack of typical dysmorphies usually delays the diagnosis[3]. The epilepsy is considered the hallmark of the syndrome helping to the early clinical suspicion, but it was only recently that such cases have been brought to clinical attention by Inoue et al.[4]. The mean age of installation of the seizures is 5.3 years of age, but in the majority starts before 10 years of age[5]. In 1997, Inoue et al.[4] emphasised that the epilepsy severity includes frequent periods of no convulsive status epilepticus of high frequency. There are electroencephalographic peculiar findings reported by some authors[4,9,12]. The brain imaging studies are less discussed than the one of genetics or electroencephalography.

Hitherto, more than 30 cases have been described, and Serrano-Castro[5] found 31 published cases "acceptably documented".

This report describes a patient submitted to serial EEG exams, brain magnetic resonance imaging (MRI) and spectroscopy by MRI, and visceral thoracic and abdominal morphological evaluation, where the cytogenetic investigation revealed a ring chromosome 20. The clinical aspects of the patient had been previously reported[13]. This report updates the patient's long term clinical follow-up and describes the cytogenetic characteristics of this rare cytogenetic abnormality.

CASE

Male patient aged 12 years born when the parents were 27 years old. The couple is healthy and non-consanguineous, and the pregnancy was apparently normal. The labour was by caesarian section with perinatal anoxia due to wrapped umbilical cord. The weight at birth was 3.050g. He was the last birth of an offspring of three. There was no history of similar case in the family. The patient presented with delayed psychomotor development associated to hypotonia and somnolence. He was examined for the first time by some of us when he was 9 years old[13]. He presented with moderated oligophrenia, emotional liability, hyperacusia with normal audiometry tests, minor mitral valve prolapse, unilateral ocular exotropy, seizures refractory to pharmacotherapy with increasing severity: myoclonic, generalized tonic-clonic and dialeptic seizures ("absences") prone to be developed by mental stressors. The first seizure was detected at 21 months of age. Any other visceral, thoracic or abdominal abnormalities was detected.

The cytogenetic studies were performed in lymphocytes cultures using standard procedures and 100 metaphases were analysed. A 46, XY, r(20)(p13q13.3) karyotype was found in 90% of the cells. In the remaining cells, 4% showed 47 chromosomes with double rings and 6% showed structurally abnormal rings presumably derived from the original r(20)(p13q13.3) chromosome. C- band investigation revealed presence of a monocentric ring in all 100 analysed. The parents karyotype were normal. Figures 1a and 1b show the patient's karyotype and partial metaphases with the ISCN (1995) chromosome 20 ideogram, respectively.

The boy has several EEG recordings along 9 years, during wakefulness, somnolence or asleep (spontaneous or induced) with variable morphology. In the first three recordings there were scattered sharp waves. Sharply contoured theta rythm was demonstrated around 6 to 9 years of age (Fig 2). Burst of spikes and wave complex (range frequency

