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Review

Emerging neuroimaging contribution to the diagnosis and management of the ring chromosome 20 syndrome

Anna Elisabetta Vaudano [a,b], Andrea Ruggieri [a], Aglaia Vignoli [c], Maria Paola Canevini [c], Stefano Meletti [a,b,*]

[a] Department of Biomedical, Metabolic, and Neural Science, University of Modena and Reggio Emilia, Modena, Italy
[b] N.O.C.S.A.E. Hospital, ASL Modena, Italy
[c] Department of Health Sciences, Epilepsy Centre, San Paolo Hospital, University of Milan, Italy

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ABSTRACT

Ring chromosome 20 [r(20)] syndrome is an underdiagnosed chromosomal anomaly characterized by severe epilepsy, behavioral problems, and mild-to-moderate cognitive deficits. Since the cognitive and behavioral decline follows seizure onset, this syndrome has been proposed as an epileptic encephalopathy (EE). The recent overwhelming development of advanced neuroimaging techniques has opened a new era in the investigation of the brain networks subserving the EEs. In particular, functional neuroimaging tools are well suited to show alterations related to epileptiform discharges at the network level and to build hypotheses about the mechanisms underlying the cognitive disruption observed in these conditions. This paper reviews the brain circuits and their disruption as revealed by functional neuroimaging studies in patients with [r(20)] syndrome. It discusses the clinical consequences of the neuroimaging findings on the management of patients with [r(20)] syndrome, including their impact to an earlier diagnosis of this disorder. Based on the available lines of evidences, [r(20)] syndrome is characterized by interictal and ictal dysfunctions within basal ganglia–prefrontal lobe networks and by long-lasting effects of the peculiar theta–delta rhythm, which represents an EEG marker of the syndrome on integrated brain networks that subserve cognitive functions.

1. Introduction

Ring chromosome 20 [r(20)] syndrome is a rare chromosomal anomaly characterized by severe epilepsy, behavioral problems, and mild-to-moderate cognitive deficits. In most cases, patients' development is normal or mildly delayed, but it is followed by cognitive and behavioral decline after seizure onset [1,2]. Epilepsy, which seems to be a constant finding, arises in childhood or adolescence and becomes refractory to antiepileptic drugs (AEDs) in the majority of the patients [3,4]. Nonconvulsive status epilepticus (NCSE) and brief motor seizures (mainly nocturnal) are among the most common seizure types [3]. Nonconvulsive status epilepticus consists of a prolonged confusional state of varying intensity [2], and it is often associated with EEG changes in the form of long-lasting slow waves with occasional spikes usually predominant over the frontal lobes [4,5]. Other types of seizures include ictal affective behaviors (mainly ictal fear–terror) associated with loss of consciousness, automatisms, or tonic activity [1]. Progressive cognitive delay and behavioral problems are frequently described [6], and the latter occasionally dominates the clinical phenotype [7]. Dysmorphic features are mostly absent or mild, hence making the diagnosis difficult, unless there is a high index of suspicion [2,3,8]. A clue is considered the presence of a typical EEG pattern consisting of long trains of theta–delta waves with sharply contoured or notched appearance, predominant over the frontotemporal regions, and occurring within normal background activity [8].

At the chromosomal level, r(20) chromosome replaces one of the two chromosomes 20 in a percentage of cells, ranging from 1% to 100% of lymphocytes. The relation between the variable mosaicism and the clinical phenotype is still controversial [2,9] although studies have shown that a high degree of mosaicism is associated with earlier age at seizure onset and dysmorphisms [10–12] but not with response to drug treatment [1,3].

Cytogenetic analysis represents the gold standard for the definitive diagnosis, but it is often delayed and not routinely performed [12]. Therefore, [r(20)] syndrome is undoubtedly an underdiagnosed condition, and the real prevalence is not known [13].

To date, the mechanisms that promote ictogenesis and the maintenance of NCSE in this condition are still unknown. The electroclinical pattern strongly suggests the involvement of the frontal lobe networks in the generation of both ictal and interictal activities. Furthermore, since one of the typical clinical features of the syndrome is the presentation with prolonged episodes of NCSE, a dysfunction in "seizure

* Corresponding author at: Department of Biomedical, Metabolic, and Neural Science, University of Modena and Reggio Emilia, Via Giardini 1355, 41126 Modena, Italy. Tel.: +39 0593961676; fax: +39 0593961336.
E-mail address: stefano.meletti@unimore.it (S. Meletti).

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control systems" has been proposed, and attention has been pointed to investigate the role of subcortical structures in this syndrome, especially the basal ganglia circuits [14,15].

In recent years, noninvasive imaging techniques, such as simultaneous recording of functional magnetic resonance imaging with electroencephalogram (EEG–fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), electric source imaging (ESI), and magnetic source imaging (MSI), have proved their usefulness in better defining the epileptic networks in both genetic and acquired epilepsies [16,17]. Furthermore, in epileptic encephalopathies (EEs), recent neurophysiologic and functional neuroimaging lines of evidences have tried to build hypotheses about the mechanisms underlying the cognitive disruption observed in these conditions by linking the neuropsychological abilities, the epileptiform discharges, and the brain networks as revealed by the neuroimaging tools [18,19]. With these aims, functional neuroimaging techniques have been applied to study patients with [r(20)] syndrome. Here, we review the main findings derived from functional neuroimaging studies performed in patients with this chromosomal disorder. Especially, we will focus on the contribution of these techniques to improve the knowledge of the following: (i) the mechanisms underlying ictogenesis in [r(20)] syndrome and (ii) the consequences of epileptic activities on brain networks that subserve normal cognition and behavior. Although limited to a relatively low number of studies, given the rarity of [r(20)] patients, this review evaluates the state of the art of this topic in order to stimulate further investigations in patients with this chromosomal disorder.

