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Specificity of electroclinical features in the diagnosis of ring chromosome 20

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ABSTRACT

Background: Ring chromosome 20 (R20) syndrome is a chromosomal disorder characterized mainly by drug-resistant frontal lobe seizures, recurrent nonconvulsive status epilepticus (NCSE), and typical EEG features. The aim of this study was to investigate if this triad is common and specific to all patients with R20.
Methods: In this cross-sectional study (from 2000 to 2011), we selected patients who fulfilled at least two out of three criteria: drug-resistant frontal lobe seizures, recurrent NCSE, and characteristic electroencephalography (EEG) features. In all patients, diagnosis was based on karyotype analysis of at least 100 metaphases.
Results: We identified 36 patients who met at least two of the selected criteria: six patients (16.7%) with R20 and 30 (83.3%) without R20 (non-R20). All patients with R20 met all three criteria. Eleven (36.7%) patients without R20, however, also displayed the full triad. In 19 patients without R20 (63.3%), one of the three clinical features was missing: frontal lobe seizures were not resistant to antiepileptic drugs (AED) in four (13.3%), recurrent NCSE was missing in six (20%), and nine (30%) patients did not have typical EEG features. Based on this data, specificity was 63.3%, positive predictive value was 35.3%, and sensitivity and negative predictive values were 100%. Additionally, a review of all publications describing the R20 phenotype revealed that 81.98% of patients with R20 display the full electroclinical triad.
Conclusions: In our study, all patients with R20 displayed the three electroclinical characteristics. This is in line with previous reports (presenting high sensitivity and negative predictive value). However, these features can also be observed in other epilepsies and are not specific to R20. Our findings suggest that in the presence of the full triad of symptoms, karyotype analysis focused on chromosome 20 should be conducted.
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1. Introduction

Ring chromosome 20 (R20) syndrome is a rare chromosomal disease. Its diagnosis depends heavily on the detection of its clinical manifestations. The presence of a ring-shaped chromosome 20, however, is the only requisite condition for an "R20 syndrome" diagnosis. It is usually assumed that this disorder has a distinct electroclinical phenotype [1–5], with the most salient features being refractory seizures with frontal lobe semiology, recurrent nonconvulsive status epilepticus (NCSE), and characteristic EEG alterations. These three electroclinical characteristics have been found repeatedly in patients with this chromosomal disorder and are, therefore, thought to be highly suggestive of R20 syndrome. Their specificity with respect to a differential diagnosis of R20 syndrome with other epilepsies still remains to be determined, however.

Our main objective in this cross-sectional study was to evaluate whether the presence of either two or three main features of this electroclinical triad distinguishes patients with R20 syndrome from patients with other types of epilepsy, which may share a similar phenotype. We have also reviewed all R20 cases described in the literature with an emphasis on the degree of compliance with the electroclinical triad.

2. Methods

2.1. Patient selection

Between the years 2000 and 2011, we identified six patients in Hospital Ruber Internacional and Hospital Niño Jesus with R20 syndrome. In the same time period, 30 consecutive patients fulfilling

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either two or three features of the electroclinical triad described, prior to the assessment in our clinic, but without a chromosomal disorder were recruited as controls. All patients underwent 24-hour video-EEG or longer, always including at least one night of spontaneous sleep and wakefulness. Only patients with seizure onset before the age of 21 years were included; this age range was selected because it is the latest epilepsy onset in R20 described in the existing literature [2].

The main features that characterize the electroclinical triad are detailed as follows:

a) Refractory frontal lobe seizures: Based on previous reports [2–4,6], three types of frontal lobe seizure were included. *Nocturnal seizures* (hyperkinetic or hypermotor seizures) are characterized by waking up, staring, mild tonic stiffening evolving to clonic movements of the face and extremities, followed by agitation and confusion. *Subtle nocturnal seizures* are expressed as minimal motor activity, such as subtle stretching, turning, or rubbing movements. *Unresponsiveness* (complex partial or automotor seizures) consists of blank staring and confusion, with or without oral or motor automatisms, frightened expression, and focal motor symptoms including head turning.
b) Recurrent NCSE: For operational purposes, patients with at least three episodes of NCSE were included. Clinical semiology during NCSE consisted of altered state of vigilance, staring, loss of emotional facial expression, reduced spontaneous motor activity, and speech production, with a slow response to questions. Associated motor symptoms, such as myoclonus, head turning were also common, as well as oral automatisms and frightened facial expression [2,4,6]. There is controversy as to whether clusters of seizures with mild impairment of consciousness and NCSE can be considered the same phenomena in R20, as very often it is difficult to distinguish them on clinical grounds. This is due to the slow onset and finalization of some frontal lobe seizures or atypical absence seizures, and the persistence of subtle manifestations between more prominent episodes in this group of patients. Because of this, and in line with other studies, we included both patients with clear-cut NCSE and seizure clusters with this type of phenomenology.
c) Typical EEG findings: According to previous reports [1,3,7–9], we selected patients who had the following patterns: brief frontal epileptic discharges and long-lasting high-voltage slow waves with occasional uni- or bilateral frontal spikes. Frequent trains of theta waves in frontotemporal areas that are not influenced by eye-opening, a pattern that has been considered very specific in the diagnosis of R20 [10], were present in all patients with R20, but not required to be present in patients without R20 in our study (Fig. 1).

2.2. Cytogenetic studies

Karyotype analysis was performed on lymphocytes. Blood was drawn into lithium heparin tubes, cultured in Lymphochrome (BioWhittaker™) medium for 72 h, and processed under standard conditions for T-G banding. For each patient, at least 100 metaphases were analyzed for the presence of ring chromosome 20.

2.3. Neuroimaging

All patients underwent a 1.5 T brain MRI. For the purpose of this study, we excluded patients with structural abnormalities depicted by the MRI that were considered to be the cause of their epilepsy. No structural abnormalities were observed in patients with R20.

2.4. Evaluation of cognitive status

To evaluate cognitive status, we used the Wechsler Adult Intelligent Scale (WAIS).

2.5. Literature search methods

To check the presence of the triad in the R20 cases published, a systematic search of the medical literature between 1978 and January 2015 was performed using the PubMed and MEDLINE databases. Search terms included ring chromosome 20, ring 20 epilepsy, and ring-20 syndrome.

2.6. Statistical analysis

Descriptive statistics were provided on demographic and clinical characteristics for both patients with R20 and patients without R20. Patients without R20 without the triad were considered *True negative* (TN); patients without R20 with the triad were *False positive* (FP); patients with R20 with the triad were *True positive* (TP); and patients with R20 without triad were *False negative* (FN). Descriptive statistics were calculated for the triad and the validation of instruments based on our series: *Specificity* [TP / TP + FP], *sensitivity* [TP / TP + FN], *positive predictive value* [TP / FP + TP], and *negative predictive value* [TN / TN + FN]. To expand on this data, we reviewed all the literature to identify the *true positive* (R20 with triad) and *false negative rate* (R20 without triad).

3. Results

3.1. Our sample of patients

Thirty-six patients who fulfilled at least two of the three electroclinical characteristics were recruited from the epilepsy clinic of Hospital Ruber Internacional. These included six patients with confirmed cytogenetic diagnoses of R20 syndrome. Clinical features of patients with R20 are shown in Table 1.

Comparing both groups, we observed some differences, although not statistically significant, which are detailed as follows: patients with R20 had a later age of epilepsy onset, and lower rate of convulsive status epilepticus and dysmorphic craniofacial features. Febrile seizures were not present in any of the six patients with R20, but were present in 16.7% of patients in the group without R20. Cognitive impairment, behavioral disturbances, and family history of epilepsy were similar in both groups (Table 2).

3.1.1. Specificity of the electroclinical triad

Seventeen out of 36 (47.2%) fulfilled the three criteria, 6/6 patients with R20 syndrome and 11/30 patients without R20 (36.7%) ($p < 0,05$). In 19 patients without R20 (63.3%), one feature was missing, nine (30%) did not have the typical EEG features, four of them (13.3%) had frontal seizures controlled with medication, and six (20%) did not have recurrent NCSE. Based on our results and according to the statistical methods previously described, the specificity of this triad for the diagnosis of R20 is 63.3%, its positive predictive value is 35.3%, while the sensitivity and negative predictive values are 100%.

3.1.2. Epilepsy syndromes in patients without R20

The group without R20 included eleven patients (36.7%) with cryptogenic frontal lobe epilepsy (3/11 with the full triad) and 19 (63.3%) with other epilepsy syndromes (8/19 with the full triad). Epilepsy syndromes in the eleven patients who had the full triad (3 + 8) are specified in Table 3.

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