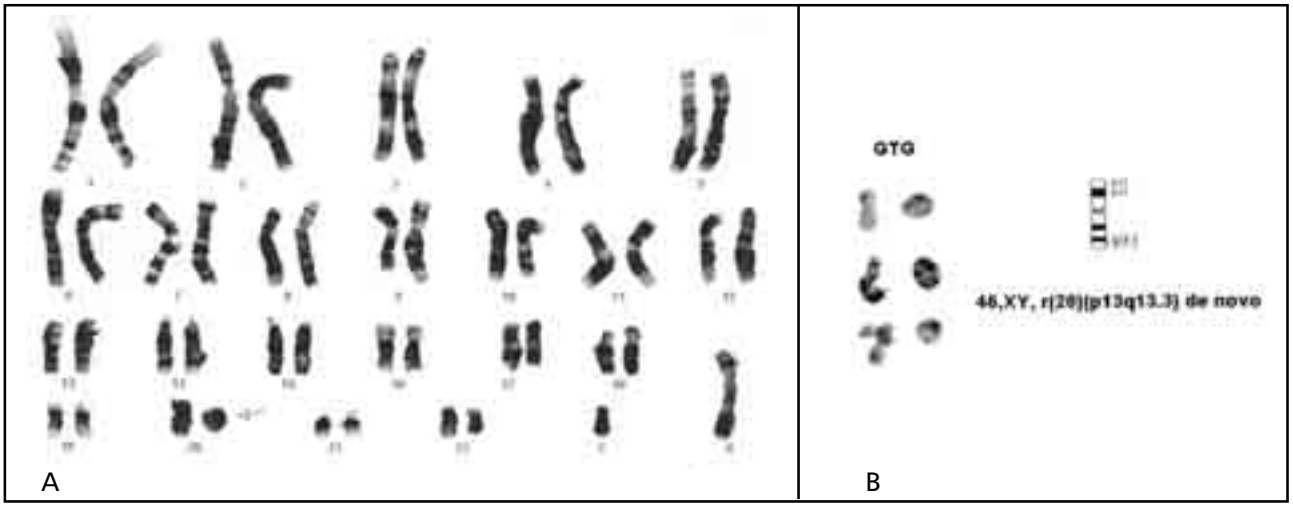

Fig 1. A. GTG karyotype of the patient. B. Partial metaphases of the patient illustrating the r(20) and chromosome 20 GTG ideogram following ISCN (1995).

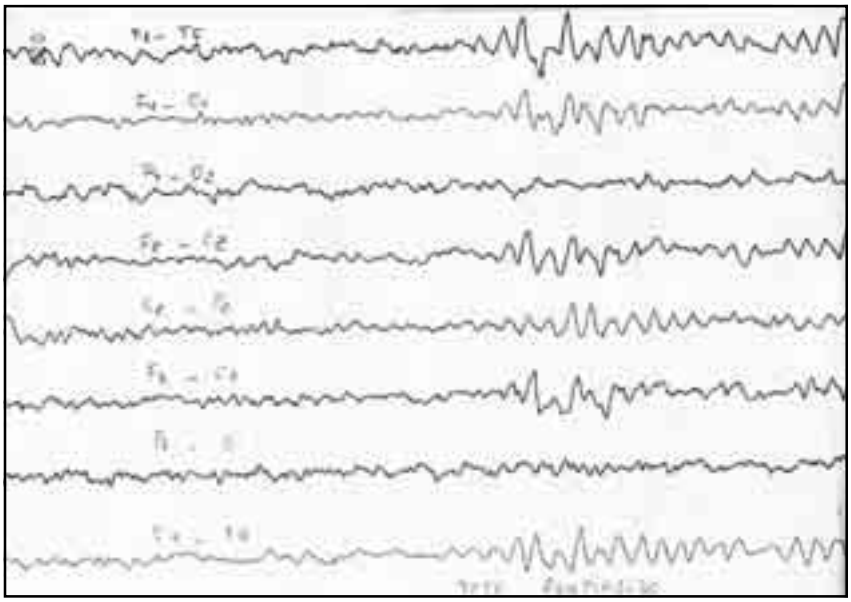

Fig 2. Sharply contoured theta rhythm.

of 2.5 to 5 Hz, of anterior predominance were more defined from 5 years of age onwards). Diffuse slow wave is also seen in the majority of the recordings with sharp format with temporal predominance and diffuse sharp accidents. The spike and wave complexes were activated by the somnolence and photo stimulation. The more recently EEG recordings shows spike and slow wave complexes discharges, of high voltage with frontal bilateral predominance (Fig 3). The EEG pattern changed with time, the sharp waves predominated in posterior and temporal regions (2 to 7 years of age). From 5 years of age onwards, it appears bursts of slow sharp-waves mainly frontal. In the last EEG exam (11 years and 6 months) it was shown slow background activity and the massive presence of spike and slow complexes also mainly frontal, of exaggerated amplitude. The summary of these findings is on Table 1. The boy was submitted to video-EEG recording in two different moments. It was shown diffuse slowness, bursts of spike and slow wave complexes associated to prolonged periods of "dialeptic" ("absence") seizures, similar to periods of *nonconvulsive status epilepticus*.

MRI shows corpus callosum, uvula, nodule and cerebellum pyramid hypoplasia, besides arachnoid cysts in the occipital region without spectral alteration of the examined area by the MR (voxels). The spectroscopy made by RMI in the temporal and frontal lobes are alike and normal (Fig 4 e 5).

