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Epilepsy in ring chromosome 20 syndrome

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ABSTRACT

Objective: Ring chromosome 20 syndrome is characterized by severe, drug resistant childhood onset epilepsy, often accompanied by cognitive impairment. We characterized the electro-clinical phenotype and the long-term course of epilepsy in a large series.
Methods: We reviewed the electro-clinical phenotype of 25 patients (aged 8–59 years), and assessed the relationship between epilepsy severity and clinical and/or genetic variables. We also searched for reports of patients diagnosed with r(20) syndrome in the literature, included those whose clinical information was sufficiently accurate, and compared their clinical features with the ones of our patients.
Results: Epilepsy exhibited an age dependent course. When seizure onset occurred in childhood (21 patients), terrifying hallucinations associated with focal motor seizures, often sleep-related (8 patients), or dyscognitive seizures (13 patients), were prominent features, often evolving into epileptic encephalopathy associated with non-convulsive status epilepticus (11 patients). In the long-term, progressive stabilization of drug resistant epilepsy associated with non-convulsive status epilepticus, focal seizures with motor and autonomic features, and eyelid myoclonia were noticed. Epilepsy onset in adolescence (3 patients) was accompanied by a milder developmental course, dyscognitive seizures and non-convulsive status epilepticus, and no cognitive decline. Only three older patients became seizure free (>5 years) We found statistically significant correlations between age at epilepsy onset and cognitive level. Although in the study cohort the relationship between r(20) ratio, age at epilepsy onset and cognitive level was non-statistically significant, it reached significance evaluating the larger cohort of patients previously published.
Significance: In ring(20) syndrome, epilepsy has an age dependent course and a worse outcome when age at seizure onset is earlier. The r(20) ratio and severity of cognitive impairment appear to be directly related to each other and inversely correlated with the age at epilepsy onset.

1. Introduction

Ring chromosome 20 [r(20)] syndrome is characterized by a distinct electro-clinical phenotype consisting of focal seizures and non-convulsive status epilepticus (NCSE), cognitive impairment, behavioral problems, and absence of a consistent pattern of dysmorphic features. Diagnosis is made through karyotype analysis, usually with high cell count, since most patients are mosaic for the ring chromosome (Daber et al., 2012).

NCSE is a key feature of the syndrome, characterized by prolonged and frequent confusional episodes, associated with clouding of consciousness of fluctuating severity, muteness, inattentiveness and slowness of response and behavior (Inoue et al., 1997). In older

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patients prolonged NCSE episodes can be associated with rhythmic myoclonia involving the perioral region (Petit et al., 1999) or the eyelids (Inoue et al., 1997; Vignoli et al., 2009). The ictal EEG pattern of NCSE in [r(20)] is characterized by long-lasting, bilateral, paroxysmal high voltage slow waves with spikes over the frontal areas, frequently associated with NCSE (Inoue et al., 1997; Petit et al., 1999; Locharernkul et al., 2005).

Frequent NCSE episodes in this syndrome might be related to deregulation of the system(s) involved in seizure initiation and termination. Deficit of striatal dopaminergic activity has been demonstrated using PET (Biraben et al., 2004) and SPECT (Del Sole et al., 2010), while f-MRI studies showed that the cortical-subcortical network plays a crucial role in the type of epilepsy manifested by the patients (Meletti et al., 2012; Vaudano et al., 2014a).

Brief motor seizures consistent with frontal lobe origin can be observed while awake and during sleep, whose ictal pattern has been described as diffuse attenuation and low-voltage fast activity, evolving into high-voltage rhythmic slow waves over the frontal regions (Kobayashi et al., 1998; Augustijn et al., 2001; Ville et al., 2006; Zambrelli et al., 2013). Even ictal bursts of diffuse – frontally predominant – fast (beta) activities associated with subtle nocturnal seizures have been reported (Augustijn et al., 2001).

Dyscognitive seizures with impaired responsiveness, staring and complex gestural automatisms, as well as generalized convulsions, have all been described in r(20) syndrome (Holopainen et al., 1994; Locharernkul et al., 2005; Herrgård et al., 2007; Conlin et al., 2011; Elens et al., 2012). A few patients were classified as having Lennox-Gastaut syndrome (Chawla et al., 2002; Alpam et al., 2005; Radhakrishnan et al., 2012).

Children with r(20) syndrome can exhibit attacks of sudden fear and terrifying hallucinations as early clinical signs (Chawla et al., 2002; Alpam et al., 2005; Radhakrishnan et al., 2012).

