Epilepsy in Ring Chromosome 20 Syndrome Might Have Variable Clinical Features

Sir,

Ring chromosome 20 [r(20)] syndrome is a rare chromosomal disorder characterized by severe epilepsy, behavioral problems, and mild-to-moderate cognitive deficits. Ring chromosomes have been identified for each of the human chromosomes, and the overall frequency is estimated at 1 in 30,000 to 60,000 births.\(^1\) Ring formation can occur in either the germline or somatic cells resulting from rare intra-chromosomal fusions. The timing of...
this fusion determines the number of cells affected. Here we report two cases of ring chromosome 20 syndrome highlighting the variations in clinical presentations. The heterogeneity in the clinical status is mostly attributed to the degree of mosaicism.

**Case 1**
9 years old boy, with normal birth and development, presented with recurrent staring episodes of about 6 months duration. Then he developed episodes of behavioral arrest with incontinence and generalized tonic-clonic seizures. Electroencephalogram (EEG) showed bilateral epileptiform abnormalities in centro-parieto-temporal regions with secondary generalization. Seizures remained refractory even after multiple antiepileptic drugs (LEV, CBZ, VPA). Cognitive and behavioral dysfunction followed with deterioration in scholastic performance and hyperactivity. He had mild facial dysmorphic features. 24-h video EEG showed multifocal and generalized epileptiform abnormalities along with runs of frontally predominant rhythmic theta waves [Figures 1 and 2]. Magnetic resonance imaging of the brain was normal. Chromosome analysis showed mosaic karyotype with two cell lines, one with normal male karyotype found in 88% of cells, another cell line with ring chromosome 20 found in 12% cells, in which breakage and reunion had occurred at bands p13 and q13.3. The segments distal to these breakpoints were deleted. He had a verbal IQ of 75, a performance IQ of 79 and a full-scale IQ of 77 indicating borderline intelligence. His antiepileptic drugs were optimized with the addition of clobazam. On the last follow-up after 3 years of the first contact, he was seizure-free on AED; had a poor scholastic performance.

**Case 2**
A 7-month-old girl, first born of second degree consanguineous parentage with a normal birth history had her first seizure at 6 months of age. All episodes were stereotyped during sleep with uprolling of eyes and generalized tonic-clonic movements. On examination, she had microcephaly, facial dysmorphism, and severe developmental delay. Interictal EEG showed generalized slow waves, ictal record captured generalized tonic-clonic seizures with diffuse EEG onset, mostly with amplitude maximum over posterior cortex [Figures 3 and 4].

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**Figures 1 and 2:** Case 1: Runs of frontally dominant theta-delta waves along with frontal spikes lasting for prolonged periods (classical pattern of ring chromosome 20 syndrome)
Magnetic resonance imaging showed widened bilateral frontal and anterior temporal subarachnoid CSF spaces with deepened Sylvian fissure. Chromosome analysis showed female karyotype with ring chromosome 20 in all the cell lines (46,XX,r(20)). She remained to have refractory epilepsy with severe developmental disabilities despite treatment with multiple AEDs and ketogenic diet.

Ring chromosome 20 syndrome is characterized by medically intractable focal epilepsy with seizure onset in childhood and an EEG demonstrating long epochs of bilateral high amplitude slow activity with intermixed frontal spikes.[1] Seizures are typically focal with impaired awareness including staring, automatisms, and focal motor symptoms.[2] Patients may describe periods of intense fear and sometimes prolonged states of confusion lasting for minutes to hours (non-convulsive status epileptics). Ictal visual hallucinations have also been described.[3] In addition, subtle nocturnal seizures with behavioral changes such as stretching, rubbing, and turning have been observed which may resemble normal arousal behavior or sometimes mistaken for non-epileptic events.

Seizures are typically difficult to control with antiepileptic medications and patients are many times subjected to epilepsy surgery workup and expensive investigations unless the diagnosis of r(20) has been made.[2] Varying degrees of intellectual impairment and behavioral problems have also been reported. Seizure onset is typically between ages 1 and 24 years, with an average of 7–9 years in mosaic patients and 2.5 years for patients with the ring in all the cell lines.[3] Earlier seizure onset is associated with more severe intellectual impairment.