2. Methods

2.1. Search methods for identification of studies

Searches were run in the following databases from 1990 to 2014: Embase, MEDLINE, PsychINFO, and PubMed. Searches were limited from 1990 to the present day, as studies carried out prior to this would necessarily have included participants without MRI or other functional/metabolic imaging techniques. The search keywords were as follows: "RING20 syndrome", "[r(20)] syndrome", "Ring Chromosome 20 Syndrome" AND "MRI", "imaging", "positron emission tomography" (or PET), "spectroscopy"(or MRS), "single-photon emission computed tomography" (or SPECT), "simultaneous functional MRI and EEG" (or EEG–fMRI), and "magnetic source imaging" (or MSI). For each citation considered, the abstract was read (when available), and articles were excluded if they were outside the scope of the review. The bibliography of each of the retrieved papers was examined to identify relevant references that could have been missed by electronic search. Only peer-reviewed original articles were accepted for inclusion in the review.

3. Results

Since its first description in 1972 [20–23], nearly 145 patients with [r(20)] syndrome in 67 reports have been described in the literature, most with intractable epilepsy, variable cognitive impairment, and/or behavioral problems. Among these, our electronic literature research revealed 12 studies, for a total of 47 patients, that used advanced morphometric and/or functional neuroimaging techniques to investigate the [r(20)] syndrome (Table 1). Instead of describing the results related to each single methodology independently, we will discuss the neuroimaging findings in relation to the different cerebral structures/networks supposed to be involved in the ictogenesis, seizure maintenance, and cognitive deficits in [r(20)] syndrome based on the electroclinical suggestions. In particular, the following brain structures/networks will be considered: (I) prefrontal cortex; (II) substantia nigra–basal ganglia networks; and (III) cortical networks involved in conscious awareness and attention.

Table 2 reports the main electroclinical and genetic features of the patient included in the present review. The patients' population

Table 1
Neuroimaging studies in [r(20)] patients.

Study	No. of patients	Methods	Main findings (no. of patients)	Correlation between neuroimaging and clinical variables
Inoue et al. [3]	6	SPECT, MEG	*SPECT interictal* (3): F or FT hypoperfusion *SPECT ictal* (2): F hyperperfusion *MEG interictal* (3): F and FT spike dipoles	N/A
da Mota Gomes et al. [24]	1	MRS	*F* and *T MRS*: normal	N/A
Biraben et al. [14]	14	[^{18}F]fluoro-L-DOPA PET, VBM	*PET*: ↓ [^{18}F]fluoro-L-DOPA uptake B Cau and Put *VBM*: normal	No correlation with patients' age, % mosaicism, seizure type.
Tanaka et al. [25]	1	MEG, I^{123}-IMP SPECT	*MEG ictal*: dipole medial F lobe	N/A
Bouilleret et al. [15]	16	[^{18}F]fluoro-L-DOPA PET	*SPECT interictal*: F hypoperfusion *PET*: ↓ [^{18}F]fluoro-L-DOPA uptake B Cau and Put	N/A
Nishiwaki et al. [26]	1	SPECT	*SPECT interictal*: normal	N/A
Jacobs et al. [27]	1	FDG-PET, SPECT	*PET interictal*: diffuse R hypometabolism *SPECT ictal*: R TP hyperperfusion	N/A
Del Sole et al. [28]	5	[^{123}I]ioflupane SPECT [^{123}I]IBZM SPECT	[^{123}I]*ioflupane SPECT*: ↓ DAT expression B Cau and Put	Negative correlation between DATs and seizure frequency and % mosaicism. Positive correlation between D2 receptor density in Put and seizure frequency and % mosaicism.
Elens et al. [9]	6	FDG-PET, SPECT	*FDG-PET interictal* (1): F hypometabolism *SPECT interictal* (3): bilateral FT hypoperfusion	N/A
Meletti et al. [29]	1	EEG–fMRI	*Ictal EEG–fMRI*: ↑ BOLD preF, Op-I, SM, Cau, and SN	N/A
Avanzini et al. [30]	12	ICA analysis and ESI	*Interictal theta–delta rhythm ESI*(12): B SM	No correlation between theta–delta activity density and % mosaicism.
Vaudano et al. [31]	11	EEG–fMRI	*Interictal theta–delta rhythm EEG–fMRI* (7): ↑ BOLD TP junction, O and SM, ↓ BOLD DAN and DMN *Ictal EEG–fMRI* (2): ↑ early BOLD preF *Group analysis EEG–fMRI* (11): ↑ BOLD B TP junction	Positive correlation between the R TP junction BOLD changes and % mosaicism

↑: increase; ↓: decrease; B: bilateral; BOLD: blood oxygen level-dependent; Cau: caudate; DAN: dorsal attentional network; DMN: default mode network; FDG: fluorodeoxyglucose; hSW: high-amplitude frontally predominant spikes and slow waves, sharp waves; I^{123}-IMP: N-isopropyl-p-[I123] iodoamphetamine; [123]IBZM: iodobenzamide; ESI: electrical source imaging; ICA: indipendent component analysis; preF: prefrontal cortex; F: frontal; FT: frontotemporal; MEG: magnetoencephalography; MRS: magnetic resonance spectroscopy; O: occipital cortex; Op-I: opercular–insular cortex; PET: positron emission tomography; Put: putamen; T: temporal; TP: temporoparietal; R: right; SM: sensory-motor cortex; SN: substantia nigra; SPECT: single-photon emission computed tomography; Th:thalamus; N/A: not available; SN: substantia nigra; VBM: voxel-based morphometry.