DISCUSSION

The reported case has several characteristics in common with others reported r(20) in the literature, but few are unusual. Our patient presents different types of pharmacoresistent seizures (tonic-clonic, partial, dialeptic -"absence", myoclonic) what has been already described in other r(20) cases[5]. He has frequent episodes of altered consciousness, automatisms, myoclonus, some episodes of no *convulsive status epilepticus,* and also frightened expression. These events can be precipitated by emotional insights as mentioned too by Roubertie et al.[14]. The epilepsy severity and periods of *no convulsive status epilepticus* are reported in the medical literature too.

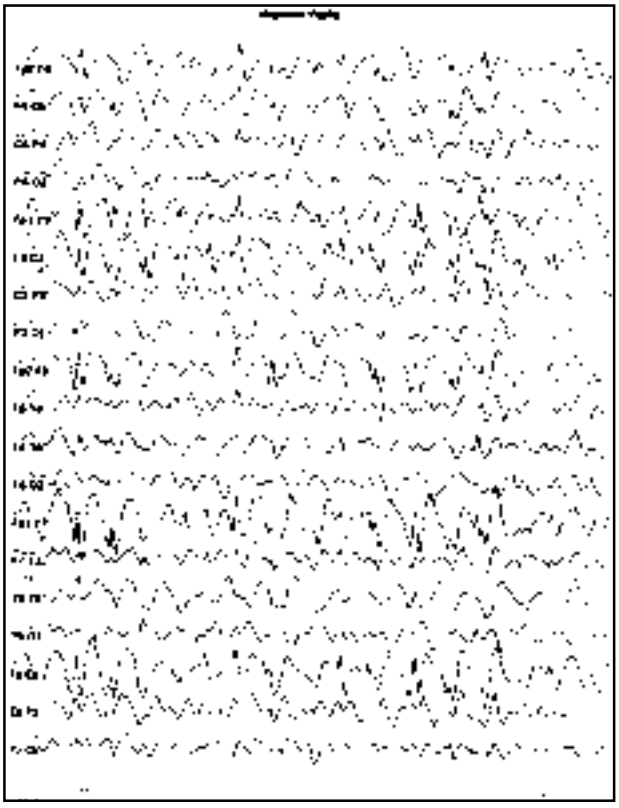

Fig 3. Spike and slow waves complexes.

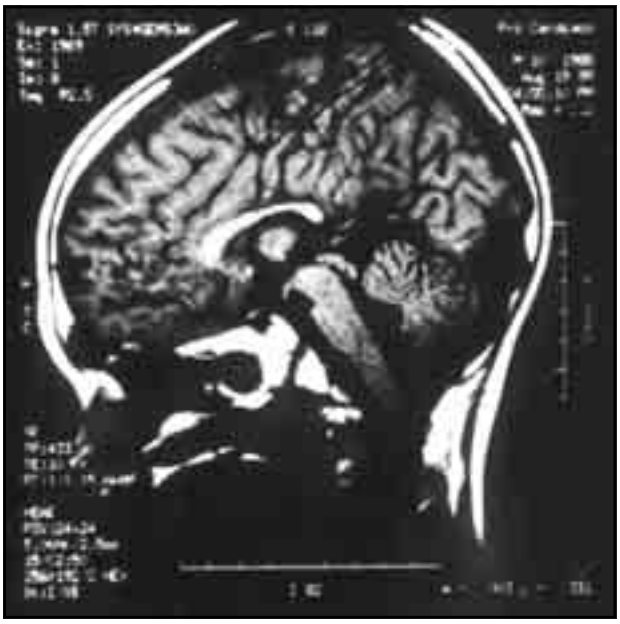

Fig 4. Corpus callosum hypoplasia.

