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Low frequency mu-like activity characterizes cortical rhythms in epilepsy due to ring chromosome 20

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HIGHLIGHTS

- A reliable 3–7 Hz cortical rhythm has been found in ring chromosome 20 patients arising from the sensory-motor system.
- Spectral features and spatial localization of the ring 20 cortical activity suggest a parallelism with the mu rhythm.
- Our methodological approach could be applied to other homogenous population of epileptic patients in order to reveal their peculiar electrical features and hence the network involved.

ABSTRACT

Objectives: To evaluate the spectral and spatial features of the cortical rhythms in patients affected by ring chromosome 20 – [r(20)]-syndrome.
Methods: Twelve patients with [r(20)] syndrome were studied. As controls we enrolled 12 patients with idiopathic generalized epilepsy (IGE) and 12 healthy volunteers (HV). Blind source separation, spectral analyses and source reconstruction were applied in all cases in order to identify reliable spatio-temporal patterns of cortical activity.
Results: A theta–delta EEG rhythm was identified in [r(20)] patients, with spectral peak ranging between 3 and 7 Hz and whose generators mapped over the sensory-motor cortices. A second peak laying at a frequency about double with respect to the first one was present in 6 cases. Analogue methodological approach in HV and IGE groups failed to show similar findings.
Conclusions: EEG of [r(20)] patients reveals the existence of a highly reproducible EEG pattern arising from the sensory-motor system.
Significance: The recognition of this peculiar EEG pattern could help the diagnostic work-up. Additionally, our findings supports the existence of a parallelism between this EEG trait and the physiological "mu" rhythm which is generate by the sensory-motor system. Such link suggests a sensory-motor system dysfunction in [r(20)] patients.

1. Introduction

The ring chromosome 20 – [r(20)]-syndrome is a chromosomal disorder in which epilepsy could be the only manifestation of the chromosomal anomaly, presenting as refractory partial seizures, often with semiology of nocturnal frontal lobe seizures and Non-Convulsive Status Epilepticus (NCSE) (Inoue et al., 1997).

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Mild-to-severe mental impairment has been reported whereas dysmorphic signs are exceptional (Canevini et al., 1998). Since its first description in 1976 (Borgaonkar et al., 1976), nearly 100 cases have been reported in the literature (Daber et al., 2012), mostly with intractable epilepsy, variable cognitive impairment and/or behavioral problems (Inoue et al., 1997; Canevini et al., 1998; Augustijn et al., 2001; Biraben et al., 2004; Vignoli et al., 2009; Elens et al., 2012; Radhakrishnan et al., 2012). A reassessment of the published cases with [r(20)] syndrome indicates that the development is generally normal or mildly delayed but it is followed by cognitive and behavioral decline after seizure onset, suggesting this syndrome to be considered as an epileptic encephalopathy (Vignoli et al., 2009; Daber et al., 2012).

The lack of dysmorphic abnormalities leads to delayed syndrome recognition and patients are often subjected to unnecessary investigations until the diagnosis with chromosomal testing has been made (Inoue et al., 1997; Ville et al., 2006). This epilepsy condition is then under-diagnosed and the real prevalence is not known. From this point of view clinical or electroencephalographic marker of this disorder could help in prompting the correct diagnosis.

The electro-clinical pattern observed in [r(20)] strongly suggests the involvement of the frontal lobes networks in the generation of ictal and interictal activities. The EEG features of [r(20)] syndrome consisted of runs of long-lasting, bilateral, paroxysmal high voltage slow waves with occasional spikes over the frontal areas. Ictal EEG show bursts of diffuse – frontally predominant – fast activities associated with clinical signs typically reported in frontal lobe seizures (Augustijn et al., 2001; Vignoli et al., 2009). The involvement of the frontal cortex in seizure generation in [r(20)] syndrome has been demonstrated by a recent MEG work that localized the source of ictal activity in the medial frontal lobe (Supplementary Motor Area) (Tanaka et al., 2004), while a PET study demonstrated a rolandic hypo-perfusion during burst of diffuse interictal slow waves (Elens et al., 2012).