The inter-ictal electroencephalographic (EEG) background may be normal or may exhibit mild slowing or bursts of sharply contoured theta activity, with a peak frequency of 5 Hz (Canevini et al., 1998). Avanzini et al. (2014) recently studied this EEG rhythm applying spectral and source localization analysis and mapped its generators over the fronto-parietal cortices.

According to the evolving concept of Epileptic Encephalopathy (EE) (Avanzini et al., 2013), mosaic r(20) syndrome falls within this definition, since children carrying the r(20) anomaly are consistently reported to be cognitively and behaviorally normal before epilepsy onset, and can experience dramatic cognitive decline and severe drug resistant seizures soon after onset (Vignoli et al., 2009).

The pathogenic mechanism underlying the seizure disorder in r(20) syndrome remains unknown, and the relationship between the percentage of mosaicism and the manifested phenotype is debated, Recent studies that applied array-CGH (Giardino et al., 2010) and SNP-array analysis (Conlin et al., 2011) failed to detect deletions on the ring chromosome, but revealed that higher percentages of r(20) chromosome cells are related to an earlier age at seizure onset, with resistance to antiepileptic drugs and major behavioral problems.

To date, roughly 150 individuals with r(20) syndrome have been reported worldwide. However, seizure semiology and the age-dependent course of epilepsy have not been fully described yet.

We describe the electro-clinical features of 25 patients with r(20) syndrome followed at six Epilepsy Centers. The aim of our study was to better characterize the electro-clinical phenotype associated with r(20) syndrome to provide clues for an earlier diagnosis, facilitate the identification of more patients, and elucidate the long-term course of epilepsy. We also compared the clinical epilepsy features and cognitive and behavioral phenotype of our sample with literature data.

2. Methods

2.1. Patients and methods

We retrospectively analyzed the clinical and video-EEG data of 25 patients with r(20) syndrome with a minimum follow-up of 2 years, evaluated at six Italian Epilepsy Centers involved in this study from 1997 to January 2015.

Informed consent was obtained from the participating subjects and/or their parents. The procedures were performed in accordance with the institutional guidelines of the recruiting centers and local Ethic Committees.

We collected epilepsy history, with details of seizure semiology (according to ILAE 2010), severity, triggering factors, AED history and response. NCSE was defined as a persistent change in behavior and or mental processes from baseline associated with continuous epileptiform EEG changes but without major motor signs. For all patients we recorded data on cognitive and psychomotor development, brain magnetic resonance imaging (MRI), and neurological examination. Cognitive ability was assessed through neuropsychological testing (WISC-III Intelligence Scale for pediatric age and WAIS Intelligence Scale for adult age) in 18 patients, and using adaptive behavior criteria based on parental description in the remaining seven. Borderline intellectual functioning was defined by the DSM IV as an IQ range that is between one to two standard deviations below the mean ($71 < IQ < 84$). We performed several video-EEG (VEEG) monitoring during wakefulness and sleep, including ictal and inter-ictal recordings, for each patient. All VEEGS have been reviewed and visually analyzed and main electro-clinical patterns have been taken into account.

We also recorded phenotypic manifestations of r(20) syndrome for each patient, including growth parameters, facial dysmorphisms, major anomalies, pigmentation anomalies and comorbidities.

Cytogenetic analysis was performed using Q banding on lymphocytes from each proband and their parents, when available. Conventional protocols were used to set up the cultures and chromosome preparations. Because of possible chromosomal mosaicism, metaphase count was extended to at least 100 cells for all patients (Giardino et al., 2010).

Our cohort includes 14 previously reported patients (Canevini et al., 1998; Vignoli et al., 2009; Giardino et al., 2010; Vaudano et al., 2014a), in whom we further defined seizure semiology and epilepsy course by reviewing the available ictal video-EEG recordings and follow-up data.

We searched for reports of patients diagnosed with r(20) syndrome through an electronic search on Pubmed using the search terms: ring 20 chromosome syndrome, ring 20 epilepsy, ring 20 seizure. We included in this study only the previously published patients, whose clinical information was sufficiently detailed ($N = 78$) (Supplementary material 1), and compared their clinical features with the ones of our patients.

2.2. Statistical analysis

Clinical, EEG and genetic data were transferred into an electronic database, located at the Epilepsy Center of San Paolo Hospital in Milan, and processed using the Statistical Package for the Social Sciences (SPSS, IBM, Chicago, IL, U.S.A.) for Macintosh, version 21.0.

Socio-demographic and clinical characteristics of our patients and those previously published were compared using chi-square test for categorized variables not normally distributed, and vari-