CASE REPORT
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Ring chromosome 20: a further contribution to the delineation of epileptic phenotype

Ring hromozom 20: doprinos boljem sagledavanju karakteristika epileptičnog fenotipa

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Abstract

Introduction. Ring chromosome 20 [r(20)] syndrome is a rare genetic abnormality where two arms of the 20th chromosome fuse forming a ring chromosome, resulting in intractable epilepsy and wide range of behavioral problems and cognitive deficits. **Case report.** We presented four patients with r (20) syndrome diagnosed between the years 2000–2018. In all patients we analyzed clinical epilepsy features (seizure semiology, seizure frequency/drug response, the presence of nonconvulsive status epilepticus), cognitive status and the phenotype characteristics. The average age of epilepsy onset was 6 years. All four patients had nocturnal epileptic events and normal brain magnetic resonance (MR) imaging. Dysmorphism was present in two children, behavioral problems also in two children and intellectual disabilities were observed in three children. R(20) syndrome mosaicism ranged between 17% and 83% of blood lymphocytes. **Conclusion.** Despite the small size of our group, we think that our findings have clinical relevance. Refractory childhood onset epilepsy and especially the occurrence of nocturnal epileptic events should help physicians to recognize this chromosomopathy. Routine karyotyping can be employed to identify the patients easily.

Key words:
chromosome aberrations; clinical medicine; cognitive dysfunction; drug resistant epilepsy; ring chromosome 20 syndrome; drug therapy.

Apstrakt

Uvod. Sindrom prstenastog hromozoma 20 (r20) je veoma retka genetička abnormalnost, gde se dva kraka 20. hromozoma spajaju i formiraju prstenasti hromozom, što dovodi do farmakorezistentne epilepsije i širokog spektra poremećaja u ponašanju i kognitivnog deficita. **Prikaz bolesnika.** Prikazana su četiri bolesnika sa r(20) sindromom dijagnostikovanim između 2000. i 2018. godine. Kod svih bolesnika su analizirane kliničke karakteristike epileptičkih napada (semiologija napada, njihova učestalost/odgovor na terapiju, prisustvo nekonvulzivnog epileptičnog statusa), kognitivni status i fenotipske karakteristike. Napadi su se u proseku javljali u uzrastu od 6 godina. Sva četiri bolesnika su imala suptilne noćne napade i normalne nalaze magnetne rezonance (MR) mozga. Dismorfizmi su bili prisutni kod dva deteta, problemi u ponašanju kod dva deteta, a kognitivni deficit kod tri deteta. Hromozomski mozaicizam r(20) kretao se između 17% i 83% limfocita krvi. **Zaključak.** Uprkos malom broju ispitanika, smatramo da dobijeni rezultati imaju klinički značaj. Farmakorezistentna epilepsija sa početkom u dečjem uzrastu i posebno pojava noćnih napada je karakteristična za sindrom prstenastog hromozoma 20, a može se jednostavno dijagnostikovati analizom kariotipa.

Ključne reči:
hromozomi, aberacije; medicina, klinička; saznanje, poremećaji; epilepsija, farmakorezistentna; ring hromozom 20 sindrom; lečenje lekovima.

Introduction

Ring chromosome 20 [r(20)] syndrome is a rare genetic abnormality that occurs in about 1/30,000 to 1/60,000 living births [1]. It was described for the first time in 1972 by Atkins et al. [2], with roughly 150 individuals reported worldwide [2–4]. It is hypothesized that telomere regions of the short arm 20p13, and long arm 20q13.3, fuse to form the ring chromosome [3, 4]. During this fusion, inversions, mutations, deletions and duplications can happen, which result in intractable epilepsy and a wide range of behavioral problems and cognitive deficits, while dys

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morphic signs are not significant [1]. The 20q13.3. locus contains at least two channel genes that have been related to epilepsy. The first one is CHRNA4 (nicotinic acetylcholine receptor) that has been related to autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). The second gene is potassium channel gene KCNQ2, which is responsible for benign familiar neonatal epilepsy (BFNE) [5, 6]. However, ADNFLE and BFNE manifest with a clearly different clinical presentation, suggesting pathogenetic mechanism whose contributions likely differ in r(20) syndrome [7].

The main concern, considering this diagnosis in a patient with epilepsy occurring in childhood or adolescence, is associated with the changes in intellectual capacities and behavior, because early diagnosis could help with adequate treatment. The ring abnormality may be seen in as few as 10% of all cells and therefore cytogenetic analysis for chromosomal mosaicism is crucial for the diagnosis. It has been recommended to use standard metaphase chromosome analysis, examining at least 50 cells to properly detect mosaicism [8].

