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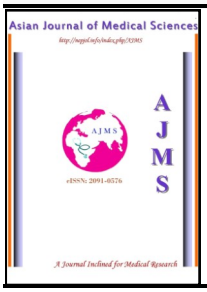

Ring Chromosome 20 Associated with Refractory Epilepsy: A Case Report

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Abstract

Ring chromosome 20 is a rare chromosomal abnormality characterized mainly by refractory epileptic seizures, cognitive and behavioral problems, and absence of definite dysmorphic features. We report a 5-year-old boy with refractory epilepsy and minimal dysmorphic features who first presented with mild developmental delay at 11 months of age. The karyotype of the child was 46,XY,r(20)(p13q13.3). Till date there are 69 cases of ring chromosome 20 reported in the literature, including mosaics and supernumerary ring chromosomes. To our knowledge, this is the first case of ring chromosome 20 with refractory epilepsy reported from the south Indian population.

Key Words: *Ring chromosome 20; epilepsy; electroencephalogram; behavioral problems*

1. Introduction

Constitutional ring chromosomes result from rare intra-chromosomal fusions occurring in about 1 in 30,000 to 60,000 births.[1] Ring chromosomes arise from unstable telomeres or subtelomeric breaks on chromosomes that resolve and stabilize by circularizing. This fusion event can produce terminal arm inversions, deletions and duplications that may involve telomeres and subtelomeres.[2] Among the most common naturally occurring constitutional ring chromosomes, ring chromosome 20 is quite common. The ring chromosome 20 syndrome is characterized by seizures, nocturnal tonic seizures, and an electroencephalogram (EEG) with long periods of bilateral high amplitude slow activity and intermixed spikes.[3] The ring chromosome 20 is increasingly recognized in recent times since its identification in 1972.[4] Clinical diagnosis is often missed or delayed because of paucity of phenotypic features. Till date 69 cases were reported including mosaics and supernumerary rings. The mosaicism ratio was unrelated to clinical phenotype, and this ratio is significantly associated with age at seizure onset, intelligence quotient and malformation, but not with seizure response to treatment.[5-6] The epilepsy associated with ring 20 constitutes a new syndrome providing an opportunity to test for a novel genetic mechanism in epilepsy.[3] A few dysmorphic features, mild to moderate mental retardation, and intractable seizures, including recurrent episodes of non-convulsive status epilepticus, frequent subtle nocturnal frontal lobe seizures, and a characteristic EEG pattern, requiring full-night video-EEG and cognitive deterioration are characteristics of this new syndrome.[7] We describe a five-year-old boy with ring chromosome 20 and refractory seizures and correlate the etiological basis for intractable seizures.

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2. Case Report

Clinical Presentation at 11months age: The proband was referred to our Genetic clinic with developmental delay. He was 11 months of age born as a second child to a non-consanguineous couple. There was no history of convulsions till then and also any family history of seizure disorder. Their first girl child was normal. Pro-band was lost for follow-up for the subsequent work-up.

Clinical Presentation at five years of age: At the age of 5 years he was brought for follow-up because of recurrent seizures since the age of 3 years. The seizures were quite atypical with brief and sudden loss of concentration followed by typical tonic-clonic seizures. He is not toilet trained and becomes restless with sudden emotional outbursts such as shouting or crying

and keeps awake during nights. Physical growth is appropriate for the age. Clinically he had a few dysmorphic features: brachycephaly, wide palpebral fissure with prominent eyes and short neck. His speech is restricted to two letter words and expresses with one to two word sentences or by gestures. He says all the alphabets but cannot write. Gross and fine motor skills are normal. He is partially independent and is restless with gravitational insecurity.

Clinical Investigations: EEG done at the onset of seizures at 3 years of age showed 6-7 Hz/sec background activities and transient spikes and wave activity of 2 Hz from left side leads with secondary generalization. A recent EEG of the sleep record showed 8-9 Hz/sec background activity of 30-50 micro-volts bihemispherically with transient spikes and waves. Assessment of Intelligence quotient (IQ) is 55 on SFB and KT scale. CT scan at the age of 2 years and recent MRI showed small ischemic/ demyelinating areas in the right corona radiata and fronto-parietal white matter. The frequency of the seizures varied from 10-15 times a day. Initially he responded to anti-epileptic drugs but started getting atypical and total seizures later. There was no response to most of the anticonvulsant drugs used in the last 3 years.