As the phenotypic spectrum of this syndrome is highly variable as depicted in this case series, karyotyping looking at a minimum of 100 metaphases may be advisable in the initial workup of drug-resistant epilepsies in children, especially if they have some dysmorphic features. Microcephaly, synophrys, dysplastic ears, small mandible, and genital hypoplasia have mostly been reported. The severity of clinical manifestations is almost always associated with the size of the deletion in the telomeric region of chromosome 20 and the degree of mosaicism. Table 1 summarizes the clinical details.
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A wide spectrum of EEG abnormalities is seen in r(20) patients probably depending upon the brain maturation and degree of mosaicism. Moreover, the EEG features are dynamic and may evolve over time in an individual patient. Interictal EEG background may be normal to mildly slow or demonstrate bursts of sharply contoured theta activity. Runs of bi-frontal spike and wave activity have been reported as a distinct pattern in r(20) syndrome.\(^2\) Ictal EEGs may point towards frontal onset with prolonged runs of diffuse slowing with frontal dominance intermixed with bi-frontal sharp wave discharges as seen with non-convulsive status epilepticus.\(^3\). In this series, case 1 had the classical EEG features described in ring 20 syndrome. Interictal SPECT and PET studies have shown, almost homogenously, a decrease in perfusion and metabolism over the bilateral frontal and frontotemporal cortices.\(^4\) Our patients have not undergone functional neuroimaging.

Both clinical and electroencephalographic findings in patients with r(20) syndrome may be confused with other refractory epilepsy syndromes. Lennox-Gastaut syndrome (LGS),

| Table 1: Clinical data (Case 1 and 2) |
|-------------------------------------|
| **Findings**                        | **Patient 1** | **Patient 2** |
| Age/sex                             | 9 years/M     | 7 months/F    |
| Family history of epilepsy          | Absent        | Absent        |
| Parental consanguinity              | Absent        | Present       |
| Age at seizure onset                | 8 years       | 6 months      |
| IQ                                  | 77            | Not done      |
| Dysmorphic Features                 | Synophrys, small posteriorly placed ears | Frontal bossing, epicanthal fold, open mouth, large pinna, microcephaly |
| MRI Brain                           | Normal        | Widened bilateral frontal and anterior temporal sub arachnoids CSF spaces with deepened Sylvian fissure |
| Seizure history                     | GTCS, staring episodes | Focal hypomotor seizures and GTCS |
| Number of AED tried                 | 4             | 5             |
| Current AED                         | VPA, CLB      | LVX, TPM, CLB |
| r(20) Mosaicism in lymphocytes      | 12%           | 100%          |