We presented four patients with the genetically confirmed diagnosis of r(20) with intent to analyze clinical parameters (sex, the age at the onset of epilepsy and the age of confirmed diagnosis, family history, the presence of dysmorphism, behavioral problems, intellectual functioning, brain magnetic resonance imaging (MRI) results, genetic findings), including clinical epilepsy features [presence of nonconvulsive status epilepticus (NCSE), seizure type and frequency], antiepileptic therapy and the refractory nature of epilepsy in patients with genetically confirmed diagnosis of r(20).

Case report

Four patients (1 male, 3 females, mean age 13 years – range from 9 to 18 years) were presented with the diagnosis of r(20) syndrome at ages 7–12. All patients had refractory epilepsy and were clinically evaluated and treated at the Clinic for Neurology and Psychiatry for Children and Youth, Belgrade, between the years 2000–2018. The electroencephalography (EEG) pattern demonstrated long-lasting, bilateral, paroxysmal high-voltage slow waves, with occasional spikes over the frontal/temporal lobes lasting for several minutes interictally or during the seizures in all patients. Karyotyping was done at University Children's Hospital-Tiršova in Belgrade. They were diagnosed by cytogenetic analysis, which was performed using G-banding on lymphocytes from each proband. 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.

In all patients, we analyzed the following parameters: sex and age of patients (years), age at seizure onset (years) and age at confirmed diagnosis of r(20) (years). Also, we evaluated the family history, the presence of dysmorphism, behavioral problems and intellectual disability [intelligence quotient (IQ) < 71]. Structural brain MRI was done and analyzed in all patients. Genetic analysis and the degree of mosaicism ranging from 1–100% of lymphocytes were evaluated in all patients, too.

We also analyzed the presenting epileptic phenotype: the presence of NCSE, seizure features and frequency, antiepileptic therapy and the refractory nature of epilepsy.

The average age of epilepsy onset was 6 years (range from 4.5 to 7 years) and the final diagnosis was made from the age of 7 to 12 years. Family history was negative pointing to a genetic syndrome. Dysmorphisms were present in two subjects (mild facial abnormalities in both) and growth failure in one, whereas behavioral problems (attention deficit and irritability) were identified in two subjects. Intellectual disabilities were observed in three subjects and absent in one. The child with normal intellectual functioning is attending regular school, while the other three require personal supervision. Brain MRIs were performed in all subjects, and were normal. Karyotype analysis in all the patients confirmed the presence of r(20) chromosomal abnormality with different percentage of mosaicism ranging between 17% and 83% of blood lymphocytes (Table 1, Figure 1).

NCSE was present in two patients. Nocturnal epileptic events were observed in all our patients, while tonic-clonic seizures and convulsive status epilepticus occurred in two patients (Figure 2). After confirming the diagnosis of epilepsy, all the patients were on multiple antiepileptic drugs in mono-and polytherapy. Seizures were drug-resistant and all patients experienced frequent (daily and weekly) seizures, in spite of the therapy with many antiepileptic drugs: carbamazepine, clobazam, lamotrigine, levetiracetam, lacosamide,

Table 1

Clinical and genetic features of ring chromosome 20 [r(20)] patients

Patient	Sex/Age at the study (years)	Epilepsy onset age (years)	Age at diagnosis (years)	FH	Dysmorphisms	Behavioral problems	Intellectual disability	MRI	r (20) mosaicism (% of blood lymphocytes)
1	F/9	4.5	7.5	NR	+ mild facial, growth failure	-	yes	N	17
2	F/13	5	11	NR	-	-	yes	N	68
3	M/11	7	7	NR	-	+ attention deficit	no	N	48
4	F/18	6	12	NR	+ mild facial	+ irritability	yes	N	83

M – male; F – female; FH – family history; MRI – magnetic resonance imaging; NR – not reported; N – normal.

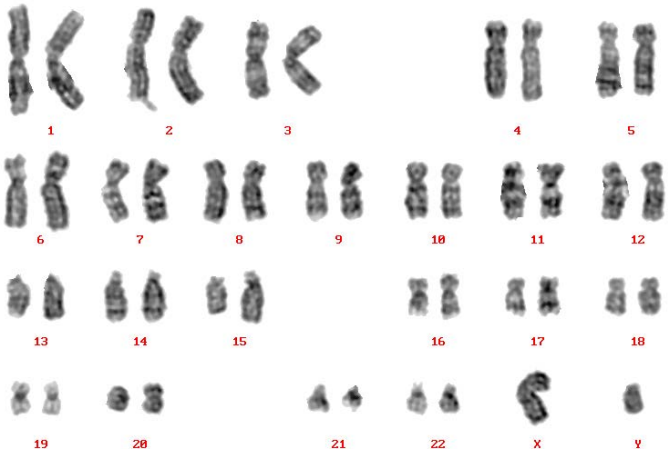


Fig. 1 – Karyotype analysis shows the presence of ring chromosome 20 [r(20)] abnormality.