Since one of the typical clinical features of the syndrome is the presentation with prolonged episodes of NCSE, a dysfunction in "seizures control systems" has been proposed and attention has been pointed to investigate the role of sub-cortical structures in this syndrome. Notably, interictal PET and SPECT studies revealed a dopaminergic dysfunction in the nigro-striatal system that could have a role in the genesis and maintenance of prolonged seizures and NCSE in [r(20)] (Biraben et al., 2004; Bouilleret et al., 2005). In accordance with, and extending these interictal findings, we recently demonstrated by means of EEG-fMRI the involvement of the nigro-striatal system and of the fronto-opercular cortex during brief ictal discharges in a patient with [r(20)] syndrome (Meletti et al., 2012).

All these elements suggest that a complex subcortical – frontal lobe network is involved in generating the seizures in [r(20)] syndrome rather than a localized frontal cortical area (Vignoli et al., 2009).

Beyond ictal EEG patterns, Canevini and colleagues reported (1998) three patients with [r(20)] who shown an apparently interictal EEG pattern constituted by trains of continuous theta–delta waves, with a peak frequency of 5 Hz (range between 3 and 7 Hz). This EEG pattern was not influenced by eyes opening or closing; it was not associated with modification of consciousness or by the injection of diazepam. This activity was located over the fronto-temporal leads and was accompanied by a normal alpha background. The complete absence of clinical signs have led the authors to hypothesize a non-epileptic nature of this peculiar activity which might resemble a "non-epileptiform" rhythm of uncertain significance. Although recognized by other studies (Inoue et al., 1997; Kobayashi et al., 1998; Daber et al., 2012), this EEG pattern has not been systematically investigated so far and dedicated EEG analysis are lacking.

In this work we report the interictal, resting state, EEG features of a population of [r(20)] patients focusing on the sub-continuous theta–delta rhythmic activity that has been described in previous reports. Thank to advanced EEG analysis approach we analyzed the morphology, frequency spectrum and source localization of this activity. We analyzed with the same methodology the presence of this peculiar rhythm in a sample of normal subjects and patients with idiopathic generalized epilepsies (IGE), as control groups. We will demonstrate this patter as highly reproducible in

Table 1
Clinical and genetic features of [r(20)] patients.

	Sex/Age at study (years)	Age at diagnosis (years)	FH	Dysmorphisms	Behavioural problems	IQ	sMRI	Genetics % r(20) mosaicism
Pt1	M/38	21	NR	Absent	Absent	130	N	8% Lymphocytes
Pt2	F/17	10	NR	Absent	Present	80	N	42% Lymphocytes
Pt3	F/17	12	NR	Absent	Present	73	N	7% Lymphocytes
Pt4	M/34	17	NR	Absent	Present	60	N	71% Lymphocytes
Pt5	F/63	44	NR	Absent	Absent	83	N	9% Lymphocytes
Pt6	F/18	9	NR	Sparse teeth	Present	74	N	40% Lymphocytes
Pt7	F/20	14	NR	Absent	Present	80	N	34% Lymphocytes
Pt8	F/45	17	NR	Absent	Present	70	N	15% Lymphocytes
Pt9	F/17	12	NR	Absent	Absent	90	N	24% Lymphocytes
Pt10	F/14	9	NR	Absent	Present	79	N	60% Lymphocytes
Pt11	F/7	Prenatal epoch	NR	Frontal bossing, inner; epicanthal folds and low nasal bridge	Absent	111	N	30% Lymphocytes
Pt12	M/12	12	NR	Absent	Present	84	N	55% Lymphocytes

M: male; F: female; FH: familiar history; IQ: intelligence quotient; sMRI: structural MRI; NR: not reported; N: normal.