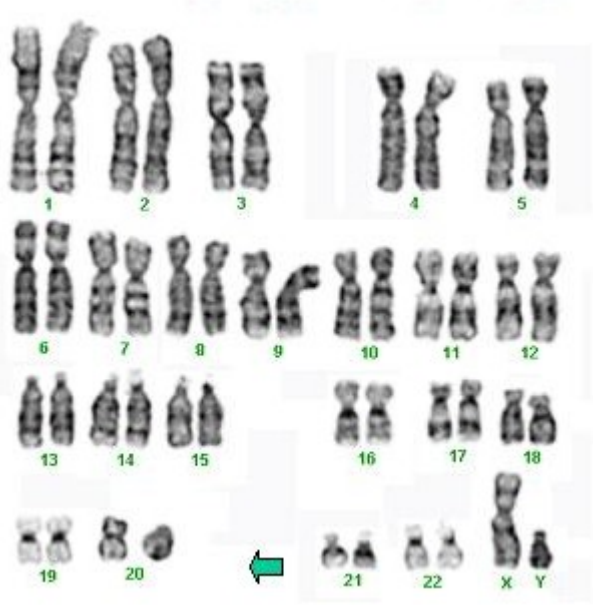

Fig-1: Karyogram showing the ring 20 chromosome (arrow)

Cytogenetic and Fluorescence *in-situ* hybridization analysis (FISH): After evaluation for developmental delay, chromosomal analysis was performed. Subsequently, chromosomal analyses were performed in the parents as well as the sister. Metaphase chromosomes were prepared from peripheral blood lymphocyte cultures using standard cytogenetic protocols. Chromosomal analysis was done on GTG-banded metaphases. FISH was carried out using whole chromosome painting probes (WCP) for chromosome 20 (VYSIS, USA). The denaturation, hybridization and signal detection were done according to the instruction manual supplied by the manufacturer.

Results: GTG-banded metaphases revealed a karyotype of 46,XY,r(20)(p13q13.3) (Fig.1). A total of 50 metaphases were studied, all metaphases showed the ring chromosome 20 indicating 100% ring formation. FISH using WCP for chromosome 20 confirmed the 20 ring in all the cells (data not shown). Parental and sister's karyotypes were normal.

3. Discussion

Ring chromosome formation occurs when there would be breaks in the chromosomal arms resulting in the fusion of the proximal broken ends. This leads to the loss of distal chromosomal material. Due to telomere dysfunction triggering fusion of reactive chromosome ends there could not be a major loss of genetic material. Ring chromosomes are rare and phenotype-genotype correlations have been extremely difficult. Almost 99% of them have a sporadic origin. Ring 20 syndrome is recently described as a separate clinical entity presenting with refractory epilepsy. The instability of the ring at mitosis, the ´´general ring syndrome`` and its dynamic mosaicism are factors that make adequate comparison of patients very difficult.

The mechanism underlying epilepsy in ring 20 syndrome remains unknown. Two possibilities have been raised previously, a structural abnormality of the ring chromosome that delays cell proliferation during development of the brain and deletions of certain telomeric genes. The typical clinical presentation of ring 20 is difficult to explain, possibly it could be a channelopathy involving the two genes CHRNA4 and KCNQ2 located on the 20q13.[8] The genetic imbalance created by these telomeric breaks during ring formation may lead to loss of these genes that are essential for control of seizure progression and ring 20 could thus be an epileptic channelopathy. For example Conlin et al in 2011 analyzed 28 cases out of which three cases had a deletion that included the candidate genes CHRNA4 and KCNQ2 genes.[9] However, a case of ring chromosome 20 syndromes without deletions of the subtelomeric and

CHRNA4-KCNQ2 gene loci was also reported.[10] Giardino et al[11] aimed at detecting the genetic mechanism underlying r(20) syndrome by FISH and array-CGH experiments, which indicated that the presence of cryptic deletions on chromosome 20 are not the cause of r(20) chromosome associated disease. They suggested that an epigenetic mechanism perturbing the expression of genes close to the telomeric regions rather than deletion of genes located at the distal 20p and/or 20q regions, may underlie the manifestation of r(20) syndrome.

It is also suggested that striatal dopamine could be modulated in ring 20 epilepsy and dysfunction of this neurotransmitter may impair the mechanism that interrupt seizures or the formation of rings may interfere with cell division and can cause the typical phenotype.[12-13]

Ring chromosome 20 epilepsy is undoubtedly a rare condition. To date there is no published data on the incidence or prevalence of this syndrome. There are 69 cases reported in the literature. To our knowledge this is the first report of ring 20 from Southern part of India with refractory epilepsy. Identification of ring 20 is essential for clinical management due to their non-responsiveness to treatment. Vagus nerve stimulation (VNS) is one of the suggested choices for the treatment for refractory epilepsy. Only one case of ring chromosome 20 treated with VNS has been reported in the literature. Chawla et.al, reported a 6-year old girl with this syndrome who responded successfully to VNS.[14] However, in other case the VNS therapy was unsuccessful in controlling seizures, but a surgical treatment (corpus callosotomy) was performed in which the severity of the tonic seizures was diminished, but frequency was unchanged.[15]

The long-term prognosis of ring 20 is variable and varies from person to person, the severity of the epilepsy and the associated learning and behavioral problems. More studies are needed to clarify the longer-term outlook for people with ring 20.

4. Conclusion

In summary we had identified a ring chromosome 20 syndrome in a boy with refractory seizures. The identification of this syndrome should alert the neurologists to perform cytogenetic analysis in patients with intractable epilepsy. Since chromosomal analysis is not a routine investigation for epilepsy, this study highlights the need for chromosomal analysis in patients manifesting refractory seizure disorders/ atypical seizures as they may go undetected.

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