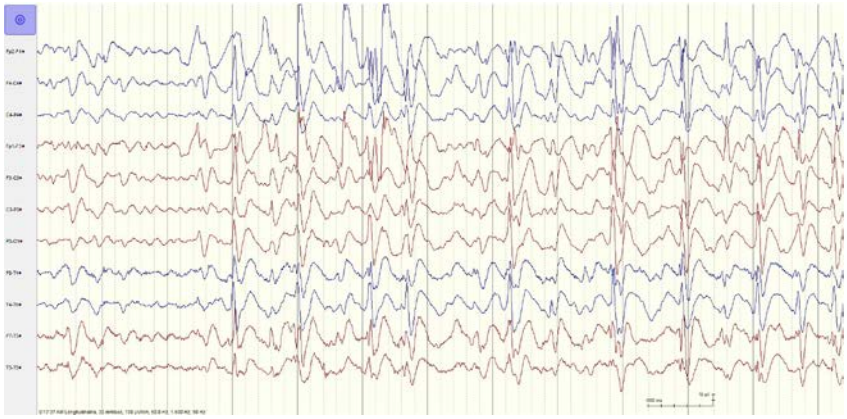


Fig. 2 – Electroencephalography (EEG) finding shows ictal EEG: atypical absence-epileptic status.

Table 2

Epilepsy features of ring chromosome 20 [r(20)] patients

Patient	NCSE	Subtle nocturnal seizures	Tonic-clonic seizures	CSE	Daily seizures	Nocturnal hypermotor seizures	Treatment	
							no improvement	improvement in seizures
1	-	+	-	-	+	+	VPA monotherapy	VPA+LTG ketogenic diet
2	+	+	+	+	+	+	TPM, OXC, VPA, LEV, LCS, PRM ketogenic diet	LTG+ETS, VNS
3	-	+	-	-	+	+	CBZ, LEV, CLB	VPA+LTG ketogenic diet
4	+	+	+	+	+	+	CBZ, VPA, TPM, ketogenic diet	LTG, VNS

NCSE – nonconvulsive status epilepticus; CSE – convulsive status epilepticus; VPA – valproate; LTG – lamotrigine; TPM – topiramate; OXC – oxcarbazepine; LEV – levetiracetam; LCS – lacosamide; PRM – primidon; ETS – ethosuximide; VNS – vagal nerve stimulation; CBZ – carbamazepine; CLB – clobazam.

ethosuximide, topiramate, valproate, oxcarbazepine, primidone. Seizures were worsened by topiramate in two patients and by carbamazepine and levetiracetam also in two patients. An antiepileptic combination therapy which offered both remarkable seizure control and tolerable quality of life was valproate and lamotrigine. In two patients this combination succeeded in reducing the seizure frequency. In one patient lamotrigine monotherapy was effective, and in another one the combination of lamotrigine and ethosuximide. In this way, the most common antiepileptic drug taken was lamotrigine. All patients were also tried on a ketogenic diet, with a significant decrease in seizures in two patients (other two patients showed no improvement on ketogenic diet and it was discontinued). Vagal nerve stimulation succeeded in reducing the seizure frequency in two patients (Table 2).

Discussion

We have described epileptic phenotype of r(20) syndrome in four patients aged 9 to 18 years. All patients with a confirmed cytogenetic diagnosis of r(20) syndrome had drug-resistant frontal lobe seizures, two of them had recurrent NCSE and all patients showed characteristic EEG pattern involving frontotemporal lobes. These three electroclinical characteristics easily recognizable in childhood have been found repeatedly in patients with this chromosomal disorders and are, therefore, thought to be highly suggestive of r(20) syndrome [9–12].

The recurrent NCSE features displayed a prolonged confusional state of varying intensity, staring, a frightened expression and mild gestural automatism, reduced spontaneous motor activity and speech production with slowness of response and befhavior [1, 4, 5]. These features were observed in two patients. Refractory frontal lobe seizures include three types of seizures and were observed in all our patients.

Nocturnal seizures (hypermotor) are manifested 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 stretching, turning of body, or rubbing. We underline the characteristic occurrence of nocturnal subtle seizures, especially in children, which should, in our opinion, be considered highly suspicious of r(20) [9]. Focal impaired awareness seizures consists of dyscognitive symptoms, blank staring, with or without oral or motor automatisms, frightened expression, sometimes evolving to bilateral tonic-clonic seizure, and focal aware seizures with motor symptoms including head turning [10]. The characteristic EEG patterns consists of brief frontal epileptic discharges, long-lasting high-voltage slow waves with occasional spikes usually predominant over the frontal lobes and frequent trains of theta waves in frontotemporal areas [13, 14].