VPA: Valproate; CLB: Clobazam; LVX: Levetiracetam, TPM: Topiramate

| Table 2: Electro clinical features of r(20) syndrome |
|-----------------------------------------------------|
| **Series**                                           | **Year of publication** | **No. of patients** | **Age at seizure onset** | **Clinical features** | **EEG characteristics** |
| Inoue *et al.*\(^4\)                                 | 1997                    | 6                   | 3-14 years               | Brief and prolonged confusing state, eyelid myoclonia, GTCS, IQ-47-95 | Interictal: Irregular high voltage, slow bilateral/unilateral synchronous and asynchronous spikes Ictal: Focal/diffuse onset with predominant bilateral or frontal evolution |
| Augustijn *et al.*\(^5\)                             | 2001                    | 4                   | 3-11.5 yrs               | CPS, GTCS, NCSE, behavioral problems with learning disability | Interictal: Diffuse slow (maximal frontotemporal) generalized and frontotemporal spikes, no ictal data |
| Ville *et al.*\(^6\)                                 | 2006                    | 6                   | Neonatal; 5-8 years      | Brief hypomotor and prolonged hypomotor CPS, Complex visual Hallucinations, IQ-60-80 | Interictal: intermittent/continuous delta or slow spike-wave discharges (frontally dominant) No ictal data |
| Jacobs *et al.*\(^7\)                               | 2008                    | 1                   | 4 years                  | NCSE, cognitive decline, died with prolonged SE | Interictal: Marked background changes, generalized rhythmic slow waves over frontal areas, very active widespread spike-and-slow wave activity over the right hemisphere. Ictal EEG: Generalized suppression, followed by 2-3 Hz rhythmic slow waves and then by a 1 Hz spike and slow-wave activity over both hemispheres, but again more prominent on the right. |
| Vignoli *et al.*\(^8\)                               | 2009                    | 3                   | 7.5-10 years             | Brief nocturnal hypomotor and prolonged hypomotor CPS with aphasia, night terrors | Interictal: Normal or frontal theta-delta Ictal: Diffuse attenuation or generalized 3 Hz spike-wave discharges (absence status) |
| Elens *et al.*\(^9\)                                | 2012                    | 6                   | 4-16 years               | Nocturnal frontal seizures, atypical absence, drug resistance | Diffuse slow waves and deceleration, frontotemporal spikes, bifrontal high-voltage spike waves |
| Avanzini *et al.*\(^10\)                             | 2014                    | 12                  | 26.3±16.7 years          | NCSE, GTCS, nocturnal fear, dyscognitive symptoms, staring, fear expression | Interictal- frontal and frontotemporal sharp and slow-waves, ictal EEG-prolonged burst of sub-continuous paroxysms of sharp wave or fast activities over the bilateral frontal regions |
| Freire de Moura M, *et al.*\(^11\)                   | 2016                    | 12                  | 17-57 years              | NCSE, CPS, GTCS | Frontopolar area bilaterally- slow waves and spikes-11 pts, slow waves-7 pts, spike-wave complexes-5 pts, spikes- 5 pts, bursts duration-4 s to 60 min |

of both the cases clearly demonstrating this phenotypic heterogeneity.

A wide spectrum of EEG abnormalities is seen in r(20) patients probably depending upon the brain maturation and degree of mosaicism. Moreover, the EEG features are dynamic and may evolve over time in an individual patient. Interictal EEG background may be normal to mildly slow or demonstrate bursts of sharply contoured theta activity. Runs of bi-frontal spike and wave activity have been reported as a distinct pattern in r(20) syndrome.\(^2\) Ictal EEGs may point towards frontal onset with prolonged runs of diffuse slowing with frontal dominance intermixed with bi-frontal sharp wave discharges as seen with non-convulsive status epilepticus.\(^3\). In this series, case 1 had the classical EEG features described in ring 20 syndrome. Interictal SPECT and PET studies have shown, almost homogenously, a decrease in perfusion and metabolism over the bilateral frontal and frontotemporal cortices.\(^4\) Our patients have not undergone functional neuroimaging.

Both clinical and electroencephalographic findings in patients with r(20) syndrome may be confused with other refractory epilepsy syndromes. Lennox-Gastaut syndrome (LGS),
characterized by medically refractory seizures but the tonic and atonic drop attacks characteristic of LGS are rarely seen in r(20) syndrome. Frontal lobe epilepsy of any etiology has seizure phenomenology and EEG similarities with r(20) syndrome. The nocturnal EEG pattern in r(20) may also have features of continuous spike and wave discharges in slow-wave sleep (CSWS).

This case series clearly demonstrates the phenotypic heterogeneity of ring chromosome 20 syndrome, which is closely related to the degree of mosaicism in the cell lines. Case 2 with 100% ring chromosomes showed an early onset of seizures with marked dysmorphism and developmental disabilities compared to case 1. The percentage of cells with the ring(20) in mosaic patients appears to be inversely correlated with the response to antiepileptic drugs.[1] This case series confirms this observation. It is advisable to add karyotyping as one of the earlier investigations in the workup of MRI negative refractory epilepsies in children.

Table 2 summarizes the major reports on this rare syndrome in the published literature.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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