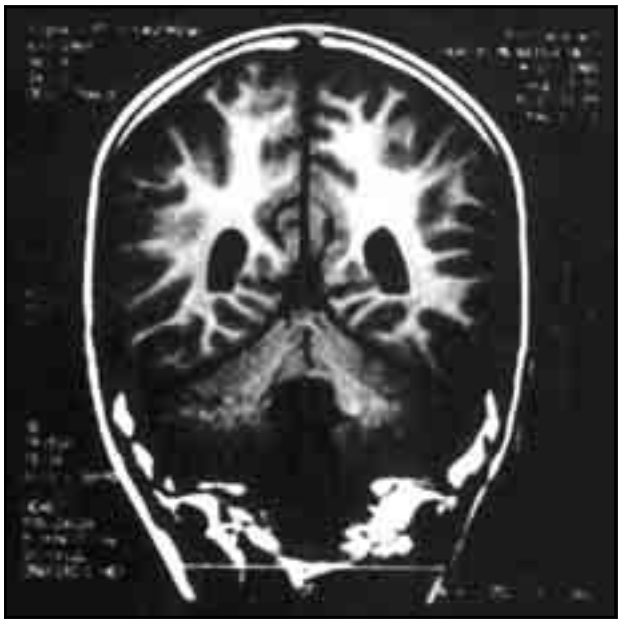

Fig 5. Cerebellum hypoplasia.

Table. Age and related EEG findings

Age	EEG findings			
	diffuse sharp wave	sharp	sharply contoured theta rithm	sharp-wave complex
2 years 1 month	+ (more posteriorly and temporal bilaterality)	-	-	-
2 years 7 months	+	-	-	-
4 years	+ (more posterior)	-	-	-
5 years	-	-	-	+
6 years	-	+ (more posterior)	+	+
7 years	-	-	-	+
8 years	-	-	+	-
9 years	-	-	+ (more posterior and temporal bilaterality)	-
9 years 1 month	-	-	+	+
11 years 6 months	-	-	-	++

The psychogenic stressors are very important in this case what can be considered as already reported by Roubertie et al.[14], as a model of psychogenetic epilepsy. Takahashi et al.[15] reported a patient with videogame-induced partial seizures what he presumes that higher brain functions can be involved in seizure induction. The simple photosensitivity was discarded. Consequently, this syndrome can be a model of epilepsy with reflex seizures based on cognitive stimulus. Our patient has emotional lability and immaturity but not aggressiveness and hyperactivity as mentioned by Roubertie et al.[14]. The hypotonia is less frequently related in the literature[7].

Canevini et al.[9] emphasized special EEG characteristics such as frequent bursts of theta waves sharply contoured and generalized spike waves. Although, Inou et al.[4] consider that the predominance is of paroxysmal high-voltage slow waves with occasional spikes. Canevini et al.[9] believe that the EEG pattern differs according to the vigilance level. Our patient presented these findings in different time of his life, but at the moment, the predominance is of slow waves usually of high voltage and synchronous with and without sharp component mainly in the frontal and front polar area, of long duration and easily diffusible. These findings are seen in the ictal and even interictal periods. These characteristics are emphasized by Kobayashi K.[12]. Maybe these variations are

related to the brain dysmophism and its different brain maturation as demonstrated in our patient.

Our case presents clinical characteristics that differ from the usually described r(20) patients, such as the brain anomalies, usually considered minor or inexistent, but in our case reported as frontal dysplasia[4,5]. These predominantly frontal anomalies are compatible with partial epilepsy conducting until complex partial seizures as proposed by Roubertie et al.[14]. The severity of the clinical expression could be related to the size of the deletion in the telomeric regions of chromosome 20, as supposed by Serrano-Castro et al.[5]. It is emphasized that most clinical symptoms, especially epilepsy, are determined by deletions involving the 20q13 region, as reviewed by Roubertie et al.[14] and Serrano-Castro et al.[5]. Furthermore, it has been suggested that the abnormal phenotype, in cases where a small deletion of either short or long arm had presumably occured, as in our example, is caused either by mosaicism or by abnormal behaviour of the ring structure or by both. In our case both conditions were present.

Mental deficiency and epilepsy without important dysmorphies are the hallmark of the ring chromosome 20. However, corpus callosum, uvula, nodule and cerebellum pyramid hypoplasias, besides arachnoid cysts in the occipital region as presented our case could expand the clinical phenotype spectrum of r(20) syndrome. These findings associated to a clear documented natural history of the disease in our patient, especially those related to the epilepsy, were very peculiar. Although, these cases may be underdiagnosed because of the lack of clear phenotypical markers.

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