In our study group, the age at the onset of seizures was between 4.5 and 7 years and ictal fear was noticed in all children. The most frequently reported patients' fears concerned animals as insects, spiders and snakes. Consistent with other studies, our data indicate that at epilepsy onset, especially in childhood, patients experience attacks of sudden fear during frontal lobe seizures, which is related to an earlier age at seizure onset [4]. It is a characteristic feature of the syndrome and may be helpful in establishing the diagnosis [4, 9, 15]. It has been confirmed that the fear feeling connected with seizures originates from frontotemporal or frontal lobes. The analysis of intracranial ictal EEGs and observations of clinical manifestations precipitated by electrical stimulation has confirmed that the limbic structures, especially the amygdale, are closely linked to fear [4]. Interictal positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies provided evidence for the participation of subcortical structures and basal ganglia in the control of epileptic seizures in r(20) syndrome [13]. They showed dopaminergic disturbances in the nigrostriatal system that could be related to the genesis and maintenance of prolonged seizures and NCSE in r(20). Furthermore, the involvement of the cortical-subcortical network in epileptic manifestation of patients with r(20) syndrome was revealed by means of ictal EEG-fMRI. Altogether, these data support a hypothesis that a dysfunction of the frontal lobes-basal ganglia network is a key feature of this chromosomal disorder [4, 13].

Concerning dysmorphism, in our series two patients displayed mild facial abnormalities and one patient growth failure. Growth failure is present in all the ring chromosome syndromes and is considered to be a constitutive feature of the majority of chromosomal abbreviations [11]. Mild to moderate cognitive impairment and behavioral problems are very frequent [4, 9]. Three of our patients, however, had cognitive impairment and two of them behavioral difficulties before the onset of epilepsy. This cognitive deficit is associated with the frontal lobe involvement, probably due to epileptiform discharges, cognitive brain network activity and dopaminergic deficits [16].

Because of the wide spectrum of clinical expressions and the rarity of this chromosomal disorder, the time gap from the onset of epilepsy to the diagnosis is usually considerable [11]. For instance, in two patients (patient 2 and 4), six years passed between the onset of epilepsy and the final diagnosis. Most of the patients have a normal brain MRI, as was seen in all our patients [17].

At the chromosomal level, r(20) replaces one of the two chromosome 20 in a percentage of cells, ranging from 1% to 100% of lymphocytes. The relation between the variable mosaicism and the clinical phenotype has been and is still controversial, although the studies have shown that a high degree of mosaicism is associated with the earlier age at the seizure onset, but not with the response to the drug treatment [1, 8]. In our series we did not see a correlation between a high degree of mosaicism compared to the age of seizure onset.

All patients with r(20) in our study group had refractory epilepsy despite multiple antiepileptic drugs tried singly or in combination. According to the results of other studies, the refractory nature of epilepsy in patients with r(20) is a common finding [4]. In all of our patients, lamotrigine was very effective. In two patients, a combination of valproate and lamotrigine allowed better seizure control and this combination is supported in the literature as very effective for treating epilepsy [4, 13]. One patient improved with a combination of lamotrigine and ethosuximide and another patient with lamotrigine as monotherapy. Two patients also improved with vagus nerve stimulation, in line with the previous reports. All patients were treated with a ketogenic diet, resulting in significant improvement in seizure control only in two patients.

In general, the prognosis is showing seizure worsening over a long period of time [11]. The histories of patients 1, 2 and 4 illustrate this unfavorable outcome. There is only one case report with favorable seizure control in patient 3 with the progressive stabilization of refractory epilepsy. He has infrequent seizures on a monthly basis, lives independently

and goes regularly to school, although refractory epilepsy prevents him from certain activities.

Conclusion

Neuroimaging-negative refractory childhood onset epilepsy, accompanied by variable cognitive delay, behavioral problems and the absence of a consistent pattern of dysmorphic features should help physicians to recognize possible genetic disorder. These patients should be referred to genetic counseling, where proper genetic testing will be offered. It is important to reduce a considerable gap between the onset of epilepsy and the diagnosis in these patients, in order to give adequate treatment and avoid long term deterioration in the patients' quality of life. We described the small group of r(20) patients, delineating semiology and age-dependent course of epilepsy. Subtle nocturnal seizures showed better sensitivity than NCSE in diagnosing r(20) syndrome. The disadvantage of that case includes the lack of the possible correlation between a delayed diagnosis and a cognitive outcome, which should be interesting to evaluate in future studies.

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